MENTAL HEALTH CLINICAL ADVISORY GROUP AGENDA
SPECIAL MEETING

Thursday, January 24, 2019
2:00 – 4:00
Human Services Building
500 Summer St
Rm 280
Salem, OR 97301

TYPE OF MEETING	Advisory Board
FACILITATOR	George Fussell
NOTE TAKER	Amanda Parish

	APPOINTED MEMBERS				OHA
	Glena Andrews, Ph.D.		Peter Grover, M.S., Ph.D., MSPsyPh		Trevor Douglass, DC, MPH
	William Beck, Pharm.D.		Lorinda Haynes, RPh		Amanda Parish
	Chris Bouneff				Jonnaliz Corbett
	Keith Cheng, MD		Bob Joondeph, JD		
	Neil Falk, MD		Nick Kashey, MD		
	George Fussell, MD		Lori Martin, MSN, PMHNP		
			Davíd Nagarkatti-Gude, MD, PhD		

DISCUSSION TOPICS	TIME	RESPONSIBLE PARTY
Call to order	5 min	George Fussell/OHA
Review of published research/practice guidelines for bipolar disorder	60 min	All
Public comment	10 min	George Fussell
Break	10 min	---------
Discussion of the most immediate research topic needs moving forward Creation of report-out points to share with the larger MHCAG regarding the research group's recommendations for the direction of the treatment care guide (e.g, evidence gaps)	35 min	All
Adjournment	----------	George Fussell

Next **Regular Meeting**: Thursday, March 7, 2019 from 1:00-4:00pm

meeting Primarily by skype conference

Human Services Building

Room # 280

500 Summer St

Salem, OR 97301

Check this website for Additional Information:

https://www.oregon.gov/oha/HSD/OHP/Pages/PT-MHCAG.aspx

MHCAG Members and the Public are welcome to attend the meeting in person in Salem or by phone at the number below

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Bipolar Disorders 2013: 15: 1–44

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Guidelines Update

Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013

Yatham LN, Kennedy SH, Parikh SV, Schaffer A, Beaulieu S, Alda M, O'Donovan C, MacQueen G, McIntyre RS, Sharma V, Ravindran A, Young LT, Milev R, Bond DJ, Frey BN, Goldstein BI, Lafer B, Birmaher B, Ha K, Nolen WA, Berk M.
Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013.
Bipolar Disord 2013: 15: 1–44. © 2012 John Wiley & Sons A/S.
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The Canadian Network for Mood and Anxiety Treatments published guidelines for the management of bipolar disorder in 2005, with updates in 2007 and 2009. This third update, in conjunction with the International Society for Bipolar Disorders, reviews new evidence and is designed to be used in conjunction with the previous publications.

The recommendations for the management of acute mania remain largely unchanged. Lithium, valproate, and several atypical antipsychotic agents continue to be first-line treatments for acute mania. Monotherapy with asenapine, paliperidone extended release (ER), and divalproex ER, as well as adjunctive asenapine, have been added as first-line options.

For the management of bipolar depression, lithium, lamotrigine, and quetiapine monotherapy, as well as olanzapine plus selective serotonin reuptake inhibitor (SSRI), and lithium or divalproex plus SSRI/bupropion remain first-line options. Lurasidone monotherapy and the combination of lurasidone or lamotrigine plus lithium or divalproex have been added as a second-line options. Ziprasidone alone or as adjunctive therapy, and adjunctive levetiracetam have been added as not-recommended options for the treatment of bipolar depression.

Lithium, lamotrigine, valproate, olanzapine, quetiapine, aripiprazole, risperidone long-acting injection, and adjunctive ziprasidone continue to be first-line options for maintenance treatment of bipolar disorder. Asenapine alone or as adjunctive therapy have been added as third-line options.

Lakshmi N Yatham[a], Sidney H Kennedy[b], Sagar V Parikh[b], Ayal Schaffer[b], Serge Beaulieu[c], Martin Alda[d], Claire O'Donovan[d], Glenda MacQueen[e], Roger S McIntyre[b], Verinder Sharma[f], Arun Ravindran[b], L Trevor Young[a], Roumen Milev[g], David J Bond[a], Benicio N Frey[h], Benjamin I Goldstein[i], Beny Lafer[j], Boris Birmaher[k], Kyooseob Ha[l], Willem A Nolen[m] and Michael Berk[n,o]

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Corresponding author:
Lakshmi N. Yatham, MBBS, FRCPC, MRCPsych (UK)
Department of Psychiatry
University of British Columbia
2255 Wesbrook Mall
Vancouver, BC V6T 2A1
Canada
Fax: 604-822-7922
E-mail: yatham@interchange.ubc.ca

Affiliations for all authors are listed before the references.

Section 1. Introduction

In 2005, the Canadian Network for Mood and Anxiety Treatments (CANMAT) published guidelines for the management of bipolar disorder (BD) (1), followed by updates in early 2007 (2) and in 2009 [in collaboration with the International Society for Bipolar Disorders (ISBD)] (3). This update includes data published in 2009 through early 2012, and is designed to be used in conjunction with the 2005 CANMAT guidelines and previous updates (1–3).

The purpose of this update is to add previously unpublished material to the guidelines. This update is designed to be used with the previous iterations of the guidelines. As in the previous updates, the guidelines are divided into eight sections (Table 1.0) and the same numbering system has been used for the sections and tables in order to facilitate ease of use. New evidence is incorporated into the management recommendations, and changes to the recommendation tables have been clearly denoted with ***bold italics*** and a footnote, and have been described in the text. The objective is to ensure that the CANMAT guidelines for treatment of BD remain current and useful for the practicing clinician.

Central to this update are the tables showing first-line, second-line, third-line, and not-recommended treatment options. These tables may assist in the selection of treatment, while the text of this update and the previous guideline iterations provide the details of the evidence that was used to make the recommendations. Similarly, the treatment algorithms condense key management information into a decision-tree flow-chart; the clinician should begin by positioning the patient in the decision tree, and then follow the arrows for subsequent management suggestions.

Search strategies and methods to assess evidence were as described in the original guidelines (1). Evidence available only in abstract form was also considered in order to ensure that the recommendations are as up to date as possible. The criteria for rating strength of evidence and making a clinical recommendation are shown in Tables 1.1 and 1.2.

We caution the readers that the evidence-based guidelines are limited by the data that are available. For instance, drugs that have patents are likely to have been more widely studied and their design was likely influenced by the goals of the sponsor to obtain approval. Generic drugs, although may be useful, may not have been widely studied because of lack of sponsorship, thus affecting their placement in the treatment algorithm. Finally, it is important to understand that the lack of evidence for a particular drug does not imply inefficacy or efficacy. Clinicians must exercise caution and choose treatments based on a careful risk–benefit analysis for each situation.

Table 1.0. Overview of guideline sections

Section 1. Introduction
Section 2. Foundations of management
Section 3. Acute management of bipolar mania
Section 4. Acute management of bipolar depression
Section 5. Maintenance therapy for bipolar disorder
Section 6. Special populations
Section 7. Acute and maintenance management of bipolar II disorder
Section 8. Safety and monitoring
Closing statement
Disclosures
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Section 2. Foundations of management

Epidemiology

Prevalence. The World Mental Health Survey Initiative, involving 61392 people in nine countries in North and South America, Europe, and Asia, reported lifetime (and 12-month) prevalence estimates of 0.6% (0.4%) for BD I, 0.4% (0.3%) for BD II, and 1.4% (0.8%) for subthreshold BD (4). However, there were large cross-national differences in rates, with the lifetime rates ranging from 0 to 1% for BD I, 0 to 1.1% for BD II, and 0.1 to 2.4% for subthreshold BD.

In the Canadian Community Health Survey–Mental Health and Well-Being (CCHS 1.2), the prevalence of BD was significantly lower among

Table 1.1. Evidence criteria

1	Meta-analysis or replicated double-blind (DB), randomized controlled trial (RCT) that includes a placebo condition
2	At least one DB-RCT with placebo or active comparison condition
3	Prospective uncontrolled trial with at least ten or more subjects
4	Anecdotal reports or expert opinion

Table 1.2. Treatment recommendation

First line	Level 1 or level 2 evidence plus clinical support for efficacy and safety
Second line	Level 3 evidence or higher plus clinical support for efficacy and safety
Third line	Level 4 evidence or higher plus clinical support for efficacy and safety
Not recommended	Level 1 or level 2 evidence for lack of efficacy

immigrant, compared to non-immigrant, subjects, but immigrants with BD were significantly less likely to report contact with mental health professionals (5).

Impact. A meta-analysis of 15 studies identified a high prevalence of lifetime suicide attempts both in patients with BD I (36.3%) and in those with BD II (32.4%) (6). In the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) (n = 4360), the completed suicide rate was 0.014 per 100 person-years (7). A large cohort study found that among men, the absolute risk of suicide was highest with BD (7.8%) compared to any other psychiatric condition, and among women, BD was associated with the second highest risk, at 4.8%, just below schizophrenia at 4.9% (8). Claims database data demonstrate the significant economic impact of suicide attempts, with one-year healthcare costs in the period post-attempt being more than double those in the year prior to an attempt (9).

The large, two-year, prospective, observational European Mania in Bipolar disorder Longitudinal Evaluation of Medication (EMBLEM) study (n = 2289) found high work impairment in 69% of patients at baseline and 41% at two years (10). Rapid cycling, high baseline work impairment, lower levels of education, recent admissions, mania symptom severity, and overall severity all predicted higher work impairment, while living in a relationship and independent housing predicted lower work impairment at follow-up. Similarly, the Understanding Patients' Needs, Interactions, Treatment, and Expectations (UNITE) global survey (n = 1300) revealed that only one-third of patients with BD were employed full-time (11). In the UNITE survey, treatment of depression, weight gain, and quality of life were identified by patients with BD as aspects of care most in need of improvement (11).

A meta-analysis of data from 12 trials (n = 1838) found that the self-esteem of patients with remitted BD was significantly lower than that of controls but significantly higher than that of patients with remitted major depressive disorder (MDD) (12). In addition, self-esteem may follow a fluctuating course during remission of BD.

In a health claims database, risk of arrest was associated with substance use, poor refill compliance, and prior arrest (13). Among patients treated with an atypical antipsychotic agent, there was a lower risk of arrest in those who had frequent outpatient visits (approximately monthly) compared to those who did not.

Course. In a sub-analysis of 771 patients in the two-year EMBLEM study, approximately one in three presented with a mixed episode, which was associated with a lower likelihood of recovery and greater use of antidepressant therapy compared to a pure manic state during follow-up (14). The Systematic Treatment Optimization Program for Early Mania (STOP-EM) project followed 53 patients presenting with a first episode of mania, and found that more than half experienced recurrence of a mood episode during the one-year follow-up, with a mean time to event of 7.9 months (15). The mean duration of mood episodes in BD I, in a longitudinal analysis of 219 patients followed for up to 25 years, was found to be 13 weeks (16).

Diagnostic assessment

The proposed fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) is scheduled to be completed by mid-2013. Revisions suggested by the International Society for Bipolar Disorders Diagnostic Guidelines Task Force (17) were summarized in the previous update to these guidelines (3). DSM-5 will have separate chapters for bipolar and related conditions, and depressive disorders. The condition 'BD not otherwise specified' (NOS) has been replaced with 'bipolar conditions not elsewhere classified'. Substance-induced BD and BD associated with a general medical condition have been added.

In the criteria for a manic episode, 'abnormally and persistently increased activity or energy' has been added to criterion A, which previously referred only to a distinct period of abnormally and persistently elevated, expansive, or irritable mood. A manic episode emerging during antidepressant treatment can qualify as a manic episode of BD, provided that the symptoms persisted beyond the physiological effects of treatment. The 'mixed episode' diagnosis has been replaced with a 'mixed features' specifier, requiring three symptoms of the opposite pole, which would apply to manic, hypomanic, and depressive episodes (18). In addition, dimensional specifiers for anxiety and suicide risk have also been proposed.

Chronic disease management

BD is a chronic illness and patients require long-term multi-disciplinary management as described in the 2005 guidelines (1). A small, cluster-randomized controlled trial (RCT) examined the effect of community mental health teams (n = 23) who received enhanced training in relapse prevention

versus treatment-as-usual (TAU) in 96 patients with BD (19). The median survival time of patients treated by the trained teams was prolonged by 8.5 weeks compared to those receiving TAU (42 weeks versus 33.5 weeks). A collaborative care model including clinician support through the use of simplified guidelines was found to result in significantly greater guideline-concordant therapy over a three-year follow-up period compared to TAU in patients with BD (n = 306) (20).

Data suggest that use of a symptom checklist can substantially increase the recognition of early warning signs for depressive or manic relapse (21). There was a positive correlation between the frequency of monitoring and social/occupational functioning.

Psychosocial interventions

When used as adjuncts to pharmacotherapy, psychosocial interventions such as group psychoeducation, cognitive behavior therapy (CBT), and interpersonal and social rhythm therapy (IPSRT) have demonstrated significant benefits, both in the treatment of acute depressive episodes and also as long-term maintenance treatment, including decreased relapse rates, mood fluctuations, need for medications, and hospitalizations, as well as increased functioning and medication adherence (1–3). Therefore, providing psychological treatments –and, in particular, brief psychoeducation, which has been demonstrated to be as effective as CBT at much lower cost (22) – is an essential aspect of managing patients with BD.

A family-focused treatment approach designed to help caregivers improve illness management skills and their own self-care was shown to effectively reduce depressive symptoms and health-risk behavior among caregivers and family members, and reduce depressive symptoms in patients (23).

The availability of internet-based strategies has grown substantially, with demonstrated efficacy in reducing depressive symptoms and improving psychological quality of life (24–27).

Section 3. Acute management of bipolar mania

Emergency management of acute mania

The acutely manic bipolar patient may present in an agitated state that acts as a barrier to therapy, interrupts the physician–patient alliance, and creates a disruptive, even hazardous, environment. Whenever possible, oral therapy should be offered first, as evidence suggests that oral agents can be as effective as intramuscular agents (28, 29). Intramuscular injections offer an alternative when oral therapy cannot be reliably administered.

Based on current data, the oral atypical antipsychotic agents, risperidone (level 2) (29, 30), olanzapine (level 2) (30), and quetiapine (level 3) (30, 31), should be considered first in the treatment of acute agitation. In patients who refuse oral medications, intramuscular olanzapine (level 2) (32–35), ziprasidone (level 2) (35–38), and aripiprazole (level 2) (39) or a combination of intramuscular haloperidol and a benzodiazepine should be considered (level 2) (29, 35, 38, 40, 41). In general, benzodiazepines should not be used as monotherapy, but are useful adjuncts to sedate acutely agitated patients (1).

New data also support the use of intravenous sodium valproate (level 3) (42) and oral divalproex ER (level 3) (31) for rapid improvement of acute mania.

Pharmacological treatment of manic episodes

Pharmacological management of acute manic episodes should follow the algorithm outlined in Figure 3.1 (1–3). New clinical trial data, and the availability of several agents, justify some changes to the recommendations. Monotherapy with asenapine, paliperidone ER, and divalproex ER, as well as adjunctive asenapine, have been added as first-line options (Table 3.3).

Step 1. Review general principles and assess medication status: Recommendations from 2005 guidelines remain unchanged.

Step 2. First-line therapies: A comprehensive meta-analysis of 68 trials supported the efficacy of pharmacotherapy for the treatment of acute mania (43). Lithium, divalproex, risperidone ER, paliperidone ER, olanzapine, quetiapine, aripiprazole, ziprasidone, and asenapine (first line), carbamazepine, and haloperidol (second line), were significantly more effective than placebo, whereas gabapentin, lamotrigine, and topiramate were not (not recommended) (43). Haloperidol was more effective than a number of antimanic agents but not olanzapine or risperidone, both of which were more effective than valproate, ziprasidone, and lamotrigine. Two other recent meta-analyses also support the efficacy of lithium/divalproex and atypical antipsychotic agents for the treatment of acute mania (44, 45).

Lithium/divalproex. The efficacy of lithium and divalproex in the management of acute mania is

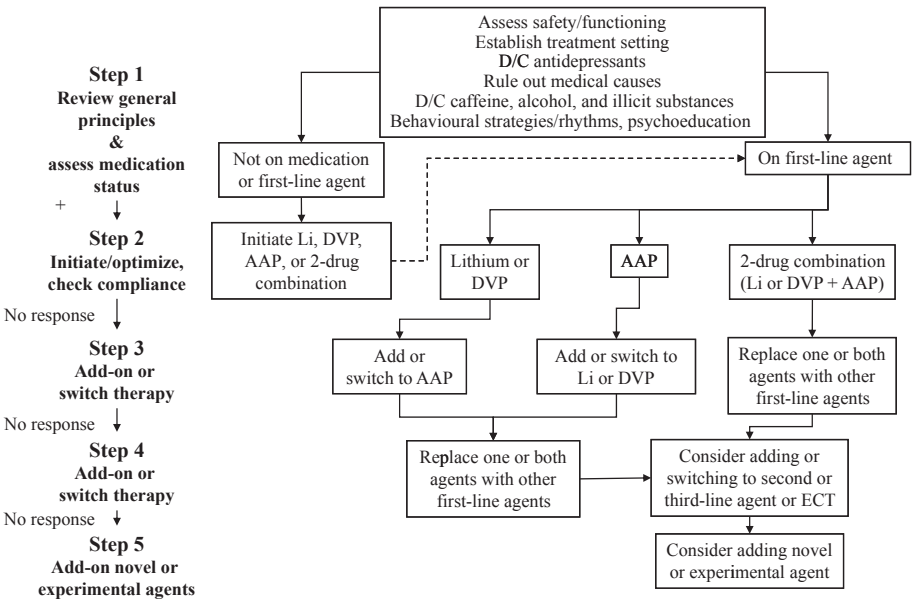


Fig. 3.1. Treatment algorithm for acute mania. Novel/experimental agents: zotepine, levetiracetam, phenytoin, mexiletine, omega-3-fatty acids, calcitonin, rapid tryptophan depletion, allopurinol, amisulpride, folic acid, memantine. D/C = discontinue; Li = lithium; DVP = divalproex; AAP = atypical antipsychotic agent.

Table 3.3. Recommendations for pharmacological treatment of acute mania

First line	Monotherapy: lithium, divalproex, ***divalproex ER***[a], olanzapine[b], risperidone, quetiapine, quetiapine XR, aripiprazole, ziprasidone, ***asenapine***[a], ***paliperidone ER***[a] Adjunctive therapy with lithium or divalproex: risperidone, quetiapine, olanzapine, aripiprazole, ***asenapine***[a]
Second line	Monotherapy: carbamazepine, carbamazepine ER, ECT, ***haloperidol***[a] Combination therapy: lithium + divalproex
Third line	Monotherapy: chlorpromazine, clozapine, oxcarbazepine, tamoxifen, ***cariprazine***[a] (not yet commercially available) Combination therapy: lithium or divalproex + haloperidol, lithium + carbamazepine, adjunctive tamoxifen
Not recommended	Monotherapy: gabapentin, topiramate, lamotrigine, verapamil, tiagabine Combination therapy: risperidone + carbamazepine, olanzapine + carbamazepine

ECT = electroconvulsive therapy; XR or ER = extended release.
[a]***New or change to recommendation***.
[b]Given the metabolic side effects, use should be carefully monitored.

well established (level 1) (1–3). Two large, 12-week, open, randomized trials comparing lithium to divalproex found comparable efficacy and tolerability of these agents for the treatment of acute mania (46, 47).

A large (n = 521), 12-week RCT compared divalproex, olanzapine, and placebo in patients with mild to moderate mania. At three weeks, improvements in mania scores were significant with olanzapine versus placebo but not with divalproex versus olanzapine or placebo. After 12 weeks of treatment, improvements in both active treatment groups were significant versus placebo, but olanzapine was significantly more efficacious than divalproex (48).

The results of two three-week RCTs assessing the efficacy of the ER formulation of divalproex for the treatment of acute mania have now been published (49, 50) One study demonstrated statistically significant improvements in manic symptoms compared to placebo (level 2) (49), while the other did not (50). In the first, Bowden et al. (49) found significantly greater improvement in manic symptoms and higher response rates (48% versus 34%, p = 0.012) with divalproex ER versus placebo, while Hirschfeld et al. (50) found no statistically significant difference in mania scores with divalproex ER versus placebo; however, discontinuation rates were over 80% and dosing may have been lower than optimal.

Given the level 1 evidence to support the immediate-release formulation of divalproex, as well as the high discontinuation rate and dosing issues in the negative trial, divalproex ER has been added as a first-line therapy, although, if prescribed, attention should be paid to dosing and serum levels.

Atypical antipsychotic monotherapy. Substantial RCT data support the efficacy of atypical antipsychotic monotherapy with olanzapine, risperidone, quetiapine, ziprasidone, and aripiprazole for the first-line treatment of acute mania (level 1) (1–3).

As reviewed earlier, a large (n = 521), 12-week RCT comparing divalproex, olanzapine, and placebo in patients with mild to moderate mania found that improvements in mania scores with olanzapine were significantly greater than with placebo after three weeks, and greater than with both divalproex and placebo after 12 weeks (48).

In a meta-analysis of six aripiprazole monotherapy RCTs in acute mania involving 2303 patients, the effect size was 0.34 versus placebo at week three, with a response generally being seen at day three (level 1) (51). A 12-week RCT of aripiprazole monotherapy in acute mania found significantly greater improvements in the Young Mania Rating Scale (YMRS) scores at week three with aripiprazole (−12.0, $p < 0.05$) or haloperidol (−12.8, $p < 0.01$) compared to placebo (−9.7), which were maintained to week 12; haloperidol was included as an active control and was not statistically compared to aripiprazole (52).

Additional data are also available comparing ziprasidone to placebo and haloperidol in a 12-week RCT. Improvements in mania scores and response rates at week three were significantly greater than with placebo for both active treatments, but haloperidol was significantly more effective than ziprasidone. During the nine-week extension phase, responses were maintained for the majority of patients receiving active treatments. Ziprasidone showed a superior tolerability profile and lower discontinuation rates during the extension phase (53).

Two three-week, double-blind RCTs demonstrating the efficacy of paliperidone ER in patients with manic or mixed episodes, which were previously cited in abstract form, have now been published (level 1) (54, 55). Paliperidone ER has been upgraded to a first-line option.

Two three-week, double-blind RCTs demonstrating the efficacy of asenapine as monotherapy for acute mania (56, 57), as well as nine-week and 40-week extension phase results demonstrating the maintenance of benefits (58, 59), which were previously cited in abstract form, have now been published (level 1). Asenapine has been upgraded to a first-line option.

Atypical antipsychotic combination therapy. As previously reported, a six-week, placebo-controlled RCT showed that adding aripiprazole to lithium or divalproex in 384 patients with an inadequate response was significantly more effective than placebo from week 1 onward (60). A 46-week open-label extension of this study found that aripiprazole as an adjunct to lithium or divalproex provided continued improvement in mania but not depression (61).

A 12-week RCT demonstrating significant improvements in mania symptoms with adjunctive asenapine added to lithium/divalproex compared to placebo that was previously cited in abstract form has still not been published, but 40-week extension results have now been reported (level 2) (62). Of the original 318 patients, 71 completed the 40-week extension; there were additional improvements in mania scores at 52 weeks in both the asenapine and placebo groups. Adjunctive asenapine has been moved to a first-line option.

Step 3. Add-on or switch therapy (alternate first-line therapies): No changes from 2005 guidelines.

Step 4. Add-on or switch therapy (second- and third-line therapies):

Second-line options. A small RCT in 44 patients with manic, mixed, or depressive episodes found that among patients who were on, or thought to benefit from, carbamazepine, there were no differences in mood ratings or in the total level of adverse events with immediate-release versus ER carbamazepine (63, 64). However, there were significantly fewer autonomic and gastrointestinal adverse events with carbamazepine ER (64).

While electroconvulsive therapy (ECT) can be an effective option, research studies have not been rigorous and therefore it continues to be recommended as a second-line therapy (level 3) (1). In an RCT of ECT as adjunct to antipsychotic therapy, bilateral, twice-weekly ECT delivered at stimulus intensities just above seizure threshold was as effective and safe as ECT administered at stimulus intensities 2.5 times the seizure threshold in rapidly resolving the symptoms of acute mania (65).

In a meta-analysis of 13 haloperidol-controlled trials, the drug was significantly more effective than lithium, divalproex, quetiapine, aripiprazole,

ziprasidone, carbamazepine, asenapine, and lamotrigine (43). Given the strong data for efficacy, haloperidol has been upgraded to a second-line option. However, haloperidol should only be used on a short-term basis to treat acute mania as continuation of haloperidol may increase the risk of a depressive episode (43).

Third-line options. A small (n = 60), 12-week RCT comparing oxcarbazepine to divalproex in patients with acute mania found no significant differences in improvements in mania scores or remission rates between the two treatments, but divalproex was associated with more adverse events (66). In another small (n = 52) RCT, adjunctive oxcarbazepine was more effective than carbamazepine as add-on therapy in patients who had previously been inadequate responders to lithium, although both agents improved manic and depressive scores versus baseline (67). As described in the previous updates to these guidelines, there are other small positive trials, but there is also a negative placebo-controlled RCT, and these new trials are small and do not include a placebo control arm; therefore, oxcarbazepine remains as a third-line option.

Cariprazine, a new dopamine D3/D2 receptor antagonist, appears promising for the treatment of acute mania, but has not yet been approved by Canadian or US regulatory agencies. The results of a three-week, phase 2, RCT, presented in abstract form, reported significant reductions in mania scores with cariprazine compared to placebo (level 2) (68).

Step 5. Add-on novel or experimental agents: Zotepine is an antipsychotic agent that has been approved in some European countries and in Japan for the treatment of schizophrenia. In a four-week, single-blind trial, adjunctive zotepine added to lithium or divalproex therapy in 45 inpatients with moderate-to-severe mania was as effective as adjunctive haloperidol in improving mania scores (69).

Two RCTs have now demonstrated the efficacy of adjunctive allopurinol for the treatment of acute mania (level 1) (70, 71). In an eight-week RCT, allopurinol as adjunct to lithium plus haloperidol was found to be significantly more effective than placebo in 82 patients hospitalized with acute mania (70). In the second RCT (n = 180), comparing the addition of allopurinol, dipyridamole, or placebo to lithium for four weeks, allopurinol led to significantly greater improvements in mania scores and remission rates versus placebo (71). Although there is level 1 evidence for the use of allopurinol, given that it can cause hepatomegaly as well as hypersensitivity reactions such as Steven–Johnson syndrome and toxic epidermal necrolysis, it is recommended only for those patients that are refractory to other first-, second, and third-line treatments.

Preliminary evidence previously suggested antimanic efficacy associated with tamoxifen (1). A six-week, placebo-controlled RCT has now demonstrated significantly greater improvements in mania scores with tamoxifen as an adjunct to lithium in 40 inpatients with acute mania compared to lithium alone (level 2) (72).

In a three-week RCT in 88 acutely manic patients on divalproex, adjunctive folic acid was significantly better than placebo in improving mania scores (level 2) (73).

A three-week, open-label, pilot trial in 33 patients with manic or mixed episode BD I found that 30–50% of patients responded to doses of memantine ranging from 20 mg to 40 mg (level 3) (74).

Given the limited data, at this time, these agents can only be recommended as add-on therapies after failure of standard therapies.

Adjunctive therapies with negative data requiring further study: A six-week RCT that found no significant improvements in manic symptoms with adjunctive flexible-dose paliperidone in patients with manic or mixed episodes who had not responded to lithium or divalproex, was previously cited in abstract form and has now been published (level 2, negative) (75). Given that paliperidone monotherapy is effective, and that lithium or valproate does not affect the metabolism of paliperidone, the lack of efficacy of combination therapy is surprising. In spite of the fact that it was a flexible-dose trial, paliperidone ER may have been under-dosed, since the monotherapy studies suggest that 12 mg/day is the most effective dose and the mean dose used was 8.1 (3.30) mg/day, with 45% of the patients receiving a final dose of 6 mg/day in this trial. In addition, a post-hoc subgroup analysis found that adjunctive paliperidone ER was superior to lithium or divalproex monotherapy for patients diagnosed with a manic episode ($p = 0.020$).

A three-week RCT in over 600 patients with BD mania/mixed episodes found no significant benefits with adjunctive ziprasidone at either high (120–160 mg/day) or low (40–80 mg/day) doses compared to placebo (76). The trial has not yet been published, but the results are available at http://www.clinicaltrials.gov.

In light of these negative trials, adjunctive use of paliperidone ER or ziprasidone, at the dosages

used by the above-noted studies, is not recommended.

Mania with psychotic features

A meta-analysis of four RCTs of aripiprazole supports its antipsychotic effects, as measured by the Positive and Negative Syndrome Scale (PANSS) score, during the acute manic and maintenance phases of BD (77). The effect sizes for aripiprazole versus placebo were highest for the PANSS–positive subscale (0.28) and the PANSS–hostility subscale (0.24).

Mixed states

A six-week RCT (n = 202) evaluating adjunctive olanzapine compared to adjunctive placebo demonstrated significantly greater and earlier reductions in manic and depressive symptoms in patients with mixed episodes inadequately controlled with divalproex (78). Post-hoc analysis of this study found that response (Clinical Global Impression–Severity decrease ≥ 1) at day two was predictive of mixed symptom remission (79).

A post-hoc analysis of two asenapine RCTs in patients with manic or mixed episodes demonstrated statistically significant decreases in depression scores with asenapine versus placebo in patients with severe baseline depressive symptoms (n = 604); differences between the active comparator olanzapine and placebo were not significant, which makes the interpretation of these results more difficult as it raises the possibility of a negative study (80).

Section 4. Acute management of bipolar depression

Pharmacological treatment of depressive episodes

Pharmacological management of acute bipolar depressive episodes should follow the algorithm outlined in Figure 4.1 (1–3). The recommendations for first- and second-line therapies are largely unchanged, except for the addition of lurasidone monotherapy and lurasidone or lamotrigine plus lithium or divalproex as second-line options. Based on negative data, ziprasidone alone or as adjunctive therapy, and adjunctive levetiracetam have been added as not-recommended options for the treatment of bipolar depression (Table 4.3).

Several meta-analyses have assessed the efficacy of atypical antipsychotic agents and other medications for the treatment of bipolar depression (81, 82). A meta-analysis of atypical antipsychotic agents for bipolar depression included five trials (two monotherapy trials with each of quetiapine

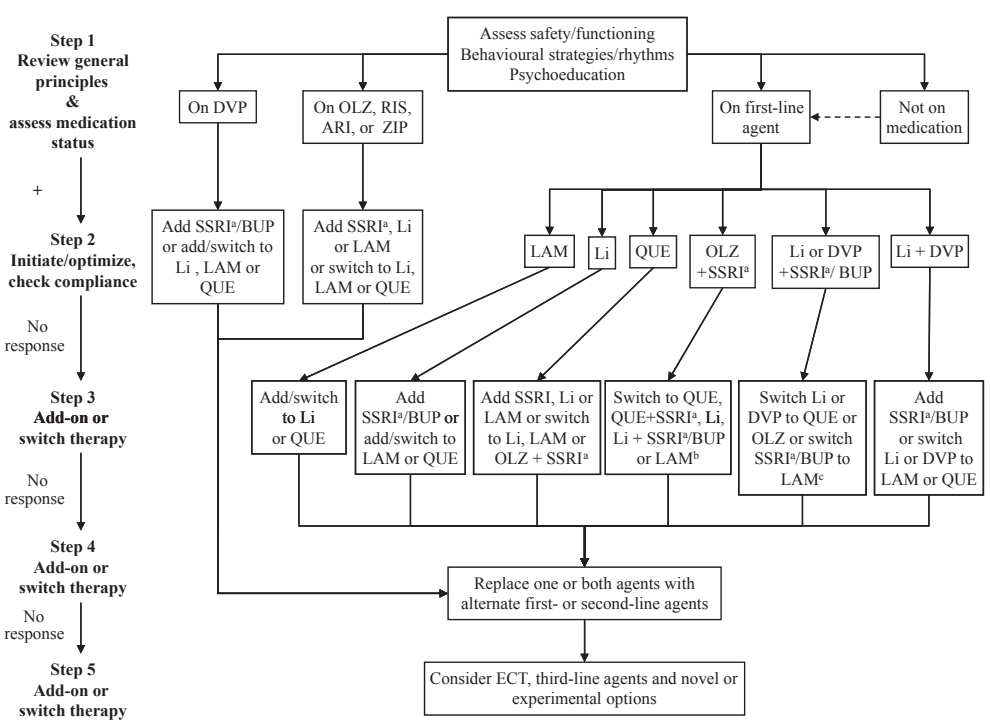


Fig. 4.1. Treatment algorithm for the management of bipolar I depression. Novel/experimental agents: adjunctive pramipexole, eicosapentaenoic acid (EPA), riluzole, topiramate, N-acetyl cysteine (NAC), ketamine, armodafinil, and chronotherapy. DVP = divalproex; OLZ = olanzapine; RIS = risperidone; ARI = aripiprazole; ZIP = ziprasidone; SSRI = selective serotonin reuptake inhibitor; BUP = bupropion; Li = lithium; LAM = lamotrigine; QUE = quetiapine; ECT = electroconvulsive therapy. [a]Except paroxetine. [b]Or switch the SSRI to another SSRI. [c]Or switch the SSRI or BUP to another SSRI or BUP.

Table 4.3. Recommendations for pharmacological treatment of acute bipolar I depression[a]

First line	Monotherapy: lithium, lamotrigine, quetiapine, quetiapine XR Combination therapy: lithium or divalproex + SSRI[b], olanzapine + SSRI[b], lithium + divalproex, lithium or divalproex + bupropion
Second line	Monotherapy: divalproex, ***lurasidone***[c] Combination therapy: quetiapine + SSRI[b], adjunctive modafinil, ***lithium or divalproex + lamotrigine***[c]***, lithium or divalproex + lurasidone***[c]
Third line	Monotherapy: carbamazepine, olanzapine, ***ECT***[d] Combination therapy: lithium + carbamazepine, lithium + pramipexole, lithium or divalproex + venlafaxine, lithium + MAOI, lithium or divalproex or AAP + TCA, lithium or divalproex or carbamazepine + SSRI[b] + lamotrigine, ***quetiapine + lamotrigine***[c]
Not recommended	Monotherapy: gabapentin, aripiprazole, ***ziprasidone***[c] Combination therapy: ***adjunctive ziprasidone***[c], ***adjunctive levetiracetam***[c]

AAP = atypical antipsychotic agent; ECT = electroconvulsive therapy; MAOI = monoamine oxidase inhibitor; TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitor; XR = extended release.

[a]The management of a bipolar depressive episode with antidepressants remains complex. The clinician must balance the desired effect of remission with the undesired effect of switching. See detailed discussion in *Clinical questions and controversies section*.

[b]Except paroxetine.

[c]***New or change to recommendation***.

[d]Could be used as first- or second-line treatment in certain situations (see text).

and aripiprazole, and one combination trial with olanzapine) and found significantly greater improvement compared to placebo for weeks 1–6 but not for weeks seven and eight (primarily accounted for by a tapering of effect in aripiprazole studies) (81). This suggests that the efficacy of these agents is not a class effect and that individual agents may show differential benefits, and, as such, generalizations on the role of atypical antipsychotic agents for depressive symptoms cannot be made. Another meta-analysis included 19 trials assessing mainly quetiapine (five trials) and lamotrigine (six trials), but also paroxetine, lithium, olanzapine, aripiprazole, phenelzine, and divalproex for the treatment of bipolar depression (82). This analysis found the highest reductions in Montgomery–Åsberg Depression Rating Scale (MADRS) scores with the olanzapine plus fluoxetine combination and quetiapine monotherapy compared to placebo. In this analysis, lamotrigine, paroxetine, aripiprazole, and lithium were not significantly different from placebo in improving depression scores. However, as cited in previous iterations, a meta-analysis of individual patient data supported the efficacy of lamotrigine monotherapy (83).

***Step 1. Review general principles and assess medication status*:** Recommendations from 2005 guidelines remain unchanged.

***Step 2. Initiate or optimize therapy and check adherence (first-line therapies)*:** Lithium, lamotrigine, quetiapine, and quetiapine extended release (XR) monotherapies, as well as lithium or divalproex plus selective serotonin reuptake inhibitor (SSRI), olanzapine plus SSRI, lithium plus divalproex, and lithium or divalproex plus bupropion all continue to be recommended as first-line choices for bipolar depression.

Data suggest that the absence of early improvement (2–3 weeks) may be a highly reliable predictor of eventual non-response, suggesting that these patients may benefit from a change in therapy (84, 85).

Lithium. The early results of the National Institute of Mental Health (NIMH) lithium treatment moderate dose use study have been presented (86). This pragmatic study randomized 283 patients with BD I or BD II to receive six months of open-label 'moderate dose' (600 mg/day) lithium plus optimized treatment [per Texas Medication Algorithms (87)] versus optimized treatment alone and found no significant differences between treatment groups. However, given that this was an open-label study, and in the absence of further study details, recommendations for adjunctive lithium use remain unchanged.

Quetiapine monotherapy. The four large published RCTs demonstrating the efficacy of quetiapine monotherapy in bipolar depression, which were cited in previous iterations of these guidelines, have now all been published: BipOLar DEpRession (BOLDER) I (88) and II (89) and Efficacy of Monotherapy SEROQUEL in BipOLar DEpres-

sioN (EMBOLDEN) I (90) and EMBOLDEN II (91) (level 1).

The eight-week RCT demonstrating significantly greater improvement in depressive symptoms with quetiapine XR monotherapy in patients with BD I or BD II depression, which was previously cited, has now been published (92).

Olanzapine + fluoxetine. There are level 1 data demonstrating the efficacy of olanzapine–fluoxetine combination (OFC) therapy for the treatment of BD I depression (1–3). Follow-up results from a previously described RCT [seven-week outcome data (93)] found significantly greater improvements in depressive and manic symptoms with OFC versus lamotrigine in 410 patients with BD I at study end (94). However, OFC treatment was associated with a significantly increased risk of treatment-emergent hypercholesterolemia and weight gain. In addition, a post-hoc analysis of a previously cited combination study (95) found that both OFC and olanzapine monotherapy were more efficacious than placebo in patients with BD I mixed depression (i.e., syndromal depression and subsyndromal mania/hypomania).

Step 3. Add-on or switch therapy (alternate first- or second-line therapies):

Second-line options

Divalproex monotherapy. Four small RCTs have assessed the efficacy of divalproex or divalproex ER for the treatment of BD I or BD II depression (level 1) (96, 97). Two meta-analyses of these trials (total n = 142), by separate groups, concluded that divalproex was more effective than placebo for the treatment of bipolar depression, but the strength of the conclusions was limited by sample size (96, 97). Therefore, given the limited evidence, divalproex continues to be recommended as a second-line option.

Lurasidone. Two six-week RCTs have demonstrated the efficacy of lurasidone as monotherapy (98) or as an adjunct (99) in patients with bipolar depression. Lurasidone monotherapy significantly reduced depressive symptoms in patients with BD I depression as early as week two compared to placebo (level 2) (98). Similarly, when used as an adjunct to lithium or divalproex, lurasidone significantly reduced depressive symptoms, and improved functioning and quality of life compared to placebo in patients with BD I depression who had an inadequate response to lithium or divalproex alone (level 2) (99). These data look very promising and if clinical experience supports efficacy, lurasidone will be upgraded to one of the first-line treatments in the next revision.

Lamotrigine + lithium or divalproex. In an eight-week RCT, the acute effect of lamotrigine was greater than that of placebo as an add-on to lithium for BD I or BD II depression (n = 124) (100). Non-responders in this trial entered a second phase in which paroxetine was added; this addition showed benefit in non-responders to lithium + placebo, but not in non-responders to lithium + lamotrigine (101). Given the slow titration required for lamotrigine, this treatment is recommended either in monotherapy or as an add-on therapy primarily for those with mild-to-moderate bipolar depression, and in particular for those with depression recurrences, given its efficacy in preventing depressive relapses.

Step 4. Add-on or switch therapy (alternate first- or second-line therapies): No changes from 2005 guideline (1).

Step 5. Add-on or switch therapy (third-line agents and novel/experimental therapies):

Third-line options

Olanzapine monotherapy. There are now two large RCTs demonstrating the efficacy of olanzapine monotherapy for the treatment of bipolar depression (level 1) (95, 102). In the earlier of these two trials, olanzapine monotherapy demonstrated a statistically significant, but clinically modest antidepressant effect in a large (n = 833), eight-week RCT in patients with bipolar depression (95), and was recommended as a third-line option (1).

In the subsequent large RCT, available in abstract form, 514 patients with bipolar depression achieved significantly greater improvement in depressive symptoms with olanzapine compared to placebo (MADRS −13.8 versus −11.7, p = 0.018) over six weeks of treatment (102). However, olanzapine was also associated with significantly greater rates of metabolic changes (102). A small (n = 20), open-label study provided additional support for the efficacy of olanzapine monotherapy in patients with BD I or BD II depression (103).

Although there is level 1 evidence, the magnitude of benefit of olanzapine monotherapy was only modestly greater than that of placebo (95, 102). In the earlier trial (95), the increased efficacy of olanzapine relative to placebo was mainly accounted for by changes in sleep, appetite, and inner tension, which are not the core symptoms of depression (81). In addition, as adverse events were

marked in the recent trial (102), this strategy continues to be recommended as a third-line option.

Quetiapine + lamotrigine. A small, open trial in 39 patients with BD I and BD II found that the combination of lamotrigine plus quetiapine was beneficial in treatment-resistant bipolar depression (level 3) (104).

Carbamazepine. There is additional evidence to support the use of carbamazepine (level 2), as a small RCT in a mixed population of 44 patients with BD found that ER carbamazepine was as effective as the immediate-release form, with fewer autonomic and gastrointestinal adverse events (63, 64).

ECT. As stated in previous iterations of the guidelines, the use of ECT should be considered earlier in patients who have psychotic bipolar depression, in those at high risk for suicide, and in those with significant medical complications due to not drinking and eating. Clinical experience and open-label data continue to accumulate and support the efficacy of ECT. In an open trial, similar rates of response and remission were observed in patients with bipolar depression (70% and 26%, respectively) and those with mixed states (66% and 30%, respectively) (105). A retrospective analysis of 201 patients with BD receiving ECT concluded that those receiving concomitant anticonvulsants achieved comparable symptomatic improvement to those not on anticonvulsants; however, they required a significantly greater number of ECT sessions to achieve this (106). Two RCTs comparing different ECT protocols found no difference in response rates in patients with bipolar or unipolar depression (107, 108).

Novel or experimental agents

Data were previously described demonstrating the benefits of adjunctive use of the following agents: pramipexole (level 2), eicosapentaenoic acid (EPA) (level 2), riluzole (level 3), topiramate (level 3), and N-acetyl cysteine (NAC) (level 2) (1–3).

Additional open-label data support the use of adjunctive riluzole and adjunctive NAC (109, 110). Patients in a small, open-label, imaging study reported improvements in depressive symptoms with riluzole (level 3) (109), while data from a large (n = 149), eight-week, open-label trial found significant improvement in depressive symptoms with adjunctive NAC in patients with BD I, II, or NOS depression (110).

Preliminary data are also available to support other novel treatments not previously investigated in patients with bipolar depression, including adjunctive ketamine, armodafinil, and chronotherapy. A two-week, crossover RCT assessing adjunctive ketamine infusion in patients with treatment-resistant bipolar depression identified a robust early antidepressant effect (within 40 min), with improvement remaining significant versus placebo through day three (level 2) (111). An eight-week RCT in 257 patients with BD I depression reported a trend toward greater improvement in depressive symptoms with adjunctive armodafinil versus placebo on some, but not all depression symptom scales (level 2) (112). Adjunctive combined chronotherapy (sleep deprivation, exposure to bright light, and sleep-phase advance) demonstrated a more rapid and sustained antidepressant response compared to medication alone (lithium + antidepressant) in a seven-week RCT in 49 patients with bipolar depression (level 3) (113). Patients receiving adjunctive chronotherapy experienced a significantly greater reduction in depressive symptoms within 48 hours, which was sustained throughout the seven weeks.

Not recommended for the treatment of acute bipolar depression:

Ziprasidone monotherapy. Data are now available from two negative RCTs of ziprasidone monotherapy in BD I depression (level 1, negative) (114, 115). The trials have not yet been published, but results are available at http://www.clinicaltrials.gov (114, 115). Both were large trials (n = 381 and n = 504, respectively) in patients with BD I depression, and both demonstrated no significant improvements in depression scores compared to placebo. While ziprasidone is not recommended for bipolar depression, patients who are using ziprasidone with benefit (initiated during mania) do not need to have it discontinued.

Adjunctive therapies with negative data requiring further study:

Adjunctive ziprasidone. A large RCT assessing adjunctive ziprasidone (mean dose 90 mg) added to therapy with lithium, divalproex, or lamotrigine in 298 patients with BD I depression found no significant difference between active treatment and placebo (level 2, negative) (116).

Adjunctive aripiprazole. While open-label trials suggest a benefit of adjunctive aripiprazole for the treatment of bipolar depression (level 3) (117, 118), a small RCT did not find a significant effect compared to placebo (level 2, negative) (119). In a six-week RCT, 23 inpatients with bipolar depres-

sion on lithium or divalproex were given open-label citalopram, and randomized to adjunctive aripiprazole or placebo. Depressive symptoms improved, with no significant differences between treatment groups (level 2 negative) (119).

In a 16-week, prospective, open-label trial, aripiprazole (add-on or monotherapy) was associated with a significant decline in depressive symptoms over 16 weeks among 85 patients with bipolar depression who were unresponsive to other medications (lithium, anticonvulsants, or antipsychotic agents) (level 3) (117). There was also a significant reduction in self-rated anhedonia among patients with BD I depression treated with aripiprazole in the same study (120). Another small (n = 20), six-week, open-label trial demonstrated improvement in depressive symptoms, with a 44% response rate with aripiprazole as add-on or monotherapy for BD I, II, or NOS depression (level 3) (118).

Adjunctive levetiracetam. A six-week RCT in 32 patients with bipolar depression found no significant differences in the change in depression scores with adjunctive levetiracetam versus placebo (level 2, negative) (121).

Clinical questions and controversies

What is the role of antidepressants in patients with bipolar depression?

The role of antidepressants in patients with bipolar depression remains one of the most controversial areas in psychiatry. Antidepressants are the most commonly used treatments for bipolar depression (122, 123) as clinicians continue to believe that, based on their clinical experience, these are effective for bipolar depression. However, the limited, but growing body of clinical trial data has not been consistent in supporting their role. For instance, OFC was shown to be more effective than placebo or olanzapine monotherapy (93, 95), but the combination of paroxetine or bupropion with a *mood stabilizer* was not more effective than a *mood stabilizer* plus placebo (124). However, this study had severe methodological limitations; most patients were also participating in a psychotherapy trial, and an unknown proportion of patients continued to use the previous antidepressant they had been on at baseline. In another study, paroxetine monotherapy (20 mg/day) was not superior to placebo in improving bipolar depressive symptoms (125). It is unknown if higher doses of paroxetine would have been more effective.

Although individual studies are contradictory, the most recent meta-analysis, which included 15 RCTs (126), found a strong trend for superiority of antidepressants over placebo for the acute treatment of bipolar depression ($p = 0.06$). Antidepressants were not associated with a significantly increased risk of manic switch (126). Most negative studies of antidepressants for bipolar depression to date have employed paroxetine as the antidepressant (91, 125, 127). A meta-analysis of the efficacy of antidepressants in unipolar depression (128) suggested that clinically important differences exist between various antidepressants in terms of efficacy and acceptability. Interestingly, paroxetine was inferior to a number of other antidepressants in this meta-analysis. The risk of manic/hypomanic switch does not appear to be a major concern with modern antidepressants when used in conjunction with a 'mood stabilizer' or an atypical antipsychotic agent, at least during short-term treatment; therefore, safety does not appear to be a significant issue during the acute treatment of bipolar depression. An important caveat is that the current definition of switch requires threshold mania; milder switches, which are common, are not captured by the default definition (129). Similarly, the metrics of cycle acceleration are not captured in current definitions or trial designs (130).

Given the above, we believe that the following conclusions and recommendations are warranted regarding the use of antidepressants for bipolar depression: (i) SSRIs (other than paroxetine) and bupropion could be used as first-line treatments in conjunction with a *mood stabilizer* for acute short-term treatment of bipolar depression, with the objective of tapering and discontinuing antidepressants 6–8 weeks after full remission of depression; (ii) avoid the use of tricyclic antidepressants and venlafaxine (131, 132) as they are associated with an increased risk of manic switch; (iii) antidepressants should not be used to treat a current mixed episode or in patients with a history of rapid cycling; (iv) monotherapy with antidepressants is **not** recommended for bipolar depression.

Section 5. Maintenance therapy for bipolar disorder

Adherence

New data provide further insight into adherence to maintenance therapy in patients with BD. In several analyses, adherence was positively associated with higher satisfaction with medication, monotherapy, a college degree, and fear of relapse, and was negatively associated with illness factors (substance use, previous hospitalization, psychotic symptoms, reduced insight into illness), medication factors (side effects, no perceived daily benefit,

difficulties with medication routines), and patient attitudes (belief that medications are unnecessary, negative attitudes toward medications, perceived change in appearance, perceived interference with life goals) (133–139). Under-dosing can also lead to higher discontinuation rates; patients receiving lower doses of ziprasidone had significantly higher discontinuation rates than those receiving medium or high doses (140).

Non-adherence has been linked to a high frequency of episodes (particularly depressive episodes), a higher risk of hospitalization and emergency room visits, as well as higher employee costs of absenteeism, short-term disability, and workers' compensation (137, 141–144). In an analysis involving UK data, the direct costs of care were two to three times higher in patients who relapsed compared to those who did not over the 6–12-month follow-up (145).

Predictors of recurrence

In observational studies, predictors of symptomatic remission and recovery during 1–2 years of follow-up in patients with manic episodes included: Caucasian ethnicity, a previous manic episode, good social functioning (no work or social impairment, living independently or with family), outpatient treatment, and being neither satisfied nor dissatisfied with life (146, 147).

In patients with rapid cycling treated with lithium or divalproex, increased risk for non-stabilization was associated with a history of recent substance use disorder (SUD), early-life verbal abuse, female gender, and late onset of first depressive episode (148). Among responders to long-term lithium therapy, the risk of recurrence was higher in those with atypical features (mainly mood-incongruent psychotic symptoms), inter-episodic residual symptomatology, and rapid cycling (149).

Psychosocial interventions for maintenance therapy

As reported in previous iterations of these guidelines, data have supported the benefits of adjunctive psychoeducation, CBT, family therapy, and IPSRT in reducing recurrences and improving symptoms in patients with BD (1–3). However, recent meta-analyses assessing the efficacy of psychotherapies for patients with BD have reached discordant conclusions. One meta-analysis of four RCTs concluded that CBT had a small effect size for depressive symptoms compared to treatment as usual or wait-list controls (150). A second analysis included 12 trials and found low to medium effect sizes associated with adjunctive CBT at the end of treatment and at follow-up (151). Another meta-analysis concluded that CBT was likely not an effective treatment strategy for the prevention of relapse in BD (152).

Given the transient benefit of CBT in the first major study of this strategy in patients with BD (153) and the negative results of a large RCT (154), the true benefit of CBT is unclear, beyond its common core element of psychoeducation (155). However, two new RCTs provide some promise. In one study comparing a group CBT intervention to treatment as usual in 50 patients, group CBT was associated with a longer median time to relapse, but no differences in time to recurrence or number of episodes (156). In a 14-week study comparing the CBT (n = 27) and control pharmacotherapy (n = 14) groups, there was a slight, although non-significant, reduction in depressive symptoms in the CBT group (157). Both of these small studies demonstrated the feasibility of group CBT rather than its efficacy, and proper replication is needed. In addition, a previously reported RCT (n = 204) (22), which has now been published, compared six sessions of group psychoeducation to 20 sessions of individual CBT. Both treatments demonstrated a significant benefit in terms of mood stability and reduction of recurrence, but there were no differences between the two treatments. Since the psychoeducation treatment was designed to be delivered by psychiatric nurses and was documented to be much less expensive than individual CBT, the study suggested that group psychoeducation should be prioritized as a first *universal* psychosocial treatment for BD.

RCTs of adjunctive group psychoeducation programs demonstrated a longer time to recurrence, fewer recurrences of any type, less time acutely ill, and fewer days of hospitalization during 1–5 years of follow-up (158, 159). A 12-week dyadic (patient–companion) group-based psychoeducation program demonstrated significantly lower relapse rates and a longer time to relapse compared to treatment as usual during a 60-week follow-up (160).

Pharmacological treatments for maintenance therapy

As discussed in previous guideline iterations, almost all modern maintenance studies have used an enriched design. The only exceptions are some of the older maintenance studies with lithium, which showed the efficacy of lithium for maintenance treatment in non-enriched samples. Given the efficacy of various treatments with enriched design studies, it makes intuitive sense that, in general, the treatment that worked during the acute phase is

Table 5.5. Recommendations for maintenance pharmacotherapy of bipolar disorder

First line	Monotherapy: lithium, lamotrigine (limited efficacy in preventing mania), divalproex, olanzapine[a], quetiapine, risperidone LAI[b], aripiprazole[b] Adjunctive therapy with lithium or divalproex: quetiapine, risperidone LAI[b], aripiprazole[b], ziprasidone[b]
Second line	Monotherapy: carbamazepine, ***paliderido ne ER***[c] Combination therapy: lithium + divalproex, lithium + carbamazepine, lithium or divalproex + olanzapine, lithium + risperidone, lithium + lamotrigine, olanzapine + fluoxetine
Third line	Monotherapy: ***asenapine***[c] Adjunctive therapy: phenytoin, clozapine, ECT, topiramate, omega-3-fatty acids, oxcarbazepine, gabapentin, ***asenapine***[c]
Not recommended	Monotherapy: gabapentin, topiramate, or antidepressants Adjunctive therapy: flupenthixol

LAI = long-acting injection; ER = extended release; ECT = electroconvulsive therapy.
[a]Given the metabolic side effects, use should be carefully monitored.
[b]Mainly for the prevention of mania.
[c]***New or change to recommendation***.

likely to be effective in the maintenance phase [please see the original 2005 guidelines: *Section 5. Maintenance therapy for bipolar disorder: General principles* (1)]. Based on new evidence, asenapine alone and as adjunctive therapy have been added as third-line options (Table 5.5) (1–3).

First-line options: Lithium, divalproex, olanzapine, and quetiapine (for both depression and mania), as well as lamotrigine (primarily for preventing depression), risperidone long-acting injection (LAI) and ziprasidone (primarily for preventing mania) continue to be first-line monotherapy options for maintenance treatment of BD (1–3). Quetiapine, risperidone LAI (mania), aripiprazole (mania), and ziprasidone (mania) are also recommended as adjunctive therapy with lithium or divalproex.

A systematic review of pharmacological interventions for the prevention of relapse in BD included 34 RCTs and quasi-RCTs, and concluded that lithium, olanzapine, and aripiprazole had significant effects in the prevention of manic relapses, as did divalproex, lamotrigine, and imipramine in the prevention of depressive symptoms (161). A meta-analysis of 20 RCTs (n = 5364) assessing the relative risk for relapse in patients with BD in remission confirmed the efficacy of lithium, divalproex, lamotrigine, and a number of atypical antipsychotic agents in preventing relapse to any episode versus placebo (162).

Lithium/divalproex. The Bipolar Affective disorder Lithium/ANti-Convulsant Evaluation (BALANCE) study randomized 330 patients with BD to open-label lithium monotherapy, divalproex monotherapy, or the combination after an active run-in period on the combination (163). Both the combination and lithium monotherapy were significantly more effective than divalproex monotherapy in preventing relapse during up to two years of follow-up. Combination therapy was not significantly more effective than lithium alone. This study, however, had a number of methodological limitations, including an open design; hence, these findings need to be confirmed in double-blind trials before firm conclusions can be drawn.

Lamotrigine. During a one-year extension phase of an RCT, median time to relapse or recurrence was longer among responders receiving lamotrigine compared to those receiving placebo as an add-on to lithium ± paroxetine (ten versus 3.5months) (164).

An open, randomized trial in patients with BD I found no differences in maintenance effectiveness between lithium (n = 78) and lamotrigine (n = 77) (165). Among patients followed for at least five years, practically no patients were maintained successfully on monotherapy with either drug.

Olanzapine. A meta-analysis of five RCTs found that olanzapine as monotherapy or an adjunct to lithium or divalproex was more effective than adjunct placebo in preventing a manic, but not any type of depressive, episode (166). The analysis concluded that olanzapine may prevent manic episodes only in patients who have responded to olanzapine for an acute episode and who have not previously had a satisfactory response to lithium or valproate.

In two recent RCTs, olanzapine was included as an active control arm, and in the continuation phase demonstrated a significantly longer time to recurrence than either risperidone LAI (167) or paliperidone ER (168).

A large, observational study (EMBLEM) included 1076 patients in a comparison of olanzapine monotherapy or as an adjunct and found no significant difference in rates of improvement, remission, or recovery, but significantly lower relapse rates with olanzapine alone compared to adjunctive olanzapine ($p = 0.01$) over the two-year follow-up (169).

Quetiapine. Three of the five large RCTs described in the 2009 guidelines (3), which demonstrated the efficacy of quetiapine alone or in combination with lithium/divalproex for maintenance therapy in BD, have now been published (level 1) (170–172). The eight-week acute-phase results of the EMBOLDEN I (90) and II (91) trials have also been published but the long-term data remain available only in abstract form.

Risperidone LAI. Risperidone LAI monotherapy (level 2) (173) and adjunct (level 2) (174) were previously recommended as first-line maintenance therapies (3), based on RCTs presented in abstract form that have now been published. An additional 18-month continuation study has now provided level 1 evidence for maintenance risperidone LAI. Time to recurrence of any mood episode was significantly longer with risperidone LAI compared to placebo (level 1) (168). However, risperidone LAI was less effective in preventing relapse compared to olanzapine.

In addition, a small ($n = 29$), long-term, open trial demonstrated improvements in treatment adherence, reductions in any relapse rates, and reductions in re-hospitalization rates with adjunctive risperidone LAI during a mean two-year follow-up (175).

Aripiprazole. Aripiprazole monotherapy has demonstrated efficacy for the prevention of manic episodes in the maintenance treatment of patients with BD I and was included in the 2009 guideline as a first-line maintenance therapy for the treatment and prevention of mania (level 1) (3).

A 52-week, relapse prevention RCT demonstrated the efficacy of aripiprazole as an adjunct to lithium or divalproex in patients with manic/mixed episodes and an inadequate response to lithium or divalproex (176). Patients ($n = 337$) in remission for 12 weeks who were randomized to continue adjunctive aripiprazole had a lower rate of relapse to manic (5% versus 15%, $p = 0.013$) but not depressive (10% versus 13%, $p = 0.384$) episodes. Since adjunctive aripiprazole demonstrated efficacy for the prevention of any mood episode or manic episodes, but not depressive episodes, it has been added as a first-line maintenance therapy for the prevention of manic episodes (level 2).

Another 52-week relapse prevention study in 351 BD I patients with a manic/mixed episode, available in abstract form, showed a non-significant trend to lower rates of manic/mixed relapse with aripiprazole versus placebo added to lamotrigine (11% versus 23%, $p = 0.058$) (177). There was a non-significant trend to lower rates of any relapse, and no effect on depressive relapse rates.

Ziprasidone. An RCT demonstrating the efficacy of adjunctive ziprasidone for maintenance treatment of BD, previously available in abstract form, has now been published (level 2) (178). Adjunctive ziprasidone (80–160 mg/day) demonstrated efficacy for the prevention of manic, but not depressive, episodes.

Second-line options:

Carbamazepine. A meta-analysis of four RCTs, including 464 patients, supports previous conclusions that maintenance treatment with carbamazepine has a similar efficacy to lithium for rates of relapses, with the caveat that there were fewer withdrawals due to adverse effects with lithium (level 2) (179). Given the significant tolerability issues with carbamazepine and the difficulty in combining this agent with other psychotropic medications because of its hepatic microsomal enzyme induction properties, carbamazepine continues to be recommended as a second-line option.

OFC. A six-month, continuation, RCT comparing OFC and lamotrigine monotherapy in patients with bipolar depression that was previously cited in abstract form has now been published (94). OFC was associated with a significantly greater improvement in depressive and manic symptoms, but there were no differences in relapse rates of bipolar depression among responders to acute treatment. In the observational EMBLEM study in 1076 patients with BD mania, adjunctive olanzapine was less effective than olanzapine monotherapy in preventing any relapse (169). By contrast, another study of open-label continuation treatment, in 114 patients with bipolar depression who were responders to OFC found that significantly more patients maintained their response to OFC compared to olanzapine monotherapy (180).

Paliperidone ER. In a three-month continuation study, continued paliperidone ER was significantly more effective than placebo in preventing relapse in prior paliperidone ER responders (level 2) (168).

However, paliperidone ER was less effective in preventing relapse compared to the olanzapine active control group.

Third-line options:

Asenapine. Nine-week and 40-week extension phase results from two pooled three-week RCTs demonstrated the maintenance of benefits with asenapine monotherapy and olanzapine in patients with BD mania (YMRS reduction −24.4 and −23.9 at week 12, −28.6 and −28.2 at week 52, respectively) (level 2) (58, 59). At one year, a worsening of mania was reported in 2.6% of asenapine patients and 1.9% of olanzapine patients, while a switch to a depressive episode occurred in 0% of asenapine and 3.0% of olanzapine patients (59). Time to response was significantly longer with asenapine compared to olanzapine ($p = 0.0127$). In this trial, patients in the placebo groups of the original RCTs were blindly switched to asenapine.

In addition, 40-week extension phase results have now been reported in abstract form from the trial of adjunctive asenapine added to lithium/divalproex compared to placebo (62). Of the original 318 patients, 71 completed the 40-week extension; improvements in mania (−17.2 versus −19.7) and depression (−3.3 versus −3.9) scores at 52 weeks were seen in both the asenapine and placebo groups, but the extension was not powered for statistical comparisons.

Based on evidence of maintenance of benefits, but in the absence of relapse prevention data and clinical experience, asenapine is recommended as a third-line option for maintenance therapy.

Rapid cycling

In a six-month RCT, patients with BD (recent manic episode), SUD, and rapid cycling, who were responders to lithium plus divalproex, were randomized to continue combination therapy or lithium alone (181). Of 149 patients enrolled into the open-label acute stabilization phase, 31 were assigned to maintenance treatment and 55% relapsed. There were no significant differences between combination and monotherapy in the rate of relapse or time to relapse. However, given the small sample size, the study was likely underpowered to detect this.

In the STEP-BD study, among patients who were responders to adjunctive antidepressants and continued this treatment, those with a rapid-cycling course had three times more depressive episodes compared to those without rapid cycling (1.29 versus 0.42 episodes/year, $p = 0.04$) (182).

Mixed states

Several open-label and post-hoc analyses provide additional insight into the role of atypical antipsychotic agents in the management of patients with mixed episodes or psychotic symptoms. In a post-hoc analysis of patients with mixed episodes ($n = 121$), where responders to olanzapine were randomized to continue olanzapine or switch to placebo, there were significant reductions in relapse rates with olanzapine compared to placebo (59.2% versus 91.1%, $p < 0.001$) (183). During 52 weeks of flexible-dosed ziprasidone (40–160 mg/day) open-label extension treatment ($n = 65$), patients with manic or mixed episodes, with or without psychotic symptoms, showed comparable improvements in mania and overall subtypes across subgroups (184). In a 24-week, open-label trial of adjunctive risperidone in 114 patients with mixed or manic episodes, significant reductions from baseline in manic, depressive, and overall symptom scores were observed with combination therapy in both the manic and mixed groups (185).

Section 6. Special populations

Issues in the management of BD in women

The management of BD in women can present additional challenges associated with the reproductive cycle.

Premenstrual syndrome (PMS)/premenstrual dysphoric disorder(PMDD): In the longitudinal STEP-BD study, among women with BD ($n = 293$), those with premenstrual exacerbation had more episodes (primarily depressive), more depressive and manic symptoms overall, a shorter time to relapse, and greater symptom severity (186). Premenstrual exacerbation may predict a more symptomatic and relapse-prone phenotype in women with BD.

A study in 61 women with BD I or BD II and 122 healthy women found that moderate-to-severe PMS/PMDD occurred significantly more frequently in patients with BD II (51.6%) compared to the healthy women (19.7%) (187). Similarly, in a study of 92 women with BD I or BD II, patients with PMDD were more likely to have BD II and cyclothymia than were patients without PMDD (188).

Among patients seen at a specialty gynecology clinic for chronic pelvic pain, those with endometriosis ($n = 27$) were more likely to have BD (44.4%) and a poorer quality of life than women with non-endometriosis pelvic pain ($n = 12$) (0%) (189).

Pre-conception: Providing appropriate education and guidance to patients considering pregnancy or who may have recently become pregnant is an important component of BD management. Pre-conception counseling should include a careful review of risks and benefits and a treatment plan for ongoing monitoring. An analysis of a large claims database including 16385 women of child-bearing age with BD or MDD revealed 1308 women who were receiving a category D (12%) or category X (1%) medication during pregnancy (190). The most frequently used psychotropic drugs were paroxetine, alprazolam, lorazepam, divalproex, lithium, and temazepam.

Pregnancy: The management of pregnant women with BD should incorporate careful planning. Updated recommendations on the use of psychiatric medications during pregnancy and lactation are available from the American Congress of Obstetricians and Gynecologists (ACOG), and the reader is referred to this Practice Bulletin for more information (191). In addition, please visit the Canadian Hospital for Sick Children Motherisk website (http://www.Motherisk.org). Therefore, in the following section, we will provide only a brief update of some of the new data in patients with BD.

The risk of teratogenicity associated with use of psychotropic medications (please see ACOG recommendations in Table 6.2) during the first trimester should be carefully weighed against the risks to the mother and the fetus of an untreated mood episode. Psychotropic medications can be used in the second and third trimester if necessary. If lithium is used during the second and third trimester, the serum lithium levels should be monitored closely because of changes in blood volume during pregnancy, and the dose should be adjusted accordingly to maintain levels in the therapeutic range.

Cohort studies in various patient populations confirm the teratogenic risk associated with divalproex (192–194) and carbamazepine (195) during pregnancy. In a case-controlled series of 52 pregnancies, topiramate was associated with reduced birth weight but no decrease in gestational age and no increase in structural defects (196).

Several cohort studies in various patient populations found that, during pregnancy, antidepressants did not confer an increased risk of major congenital anomalies compared to unexposed controls (197, 198). However, in one analysis antidepressant use was associated with increased rates of pregnancy complications, including induced delivery, caesarean section, and preterm birth, as well as increased risk of persistent pulmonary hypertension of the newborn (199).

Some analyses suggest increased risks with individual antidepressants (198–200), while others do not (197). In one analysis, there were associations of fluoxetine with ventricular septal defects, paroxetine with right ventricular outflow tract defects, and citalopram with neural tube defects, although the absolute risk for these specific effects was small (198). The rate of major anomalies (primarily cardiovascular) in birth outcome among pregnant patients (n = 314) with first trimester exposure was 4.7% with fluoxetine and 5.2% with paroxetine, compared to 2.5% in control patients (n = 1467), in a multicentre, prospective, controlled study (200). Cardiovascular defects have also been associated with paroxetine (199, 201) and tricyclic antidepressant exposure (199).

A Canadian neonatal record analysis (n = 119547 live births) concluded that prenatal exposure to combination therapy with SSRI and benzodiazepines conferred a higher incidence of congenital heart disease when compared to no exposure (202). SSRI monotherapy was not associated with an increased risk for major congenital anomalies, but was associated with an increased incidence of atrial septal defects.

A retrospective chart review including 30092 total deliveries identified one major malformation among 16 of the mothers who were treated with atypical antipsychotic agents during their pregnancy (203). The Food and Drug Administration (FDA) issued a safety alert regarding the risks to newborns associated with prenatal exposure to typical or atypical antipsychotic drugs (204). The new drug labels now contain information about the potential risk for abnormal muscle movements and withdrawal symptoms including agitation, abnormal muscle tone, tremor, sleepiness, breathing, and feeding difficulties in newborns.

In an observational, prospective study in 14 women with BD undergoing maintenance treatment with lithium during pregnancy, the lithium concentration ratio from infant to mother was 0.96 and congenital malformations were greater in those receiving higher doses versus lower doses; however, no significant differences in neonatal outcomes (gestational age/weight, Apgar scores, or hospital stay) were noted (205).

Postpartum period: Distinguishing bipolar depression from MDD can be challenging in the postpartum period because of a lack of screening instruments designed specifically for use during this period (206). A Mood Disorder Questionnaire (MDQ) validation study concluded that, with

Table 6.2. Psychiatric medications in pregnancy and lactation

Agent	Pregnancy risk category[a]	American Academy of Pediatrics rating	Lactation risk category[b]
Anxiolytic medications			
Benzodiazepines			
Alprazolam	D	Unknown, of concern	L3
Chlordiazepoxide	D	N/A	L3
Clonazepam	D	N/A	L3
Clorazepate	D	N/A	L3
Diazepam	D	Unknown, of concern	L3, L4 if used chronically
Lorazepam	D	Unknown, of concern	L3
Oxazepam	D	N/A	L3
Benzodiazepines for insomnia			
Estazolam	X	N/A	L3
Flurazepam	X	N/A	L3
Quazepam	X	Unknown, of concern	L2
Temazepam	X	Unknown, of concern	L3
Triazolam	X	N/A	L3
Non-benzodiazepine anxiolytics and hypnotics			
Buspirone	B	N/A	L3
Chloral hydrate	C	Compatible	L3
Eszoplicone	C	N/A	N/A
Zaleplon	C	Unknown, of concern	L2
Zolpidem	B	N/A	L3
Antiepileptic and mood-stabilizing medications			
Lithium carbonate	D	Contraindicated	L4
Valproic acid	D	Compatible	L2
Carbamazepine	D	Compatible	L2
Lamotrigine	C	Unknown	L3
Antidepressants			
Tricyclic and heterocyclic antidepressants			
Amitriptyline	C	Unknown, of concern	L2
Amoxapine	C	Unknown, of concern	L2
Clomipramine	C	Unknown, of concern	L2
Desipramine	C	Unknown, of concern	L2
Doxepin	C	Unknown, of concern	L5
Imipramine	C	Unknown, of concern	L2
Maprotiline	B	N/A	L3
Nortriptyline	C	Unknown, of concern	L2
Protriptyline	C	N/A	N/A
Selective serotonin reuptake inhibitors			
Citalopram	C	N/A	L3
Escitalopram	C	N/A	L3 in older infants
Fluoxetine	C	Unknown, of concern	L2 in older infants, L3 if used in neonatal period
Fluvoxamine	C	Unknown, of concern	L2
Paroxetine	D	Unknown, of concern	L2
Sertraline	C	Unknown, of concern	L2
Other antidepressants			
Bupropion	B	Unknown, of concern	L3
Duloxetine	C	N/A	N/A
Mirtazapine	C	N/A	L3
Nefazodone	C	N/A	L4
Trazodone	C	Unknown, of concern	L2
Venlafaxine	C	N/A	L3
Antipsychotic medications			
Typical antipsychotic agents			
Chlorpromazine	C	Unknown, of concern	L3
Fluphenazine	C	N/A	L3
Haloperidol	C	Unknown, of concern	L2
Loxapine	C	N/A	L4
Perphenazine	C	Unknown, of concern	N/A
Pimozide	C	N/A	L4

Table 6.2. (Continued).

Agent	Pregnancy risk category[a]	American Academy of Pediatrics rating	Lactation risk category[b]
Thioridazine	C	N/A	L4
Thiothixene	C	N/A	L4
Trifluoperazine	C	Unknown, of concern	N/A
Atypical antipsychotic agents			
Aripiprazole	C	N/A	L3
Clozapine	B	Unknown, of concern	L3
Olanzapine	C	N/A	L2
Quetiapine	C	Unknown, of concern	L4
Risperidone	C	N/A	L3
Ziprasidone	C	Unknown, of concern	L4

[Copyright (2008) Wolters Kluwer Health; reprinted with permission from (191)]. N/A = not available.
[a]The US Food and Drug Administration classifies drug safety using the following categories: A = controlled studies show no risk; B = no evidence of risk in humans; C = risk cannot be ruled out; D = positive evidence of risk; X = contraindicated in pregnancy.
[b]Lactation risk categories are listed as follows: L1 = safest; L2 = safer; L3 = moderately safe; L4 = possibly hazardous; L5 = contraindicated.

alternate scoring, the MDQ may be a useful screening instrument for BD in the postpartum period (206, 207). The optimal cut-off score was eight or more endorsed symptoms without the supplementary questions (sensitivity 88% and specificity 85%) (208).

In a well-designed longitudinal study involving 344 pregnant women, there was an 8.4-fold increase in hypomanic symptoms in the early postpartum period (11.7%) compared to during the first trimester (1.4%) and to eight weeks postpartum (4.9%) (209). Although hypomanic symptoms are common in the early puerperium, they are often overlooked, leading to a misdiagnosis of MDD (210). This may be due in part to the absence of hypomania from the postpartum-onset specifier in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition–text revised (DSM-IV-TR) (211). However, a study from Spain suggested reconsideration of the DSM postpartum-onset specifier, as it did not appear to influence prognosis or functioning in women with BD (212).

According to a Danish population-based study of new mothers, the period of highest risk for psychiatric readmission was 10 to 19 days postpartum [relative risk (RR) = 2.7], and the period of lowest risk was during pregnancy (RR = 0.5). Previous diagnosis of BD was the strongest predictor of readmissions 10–19 days postpartum (RR = 37.2), with 27% of women with BD being readmitted within the first year (213). Similarly, psychotic illness has been shown to peak immediately following a first childbirth (214).

ACOG recommendations for the use of psychiatric medications during lactation are also shown in Table 6.2 (191).

Menopause: In a STEP-BD analysis of 164 patients with BD followed for an average of 30 months, menopausal transition was associated with significantly more visits due to depressive symptoms and fewer euthymic visits compared to a comparison group of non-menopausal women and men (215).

Issues in the management of BD in children and adolescents

Complete treatment recommendations for pediatric BD are beyond the scope of these guidelines; the reader is referred to specific guidelines for the management of children and adolescents with BD, such as those developed by the American Academy of Child and Adolescent Psychiatry (AACAP) (216). Therefore, in the following section, we will provide only a brief overview of some of the issues in this population without offering recommendations for levels of treatment.

Presentation and diagnosis: Across the world, BD is the fourth leading cause of disability among adolescents (15–19 years) (217). The presentation and diagnosis of BD in children and adolescents remains controversial. Increasing billing and discharge diagnoses of pediatric BD contradict a stable epidemiologic prevalence, suggesting that diagnostic criteria for BD may not be systematically applied in some clinical settings (218, 219). However, much of the controversy regarding pediatric BD has focused on the group of youth with severe, chronic, non-episode irritability, which has led to the proposed DSM-5 diagnosis of 'disruptive mood dysregulation disorder' (DMDD) (220). The reader is referred to recent publications focusing specifically on differential diagnosis and developmental considerations in ascertaining

manic symptoms (221, 222), and regarding concerns about the DMDD diagnosis (223). Prospective studies of children and adolescents with rigorously defined BD demonstrate that this is an episodic illness that continues into young adulthood and is characterized by substantial impairment and morbidity (224–226).

Based on a meta-analysis of 12 epidemiological studies in patients between the ages of seven and 21 years (n = 16222), the overall prevalence of BD was 1.8% (219). Of note, rates of BD in these epidemiologic studies did not increase over time and did not differ for studies within versus outside of the USA. Among Canadian adolescents and young adults (15–24 years), the CCHS 1.2 survey recorded a lifetime prevalence of BD of 3.0% (2.1% in those aged 15–18 years; 3.8% in those aged 19–24 years) (227). In a claims database, the one-year rate of a new diagnosis of BD among patients ≤17 years of age was 0.23%. Misdiagnosis was common, with 47% being diagnosed with depressive disorder and 37% with disruptive behavior disorder in the previous year (228). In the Course and Outcome of Bipolar Youth (COBY) study (n = 364), first episodes in patients ≥ 12 years were generally depressive, while those in patients < 12 years were more likely to be subsyndromal manic/hypomanic symptoms (229).

A claims analysis of younger (age 6–18 years) patients with BD (n = 423) showed that the majority did not receive guideline-concordant care, with only 26% receiving anti-manic treatments and 33% receiving antidepressant monotherapy (230). Similarly, eight-year follow-up data from an NIMH study on the course of BD I in children found that 37% of patients had never received anti-manic treatment (231).

Over a five-year follow-up period in the COBY study (n = 413) in youth (age 7–17 years), the rate of suicide attempts was 18%. (232). Predictive variables included female gender, severity of depressive symptoms, familial history of depression, and lifetime history of exposure to antidepressants. Non-suicidal self-injury has also been reported in more than 20% of children and adolescents with BD (233).

Comorbidities and mimics: In the COBY study, 44% of youth had at least one lifetime anxiety disorder, and nearly 20% had two or more, with the most prevalent being separation anxiety (24%) and generalized anxiety disorder (GAD) (16%) (234). A family history study that included 157 patients (age 6–17 years) with BD I revealed extremely high rates of comorbid attention-deficit hyperactivity disorder (ADHD) (85%), oppositional defiant disorder (90%), two or more anxiety disorders (64%), conduct disorder (51%), and SUD (12%) (235).

Early BD onset (age < 12 years) has been associated with ADHD, whereas later BD onset (age ≥ 12 years) was associated with panic, conduct, and SUD (229). Psychotic symptoms have been reported in about one-third of youth with BD, and confer a significantly greater likelihood of lifetime GAD, agoraphobia, social phobia, and obsessive compulsive disorder (OCD) (236).

Medical comorbidities including obesity, type 2 diabetes mellitus, other endocrine disorders, migraine headaches, central nervous system disorders/epilepsy, organic brain disorders/mental retardation, cardiovascular disorders, and asthma in a large cohort study were significantly more prevalent among children and adolescents with BD (n = 1841) compared to a control group (n = 4500) (237). In the COBY study (n = 348), overweight/obesity was seen in 42% of youth with BD, and was associated with increased psychiatric burden (238). Moreover, in a pilot study on inflammatory markers among 30 adolescents in the COBY study, 40% had levels of high-sensitivity C-reactive protein that are considered to confer a high risk for cardiovascular disease among adults (≥ 2 μg/mL) (239).

Acute and maintenance treatment of pediatric BD: Most RCTs in youth with BD have investigated the acute treatment of manic/mixed symptoms, with few assessing maintenance therapy. Thus, taking into account that not all treatments that are efficacious in adults will also be so in children and adolescents, and until further studies become available, the guidelines developed for adults with BD should be cautiously applied to youth.

Psychosocial interventions

The two-year follow-up results of an RCT in adolescent patients (n = 58) with BD which compared adjunctive family-focused treatment (FFT) and enhanced care found no differences in time to recurrence of depression or mania, but patients in the FFT group spent fewer weeks in depressive episodes (240). In a one-year open trial, a modified FFT was associated with improved depression, hypomania, and psychosocial functioning scores in youth who were thought to be at high risk for developing BD (241). Preliminary findings suggest that child and family-focused CBT (242), dialectical behavior therapy (DBT) (243), and IPSRT (244) may be promising in the management of BD in this patient population.

Pharmacological management

Atypical antipsychotics. The AACAP published a practice parameter on the use of psychotropic medication in children and adolescents, and the reader is referred to those guidelines for more details (245). Provided below is an overview of current data of the efficacy of atypical antipsychotic agents for the treatment of BD in younger patients.

The US FDA has now approved quetiapine for the first-line treatment of acute manic/mixed episodes in pediatric patients. In light of safety/tolerability concerns, olanzapine (weight gain and metabolic disturbances) and ziprasidone (QT prolongation) were approved as second-line treatments only (246).

A meta-analysis of nine RCTs included 1609 pediatric patients with acute BD mania and found significantly greater improvements in YMRS scores in the atypical antipsychotic agent group and *mood stabilizer* group relative to placebo. The effect sizes were greater for the atypical antipsychotic agent group compared to a *mood stabilizer* group (effect size 0.65 versus 0.20). However, the *mood stabilizer* group included studies on topiramate and oxcarbazepine, neither of which demonstrated efficacy as *mood stabilizers*. Further, medication-associated weight gain was greater with atypical antipsychotic agents than with *mood stabilizers* (effect size 0.53 versus 0.10) (44).

In a small eight-week RCT in 32 adolescents (age 12–18 years), quetiapine monotherapy was not significantly better than placebo for the treatment of bipolar depression (247). This negative trial requires replication in light of the small sample size, high placebo response rates, and robust evidence of quetiapine efficacy in bipolar depression in adults group (1–3). Quetiapine monotherapy has also demonstrated efficacy as acute and maintenance treatment in small, open-label studies (248, 249).

A pooled analysis of four olanzapine trials (two RCTs, two open-label) in adolescents (age 13–17 years) with BD or schizophrenia revealed significantly more weight gain compared to adult patients (7.4 kg versus 3.2 kg) in up to 32 weeks of treatment (250). Adolescents also experienced significant changes in fasting glucose, total cholesterol, triglycerides, alanine aminotransferase, and prolactin. In an eight-week, open-label study the addition of topiramate to olanzapine therapy in 40 pediatric patients with BD resulted in significantly less weight gain than with olanzapine monotherapy, with no differences in mania symptom scores (251).

In addition to the previously cited RCT data, further open-label data support the efficacy and tolerability of ziprasidone therapy in youth with BD (252, 253).

A three-week RCT in 169 pediatric patients with BD mania/mixed episodes demonstrated greater reductions in mania scores with risperidone versus placebo (254). In a six-week RCT in 66 youth, risperidone resulted in more rapid improvement in manic symptoms and a significantly greater rate of remission (63% versus 33%) compared to divalproex (255). Primary outcomes from the eight-week Treatment of Early-Age Mania (TEAM) study of 279 medication-naïve youth (age 6–15 years) with BD I mania/mixed episodes were recently published (256). TEAM was a controlled, randomized, no-patient-choice study comparing lithium, divalproex, and risperidone. The response rate for risperidone (68.5%) was significantly greater than for lithium (35.6%) and divalproex (24.0%), which did not differ significantly from each other. However, increased weight gain, body mass index (BMI), and serum prolactin levels were also significantly greater with risperidone than with the other medications. Similar results were seen in a small cohort study in which risperidone resulted in a faster and greater reduction of symptom scores versus divalproex (257). Hence, although it is premature to conclude that atypical antipsychotic agents have greater efficacy than *mood stabilizers* in pediatric mania, a convergence of data suggest that this may be the case.

An RCT demonstrating the efficacy of aripiprazole for BD I manic/mixed episodes in pediatric patients that was previously cited in abstract form has now been published (258). Another six-week RCT in 43 pediatric patients with BD manic /mixed episodes and comorbid ADHD demonstrated significant reductions in manic, but not depressive or ADHD, symptoms with aripiprazole versus placebo (level 1) (259).

Analyses suggest a poorer response to atypical antipsychotic agent therapy in pediatric patients with BD and comorbid OCD, but not in those with comorbid autism (260, 261).

Anticonvulsants. Several small, open-label trials demonstrated significant improvements with lamotrigine monotherapy in both manic and depressive clinical endpoints (262, 263), and as an adjunct to atypical antipsychotic agents (264) in youth with BD mania/mixed episodes during 3–6 months of follow-up.

A four-week RCT of divalproex ER in 150 pediatric patients (age 10–17 years) with BD mania/mixed episodes found no benefit of active

treatment over placebo on primary or secondary outcomes, and there was only modest improvement in mania scores during the six-month, open-label extension phase (265). However, a six-month, open-label study in 226 youth with BD I mania/mixed episodes found that divalproex ER reduced mania scores and was generally well tolerated (266).

In an eight-week, open-label trial in 27 youth with bipolar spectrum disorders, carbamazepine ER was associated with improvements in mania, depression, psychosis, and ADHD symptoms, but drop-out rates were high (267).

Issues in the management of BD in older patients

Presentation and course: The two-year EMBLEM study included 475 patients >60 years with acute BD mania/mixed, and found that older patients had a history of more rapid cycling, fewer suicide attempts, and less severe manic and psychotic symptoms, but no difference in depressive symptomatology (268). Older patients with late-onset BD (age ≥ 50 years) experienced a better 12-week outcome with a faster recovery and earlier discharge compared to older patients with early-onset BD (age <50 years). The prevalence of mixed episodes was reported at 10% in patients ≥ 60 years in an RCT (269).

Comorbidity: In a case-controlled study, there was a higher prevalence among older patients (n = 82, age >60 years) with BD of diabetes mellitus (27%), atopic diseases (20%), smoking (24%), and unfavourable social functioning (22%) when compared to age-matched controls (270).

A large survey of geriatric patients in a Veterans Health Administration database found the use of anticonvulsants to be associated with an over twofold increased risk of fracture. In addition, patients with BD had a 20% increased risk of fracture compared to those without BD, independent of the use of anticonvulsants (271).

Older adults with BD have been shown to have greater levels of cognitive dysfunction than age-matched mentally healthy control subjects (272–275). Among older patients with BD, a greater burden from vascular risk factors has been associated with poorer outcomes on some cognitive measures (276, 277). Several analyses have failed to detect a significant association between dementia or cognitive performance in older patients and the use of lithium (277, 278).

Treatment of BD in older patients: Data assessing pharmacotherapy specifically in older patients with BD remain scarce. In a post-hoc, pooled analysis of two quetiapine monotherapy RCTs in patients with acute BD mania, subgroup analysis of 59 older adults (age ≥ 55 years) demonstrated a significant improvement in manic symptoms as early as day four, and this was sustained over the 12 weeks of follow-up versus placebo (279).

At 12 weeks, the results from an open-label study of adjunctive lamotrigine in older patients (n = 57, age ≥ 60 years) with BD I or BD II indicated an overall significant decline in depressive symptoms, with a 65% response rate and a low rate of discontinuations because of adverse events (10%) (280).

Issues in the management of BD in patients with comorbid conditions

The reader is also referred to a task force report on the management of patients with mood disorders and comorbid psychiatric and medical conditions developed by the CANMAT Comorbidity Task Force (281).

Prevalence and impact

Medical. In the large US National Epidemiologic Survey on Alcohol and Related Conditions study, which included 1548 patients with BD I, the prevalence of one or more general medical conditions was 32% (282). In another analysis, patients with BD I or BD II were found to have a mean of 2.5 comorbid medical conditions (283). Cardiovascular disease and hypertension were almost fivefold more prevalent among patients with BD than controls (284). The risk of cardiovascular mortality was found to be more than double in patients with BD I compared to those with BD II, in a long-term follow-up study (285). In addition, patients with BD had a significantly greater risk for hospital readmission due to a cardiovascular event (286).

The increased rate of metabolic syndrome in patients with BD, by up to twofold compared to the general population, has been documented in countries around the world (287). Comorbid metabolic disturbances in patients with BD have been associated with a more complex illness presentation, less favourable response to treatment, and worse course of illness (283, 287, 288).

In patients with BD, a higher BMI has been associated with more frequent manic and depressive relapses, more suicide attempts, and poorer psychosocial functioning, as well as a greater frequency of type II diabetes, hypertension, and subthreshold anxiety disorders (289–291). Over-

weight/obesity has also been shown to have a negative impact on long-term treatment response (283, 289) and on cognitive function in euthymic patients with BD (292).

Comorbid migraine affects nearly one in four patients with BD (293), and confers significantly increased risk for suicidal behavior, comorbid psychiatric disorders, and rapid cycling, as well as a greater number of mood episodes and lifetime hospitalizations compared to patients without migraine (293, 294). The prevalence of migraine is reportedly higher in patients with BD II than in those with BD I (35% versus 19%) (293).

Up to 12% of patients with epilepsy may have a diagnosis of BD; however, only 1.4% had *pure* BD, as all other cases were associated with differing states relating to the primary diagnoses of epilepsy (295).

Psychiatric. A retrospective analysis of four trials including 566 patients with rapid-cycling BD I or BD II found lifetime rates of anxiety disorders and SUD of 46% and 67%, respectively (296). Comorbid SUD has been linked to an increased risk of suicide and other unnatural deaths, suicide attempts, nicotine dependence, and other SUDs in patients with BD (297–299). Patients with BD have a fivefold higher risk of current cigarette smoking compared to the general population (300). Cigarette smoking has also been associated with suicidal behavior in patients with BD (301, 302). In addition, suicidal behavior has been associated with borderline personality disorder (BPD), panic disorder, alcoholism, other drug addictions, and GAD, although only BPD and alcoholism were independently associated (301). Comorbid SUD in patients with BD confers substantially greater impairment in social functioning compared to patients without SUD (303).

In patients with rapid-cycling BD, comorbid SUD was associated with a twofold increased risk of being incorrectly medicated (not receiving a *mood stabilizer* after the onset of first mania/hypomania) (296). In addition, an uncontrolled study suggested that comorbid SUD may be associated with a very high risk of antidepressant-induced switch to mania (76%) (304, 305).

A functional assessment of patients (n = 206) with BD I or BD II noted that more than one-third had missed ≥ 2 years of work time over a five-year period, and extended unemployment was associated with increased rates of panic disorder and alcohol abuse (306). The presence of comorbid panic disorder in patients with BD I (compared to those with no panic disorder) was associated with significantly more depressive, manic, and any mood episodes, as well as increased risk of lifetime SUD or eating disorders (307). In the NIMH Collaborative Depression Study, the presence of psychic and somatic anxiety symptoms was associated with a greater proportion of weeks in depressive episodes during long-term follow-up (mean 17 years) of patients with BD (308). The prevalence of lifetime eating disorders, particularly binge eating disorder, is high (14%) in patients with BD (309).

It is of note that patients with BPD are at high risk of being misdiagnosed as having BD, and vice versa (310, 311).

The International Mood Disorders Collaborative Project reported the prevalence of lifetime ADHD in adults with BD as 18%, which was substantially higher than that found in patients with MDD (5%). Comorbid ADHD has been associated with a greater number of comorbid psychiatric conditions (312), a negative impact on the course of BD in adulthood (313), impaired psychosocial functioning, and poorer overall quality of life (312, 314).

Treatment of BD in patients with comorbidities: In a retrospective analysis, a bipolar collaborative chronic care model was as effective in patients with BD and comorbid conditions (SUD, psychiatric, and/or medical) as in those without, although it may be necessary to pay specific attention to physical quality of life in patients with cardiovascular disease (315). A six-month pilot study of a BD medical care model demonstrated a slowing of decline in physical health-related quality of life compared with usual care in patients with BD and cardiovascular disease-related risk factors (316). Improvements in mental health-related quality of life were also seen, but were not significant.

Medical. A small (n = 10), 14-week pilot study of an integrated psychosocial treatment model including three treatment modules (nutrition/weight loss, exercise, and wellness treatment) administered in group sessions, as well as weekly exercise, demonstrated improvements in quality of life, depressive symptoms, and weight (317). Open-label adjunctive ziprasidone was effective in significantly improving weight-related parameters while maintaining or improving mood symptoms in 25 obese/overweight patients with BD taking atypical antipsychotic agents, lithium, or divalproex (318).

In a recent report, bariatric surgery for weight reduction was as effective in patients with BD as in those without (319).

Psychiatric. An RCT in 61 patients with BD and comorbid SUD compared a modified version of

integrated group therapy (12 sessions instead of 20) to group drug counseling (320). The integrated group therapy, which employed a cognitive-behavioral model integrating treatment of both conditions, resulted in an increased likelihood of achieving total abstinence and a better overall composite outcome compared to regular group counseling. A review of psychosocial interventions for the treatment of comorbid anxiety in patients with BD concluded that CBT, mindfulness-based CBT, and relaxation training may be effective, while interpersonal and family therapy, and psychoeducation alone did not seem to be beneficial in treating comorbid anxiety (321).

Two large, 12-week RCTs (n = 362 and n = 115) of adjunctive quetiapine in patients with BD and comorbid alcohol abuse or dependence did not show significant improvements in measures of alcohol use and dependence compared to placebo, although depressive symptoms improved in one trial (322, 323). A 12-week RCT of adjunctive naltrexone in 50 patients with BD I or BD II and comorbid alcohol dependence demonstrated a trend toward greater decrease in alcohol-related outcomes compared to placebo (324). Response to naltrexone was significantly related to medication adherence.

In a 20-week RCT involving 80 patients with BD and comorbid SUD (cocaine or methamphetamine dependence), both quetiapine and risperidone improved manic and depressive symptoms, as well as drug cravings and use, with no significant differences between treatments (325); however, this study lacked a placebo group. In another placebo-controlled, 12-week RCT, involving 44 patients with BD I or BD II and cocaine dependence, citicoline significantly improved some aspects of declarative memory and cocaine use, but not mood (326).

In a small RCT involving 31 patients with rapid-cycling BD and comorbid SUD who were stabilized on the combination of lithium plus divalproex, there was no significant difference in mood relapse rates between patients randomized to continue combination therapy and those who received lithium alone (181). An analysis of 98 patients from the acute open-label phase of this study found that these patients have a poor response to treatment and a high burden of serious medical comorbidity (327).

A small, six-week RCT in 43 pediatric patients with BD manic/mixed episodes and comorbid ADHD demonstrated significant reductions in manic, but not depressive or ADHD, symptoms with aripiprazole versus placebo (level 1) (259).

In a randomized, crossover trial in 16 youth with BD (age 8–17 years) who had responded to aripiprazole, the addition of methylphenidate did not result in significant improvements in ADHD or mania symptoms compared to placebo (328); however, depressive symptoms did improve.

In an eight-week RCT of risperidone in 111 patients with BD and comorbid panic disorder or GAD, risperidone was no more effective than placebo on any of the anxiety measures (329).

A post-hoc analysis of the BOLDER I and BOLDER II trials including 1051 patients with BD I or BD II depression reported significant improvements in anxiety symptom scores as early as week one, and these were sustained through week eight with quetiapine compared to placebo (330). This suggests that quetiapine should be investigated in patients with BD and comorbid anxiety disorders.

Section 7. Acute and maintenance management of bipolar II disorder

Acute management of hypomania

The preponderance of depressive symptoms in patients with BD II likely contributes to the under-investigation of treatments for hypomania in this patient group. The only studies carried out to date examined mixed samples of patients with BD I and BD II and did not report results separately for BD II. Nonetheless, due to the paucity of information on the treatment of hypomania, we will describe them briefly here. Two small, eight-week RCTs indicated that quetiapine (n = 39) (331) and divalproex ER (n = 60) (332) were superior to placebo in treating patients with hypomania or mild mania. In addition, a previously described six-month, open-label trial suggested efficacy for risperidone (333).

Table 7.2. Recommendations for pharmacological treatment of acute bipolar II depression

First line	Quetiapine, ***quetiapine XR***[a]
Second line	Lithium, lamotrigine, divalproex, lithium or divalproex + antidepressants, lithium + divalproex, atypical antipsychotic agents + antidepressants
Third line	Antidepressant monotherapy (primarily for those with infrequent hypomanias), switch to alternate antidepressant, ***quetiapine + lamotrigine***[a], ***adjunctive ECT***[a], ***adjunctive NAC***[a], ***adjunctive T3***[a]
Not recommended	See text on antidepressants for recommendations regarding antidepressant monotherapy

ECT = electroconvulsive therapy; NAC = N-acetylcysteine; T3 = triiodothyronine; XR = extended release.
[a]***New or change to recommendation***.

Due to the methodological limitations of these trials, and the lack of systematic study of many commonly used mood-stabilizing medications, it is difficult to formulate evidence-based treatment recommendations for hypomania. However, clinical practice suggests that medications that are effective in mania are efficacious in treating hypomanic symptoms. Thus, in patients with persistent and/or impairing symptoms of hypomania, clinicians should treat according to their clinical judgment, using lithium, divalproex, or atypical antipsychotic agents and tapering potentially contributory medications such as antidepressants.

Acute management of bipolar II depression

Psychotherapy: The role of psychotherapy in the treatment of BD II depression has also been understudied. Nonetheless, the predominance of depressive symptoms in patients with BD II, and the fact that BD II depression shares many clinical characteristics with MDD suggest that psychotherapy may improve outcomes in these patients. Supporting this is one small (n = 17), 12-week feasibility study demonstrating that 41% of patients with BD II depression achieved a response (≥ 50% reduction in depression scores) with IPSRT monotherapy without an increase in mania scores (334).

Pharmacotherapy: Table 7.2 illustrates the recommendations for the pharmacological treatment of acute BD II depression (1–3). Quetiapine XR joins quetiapine as a first-line option. Quetiapine plus lamotrigine, adjunctive NAC, and adjunctive triiodothyronine (T3) have been added as third-line options.

First-line options

Quetiapine. The four large RCTs demonstrating the efficacy of quetiapine monotherapy in combined groups of patients with BD I or BD II depression, which were cited in previous iterations of these guidelines, have now all been published: BOLDER I (88) and II (89), and EMBOLDEN I (90) and EMBOLDEN II (91). A pooled analysis of data in 776 patients with BD II from all four studies has been presented in abstract form (level 1) (335). Quetiapine doses of 300 mg/day and 600 mg/day were both associated with significantly greater improvements in MADRS total scores compared to placebo, beginning at week one and continuing through week eight. Response and remission rates were also significantly greater with both doses of quetiapine than placebo. There were significant improvements in core depressive symptoms, including reported sadness, anhedonia, negative thoughts, and suicidality, as well as anxiety symptoms.

In an eight-week RCT in patients with BD I and BD II depression, among the patients with BD II (n = 53), quetiapine XR 300 mg/day was associated with a significantly greater improvement in MADRS total score at study end compared to placebo (level 2) (92).

Second-line options

Lithium. The EMBOLDEN I trial included a lithium comparator arm, and provides the only placebo-controlled, parallel-group RCT data for lithium in acute BD II depression (90). In this trial, neither lithium nor quetiapine were superior to placebo in improving depression scores in patients with BD II, raising the possibility that this was a failed, rather than negative, trial. In addition, the mean lithium levels were < 0.8 mEq/L.

Divalproex. A meta-analysis of four small studies (total n = 142) in patients with BD I or BD II depression found that the RR of response was double, and of remission almost two-thirds greater, with divalproex monotherapy compared to placebo (96). Two of the trials reported results separately for BD I and BD II, with one reporting greater improvement in patients with BD I than BD II (as outcomes for the BD II group showed no separation from placebo) (336), and the other reporting greater improvements in BD II than BD I (337). Additional, open-label data supporting the efficacy of divalproex ER in BD II depression, previously cited in abstract form, have now been published (338). Thus, the data in aggregate are mixed. Further studies are clearly warranted to fully understand the role of divalproex in BD II depression.

Lamotrigine. The results of two previously unpublished RCTs of lamotrigine have been published in a review article (339). In the first study, 221 patients with BD II received lamotrigine 200 mg/day or placebo for eight weeks, while in the second 206 patients with BD I or BD II depression were randomized to lamotrigine 100–400 mg/day or placebo. In neither trial was lamotrigine superior to placebo. The negative results may be related to the slow titration of lamotrigine and high placebo response rates. Further, a meta-analysis of lamotrigine trials in BD I or BD II depression showed greater response

rates with lamotrigine than placebo, although the effect size was very modest (83). Based on this evidence, and its excellent tolerability profile, lamotrigine continues to be recommended as a second-line option for the acute treatment of BD II depression.

Third-line options

Antidepressant monotherapy. Relatively few studies have assessed antidepressant monotherapy in BD II because of concerns about induction of mood elevation. A paroxetine comparator arm in the EMBOLDEN II trial represents the largest placebo-controlled sample to evaluate antidepressant monotherapy in BD II depression (91). Paroxetine was not superior to placebo, although the dose may be considered low (20 mg), and quetiapine did not separate from placebo in this study, suggesting that this was a failed, rather than negative, study. Interestingly, switch rates into hypo/mania were similar with paroxetine and placebo.

In a 14-week, open-label study of fluoxetine monotherapy (n = 148), 60% of patients responded and 58% remitted (340). Although about 24% experienced hypomania/subsyndromal hypomania, this did not result in treatment discontinuation. In a post-hoc analysis of a previously reported open-label study in 83 patients with BD II, the significantly greater improvements in depression scores with venlafaxine compared to lithium were independent of rapid-cycling status, and venlafaxine did not result in a higher proportion of mood conversions (versus lithium) in either the rapid or non-rapid-cycling patients (341). Patients in this study who were unresponsive to lithium therapy (n = 14) and who were subsequently crossed over to venlafaxine experienced significantly greater reductions in depression and overall mood scores, with no differences in mania scores versus prior lithium (342). The main limitation of these studies is their open-label design.

Quetiapine + lamotrigine. A 12-week, open-label trial assessed the benefit of adding lamotrigine or quetiapine to pre-existing therapy in a mixed sample of patients with BD (BD I n = 15, BD II n = 22, or BD NOS n = 1) on multiple medications (level 3) (104). Adding quetiapine to lamotrigine in patients who had not responded to lamotrigine (n = 17 patients with BD II), and adding lamotrigine to quetiapine in patients who had not responded to quetiapine, was associated with improvements in the overall sample (level 3) (104). Data were not reported separately for patients with BD II.

Adjunctive ECT. An open-label study of twice-weekly bilateral ECT included patients with BD II who were medication refractory (n = 67). They achieved a response rate of 79% and a remission rate of 57% (343). This response rate was intermediate between patients with MDD (94%) and those with BD I (67%).

Novel treatments. In a sub-analysis of a small number of patients with BD II (n = 14) participating in a 24-week RCT, significantly more patients achieved full remission of both depressive and manic symptoms with adjunctive NAC compared to placebo (344). In a retrospective chart review of patients with treatment-resistant BD II or BD NOS depression (n = 159), treatment with supraphysiologic doses of T3 was associated with response in a majority of patients (345).

Maintenance therapy for bipolar II disorder

Psychotherapy: A post-hoc analysis of 20 patients with BD II who participated in a single-blind RCT demonstrated the benefits of adjunctive psychoeducation (21 sessions over six months) compared to unstructured support groups, with lasting benefits for up to five years (346). Significantly fewer patients in the psychoeducation group experienced any mood, depressive, or hypomanic relapse during follow-up, and had significantly better psychosocial functioning at both two- and five-year follow-up.

Pharmacotherapy: The major focus of maintenance therapy for patients with BD II is prevention of depressive episodes. New data support the addition of quetiapine monotherapy as first-line, and adjunctive quetiapine as second-line options for maintenance treatment for BD II (Table 7.4) (1–3). Lithium and lamotrigine continue to be recommended as first-line agents and fluoxetine has been added as a third-line treatment option.

First-line options

Quetiapine. A pooled analysis of maintenance data from the EMBOLDEN I and II trials has been presented in abstract form (335). Among patients with BD II (n = 231) who achieved remission during acute-phase treatment with quetiapine, those who continued quetiapine monotherapy for up to 52 weeks were significantly less likely to experience relapse into any mood episode [hazard ratio (HR) 0.47 for 300 mg and 0.18 for 600 mg] or depressive mood episode (HR 0.35 and 0.21) compared to those who switched to placebo (level 1).

Table 7.4. Recommendations for maintenance treatment of bipolar II disorder

First line	Lithium, lamotrigine, ***quetiapine***[a]
Second line	Divalproex; lithium or divalproex or atypical antipsychotic + antidepressant; ***adjunctive quetiapine***[a]; ***adjunctive lamotrigine***[a]; *combination of two of: lithium, divalproex, or atypical antipsychotic*
Third line	Carbamazepine, oxcarbazepine, atypical antipsychotic agent, ECT, ***fluoxetine***[a]
Not recommended	Gabapentin

ECT = electroconvulsive therapy.
[a]***New or change to recommendation***.

Rates of mania/hypomania were low, and similar for quetiapine and placebo.

Second-line options

Adjunctive lamotrigine. In a 52-week, open-label study in 109 patients with treatment-refractory BD II, adjunctive lamotrigine was associated with a significant improvement in depressive symptoms and sustained response (level 3) (347). Depressive symptoms continued to improve over a 52-week period, suggesting that the two negative acute-phase RCTs discussed above may have been too short to detect a difference between lamotrigine and placebo. Similarly, a retrospective chart review reported that the majority of 31 patients with treatment-resistant BD II depression who received adjunctive lamotrigine for ≥ 6 months were much or very much improved (348). The mean dose of lamotrigine was 199 mg/day and the maximum 400 mg/day, suggesting that a substantial number of patients required ≥ 200 mg for maximal benefit.

Adjunctive quetiapine. Naturalistic studies in combined populations of patients with BD I and BD II demonstrated high rates of sustained euthymia with adjunctive quetiapine, in spite of the fact that the quetiapine doses used in clinical practice were substantially lower than those used in clinical trials (level 3) (349, 350). Unfortunately, neither of these studies reported separate results for patients with BD II.

Third–line options

Carbamazepine/oxcarbazepine. In an RCT in BD I (n = 27) or BD II (n = 25) patients who displayed residual manic or depressive symptoms on maintenance lithium treatment, the addition of eight weeks of carbamazepine or oxcarbazepine resulted in significant symptom reduction, with oxcarbazepine being more effective than carbamazepine (67). Results were not presented separately for patients with BD II.

Fluoxetine monotherapy. There are now two small RCT extension studies with fluoxetine in patients with BD II depression. The first was a six-month RCT in patients with BD II and BD NOS who had responded to fluoxetine, in which relapse rates were 43% with continued fluoxetine versus 100% with placebo (p = 0.08) (351). The second was a one-year RCT (n = 81) in patients with BD II depression who had responded to fluoxetine. It reported that patients were significantly more likely to remain well if they continued on fluoxetine than if they switched to lithium (352). However, neither fluoxetine nor lithium was significantly better than placebo in mean time to relapse (fluoxetine 249.9 days, lithium 156.4 days, placebo 186.9 days). The lack of superiority of fluoxetine over placebo in these studies may be related to a lack of statistical power due to a smaller sample size.

Data from STEP-BD and other naturalistic studies provided additional information on the efficacy and safety of antidepressants in real-world settings. In a STEP-BD randomized, open-label trial, patients with depressive symptoms (n = 70; n = 21 with BD II) who responded acutely to adjunctive antidepressants had a significantly longer time until relapse into depression if they continued the antidepressant for 1–3 years versus discontinuing after resolution of the depression (182). Patients with BD II in this trial showed similar benefits to those with BD I, with no increase in hypo/manic switch. Similarly, in the entire STEP-BD sample (n = 3640; 30.7% with BD II), there was no increased frequency of switch from depression to hypo/mania without an intervening period of wellness in antidepressant-treated patients (19.6%) compared to patients receiving non-antidepressant treatments (24.9%) (353). Consistent with previous studies (354), the risk of antidepressant-associated switch was lower in BD II than BD I. The results from another open-label study in patients with BD II who discontinued antidepressant treatment showed that relapse occurred 2.5 times more quickly when discontinuation was rapid versus gradual (355).

ECT. Information on the use of ECT in BD II remains limited. In one small case series of 14 patients with rapid-cycling BD (nine with BD II) who received maintenance ECT for a mean of

21 months, all patients experienced significant improvement and a resolution of rapid-cycling status (356).

Clinical questions and controversies

Is cognitive dysfunction an issue in patients with BD II?

Persisting cognitive dysfunction is common and debilitating in patients with BD II. In a meta-analysis, patients with BD II had lower performance scores than healthy controls in all cognitive domains (357). In addition, cognitive impairment in BD II was as severe as in BD I, with the exception of memory and semantic fluency.

In a case series of 58 BD I, BD II, or BD NOS patients who received donepezil for memory problems, 84% with BD II (36/43) showed improvement, compared to 0% of patients with BD I (0/7) and 50% of patients with BD NOS (4/8) (358). More than half of the patients with BD I had worsening of affective symptoms compared to only 2% of those with BD II and 25% of those with BD NOS.

Do the clinical features of depressive episodes inform treatment decisions in BD II?

Data from STEP-BD show that mixed hypomanic symptoms are common during depressive episodes, occurring in 70% of patients with BD II, compared to 66% of patients with BD I (129). Adjunctive antidepressants did not lead to greater recovery rates among patients with mixed symptoms in STEP-BD, and were in fact associated with greater manic symptom severity at the three-month follow-up (359). Although recovery rates were not reported separately for patients with BD II in this sample, this suggests that antidepressants should be avoided in BD II depressive episodes with concomitant hypomanic symptoms.

Psychotic symptoms are also relatively common in BD II depression, and were present in 20% of patients with BD II in a Spanish study (n = 164) (360). There is little information to guide the treatment of psychotic depression in patients with BD II, but clinical experience and studies in MDD suggest that antipsychotic medications either as monotherapy (e.g., quetiapine) or in combination with mood stabilizers may be required.

Bipolar spectrum disorders

Diagnosis: Formulating treatment recommendations for patients with bipolar spectrum disorders (BSDs; also referred to as 'BD NOS' in the DSM-IV) remains hampered by both a lack of consensus regarding which disorders should be included in this category, and also an almost complete absence of well-designed clinical trials in this patient group. The issue is further compounded by uncertainty regarding the diagnostic stability of BSDs. In fact, BSDs may be prodromal to BD I and BD II in a substantial number of patients, according to one longitudinal study of 57 people with cyclothymia or BD NOS, where 42% progressed to BD II and 10% to BD I over a 4.5-year follow-up period (361).

Epidemiology: The results from two large studies which measured the prevalence of BSDs indicate that they are relatively common in the general population. The World Mental Health Survey Initiative, including 61392 people in nine countries in North and South America, Europe, and Asia, reported that 1.4% of the population met lifetime criteria for subthreshold BD (4). This was similar to the lifetime prevalence of 2.4% reported in the National Comorbidity Survey Replication (NCS-R) in the USA (n = 9282) (362). In both studies, the prevalence of BSDs was greater than those of BD I and BD II combined. The NCS-R further suggested that BSDs are also common in clinical populations, as over 35% of people with major depressive episodes also met the lifetime criteria for subthreshold hypomania (363). Although a liberal definition of subthreshold hypomania was utilized (lifetime presence of ≥ 1 hypomanic symptom), the NCS-R reported that, compared to people with major depressive episodes alone, those who had subthreshold hypomania shared a number of clinical features with those suffering from BD I or BD II, including an earlier age of onset, more frequent depressive episodes, a greater number of suicide attempts, and higher rates of comorbidity.

Management: Very few studies have investigated treatment options for BSDs. The only RCT that has been reported to date was conducted in 56 youth with BSD or cyclothymia who were randomized to divalproex or placebo for up to five years. At study end there were no differences between treatment groups in time to study discontinuation due to a mood episode or for any reason, severity of mood symptoms, or psychosocial functioning (364).

A small case series reported rapid and sustained symptom remission in four patients with BD NOS and depressive or mixed symptoms with low-dose quetiapine (50–75 mg) (365). In addition, a

retrospective chart review of 34 patients with treatment-refractory BD NOS found that adjunctive treatment with supraphysiologic doses of T3 was associated with an improvement in depressive symptoms in 85% of patients, and remission in 38% (345). In a case series of 58 patients with BD prescribed donepezil for memory problems, 50% of those with BD NOS (4/8) had improvements in memory; however, 25% had a worsening of affective symptoms (358).

In the absence of well-designed clinical trials, specific treatment suggestions for patients with BD NOS cannot be made. Clinicians should formulate treatment plans based on patients' presenting symptoms, course of illness, previous treatment responses, and family history. Given the probability that subthreshold bipolarity is present in a substantial proportion of patients with MDD, clarifying the nature and best treatment options for BD NOS is a major unmet need in mood disorders research.

Section 8. Safety and monitoring

Monitoring

Previous iterations of the guidelines provided recommendations for initial and follow-up laboratory investigations and monitoring strategies for patients with BD (1–3). BD and some of its treatments can increase the risk of comorbid medical conditions, as well as risk factors for cardiovascular disease such as overweight/obesity, diabetes, metabolic syndrome, and dyslipidemia. Complete medical and laboratory investigations should be performed at baseline, with ongoing monitoring for weight changes and adverse effects of medication.

The ISBD has also published consensus recommendations for general safety monitoring for all BD patients receiving treatment, as well as specific monitoring recommendations for individual agents, and the reader is also referred to this document for more details (366).

Unfortunately, the UNITE global survey of 1300 patients with BD found that monitoring of safety parameters does not occur in the majority of patients, with less than 30% undergoing weight and blood pressure measurements, and less than 5% undergoing a physical examination or blood tests during interactions with their principal health care provider (11).

Safety and tolerability of pharmacotherapy for BD

The previous iterations of the guidelines have extensively reviewed the safety and tolerability of pharmacotherapeutic options; only new data are included here (1–3).

An analysis of 48 RCTs in patients with BD or schizophrenia found that, compared to risperidone, quetiapine was associated with significantly less anxiety, restlessness, and extrapyramidal symptoms (EPS); and also compared to risperidone, olanzapine was associated with increased weight gain and ziprasidone with decreased weight gain (367).

Weight gain: The naturalistic STOP-EM trial concluded that, in 47 patients with BD receiving maintenance therapy following their first manic episode, the mean 12-month weight gain was significantly greater compared to healthy control subjects (4.76 kg versus 1.50 kg; $p = 0.047$). In addition, 12-month rates of overweight/obesity were > 50% in patients with BD, almost double those in healthy subjects (368).

A review of RCTs confirmed that long-term olanzapine treatment (≥ 48 weeks) was associated with a substantial weight gain (mean 5.6 kg), with 64% of patients gaining ≥ 7% of their baseline weight (369). During short-term treatment, olanzapine orally disintegrating tablet was not associated with any reduction in weight gain compared to the standard tablet formulation (370). By contrast, a post-hoc analysis of a six-month RCT found that adjunctive ziprasidone had no negative impact on metabolic parameters or body weight compared to adjunctive placebo (371). Post-hoc analyses of two studies found a modest increase in weight with adjunctive aripiprazole that was not significantly different from that using lithium/divalproex alone (372). When used as an adjunct to lamotrigine, aripiprazole plus lamotrigine was associated with an increased weight gain compared to lamotrigine alone, which was associated with decreased body weight over the one-year period.

The non-randomized Second-generation Antipsychotic Treatment Indications, Effectiveness and Tolerability in Youth cohort study found that after a median of 10.8 weeks of treatment, weight increased by 8.5 kg with olanzapine ($n = 45$), 6.1 kg with quetiapine ($n = 36$), 5.3 kg with risperidone ($n = 135$), and 4.4 kg with aripiprazole ($n = 41$) compared to 0.2 kg in the untreated group ($n = 15$) (373).

An 11-month, RCT in 50 patients on pharmacotherapy for BD found that a multimodal lifestyle intervention (11 group sessions and weekly fitness training) significantly reduced BMI, at end of treatment (five months) and at a six-month follow-up, compared to a wait-list control group; however, the effect was only significant in women (374).

Metabolic syndrome and type 2 diabetes: Additional data continue to demonstrate high rates of diabetes and metabolic syndrome associated with atypical antipsychotic agent use in patients with BD (375). However, in a post-hoc analysis of a six-month RCT, the incidence of metabolic syndrome with aripiprazole maintenance therapy was similar to that of placebo (376).

Additional data confirm the potential for metabolic disturbances with divalproex treatment. In a cohort study, divalproex was associated with significantly higher plasma insulin, triglyceride levels, and BMI, as well as lower fasting glucose and high-density lipoprotein cholesterol (HDL-C) levels (377).

Dyslipidemia: Dyslipidemia is an important cardiovascular risk factor. As discussed in previous iterations of the guidelines, atypical antipsychotic agents, as well as lithium/divalproex, can cause dyslipidemia (1–3). Additional data from a cohort study found that divalproex was associated with low HDL-C levels and high adiponectin levels in patients with BD compared to non-psychiatric matched control subjects (378). Lipid profiles should be monitored and appropriate lipid-lowering medications prescribed as needed, according to published recommendations for the management of dyslipidemia.

Endocrine side effects: The results from a case-controlled study indicated higher risks of hypothyroidism in patients with BD who had used carbamazepine alone [odds ratio (OR) = 1.68], combination lithium and valproate (OR = 2.40), combination lithium and carbamazepine (OR = 1.52), or all three agents (OR = 2.34) compared to patients who had never used any of these agents (379). A meta-analysis of 390 RCTs and observational studies found that lithium was associated with an increased risk of clinical hypothyroidism (OR = 5.78), as well as increases in thyroid-stimulating hormone and parathyroid hormone (380).

Suicide: A 2.5-year RCT of 98 patients with BD and past suicide attempts found no significant differences between lithium and divalproex in time to suicide attempt or suicide event, although the trial was statistically underpowered to detect differences (381).

Cognitive impairment: Three meta-analyses have demonstrated persistent cognitive impairments in euthymic patients with BD, including deficits in executive functions, verbal memory, learning, processing speed, and attention (357, 382, 383). In addition, patients tested during a manic/mixed or depressed state showed exaggerated impairment on measures of verbal learning (383).

Several cohort studies have demonstrated greater cognitive dysfunction in euthymic patients with BD taking antipsychotic medications compared to healthy control subjects (384–386) or to those not taking antipsychotic agents (385). Two cohort studies have shown fewer cognitive impairments associated with quetiapine than with olanzapine or risperidone (385, 387).

An eight-week RCT in 35 euthymic patients with BD found that adjunctive pramipexole significantly improved visual–verbal processing speed and working memory compared to placebo (388). A small (n = 16), three-month RCT in minimally symptomatic patients with BD found that adjunctive galantamine improved episodic memory performance; however, placebo improved processing speed (389).

Hypersensitivity and dermatological reactions: Additional data demonstrate the risk of serious rash, erythema multiforme, Stevens–Johnson syndrome, or toxic epidermal necrolysis with lamotrigine, carbamazepine, and divalproex (390, 391). A 12-week trial demonstrated a statistically significant reduction in the development of rashes with a slow titration of lamotrigine compared to a standard titration schedule (392).

The US FDA issued a warning that type I hypersensitivity reactions (including anaphylaxis and angioedema) can occur with asenapine use, after as little as one dose (393).

Sedation: In a pooled analysis of data from three short-term trials in patients with BD, asenapine monotherapy and as an adjunct was associated with higher rates of somnolence than placebo, which occurred after 1–9 days of treatment and persisted for 1–4 weeks (394).

Gastrointestinal symptoms: In a three-month RCT, ER carbamazepine resulted in significantly fewer autonomic and gastrointestinal adverse events compared to the immediate-release formulation (64).

Neurological side effects including EPS: An increased risk of neuroleptic malignant syndrome associated with the use of antipsychotic medications (OR = 2.36) has been reported in patients with BD (395).

A post-hoc analyses of pooled data in patients with a mood disorder reported an increased rate of akathisia in patients receiving aripiprazole (18%) compared to placebo (5%) (396).

Fracture risk: In a Veteran's Administration prospective cohort study, the use of anticonvulsants was associated with a twofold greater risk of fracture among patients (age ≥ 50 years) with BD (271). In addition, a diagnosis of BD was associated with a 20% increased risk of fracture, independent of anticonvulsant use. Antidepressants and antipsychotic agents can similarly decrease bone mineral density (397). Screening for bone mineral density may be indicated in high-risk populations (398).

Closing statement

The purpose of this update is to add previously unpublished material to the CANMAT guidelines for the treatment of BD, ensuring that they remain current and practical. When a first-line treatment is unsuccessful, clinicians are advised to try alternative first-line treatments before proceeding to second-line options, and the same recommendation applies when second-line treatments fail. Judicious use of psychosocial interventions, alternative somatic treatments such as ECT, and the numerous experimental agents offer additional promise for the management of BD.

Affiliations

[a]Department of Psychiatry, University of British Columbia, Vancouver, BC, [b]Department of Psychiatry, University of Toronto, Toronto, ON, [c]Department of Psychiatry, McGill University, Montreal, QC, [d]Department of Psychiatry, Dalhousie University, Halifax, NS, [e]Department of Psychiatry, University of Calgary, Calgary, AB, [f]Department of Psychiatry, University of Western Ontario, London, ON, [g]Department of Psychiatry, Queen's University, Kingston, ON, [h]Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, [i]Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [j]Institute of Psychiatry, University of São Paulo Medical School, São Paulo, Brazil, [k]Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh, Pittsburgh, PA, USA, [l]Department of Psychiatry, Seoul National University, Seoul, Korea, [m]Department of Psychiatry, University Medical Center, Groningen, The Netherlands, [n]School of Medicine, Deakin University, Geelong, [o]Department of Psychiatry, University of Melbourne, Parkville, Victoria, Australia

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RESEARCH ARTICLE

Efficacy of cognitive-behavioral therapy in patients with bipolar disorder: A meta-analysis of randomized controlled trials

Kai-Jo Chiang[1,2], Jui-Chen Tsai[1,3], Doresses Liu[1,4], Chueh-Ho Lin[1,5,6], Huei-Ling Chiu[1], Kuei-Ru Chou[1,3,7]*

1 School of Nursing, College of Nursing, Taipei Medical University, Taipei, Taiwan, **2** Department of Nursing, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan, **3** Department of Nursing, Taipei Medical University-Shuang Ho Hospital, Taipei, Taiwan, **4** Department of Nursing, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan, **5** School of Gerontology Health Management, College of Nursing, Taipei Medical University, Taipei, Taiwan, **6** Master's Program in Long-Term Care, College of Nursing, Taipei Medical University, Taipei, Taiwan, **7** Psychiatric Research Center, Taipei Medical University Hospital, Taipei, Taiwan

* kueiru@tmu.edu.tw

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Abstract

Background

Although cognitive behavioral therapy (CBT) is considered a promising adjuvant to pharmacotherapy for treating bipolar disorder (BD), its efficacy is unproven. The present review and meta-analysis evaluated the treatment outcomes of patients with BD treated with CBT plus medication and compared these data with the outcomes of those who received standard care alone.

Methods

Electronic searches from inception to July 31, 2016, were performed using PubMed, Medline OVID, Cochrane Library, EMBASE, CINAHL plus, and PsycINFO. In the extensive electronic literature search, keywords such as "bipolar disorder," "manic-depressive psychosis," "bipolar affective disorder," "bipolar depression," "cognitive therapy," "cognitive-behavioral therapy," and "psychotherapy" were transformed into MeSH terms, and only randomized controlled trials (RCTs) were included. The pooled odds ratios (ORs) of relapse rates and Hedges's g, along with 95% confidence intervals (CIs), for the mean differences in the levels of depression, mania, and psychosocial functioning were calculated. Further subgroup analyses were conducted according to the characteristics of the CBT approaches, patients, and therapists, if the data were available.

Result

A total of 19 RCTs comprising 1384 patients with type I or II BD were enrolled in our systematic review and meta-analysis. The main analysis revealed that CBT could lower the relapse rate (pooled OR = 0.506; 95% CI = 0.278 −0.921) and improve depressive symptoms (g =

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−0.494; 95% CI = −0.963 to −0.026), mania severity (g = −0.581; 95% CI = −1.127 to −0.035), and psychosocial functioning (g = 0.457; 95% CI = 0.106–0.809).

Conclusions

CBT is effective in decreasing the relapse rate and improving depressive symptoms, mania severity, and psychosocial functioning, with a mild-to-moderate effect size. Subgroup analyses indicated that improvements in depression or mania are more potent with a CBT treatment duration of ≥90 min per session, and the relapse rate is much lower among patients with type I BD.

Introduction

Bipolar disorder (BD) is a severe mental disease with a lifelong course and considerable morbidity and mortality. BD has a lifelong prevalence rate of 1%–1.5% and is characterized by recurrent episodes of mania, depression, or a mixture of both phases [1]. BD can cause impaired cognition [2], functional decline [3], poor health outcomes [4], and a high frequency of suicidal behavior [5]. The inter-personal relationships of patients with BD are also highly affected by the dramatic alternation of manic/hypomanic and depressive mood cycles. A BD cohort study with a relatively large sample size (n = 1469) demonstrated that 58% of patients with BD types I and II recovered, but approximately half of them experienced recurrence within 2 years [6]. In the United States, the direct and indirect costs of BD were estimated to be USD 151 billion in 2009 [7]. Millions of patients worldwide are affected by this severe mood illness, incurring costs of billions of USD for the years lived with disability [8].

Given the biological and hereditary underpinning of BD, pharmacotherapy is the first-line treatment. However, a growing body of literature suggests that combined pharmacotherapy and psychotherapy is more effective in treating patients with BD than is medication alone [9]. As an adjuvant therapy, psychotherapy helps patients with BD in improving their compliance, awareness, and coping skills for life events, which collectively results in an improved response to pharmacotherapy [10–13, 32]. Among the psychological therapies that are potential adjuncts to medications for patients with BD, cognitive-behavioral therapy (CBT) is a promising treatment option but has inconclusive findings [14].

In clinical settings, CBT is the non-pharmaceutical intervention of choice for patients with depression and anxiety, the core concept and treatment practice model were developed by Beck et al. more than 40 years previously [15, 16]. Randomized controlled trials (RCTs) published within the past 10 years have disclosed the potential benefits of CBT as an adjunct to mood stabilizers for preventing relapse, relieving symptoms, and enhancing drug adherence [9]. Currently, some meta-analyses have evaluated the efficacy of CBT for BD [17–23]. These studies have demonstrated that CBT has a small impact on clinical symptoms [17–19], but the evidence remains incomprehensive and inconclusive due to limited data. In a meta-analysis, Ye et al described the short-term efficacy of CBT in lowering the relapse rate of BD [19]. In our study, an in-depth subgroup analysis of the meta-analyses on this topic was conducted to provide insights for psychiatrists and psychologists. Accordingly, we performed a meta-analysis, as well as extensive searches of multiple databases and further subgroup analysis, to determine the efficacy of CBT in improving depressive symptoms, mania severity, relapse rates and social functioning.

Materials and methods

Reporting standards for meta-analyses

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement for the meta-analyses of RCTs. The PRISMA checklist(S1 Checklist) is provided as Supplementary Material.

Search strategy for systematic literature reviews

Electronic searches from the date of inception to July 31, 2016 were performed using PubMed, Medline OVID, the Cochrane Library, EMBASE, CINAHL Plus, and PsycINFO. To identify specific and relevant studies, we developed a search strategy based on the patient population (BD), treatment (CBT), and study design (RCT; S1 Table). In extensive electronic literature searches, keywords such as "bipolar disorder," "manic-depressive psychosis," "bipolar affective disorder," "bipolar depression," "cognitive therapy," "cognitive-behavioral therapy," and "psychotherapy" were transformed into exploded MeSH terms. The references from selected articles were also accessed for eligibility in the review process. All the candidate articles were evaluated by two independent reviewers through systematic approaches involving the inclusion and exclusion criteria.

Selection criteria

In this systematic review, eligible studies fulfilled the following inclusion criteria: (1) RCT, (2) patients with BD aged $\geq$18 years, (3) presence of two study groups: a comparison group receiving the usual interventions and a CBT group receiving CBT plus the intervention given to the control group, and (4) availability of at least one relevant outcome such as changes in the relapse rate, depressive symptoms, mania severity, and psychosocial functioning. The depressive symptoms were assessed using the Hamilton Rating Scale for Depression (HRSD), Beck Hopelessness Scale (BHS), Beck Depression Inventory (BDI), or Montgomery–Asberg Depression Rating Scale (MADRS); the mania severity was assessed using the Mania Rating Scale (MRS) or Young Mania Rating Scale (YMRS); and the level of psychosocial functioning was assessed using the Global Assessment of Functioning (GAF), Dysfunctional Attitude scale (DAS), or Social Performance Scale (SPS).

The exclusion criteria were as follows: (1) no relevant data were available for further meta-analysis and (2) article types other than RCTs, such as comments, letters, and reviews. In addition, for duplicated publications with the same study participants, only those studies with the most relevant and comprehensive data were considered, and the other studies were discarded. Furthermore, during the selection process for systematic reviews, we verified whether CBT or the relevant variants were included in the psychological interventions of each study. However, some studies used psychological therapies based on CBT or CBT-modified programs. After careful discussion, we included such studies because their core psychological intervention was CBT.

Data extraction, data verification, and quality assessment

Data extraction was performed by two independent reviewers who used a specific work sheet designated before the literature search. A consensus meeting was held with a third researcher to resolve disparities between the two reviewers. Data extraction was conducted from full-text versions of the RCTs, where available. A quality-control process for the data extraction was undertaken by another researcher to verify all the extracted data against the original sources. The data regarding basic characteristics and outcome measures, including the study identity

(first author plus publication year), country, study design, number of study participants, mean or median age, gender, intervention characteristics, and all relevant outcomes, were extracted for all studies. Quality assessment of the selected RCTs was conducted according to Cochrane Collaboration's tool for assessing the risk of bias in randomized trials [24]. If the study populations were duplicated, the most updated findings or most comprehensive outcome measures were chosen. Some of the follow-up studies of the original RCTs focused on cost-effectiveness and could not be included in this meta-analysis.

Statistical analysis

All data analyses were performed using Comprehensive Meta-Analysis, Version 3.3 (Biostat Inc., Englewood, NJ, USA). The efficacy of CBT in lowering the relapse rate was evaluated from the overall odds ratio (OR). The average changes in the scores for depressive symptoms, mania severity, and psychosocial functioning were calculated from baseline to the study end. Furthermore, Hedges's g was used to determine the effect size of continuous outcomes, with g values of 0.2–0.4, 0.5–0.7, and $\geq$0.8 representing small, moderate, and large effect sizes, respectively. The significance of the ORs and Hedges's g was determined using a Z test. A two-tailed $P < 0.05$ was considered statistically significant. The heterogeneity among RCTs was determined using the Cochran's Q test and I^2 statistic, with I^2 values of 75%, 50%, 25%, and 0% indicating high, moderate, low, and no heterogeneity, respectively. Data from individual RCTs were summarized using a random-effects model for obtaining more statistically conservative estimates compared with those obtained using a fixed-effects model. In addition, further subgroup analysis was conducted according to the characteristics of CBT approaches, patients, and therapists, if the data were available for assessing the impact of different characteristics on the efficacy of CBT in treating BD. Sensitivity analyses were performed using the leave-one-out approach to elevate the robustness of the pooled estimates. Publication bias was evaluated using a funnel plot with Egger's test.

Results

Characteristics of the included studies

Fig 1 depicts the entire literature review process. Initially, 973 research reports were identified. Through independent reviews based on the inclusion/exclusion criteria, 19 RCTs evaluating the efficacy of CBT for patients with BD were included in this meta-analysis [25–43]; these studies comprised a total of 716 patients with CBT and 668 controls. Of the 19 RCTs, three included only patients with BD I, and other studies included patients with BD I or II. The mean age of the patients at enrollment ranged from 34.7 to 44 years. Most of these RCTs (n = 10) used individual-based CBT, and other studies (n = 9) used group-based CBT. The number of CBT sessions ranged from 8 to 30, and the duration of each session ranged from 45 to 120 min. All the included RCTs were published between 2000 and 2015. Other details are summarized in Table 1.

Primary outcome: Depressive symptoms and mania severity

In 13 RCTs reporting treatment outcomes concerning depression [25–28, 31–34, 36, 39–42], which employed the BDI, BHS, HRSD, and MADRS, the pooled effect size indicated that patients who underwent CBT exhibited a more favorable response in terms of decreased depression levels compared with those treated as usual (Hedges's g = −0.494; 95% CI = −0.963 to −0.026; P = 0.039, with a moderate effect size; Fig 2). Large heterogeneity was observed in this analysis (Q = 116.179; $P < 0.001$; I^2 = 89.671%).

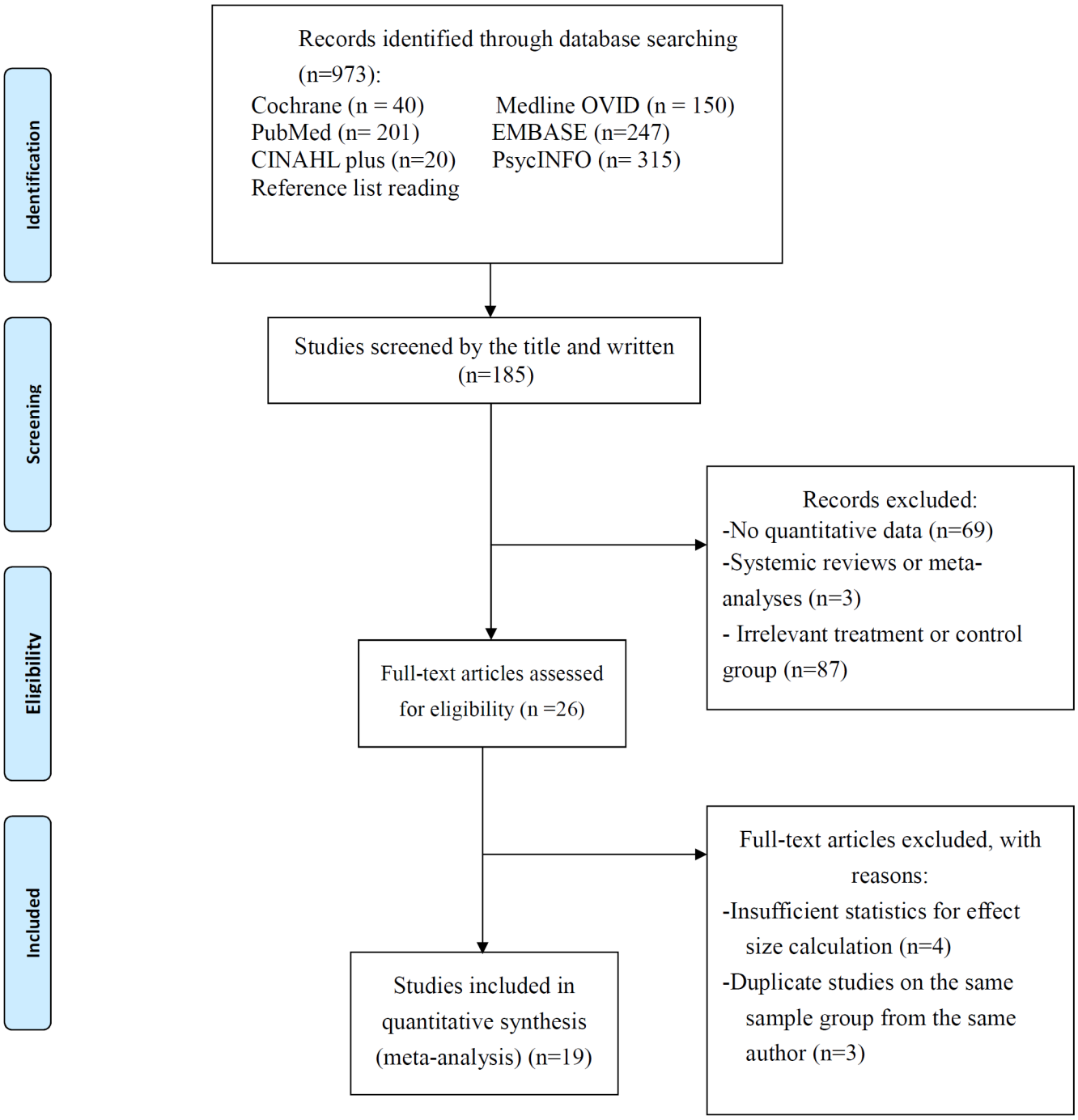


Fig 1. PRISMA 2009 flow diagram.

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In 11 RCTs reporting the treatment efficacy with respect to mania [25, 27, 28, 33, 34, 36, 37, 39–42], which employed the MRS and YMRS, the pooled effect size indicated that CBT significantly reduced the severity of mania in patients with BD (Hedges's g = −0.581; 95% CI = −1.127 to −0.035; P = 0.037, with a moderate effect size; Fig 3). Large heterogeneity was noted in this analysis (Q = 106.210; P < 0.001; I^2 = 90.585%).

Table 1. Characteristics of cognitive-behavioral therapy for patients with bipolar disorder in the randomized controlled trials included in the meta-analysis (N = 19).

Study	Country	Intervention (experimental/ control)	Design	Sample size (patients)	Intervention characterization	Outcome	Study quality/ Cochrane tool
Lam et al. (2000) [25]	UK	CBT/TAU	RCT	• Total N: 25	• Number of sessions treated: 12–20	• Relapse rate (episodes)	7/
				• Complete N (T/ C): 12/11	• Treatment length (min): -	• Depression level (BDI, BHS, HDRS)	AA: low
				• Mean age (years):39.0	• Each group size (people): individual	• Mania severity (MRS)	AC: unclear
				• Gender (M/F): 12/13	• CBT therapist: certified professional	• Function (SPS)	BAO: low
				• Bipolar I: 25		• Assessed time points (months): 6, 12	IO: low
							SRO: low
Scott et al. (2001) [26]	UK	CT/WLC	RCT	• Total N: 42	• Number of sessions treated: 25	• Relapse rate (episodes)	7/
				• Complete N (T/ C): 21/21	• Treatment length (min): 45	• Depression level (BDI)	AA: low
				• Mean age (years):38.8	• Each group size (people): individual	• Symptom (ISS)	AC: unclear
				• Gender (M/F): 17/25	• CBT therapist: certified professional	• Function (GAF)	BAO: unclear
				• Bipolar I: 34 • Bipolar II: 8		• Assessed time points (months): 6, 12, 18	IO: low
							SRO: low
Lam et al. (2003) [27]	UK	CT/TAU	RCT	• Total N: 103	• Number of sessions treated: 12–18	• Relapse rate (episodes)	6/
				• Complete N (T/ C): 43/44	• Treatment length (min): -	• Depression level (BDI, HDRS)	AA: low
				• Mean age (years):44.0	• Each group size (people): individual	• Mania severity (MRS)	AC: unclear
				• Gender (M/F): 45/58	• CBT therapist: certified professional	• Function (SPS, DAS)	BAO: unclear
				• Bipolar I: 103		• Assessed time points (months): 6, 12, 18	IO: low
							SRO: low
Ball et al. (2006) [28]	Australia	CT/TAU	RCT	• Total N: 52	• Number of sessions treated: 20	• Relapse rate (episodes)	7/
				• Complete N (T/ C): 25/27	• Treatment length (min): 60	• Depression level (BDI, BHS, HDRS, MADRS)	AA: low
				• Mean age (years):42.0	• Each group size (people): individual	• Mania severity (YMRS)	AC: unclear
				• Gender (M/F): 22/30	• CBT therapist: certified professional	• Function (GAF, SAS, SPS, DAS)	BAO: low
				• Bipolar I or II: 52		• Assessed time points (months): 3, 6, 9, 12	IO: low
							SRO: low
Scott et al. (2006) [29]	UK	CBT/SC	RCT	• Total N: 253	• Number of sessions treated: 22	• Recurrence rate (episodes)	8/
				• Complete N (T/ C): 127/126	• Treatment length (min): -	• Depression level (LIFE-II score for depression)	AA: low
				• Mean age (years):41.2	• Each group size (people): individual	• Mania severity (LIFE-II score for mania)	AC: unclear

(*Continued*)

Table 1. (*Continued*)

Study	Country	Intervention (experimental/ control)	Design	Sample size (patients)	Intervention characterization	Outcome	Study quality/ Cochrane tool
				• Gender (M/F): 89/164	• CBT therapist: certified professional	• Assessed time points (months): 6, 12, 18	BAO: low
				• Bipolar I: 238 • Bipolar II: 15			IO: low
				• Recurrent Bipolar			SRO: low
Miklowitz et al. (2007) [30]	USA	IPT/CC	RCT	• Total N: 152	• Number of sessions treated: 30	• Depression level (MADRS)	8/
				• Complete N (T/ C): 84/68	• Treatment length (min): 60	• Function (LIFE-RIFT)	AA: low
				• Mean age (years):41.1	• Each group size (people): individual	• Assessed time points (months): 3, 6, 9	AC: unclear
				• Gender (M/F): 64/88	• CBT therapist: unclear		BAO: low
				• Bipolar I: 105 • Bipolar II: 47			IO: low
							SRO: low
William et al. (2008) [31]	UK	MBCT/WLC	RCT	• Total N: 68	• Number of sessions treated: 8	• Depression level (BDI-II)	8/
				• Complete N (T/ C): 28/27	• Treatment length (min): 120	• Anxiety level (BAI)	AA: low
				• Age (years):18–65	• Each group size (people): 12–15	• Assessed time points (months): post-treatment	AC: unclear
				• Gender (M/F): 12/13	• CBT therapist: certified professional		BAO: low
				• Unipolar: 51 • Bipolar: 17			IO: low
							SRO: low
Zaretsky et al. (2008) [32]	Canada	CBT/PE	RCT	• Total N: 79	• Number of sessions treated: 14	• Depression level (HDRS)	6/
				• Complete N (T/ C): 29/24	• Treatment length (min): -	• Mania severity (CARS-M)	AA: low
				• Mean age (years): 40.7	• Each group size (people): individual	• Function (SPS, DAS)	AC: unclear
				• Gender (M/F): unclear	• CBT therapist: certified professional	• Assessed time points (weeks): 2, 6, 12	BAO: unclear
				• Bipolar I: 52 • Bipolar II: 27			IO: low
							SRO: low
Perlick et al. (2010) [33]	USA	FF-CBT/HE	RCT	• Total N: 46	• Number of sessions treated: 12–15	• Depression level (HDRS)	8/
				• Complete N (T/ C): 22/18	• Treatment length (min): 45	• Mania severity (YMRS)	AA: low
				• Mean age (years):34.7	• Each group size (people): family-based	• Assessed time points (months): post-treatment	AC: unclear
				• Gender (M/F): 15/25	• CBT therapist: unclear		BAO: low
				• Bipolar I: 40 • Bipolar II: 6			IO: low
							SRO: low

(*Continued*)

Table 1. (*Continued*)

Study	Country	Intervention (experimental/ control)	Design	Sample size (patients)	Intervention characterization	Outcome	Study quality/ Cochrane tool
Costa et al. (2011) [34]	Brazil	CBGT/TAU	RCT	• Total N: 41	• Number of sessions treated: 14	• Depression level (BDI, BHS)	7/
				• Complete N (T/ C): 27/12	• Treatment length (min): 120	• Mania severity (YMRS)	AA: low
				• Mean age (years):40.5	• Each group size (people): group	• Anxiety level (BAI)	AC: unclear
				• Gender (M/F): 12/25	• CBT therapist: certified professional	• Assessed time points (weeks): 7, 14	BAO: low
				• Bipolar I: 35 • Bipolar II: 6			IO: low
							SRO: low
Gomes et al. (2011) [35]	Brazil	CBGT/TAU	RCT	• Total N: 50	• Number of sessions treated: 18	• Relapse rate (episodes)	7/
				• Complete N (T/ C): 25/22	• Treatment length (min): 90	• Assessed time points (months): post-treatment	AA: low
				• Median age (years):38.0	• Each group size (people): 4.4		AC: unclear
				• Gender (M/F): 12/38	• CBT therapist: certified professional		BAO: low
				• Bipolar I: 38 • Bipolar II: 12			IO: low
							SRO: low
Meyer et al. (2012) [36]	Germany	CBT/ST	RCT	• Total N: 76	• Number of sessions treated: 20	• Recurrence rate (episodes)	8/
				• Complete N (T/ C): 38/38	• Treatment length (min): 50–60	• Depression level (BDI, BHS)	AA: low
				• Mean age (years):44.0	• Each group size (people): individual	• Mania severity (SRMI)	AC: low
				• Gender (M/F): 38/38	• CBT therapist: certified professional	• Function (GAS)	BAO: unclear
				• Bipolar I: 38 • Bipolar II: 38		• Assessed time points (months): post-treatment	IO: low
							SRO: low
Harvey et al. (2015) [37]	USA	CBT/PE	RCT	• Total N: 58	• Number of sessions treated: 8	• Relapse rate (episodes)	8/
				• Complete N (T/ C): 30/28	• Treatment length (min): 50–60	• Insomnia (ISI, SD-SE, PSQI)	AA: low
				• Mean age (years):36.6	• Each group size (people): individual	• Depression level (IDS-C)	AC: unclear
				• Gender (M/F): 22/36	• CBT therapist: certified professional	• Mania severity (YMRS)	BAO: low
				• Bipolar I: 58		• Function (SDS)	IO: low
						• Assessed time points (months): post-treatment, 6 month follow-up	SRO: low
Colom et al. (2003) [38]	Spain	GPE/SC	RCT	• Total N: 120	• Number of sessions treated: 21	• Recurrence rate (episodes)	8/
				• Complete N (T/ C): 60/60	• Treatment length (min): 90	• Hospitalization	AA: low

(*Continued*)

Table 1. (*Continued*)

Study	Country	Intervention (experimental/ control)	Design	Sample size (patients)	Intervention characterization	Outcome	Study quality/ Cochrane tool
				• Mean age at onset (years): 22.8	• Each group size (people): 8 to 12	• Assessed time points (months): 6, 12, 18, 24-month follow-up	AC: unclear
				• Gender (M/F): 44/76	• CBT therapist: certified professional		BAO: low
				• Bipolar I: 100 • Bipolar II: 20			IO: low
							SRO: low
González-Isasi et al. (2010) [39]	Spain	CT/SC	RCT	• Total N: 40	• Number of sessions treated: 20	• Relapse	8/
				• Complete N (T/ C): 20/20	• Treatment length (min): 90	• Depression level (BDI)	AA: low
				• Mean age (years): 41.3	• Each group size (people): 10	• Mania severity (YMRS)	AC: low
				• Gender (M/F): 21/19	• CBT therapist: certified professional	• Anxiety level (STAI-S)	BAO: unclear
				• Bipolar I/II: 40 • Refractory Bipolar		• Inadaption scale	IO: low
						• Assessed time points (months): post-treatment, 6, 12 months follow-up	SRO: low
Weiss et al. (2007) [40]	USA	IGT/SC	RCT	• Total N: 62	• Number of sessions treated: 20	• Substance use	8/
				• Complete N (T/ C): 31/31	• Treatment length (min): 60	• Depression level (HAM-D)	AA: low
				• Mean age (years):41.9	• Each group size (people): -	• Mania severity (YMRS)	AC: unclear
				• Gender (M/F): 30/32	• CBT therapist: certified professional	• Assessed time points (months): post-treatment, 3, 5, 8 months follow-up	BAO: low
				• Bipolar I: 40 • Bipolar II: 22			IO: low
				• SUD			SRO: low
Weiss et al. (2009) [41]	USA	IGT/GDC	RCT	• Total N: 61	• Number of sessions treated: 12	• Substance use	8/
				• Complete N (T/ C): 31/30	• Treatment length (min): 60	• Relpase rate (episode)	AA: low
				• Mean age (years): 38.3	• Each group size (people): -	• Addiction (ASI)	AC: low
				• Gender (M/F): 36/25	• CBT therapist: certified professional	• Depression level (HDRS)	BAO: unclear
				• Bipolar I: 48 • Bipolar II: 9		• Mania severity (YMRS)	IO: low
				• BD, NOS: 4 • SUD		• Assessed time points (months): post-treatment, 3, 6 months of follow-up	SRO: low
Perich et al. (2013) [42]	Australia	MBCT/TAU	RCT	• Total N: 95	• Number of sessions treated: 8	• Recurrence rate (episodes)	8/
				• Complete N (T/ C): 48/47	• Treatment length (min): 120–150	• Depression level (MADRS, DASS)	AA: low

(*Continued*)

Table 1. (*Continued*)

Study	Country	Intervention (experimental/ control)	Design	Sample size (patients)	Intervention characterization	Outcome	Study quality/ Cochrane tool
				• Mean age (years):-	• Each group size (people): individual	• Mania severity (YMRS)	AC: unclear
				• Gender (M/F): 33/62	• CBT therapist: certified professional	• Anxiety level (STAI)	BAO: low
				• Bipolar I: 59 • Bipolar II: 35		• Assessed time points (months): post-treatment, 3, 6, 9, and 12 months of follow-up	IO: low
				• Bipolar NOS: 1			SRO: low
González-Isasi et al. (2010) [43]	Spain	CBT/SC	RCT	• Total N: 20	• Number of sessions treated: 13	• Relapse	8/
				• Complete N (T/ C): 20/20	• Treatment length (min): 90	• Depression level (BDI)	AA: low
				• Mean age (years): 38.5	• Each group size (people): 10	• Mania severity (YMRS)	AC: low
				• Gender (M/F): 6/14	• CBT therapist: certified professional	• Function (GAF)	BAO: unclear
				• Bipolar I/II: 40 • Refractory Bipolar		• Assessed time points (months): post-treatment, 6, 12 months follow-up	IO: low
							SRO: low

CBT: cognitive-behavioral therapy, TAU: treatment as usual, WLC: waiting list control, MM: medication monitoring, SC: standard care, SUD: substance use disorder, IPT: intensive psychosocial treatment, CC: collaborative care, MBCT: mindfulness-based cognitive therapy, PE: psychoeducation, FF-CBT: family-focused, cognitive behavioral therapy, treatment-health promoting intervention, HE: health education, ST: supportive therapy

https://doi.org/10.1371/journal.pone.0176849.t001

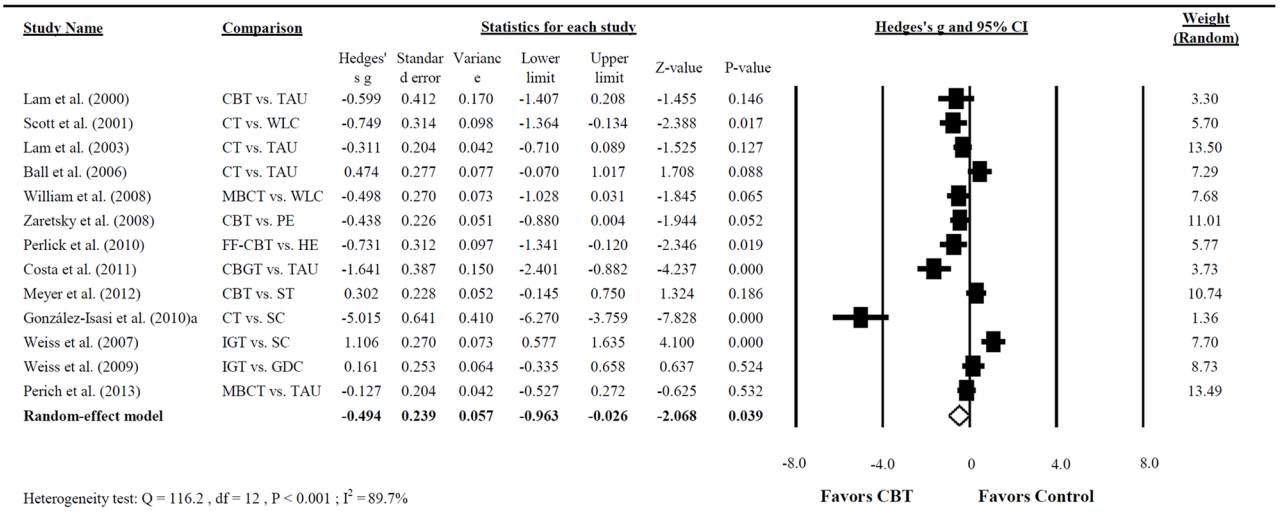


Fig 2. Forest plot of the meta-analysis for reducing depressive symptoms in BD among patients treated with CBT compared with controls (n = 13 studies).

https://doi.org/10.1371/journal.pone.0176849.g002

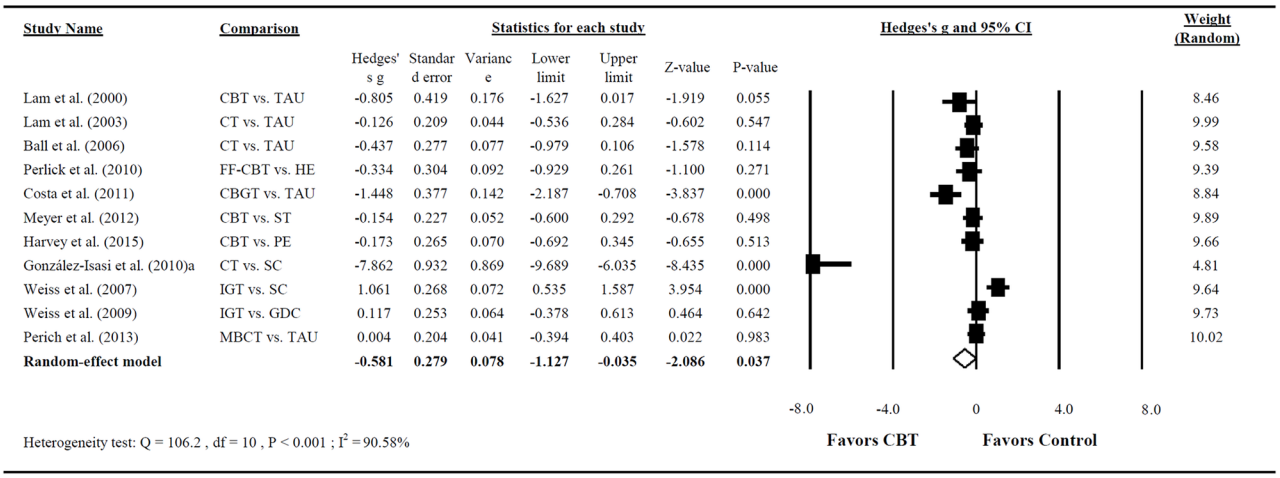


Fig 3. Forest plot of the meta-analysis for reducing mania severity in BD among patients treated with CBT compared with controls (n = 11 studies).

https://doi.org/10.1371/journal.pone.0176849.g003

Secondary outcomes: Relapse rate and psychosocial functioning

A total of 10 RCTs provided adequate statisticsal data for calculating the relapse rate [25–29, 32, 35–38]. The pooled OR indicated that compared with the control group, patients with CBT had significantly lower relapse rates at follow-up (Fig 4; pooled OR = 0.506; 95% CI = 0.278–0.921; P = 0.026). Large heterogeneity was observed in this analysis (Q = 29.676; P < 0.001; I^2 = 69.672%).

In addition, our meta-analysis revealed the potential clinical benefits of CBT for improving psychosocial functioning (assessed through GAF, SPS, or DAS), according to the pooled findings of seven RCTs [25–28, 30, 32, 43] (Hedges's g = 0.457; 95% CI = 0.106–0.809; P = 0.011, with a moderate effect size; Fig 5). Large heterogeneity was noted in this analysis (Q = 18.769; P < 0.001; I^2 = 68.032%).

In summary, the overall effect size of CBT for patients with BD is shown in Table 2.

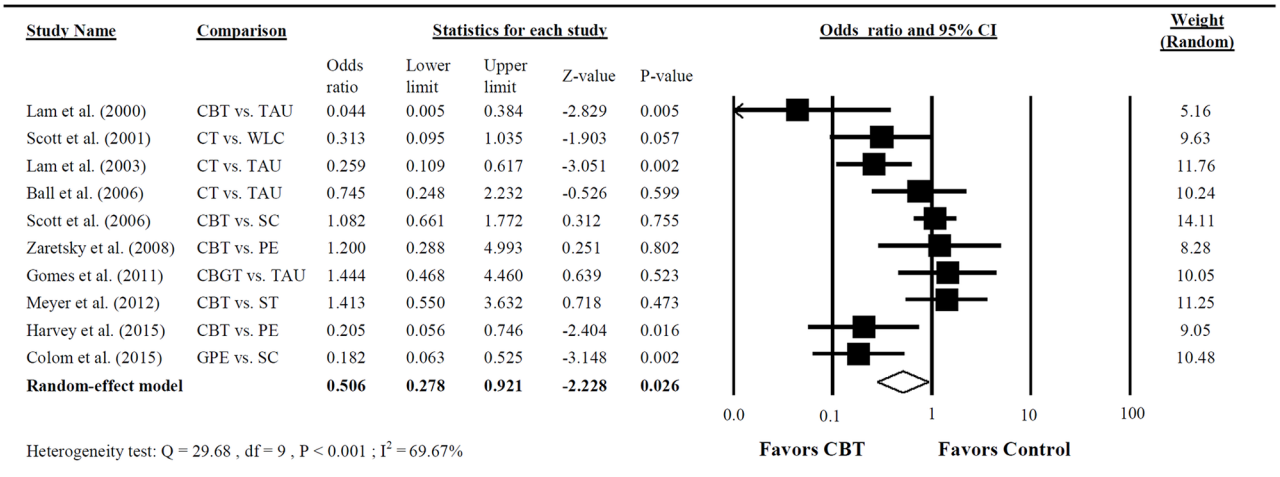


Fig 4. Forest plot of the meta-analysis for lowering the relapse rate of BD among patients treated with CBT compared with controls (n = 10 studies).

https://doi.org/10.1371/journal.pone.0176849.g004

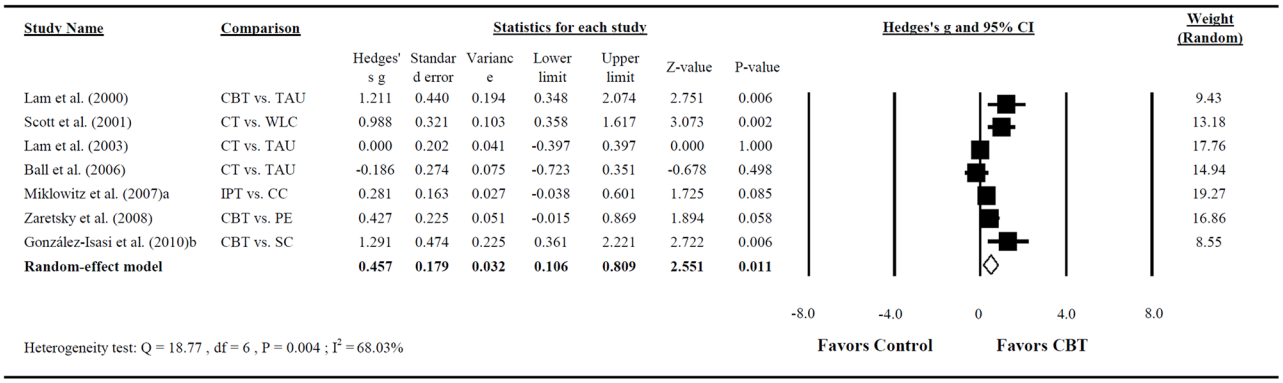


Fig 5. Forest plot of the meta-analysis for improving psychosocial functioning in BD among patients treated with CBT compared with controls (n = 7 studies).

https://doi.org/10.1371/journal.pone.0176849.g005

Sensitivity analysis

S1 Fig displays the effect of removing every single study on the overall estimate. In the random-effects model, the pooled ORs for the relapse rate did not exhibit marked dispersion, and similar findings for Hedges's g were observed with regard to the level of depression, severity of mania, and level of psychosocial functioning. These findings consolidate the robustness of this meta-analysis, indicating that none of the studies would dominate the summarized results.

Publication bias

S2 Fig illustrates the funnel plot for evaluating potential publication bias. The funnel plot shows symmetry, and the publication bias does not seem significant for the relapse rate, according to Egger's test (P = 0.107).

Subgroup analysis

Tables 3 and 4 present all the subgroup analyses for efficacy outcomes, according to the characteristics of the patients, therapists, and therapies. The subgroup analysis for the relapse rate revealed that studies assessing only patients with BD I reported a greater reduction in relapse rate after CBT than did studies assessing patients with BD I and II ($Q_B = 7.889$; $P < 0.001$). The subgroup analysis for the recovery of depressive symptoms indicated that the effect size was significantly larger for treatment durations of ≥90 min per session compared with that for

Table 2. Overall effect size of cognitive behavioral therapy for patients with bipolar disorder.

		Effect size	95% CI		Null hypothesis (two-sided)		Homogeneity			
Outcomes	Sample size (studies)		Lower	Upper	Z value	P value	Q value	P value	I^2	τ^2
• Depression	13	−0.494[a]	−0.963	−0.026	−2.068	0.039	116.179	<0.001	89.671	0.644
• Mania	11	−0.581[a]	−1.127	−0.035	−2.086	0.037	106.210	<0.001	90.585	0.734
• Relapse rate	10	0.506[b]	0.278	0.921	−2.228	0.026	29.676	<0.001	69.672	0.599
• Psychosocial functioning	7	0.457[a]	0.106	0.809	2.551	0.011	18.769	<0.001	68.032	0.141

CI, confidence interval

[a] Hedges' g

[b] Odds ratio

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Table 3. Subgroup analysis of cognitive behavioral therapy for patients with bipolar disorder: Depression and mania.

	Depression (n = 13)					Mania (n = 11)				
	Sample size (studies)	Hedges' g (95% CI)	P_A	Q_B	P_B	Sample size (studies)	Hedges' g (95% CI)	P_A	Q_B	P_B
Disease type										
• Bipolar I	2	-0.367 (-0.725, -0.009)	0.044	0.211	0.646	3	-0.239 (-0.556, 0.078)	0.139	1.521	0.218
• Bipolar I/II	11	-0.523 (-1.081, 0.035)	0.066			8	-0.762 (-1.531, 0.006)	0.052		
Therapist background										
• Psychologists	12	-0.510 (-1.027, 0.006)	0.053	0.043	0.835	11	-0.581 (-1.127, -0.035)	0.037	0.000	1.000
• Nonpsychologists	1	-0.438 (-0.880, 0.004)	0.052			0				
Therapy delivery										
• Individual	7	-0.176 (-0.483, 0.131)	0.261	1.880	0.170	6	-0.186 (-0.383, 0.010)	0.063	2.491	0.114
• Group	6	-1.000 (-2.137, 0.137)	0.085			5	-1.407 (-2.910, 0.096)	0.067		
Treatment sessions										
• ≥12	8	-0.648 (-1.487, 0.192)	0.130	0.659	0.417	7	-0.951 (-1.893, -0.009)	0.048	3.080	0.079
• <12	2	-0.271 (-0.624, 0.083)	0.134			2	-0.062 (-0.378, 0.255)	0.703		
• undisclosed	3					2				
Treatment frequency										
• Otherwise	4	-0.510 (-1.228, 0.209)	0.164	0.000	0.994	5	-0.456 (-0.885, -0.027)	0.037	0.444	0.505
• Weekly	9	-0.506 (-1.135, 0.123)	0.115			6	-0.824 (-1.817, 0.170)	0.104		
Treatment duration										
• ≥90 min	4	-1.695 (-3.110, -0.280)	0.019	5.456	0.019	3	-2.902 (-5.683, -0.122)	0.041	4.135	0.042
• <90 min	6	0.110 (-0.429, 0.649)	0.689			6	0.017 (-0.410, 0.443)	0.940		
• undisclosed	3					2				

P_A, subgroup effect on outcome variable; P_B, heterogeneity among subgroups (moderator); CI, confidence interval

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treatment durations of <90 min per session (Q_B = 5.456; P = 0.019), and this effect with regard to treatment duration was also observed in the subgroup analysis for the reduction in mania severity (Q_B = 4.135; P = 0.042).

Discussion

In the current study, we systematically reviewed the results of 19 RCTs and compared the treatment outcomes obtained by using CBT as an adjuvant therapy to pharmacotherapy and those obtained by using standard care for treating patients with BD. The research quality of the selected studies, including the quality of the study design, patients, outcome measures, statistical analysis, and results, was assessed using the approach described by Brodaty, Green, and Koschera [44]. According to the guidelines of the Cochrane Collaboration, a research quality

Table 4. Subgroup analysis of cognitive behavioral therapy for patients with bipolar disorder: Relapse rate and psychosocial functioning.

	Relapse rate (n = 10)					Psychosocial functioning (n = 7)				
	Sample size (studies)	Odds ratio (95% CI)	P_A	Q_B	P_B	Sample size (studies)	Hedges's g (95% CI)	P_A	Q_B	P_B
Disease type										
• Bipolar I	3	0.198 (0.094, 0.416)	< 0.001	7.889	0.005	2	0.562 (-0.663, 1.786)	0.368	0.018	0.893
• Bipolar I/II	7	0.755 (0.428, 1.333)	0.333			5	0.474 (0.062, 0.885)	0.024		
Therapist background										
• Psychologists	9	0.465 (0.245, 0.884)	0.020	1.411	0.235	4	0.448 (-0.191, 1.088)	0.169	0.014	0.906
• Nonpsychologists	1	1.200 (0.288, 4.993)	0.802			3	0.495 (0.074, 0.916)	0.021		
Therapy delivery										
• Individual	8	0.510 (0.265, 0.983)	0.044	0.000	0.997	6	0.373 (0.027, 0.719)	0.035	3.440	0.064
• Group	2	0.508 (0.067, 3.870)	0.513			1	1.348 (0.377, 2.319)	0.006		
Treatment sessions										
• ≥12	9	0.555 (0.298, 1.033)	0.063	1.850	0.174	5	0.466 (0.063, 0.869)	0.023	0.014	0.905
• <12	1	0.205 (0.056, 0.746)	0.016			2	0.542 (-0.638, 1.723)	0.368		
Treatment frequency										
• Otherwise	5	0.415 (0.141, 1.221)	0.110	0.243	0.622	3	0.355 (-0.128, 0.838)	0.150	0.285	0.593
• Weekly	5	0.578 (0.273, 1.222)	0.151			4	0.562 (-0.024, 1.148)	0.060		
Treatment duration										
• ≥90 min	2	0.508 (0.067, 3.870)	0.513	0.005	0.946	1	1.291 (0.361, 2.221)	0.006	3.004	0.083
• <90 min	4	0.548 (0.231, 1.300)	0.172			3	0.335(-0.218, 0.887)	0.235		
• undisclosed	4					3				

P_A, subgroup effect on outcome variable; P_B, heterogeneity among subgroups (moderator); CI, confidence interval

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score of 6–10 is acceptable. The 19 RCTs that received a total research quality score of >6 were included in the meta-analysis.

The meta-analysis indicated that CBT has a positive impact on patients with BD in terms of reducing depression levels, improving mania severity, decreasing relapse rates and increasing psychosocial functioning, with a moderate effect size. Our findings were similar to those of Jan [20] and Lam [21]. Compared to previous meta-analyses [17–19], we considered a greater number of databases and identified more RCTs that included four outcome measures (depression, mania, relapse rate, and psychosocial functioning) in the meta-analysis. In addition, we performed subgroup analyses of various characteristics, including disease type, therapists background, and treatment characteristics (such as therapy delivery type and session frequency and duration). Taken together, this meta-analysis derived more insights than previous studies through a comprehensive search and sophisticated analytic approaches.

Similar to that in unipolar patients, the underlying hypothesis for CBT application in BD is that these patients have distorted cognitions, which might lead to negative mood states. Nevertheless, CBT for BD also deals with distorted cognitions during manic states, termed "hyperpositive thinking," which was not a treatment target in conventional CBT for patients with depression [45]. Although the role of regular treatment of BD episodes with antidepressants has yet to be established, the impressive results obtained for the use of CBT as an acute phase therapy for BD episodes suggest a critical avenue for future studies. Our findings suggest that CBT demonstrated greater effectiveness for reducing the relapse rate in patients with BD I compared with that in patients with BD I and II. This might be due to the relative homogeneity of the treatment population within these studies [25, 27, 37]. One possible explanation is the difference in disease course between BD I and BD II. The relapse rate for major depression tends to be higher in BD II than in BD I. In particular, determining the efficacy (or effectiveness) of CBT in real-world practice—both alone and as an adjuvant to monotherapy—for patients with BD II, in whom pharmaceutical therapy with mood stabilizers have unclear benefits, moreover, only one second-generation antipsychotic drug, quetiapine, has received Food and Drug Administration approval [14].

Our subgroup analysis revealed that treatment durations of $\geq$90 min per session were much more effective than were shorter treatment durations, and this treatment duration led to significantly improved depressive symptoms or mania severity. Previous studies on CBT with intervention durations ranging from 45 to 120 min per session have reported different extents of reduction in depression or mania levels [25–43], implying that the treatment duration is a potential moderator for treatment efficacy. Because CBT is a form of psychotherapy, it relies on a strong collaborative relationship between therapists and patients; this connection is strengthened by a more thorough process and longer treatment duration. In the future, treatment durations of $\geq$90 min might be implemented to increase effectiveness.

Among the 19 selected RCTs, patients with refractory BD were reported in two studies [39,43]. In the meta-analysis for determining the effect of CBT treatment on reducing depression and mania levels, the findings suggested that CBT had an impressive effect in patients with refractory BD [39]. Clearly, pharmacotherapy is an absolute necessity in this clinical syndrome, although this is not sufficient, at least in treatment-resistant patients. Combined CBT and pharmacotherapy might be an effective treatment strategy among patients with refractory BD.

Similar to most meta-analysis studies, the current study has some limitations. First, some comparisons were limited by the sample size. Only four studies [27, 29, 30, 38] had more than 100 patients, and the other RCTs involved small samples. Second, moderate-to-high heterogeneity was observed in the overall and subgroup analyses, indicating that a certain set of confounders (or possible personal and psychosocial factors), such as age, gender, and CBT style/approach, might be one of the heterogeneity sources affecting the results. Third, an important concern in meta-analyses is the "file-drawer" problem. Nonsignificant findings might not have been published, thus biasing the present results in a favorable direction for CBT. Although we conceive that this is not the case here (for example, the largest published RCTs of CBT in BD [29] had null findings), we calculated the number of studies with an effect size of zero that would be needed to reduce the present effect size to zero [46]. For the four different outcomes, depressive level, mania severity, relapse rate, and psychosocial functioning, 58, 43, 28, and 28 studies with no effect, respectively, would be needed to reduce the observed effect size to zero. These numbers are unlikely, considering that many of the published studies reported nonsignificant results. Collectively, more RCTs with larger sample sizes are warranted in the future to overcome these limitations, and the optimized and systematic approaches of CBT should be further investigated to prevent the effect of these factors in future studies. In addition,

international, multicenter studies of a BD cohort with CBT might be valuable in establishing a database for the long-term evaluation of patient outcomes to facilitate evidence-based practices [47].

In conclusion, this meta-analysis recommends the use of CBT as an adjunctive therapy to medications in patients with BD because of the positive effects observed post-treatment and at follow-up. The benefits include decreased levels of depression and mania, decreased relapse rates, and increased levels of psychosocial functioning. The subgroup analysis indicated that the improvement in depression or mania levels was more profound with a CBT treatment duration of $\geq$ 90 min per session, and the relapse rate was lower among patients with BD I. Additional studies should investigate optimal patient selection strategies to maximize the benefits of adjunctive CBT and thereby the cost-effectiveness of treatment for patients with BD who do not rapidly respond to first-line interventions.

Supporting information

S1 Fig. Sensitivity analysis. Sensitivity analysis with leave-one-out approach of meta-analysis for (a) relapse rate, (b) level of depression, (c) severity of mania, and (d) level of psychosocial functioning of bipolar disorder among patients treated with CBT compared to control group.
(DOCX)

S2 Fig. Funnel plot. Funnel plot for evaluating publication bias of meta-analysis for (a) relapse rate (Egger's test: t = 1.81, df = 8, P-value = 0.107), (b) level of depression (Egger's test: t = 2.83, df = 11, P-value = 0.016), (c) severity of mania (Egger's test: t = 3.86, df = 9, P-value = 0.004), and (d) psychosocial functioning (Egger's test: t = 2.08, df = 5, P-value = 0.092) of bipolar disorder among patients treated with CBT compared to control group.
(DOCX)

S1 Table.
(DOCX)

S1 PRISMA Checklist.
(DOC)

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Author Contributions

Conceptualization: KJC KRC.

Data curation: KJC KRC.

Formal analysis: KJC KRC.

Investigation: KJC KRC.

Methodology: KJC KRC.

Project administration: KRC.

Resources: KRC.

Software: KJC HLC.

Supervision: KJC KRC.

Validation: KJC JCT DL CHL HLC KRC.

Visualization: KJC JCT DL CHL HLC KRC.

Writing – original draft: KJC KRC.

Writing – review & editing: KJC JCT DL CHL HLC KRC.

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REVIEW

WILEY BIPOLAR DISORDERS

An update on adjunctive treatment options for bipolar disorder

Olivia M Dean[1,2,3] | Emma Gliddon[1,3] | Tamsyn E Van Rheenen[4,5,6] | Francesco Giorlando[3] | Sandra K Davidson[7] | Manreena Kaur[6] | Trung T Ngo[8,9] | Lana J Williams[1]

[1]IMPACT Strategic Research Centre, Deakin University, Geelong, Vic., Australia

[2]Florey Institute for Neuroscience and Mental Health, University of Melbourne, Parkville, Vic., Australia

[3]Department of Psychiatry, University of Melbourne, Parkville, Vic., Australia

[4]Melbourne Neuropsychiatry Centre, Department of Psychiatry, University of Melbourne, Melbourne, Vic., Australia

[5]Centre for Mental Health, Swinburne University, Melbourne, Vic., Australia

[6]Monash Alfred Psychiatry Research Centre, Central Clinical School, Monash University and The Alfred Hospital, Melbourne, Vic., Australia

[7]Department of General Practice, Melbourne Medical School, University of Melbourne, Carlton, Vic., Australia

[8]Mater Research Institute-UQ, Faculty of Medicine, The University of Queensland and Translational Research Institute, Brisbane, Qld, Australia

[9]Genetic Epidemiology Laboratory, QIMR Berghofer Medical Research Institute, Brisbane, Qld, Australia

Correspondence
Olivia M. Dean, IMPACT Strategic Research Centre, Deakin University, Geelong, Vic., Australia.
Emails: olivia.dean@barwonhealth.org.au; oliviad@barwonhealth.org.au

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Objectives: Bipolar disorder is a complex illness often requiring combinations of therapies to successfully treat symptoms. In recent years, there have been significant advancements in a number of therapies for bipolar disorder. It is therefore timely to provide an overview of current adjunctive therapeutic options to help treating clinicians to inform their patients and work towards optimal outcomes.

Methods: Publications were identified from PubMed searches on bipolar disorder and pharmacotherapy, nutraceuticals, hormone therapy, psychoeducation, interpersonal and social rhythm therapy, cognitive remediation, mindfulness, e-Health and brain stimulation techniques. Relevant articles in these areas were selected for further review. This paper provides a narrative review of adjunctive treatment options and is not a systematic review of the literature.

Results: A number of pharmacotherapeutic, psychological and neuromodulation treatment options are available. These have varying efficacy but all have shown benefit to people with bipolar disorder. Due to the complex nature of treating the disorder, combination treatments are often required. Adjunctive treatments to traditional pharmacological and psychological therapies are proving useful in closing the gap between initial symptom remission and full functional recovery.

Conclusions: Given that response to monotherapy is often inadequate, combination regimens for bipolar disorder are typical. Correspondingly, psychiatric research is working towards a better understanding of the disorder's underlying biology. Therefore, treatment options are changing and adjunctive therapies are being increasingly recognized as providing significant tools to improve patient outcomes. Towards this end, this paper provides an overview of novel treatments that may improve clinical outcomes for people with bipolar disorder.

KEYWORDS

bipolar disorder, cognition, e-health, hormones, neuromodulation techniques, nutraceuticals, psychological therapies, transcranial magnetic stimulation

1 | INTRODUCTION

The lifetime prevalence of bipolar disorder is between 0.1 and 4.4 percent.[1,2] Bipolar disorder may be associated with poor symptomatic, physical and psychosocial outcomes and is generally considered a lifelong condition.[3] Patients are therefore often prescribed a combination of therapy types, all aiming to improve functional outcomes for the individual. Thus, the aim of treatment is to reduce the frequency, duration and severity of active episodes and increase time spent in remission.

While there have been some recent developments in modified drugs for bipolar disorder (eg, divalproex), and using anti-epileptic and

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antipsychotic medications as adjuvants (eg, lamotrigine and quetiapine), no novel agents have significantly altered the pharmacological landscape over the last decade. Lithium remains the most common treatment and persistent bipolar depression remains difficult to treat.[4,5] Similarly, while there is efficacy with psychological therapies, these are mainly adjunctive and there is still a paucity of therapies that are specific to bipolar disorder and effective as monotherapy.[6] Finally, there is the option of exploring electroconvulsive therapy (ECT), used predominantly as a 'last line', which can show profound improvements, but also severe side-effects, with efficacy predominantly in depression and a waning effect that does not appear to last over the longer term.[7]

Therefore, there has been a renewed search for novel approaches to treatments for bipolar disorder. It has resulted in an number of therapies undergoing evaluation through investigator-initiated studies, encompassing pharmacological, psychological and neuromodulation approaches.[8] This review provides an update on novel adjunctive treatment options for bipolar disorder to assist clinicians in working towards better functional recovery for patients.

2 | TREATMENTS

2.1 | Repurposed agents

There is now significant evidence implicating inflammation, altered antioxidant defense and mitochondrial dysfunction in the pathophysiology of bipolar disorder.[9] A multitude of novel trials have utilized this new biological understanding to trial agents that specifically target these pathways.[10] By utilizing existing agents with known safety profiles and repurposing them for psychiatric indications, the development of a new therapy can be accelerated compared to *de novo* drug discovery. *N*-acetyl cysteine, traditionally used as an antidote to paracetamol overdose, is an agent that has been successfully repurposed for bipolar depression.[11] There have been several randomized controlled trials, aggregated in a recent meta-analysis,[11] showing benefits of *N*-acetyl cysteine as an adjunctive therapy for bipolar depression. To date, the dosing has been 2000 mg/day in addition to treatment as usual, with minimal side effects and no apparent interactions with usual treatment.[12]

Other anti-inflammatory agents have also been trialled, and some efficacy has been shown with adjunctive celecoxib treatment. A randomized controlled trial of participants experiencing mixed or depressed bipolar episodes (and undergoing ECT) found that 200 mg twice a day (ie, 400 mg/day) of adjunctive celecoxib attenuated increases in tumor necrosis factor (TNF)-alpha levels. No other changes were noted. In a more recent study, adjunctive celecoxib (400 mg/day) was effective in mania over 6 weeks of treatment.[13] There is current interest in a variety of other adjunctive anti-inflammatory agents in varying stages of clinical trials. Adjunctive minocycline was shown to improve symptoms in a case report of bipolar depression. Following a week of minocycline treatment (150 mg/day), the patient was noted to have improved symptoms.[14] A randomized controlled trial is currently underway to provide definitive evidence of minocycline's potential in bipolar disorder (ClinicalTrials.gov: NCT01429272).[15] There are also a number of other psychiatric minocycline trials, including a trial in patients with major depressive disorder, the results of which were positive in terms of functional and quality of life outcomes.[16,17] In addition, ketamine is currently being explored as an adjunctive therapy for bipolar disorder. A recent meta-analysis suggested that adjunctive ketamine in combination with ECT is not efficacious.[18] However, when explored as an adjunct to any other therapy and specifically for bipolar depression, adjunctive ketamine has been found to be useful.[19] Given the lack of targeted therapies for bipolar depression, such treatment options in this domain need to be seriously considered.

2.2 | Nutraceuticals

There has been an explosion in the field of nutritional psychiatry recently.[20] Several nutraceutical agents have been trialled as adjunctive therapies to improve treatment for the symptoms of bipolar disorder (eg, *N*-acetyl cysteine, also considered a health supplement).[21] While there is growing popularity in the community of the use of omega-3 fatty acids, varying efficacy has been found in bipolar disorder.[22] Overall, it appears that adjunctive omega-3 treatment favors improvement in bipolar disorder; however, methodological issues remain such as trial design and sample size, which make definitive statements difficult.[23] Similar findings have been reported with adjunctive inositol, with one study finding statistical improvements, but another two studies showing only small effects which did not reach statistical significance on the primary outcomes. These results leave the utility of inositol for bipolar disorder in doubt.[24] Folic acid has also been trialled as an adjunctive treatment for bipolar disorder, although only two trials have been published to date. An early study found no improvement in people with bipolar depression (n = 17) who were taking lithium following adjunctive folate treatment (200 μg/day).[25] However, the study also included individuals with unipolar depression (in which some benefit was shown) and the sample size may have been a significant limiting factor. More recently, a study of 88 participants showed benefits of high-dose folic acid (3 mg/day) as an adjunct to sodium valproate for bipolar mania.[26] Magnesium, melatonin and choline have also been suggested as potentially useful adjunctive agents, but only small trials have been conducted and further work is required.[23] There is also current interest in investigating combinations of adjunctive nutraceutical agents.[10,27,28] However, results from randomized controlled trials are required.

2.3 | Hormone treatments

Recent evidence indicates that the selective estrogen receptor modulator tamoxifen, a protein kinase C (PKC) inhibitor, may confer some benefit in reducing manic symptomatology.[29] It has been postulated that, alongside its PKC-inhibiting effects, tamoxifen may stimulate ovarian steroid genesis which increases estrogen levels.[30] Several studies have demonstrated mood-symptom improvement as a result of tamoxifen augmentation.[31-34] For example, Amrollah and colleagues[35] recently showed the effectiveness of adjunctive tamoxifen compared to lithium alone for the rapid reduction of

manic symptoms in 40 in patients with bipolar disorder. This potential effect—coupled with known differences between men and women in the clinical course of bipolar disorder and an increased risk for relapse in women at times corresponding to major reproductive events—suggests that estrogen may play a role in bipolar disorder symptomatology. Correspondingly, Kulkarni et al. observed that adjunctive augmentation with the progestin medroxyprogesterone (MPA) had a modulating effect on manic symptomatology in comparison to tamoxifen or placebo.[36] Although the reason for the lack of effect with tamoxifen is unclear, the anti-manic effect of MPA was postulated as being related to its estrogenic effect. At this point, understanding of the effects of estrogen in bipolar disorder remains limited, but there is at least some evidence that it may play some role in the disorder's pathophysiology.[30] Further work exploring the efficacy of tamoxifen and MPA is thus required.

2.4 | Psychoeducation

Psychoeducation as an adjunctive therapy for bipolar disorder has evolved from providing patients with information exclusively related to a biological understanding of the disorder and related pharmacological treatments to an integrative approach emphasizing illness and symptom awareness, treatment adherence, self-management, the importance of regular habits, avoiding drug misuse and promoting good physical health.[37,38] Although the active ingredients of this treatment are yet to be clearly established, it is speculated that psychoeducation helps individuals recognize early signs and symptoms and adopt behavioral measures to prevent a full-blown episode.[37,39,40] The superiority of group psychoeducation over individual psychoeducation further suggests that the opportunity to share personal experiences and insights in a supportive peer setting confers additional benefit.[41-43]

Psychoeducation as an adjunctive treatment has shown encouraging results in both bipolar I and bipolar II disorder and across a range of therapeutic targets. Studies show that psychoeducation increases adherence to medication and other elements of treatment[39,41,44-47] and reduces time spent in manic, hypomanic, mixed and depressive episodes.[45,48,49] Long-lasting improvements in overall relapse rates, time spent ill, hospitalization readmission and number of hospitalization days have also been demonstrated.[41,48,50,51] Recent studies report that psychoeducation is associated with increased perceptions of control[47] and reduced self-stigma among people with bipolar disorder.[52]

Evidence suggests that the efficacy of psychoeducation diminishes as the number of episodes increase, highlighting the importance of delivering this treatment as early as possible.[39,53] Ideally, psychoeducation should be delivered when patients are euthymic and are best able to comprehend and retain the information; however, patients with mild depressive episode can also benefit.[54]

Overall, psychoeducation is a clinically effective and cost-effective[55] adjunctive therapy for bipolar disorder and is increasingly considered a standard component of care. Further research is needed to identify the causal mechanisms in psychoeducation that lead to positive outcomes, to clarify the optimal dose and mode of delivery, and to understand how to best personalize treatment. In the following sections, we review the novel psychological therapies available that have been investigated for bipolar disorder.

2.5 | Interpersonal and social rhythm therapy

The main therapeutic goals of interpersonal and social rhythm therapy (IPSRT) are to regulate social and circadian rhythms, maintain regular routines, promote positive social relationships and social roles, and to reduce interpersonal conflict.[56] Given that such rhythms are often dysregulated in bipolar disorder, this line of therapy could be useful.[57] This approach has shown some efficacy in bipolar disorder, with significantly higher regularity of social rhythms and a significant reduction in the likelihood of mood recurrence.[56] A more recent pilot study comparing IPSRT to quetiapine for people with bipolar II disorder showed promising results.[58] Both groups had significant improvements in depression and mania rating scores over 12 weeks and had high satisfaction ratings, and there were no differences in treatment preferences of participants, suggesting that IPSRT could be effective as a standalone treatment for bipolar II. These results show that IPSRT plays an important role in the psychosocial treatment of this illness.

2.6 | Mindfulness

Mindfulness is a form of cognitive awareness that focuses on stress reduction by improving concentration and encouraging relaxation.[59] This approach promotes the conscious awareness of distressing thoughts and feelings, and aims to provide individuals with the ability to disengage from these thoughts and feelings rather than counter them.[60] When used as a psychological therapy tool, mindfulness is often incorporated into cognitive therapy (ie, mindfulness-based cognitive therapy [MBCT]). MBCT was first used as a psychological intervention for anxiety disorders,[59] and has since been applied to a range of mental health conditions, including bipolar disorder. Results of MBCT in bipolar disorder have been positive overall, ranging from significant improvements in executive functioning, memory, task completion, and attentional readiness,[60,61] to significant decreases in depression scores, anxiety scores, and dysfunctional attitudes about achievement.[62-64] These findings are promising; however, it is not yet clear how long-lasting the effects of MBCT are in bipolar disorder.

2.7 | Cognitive remediation

Over the last two decades, there has been an increased focus on the neurocognitive profile of bipolar disorder. There is now significant evidence indicating that people with the illness have substantial impairments in cognitive function, ranging from lower order deficits in processing speed to higher order deficits in executive functioning.[65-67] Cognitive abnormalities have been consistently demonstrated in patients during both symptomatic and euthymic mood states as well as during the first bipolar episode,[68,69] with recent evidence also suggesting that cognitive impairments may be present prior to illness onset in some individuals.[70,71] These findings—coupled with growing research indicating that individuals at increased genetic risk for the

disorder also exhibit neuropsychological impairment in certain cognitive domains—suggest that aberrant cognition may represent a trait-like endophenotype of the illness.[72-74]

To this end, an emerging theme in the bipolar disorder literature is the use of cognitive remediation therapy (CRT).[75] CRT seeks to remediate cognitive dysfunction through lasting, generalizable improvements in neuropsychological and, subsequently, psychosocial ability.[76] Given that cognitive processes are underpinned by structural and functional brain mechanisms known to be dynamic in nature, cognitive remediation partially draws on the principle that the brain is plastic and capable of change.[77] In practical terms, it is a behavioral intervention designed to improve attention, memory, executive functioning and other neuropsychological processes through the use of computer-based and face-to-face training programs which teach drill and practice, and adaptive and compensatory strategies, usually over a period of 10 sessions or more.

CRT has been studied increasingly in the context of psychotic disorders.[78] Relatively few cognitive remediation studies have been carried out in bipolar disorder, although preliminary research indicates that some of the same cognitive improvements seen in psychosis may also apply.[75,79] A systematic review by Anaya and colleagues[80] reported a significant, moderate pooled effect size for pre- to post-intervention change in cognitive performance in an aggregate sample of bipolar disorder and unipolar disorder subjects (ie, combined across seven small studies). Importantly, one of the studies included in the analysis also indicated reductions in depressive symptoms, and improvements in occupational and general psychosocial functioning.[81] Furthermore, recent investigation in a group of euthymic bipolar disorder I subjects showed that, compared to treatment as usual, functional remediation (where improvements in functional endpoints are emphasized) had an efficacious effect on daily functioning.[82] Other evidence suggests that this form of remediation may also be efficacious for individuals with euthymic bipolar disorder II.[83] Moreover, neuroimaging studies suggest that it may have measurable implications for brain changes, as improvements in working memory and indirect changes in functional brain activation were observed in individuals with unipolar/bipolar depression after 10 weeks of computer-assisted cognitive remediation.[84] One caveat to note is that the "euthymic" state is hard to define and thus studies are difficult to compare. Moreover, there may be residual effects that last a long time after the last episode. Thus, it may be difficult to disentangle inter-episode improvement from therapeutic effects.

2.8 | e-Health approaches

A number of internet-based programs for mental health have been developed based on successful face-to-face psychological therapy approaches. These online interventions are becoming increasingly common and have shown significant efficacy across a variety of mental health conditions.[85] It has been suggested that, in bipolar disorder, online programs may help people to overcome a number of barriers commonly faced when attempting to access self-management programs.[86]

Few internet-based interventions have been evaluated for use as adjunctive treatments for bipolar disorder, and the results for these programs have been varied.[87] While some interventions have shown no significant improvements in outcomes when compared with control conditions,[47,88,89] one study found significant reductions in mania symptom severity.[90] Other programs have also shown promise when evaluated in pilot studies[91,92] and further evaluations of these programs are anticipated.

Nearly all of the existing online programs for bipolar disorder have incorporated elements of psychoeducation and cognitive behaviour therapy (CBT).[47,88-90,93,94] One program has utilized social rhythm therapy[92] (a key element of IPSRT), while the most recent program was based on mindfulness.[91] A recent review of optimization strategies for the delivery of e-health interventions in bipolar disorder suggested that the inclusion of peer support, such as discussion forums and peer coaching, could help to improve program engagement.[86] Two studies have suggested that peer coaching can significantly improve program adherence;[47,94] however, further research is required to determine the impact of discussion forums in online interventions for bipolar disorder. Programs developed for bipolar disorder to date have focused on self-help interventions with minimal therapist assistance; however, therapist-guided interventions are also an option. Based on the current literature, it is unclear which therapeutic approach works best in online programs for the disorder.

More recently, a number of smartphone-based applications (apps) have been developed for use as self-management tools for bipolar disorder. While many of these apps are available on the commercial market,[95] research into the efficacy of this approach appears to be ongoing.[96] A recent systematic review reported that, while a number of apps for bipolar disorder were commercially available, the quality of these apps was very poor.[95] The review found that the content provided within informational apps was not in line with practice guidelines and core psychoeducation principles, and information sources were rarely cited. This review also reported that the majority of symptom monitoring apps failed to monitor key areas such as sleep and medication intake, and screening apps did not use validated screening measures.[95]

To date, only one smartphone app has been evaluated by a randomized controlled trial. Results showed no significant improvements in symptoms of both depression and mania in those using the smartphone app for daily mood monitoring.[97]

In addition to smartphone apps, other portable electronic devices such as mobiles phones and personal digital assistants (PDAs) have been utilized in a number of ways as adjunctive treatment tools for bipolar disorder. Face-to-face psychoeducation followed by mobile phone-based mood monitoring has been shown to significantly improve symptoms of depression when compared with paper-based mood monitoring in people with bipolar disorder.[98] Pilot data on an ecological momentary intervention delivered via PDA also showed a significant decrease in depression symptoms, as well as high rates of treatment adherence.[99]

Delivering psychotherapeutic material at a distance comes with a range of unique ethical considerations and safety concerns. Ensuring appropriate user safety monitoring, maintaining secure data privacy controls, and clearly communicating the adjunctive nature of an intervention are crucial.[100] Online and mobile technologies provide a

number of solutions to these issues through automated safety assessments, password-protected and encrypted data files, and automated reminder notifications to seek face-to-face care when required.[100]

Considering the rate at which technology continues to advance, it is likely that incorporating technologies such as computers and smartphones into treatment will continue to be a focus of research for the foreseeable future.

2.9 | Repetitive transcranial magnetic stimulation

While ECT was introduced almost a century ago as the first form of therapeutic brain stimulation, the last two decades have been momentous for the advancement of brain stimulation techniques. Undoubtedly, the most significant has been the establishment of repetitive transcranial magnetic stimulation (rTMS) on the left dorsolateral prefrontal cortex (DLPFC), as a safe and efficacious treatment for depression with a low side-effect profile.[101-103]

The first of these trials provided evidence that high-frequency rTMS on the left DLPFC (the most common of the depression rTMS treatment protocols) was efficacious for bipolar depression.[104] In contrast, a subsequent trial that also applied high-frequency rTMS on the left DLPFC found that rTMS was not significantly better than sham for treating bipolar depression.[105] It is relevant to note, however, that this study adopted more conservative treatment parameters; that is, a lower frequency of stimulation and a much shorter duration of treatment course compared with the previous study as well as most studies in the depression literature. Notwithstanding this, Fitzgerald and colleagues (2016)[106] employed a more intensive treatment protocol with sequential bilateral DLPFC stimulation, but similarly showed no significant benefit of active compared with sham rTMS in the largest trial to date (n = 49). This study, importantly, provided a basis for the authors to carry out post hoc power analysis, which revealed that a sample of 157 would be required to show therapeutic effects. Thus, all the aforementioned studies were underpowered and their results should be interpreted with caution. Notably, a large-sample naturalistic study (n = 240) recently provided evidence that rTMS is similarly effective for bipolar depression compared with unipolar depression, and taken together with findings of sham-controlled trials, this work indicates further investigation into rTMS treatment for bipolar depression is warranted.[107]

In evaluating rTMS treatment for bipolar depression, it should be recognized that the confounding effects of limitations in study design are likely to be important. In the rTMS for depression literature, a progressive overall pattern of improved therapeutic benefit of rTMS for depression is apparent, and a meta-analysis has shown that effect sizes reported in more recent studies are larger than in older studies.[108] More recent studies were better designed, and this likely contributed to their superior effect size findings. For instance, recent studies recruited larger samples and employed more intensive treatment protocols providing 20 (or more) rTMS sessions, whereas earlier smaller sample studies typically adopted a more conservative number of sessions (eg, 10). It is also plausible that patients selected in later studies may have been less treatment-resistant, a feature that has been shown to correspond with better rTMS response.[109]

It is possible that further research into rTMS for bipolar depression has been deterred due to the reports of induction of hypomania/mania in this population.[110] However, it has been shown that the risk of developing mania is low, and not significantly different when comparing active and sham rTMS, and not higher when compared to antidepressant treatment.[111] This evidence suggests that switching to hypomania/mania is a change in clinical status that may or may not occur during the course of rTMS treatment and an appropriate level of clinical management is advisable (for further information, see Fitzgerald and Daskalakis).[110] Despite being extremely uncommon, it is critical to consider seizure induction as a possible adverse event, which has been documented in depressed and healthy patients during or immediately after rTMS.[112] Reports of seizures with rTMS occurred in cases where stimulation exceeded established TMS safety guidelines[113] or in patients with existing neurological disorders (eg, epilepsy and multiple sclerosis).[112] It is therefore strongly advisable that the provision of rTMS to patients with neurological disorders is carefully and appropriately considered.

3 | DISCUSSION

Effective treatment of bipolar disorder is an ongoing challenge for patients and clinicians. Given that many people do not respond adequately to monotherapy and combination regimens are the rule rather than the exception,[114] it is imperative that clinicians and patients are provided with up-to-date information on novel tools for bipolar disorder management. Indeed, with mental health care resources being limited and with ongoing advances in technology, the use of self-directed learning and treatment in the online space is gaining momentum.[115] Furthermore, the departure from large-scale pharmaceutical company investments in mental health treatments has been paralleled by a significant expansion of investigator-initiated research leading to the development of novel therapies. It is imperative that information on novel interventions is widely disseminated, given the critical need for new effective therapies, the shift towards treatment in the primary care setting, and the paucity of marketing resources in investigator-initiated studies.

By bringing together all the available information, clinicians can more readily identify potential new treatment options for their patients. Some of these new therapies are more patient-centered, especially in the context of internet-based therapies. It shifts the focus back onto the patient and enables a greater sense of direction and control in the management of their illness. Such patient-directed care also facilitates individualized tailored health care, thus maximizing the opportunity for full recovery. Indeed, the inclusion of therapies adjunctive to conventional treatment regimens has been one very useful pathway to make up the shortfall towards full functional recovery for patients.

With enormous growth in biology psychiatry research over recent years, a plethora of novel agents have been focused on biologically relevant pathways, some of which have shown efficacy in bipolar disorder. There has been particular interest in bipolar depression in the

field because it is the condition that has the greatest unmet need in terms of treatment outcomes. Adjunctive agents are being used more commonly by clinicians and this review should assist in informing both clinicians and patients in the mental health space of what is available and what has been found to be useful.

Advances in brain stimulation techniques have provided an alternate strategy for targeting aberrant neurobiological pathways in bipolar depression; that is, highfrequency rTMS applied to the left DLPFC. Although efforts to investigate rTMS treatment specifically for bipolar depression to date have been scant, it is a promising, relatively safe and low-risk treatment for bipolar depression. Given that bipolar depression patients are included in most rTMS treatment for depression studies and the shared diathesis between bipolar and unipolar depression, there is clearly further potential for rTMS to be established as a treatment of bipolar depression. However, studies utilizing larger sample sizes with more advanced treatment protocols are required before the efficacy of rTMS for bipolar depression can be better determined.

In regard to psychological therapies, while more research is required into the potential benefits of CRT for people with bipolar disorder, current evidence suggests that it is imperative for treating team members to recognize that cognitive deficits may be present in individuals with the illness. Indeed, the assessment of cognitive ability in clinical practice is an area that has been largely ignored thus far. Yet, in the context of persistent functional impairments that remain even beyond symptom remission,[116] it is a major impediment to holistic disease management. Progress toward rectifying this issue will no doubt require increased dissemination of research knowledge from scientists to clinicians and greater collaboration between primary health care providers, neuropsychologists, psychiatrists and, moreover, policy makers.

While advances in technology may provide new opportunities to enhance treatment, they also present an interesting challenge for clinicians. The internet is becoming an increasingly acceptable source of information, with 21% of US adults using the internet to search for mental health information.[117] While a number of evidence-based e-health and m-health tools for bipolar disorder exist, so too do commercially driven products with little regard for clinical guidelines.[95] With rapid growth in this area, it is becoming increasingly important for clinicians to stay up to date and technologically savvy so that they can recognize poor-quality tools and information, and best advise their patients accordingly.

4 | CONCLUSION

In conclusion, current treatments for bipolar disorder can reduce episode frequency. It is a promising time for new therapies to be produced. A more complete understanding of how bipolar disorder develops and persists may lead to improved prediction of episodes, new approaches for treatment-resistant patients and even curative interventions. There is significant work being completed to provide information regarding stage of illness, illness severity and relevance to treatment outcomes.[118] Further studies are required to accurately position novel therapies in the context of stage of illness. However, individualized therapy, chronicity and severity of symptoms are the current focus in psychiatry.[119,120] There are a range of updated tools, summarized in this review, that provide new options for the treatment of bipolar disorder and may help to improve functional health outcomes for patients.

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ORCID

Olivia M Dean http://orcid.org/0000-0002-2776-3935
Emma Gliddon http://orcid.org/0000-0002-5897-820X
Francesco Giorlando http://orcid.org/0000-0002-2458-945X
Trung T Ngo http://orcid.org/0000-0002-1909-134X

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Review article

Psychological interventions for adults with bipolar disorder: systematic review and meta-analysis

Matthijs Oud, Evan Mayo-Wilson, Ruth Braidwood, Peter Schulte, Steven H. Jones, Richard Morriss, Ralph Kupka, Pim Cuijpers and Tim Kendall

Background
Psychological interventions may be beneficial in bipolar disorder.

Aims
To evaluate the efficacy of psychological interventions for adults with bipolar disorder.

Method
A systematic review of randomised controlled trials was conducted. Outcomes were meta-analysed using RevMan and confidence assessed using the GRADE method.

Results
We included 55 trials with 6010 participants. Moderate-quality evidence associated individual psychological interventions with reduced relapses at post-treatment (risk ratio (RR) = 0.66, 95% CI 0.48–0.92) and follow-up (RR = 0.74, 95% CI 0.63–0.87), and collaborative care with a reduction in hospital admissions (RR = 0.68, 95% CI 0.49–0.94). Low-quality evidence associated group interventions with fewer depression relapses at post-treatment and follow-up, and family psychoeducation with reduced symptoms of depression and mania.

Conclusions
There is evidence that psychological interventions are effective for people with bipolar disorder. Much of the evidence was of low or very low quality thereby limiting our conclusions. Further research should identify the most effective (and cost-effective) interventions for each phase of this disorder.

Declaration of interest
R.M. and S.H.J. are authors of three included studies.

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Bipolar disorder affects approximately 1.5% of the population,[1–5] and often takes a chronic course with recurrent manic, hypomanic, depressive and mixed episodes. Bipolar disorder is associated with poor psychosocial functioning,[6] a high economic burden,[7–10] and early mortality.[11] People with bipolar disorder are symptomatically ill almost half the time.[12] Although mania often results in hospital admission,[13] depressive symptoms and episodes account for most illness-related disability.[1] In trying to manage the illness, people with bipolar disorder use pharmacological interventions, but 60% of people who commence out-patient maintenance treatment will have an episode within 2 years.[13] As an additional strategy, many people with bipolar disorder wish to use psychological interventions to improve symptoms and reduce relapse rates. Previous meta-analyses have evaluated evidence for specific psychological interventions such as cognitive–behavioural therapy (CBT),[14–18] family interventions and psychoeducation,[17–19] some during acute episodes and some during euthymic periods, with varying durations of intervention and follow-up. The number of relevant trials has tripled since the last meta-analysis and a new comprehensive review is needed to inform the selection of psychological interventions for each stage of bipolar disorder. We therefore conducted a systematic review and meta-analysis of psychological interventions for adults with bipolar disorder compared with control groups (treatment as usual, waiting list, attention control or an active intervention) on symptoms of depression and mania, response, relapse, discontinuation, hospital admission, quality of life and psychosocial functioning. This review informed the guidelines on the management of bipolar disorder issued by the National Institute for Health and Care Excellence (NICE) and The Netherlands Psychiatric Association and Trimbos Institute,[20,21] and is reported here following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[22]

Method

We included randomised controlled trials (RCTs) of all individual, group and family psychological interventions for adults (18 years and older). We also included service-level interventions with (elements of) psychological interventions such as collaborative care. Eligible comparison groups were control groups (treatment as usual, waiting list or attention control) or other active interventions. Trials were eligible if at least 66% of the sample had bipolar disorder or if disaggregated data were reported for participants with the disorder. For trials including people with other mental disorders (e.g. major depressive disorder or schizophrenia) we requested disaggregated data.

Search strategy

We searched CINAHL, EMBASE, Medline, PreMedline, PsycINFO, CDSR, DARE, HMIC and CENTRAL from inception to January 2014 using terms for bipolar disorder and randomised clinical trials (see online data supplement). Searches were not restricted by language. Authors M.O. and R.B. assessed the eligibility of studies for inclusion and discussed disagreements with a third author (E.M.-W.). We then searched the reference lists of the included studies, excluded studies and previous reviews. We contacted study authors and experts to request additional reports of trials. German language reports were translated by P.S.

Assessment of bias

Studies were assessed and rated independently by two authors (M.O., P.C.) using the Cochrane Collaboration risk of bias assessment tool.[23] Disagreements were discussed with a third author (E.M.-W.) and resolved by consensus. Each study was rated

for risk of bias due to sequence generation; allocation concealment; masking (blinding) of participants, assessors and providers; selective outcome reporting (e.g. reporting incomplete data or not all of the outcomes measured); and incomplete data. Risk of bias for each domain was rated as high (seriously weakens confidence in the results), low (unlikely to seriously alter the results) or unclear.

Data management

Patient outcomes included reduction of symptoms of depression and mania (response), relapse (any type, depression, mania or mixed), hospital admission, quality of life, suicide, psychosocial functioning and study discontinuation. We also extracted treatment format, number and length of sessions, method of recruitment, inclusion and exclusion criteria, age, gender, setting, study location and number of people with type 1 bipolar disorder. Study characteristics are reported in online Table DS1. Treatment in the acute phase typically aims at remission of the index episode, and if symptoms of the index episode reappear after a short period the term 'relapse' is often used. Long-term management aims to prevent future episodes, often termed 'recurrence'.[24] In this review it was impossible to distinguish between relapse and recurrence because studies included participants with acute symptoms as well as those who were euthymic without reporting disaggregated data; we have used the term 'relapse' for both outcomes.

Statistical analysis

Psychological treatments developed for bipolar disorder may differ in the underlying therapeutic tradition (e.g. CBT, interpersonal therapy, psychoeducation) and delivery, but they share non-specific treatment factors (e.g. contact with a caring professional, problem-solving, coping with stigma),[25] so their effects may be aggregated in meta-analysis to explore the range of potential effects. In this review, psychotherapies were aggregated by method of delivery, comprising individual treatment, group treatment, family therapy and collaborative care. Information about the effects of interventions with different therapeutic traditions were analysed in subgroups. For continuous outcomes we calculated the standardised mean difference (SMD), Hedges' g for between-group differences. For dichotomous outcomes we calculated the risk ratio (RR) for events. All outcomes are reported with 95% confidence intervals. Overall effects were calculated using random effects models. Continuous effects were weighted by the inverse of variance; dichotomous effects were weighted using the Mantel–Haenszel method.[23] Because time-to-event data were reported inconsistently, and often incompletely (e.g. as curves without associated events or statistics), we were unable to analyse these results; however, most studies were short and similar in duration, and hazard ratios would be similar to the relative risks reported here.

Missing data were noted for each outcome. When missing cases were not reported we contacted the authors. If continuous outcomes were reported for those completing the trial as well as controlling for missing data (for example, imputed using regression methods), we used the data that controlled for missing data. Statistical heterogeneity was assessed by visual inspection of forest plots, by χ^2-tests (assessing the P-value) and by calculating the I^2 statistic, which describes the percentage of observed heterogeneity that would not be expected by chance. If $P<0.10$ and I^2 exceeded 50% we considered heterogeneity to be substantial. Meta-analyses of comparisons and subgroups were conducted using RevMan 5.2;[26] owing to the few studies per type of intervention a meta-regression would not be meaningful and was therefore not conducted. Confidence in the results was assessed by M.O. and E.M.-W. using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) method,[27] which is a structured assessment of the quality of evidence attending to the following factors: risk of bias, inconsistency, indirectness, imprecision and publication bias.

Results

Of 13 641 potentially relevant citations and 4 from other sources we retrieved 59 papers, which were assessed for inclusion (Fig. 1). Of these, three were excluded because only a minority of participants had bipolar disorder and we could not obtain disaggregated data,[28–30] and one was a trial of a measurement instrument.[31] Fifty-five randomised controlled trials were therefore included: four were unpublished at the time of inclusion,[32–35] two had been recently published,[34,35] and fifty-one trials had been published between 1984 and 2014. Seven were not included in the meta-analysis because they did not report usable outcomes, which remained unavailable after we contacted the authors.[36–42]

Study characteristics

Table DS1 presents study characteristics for each trial. Included studies randomised 6010 participants, ranging from 19 to 441 per study. Studies were conducted in North America ($k=22$), England and Ireland ($k=12$), central Europe ($k=11$), Australia ($k=5$), Brazil ($k=3$) and Iran ($k=2$). Participants were recruited

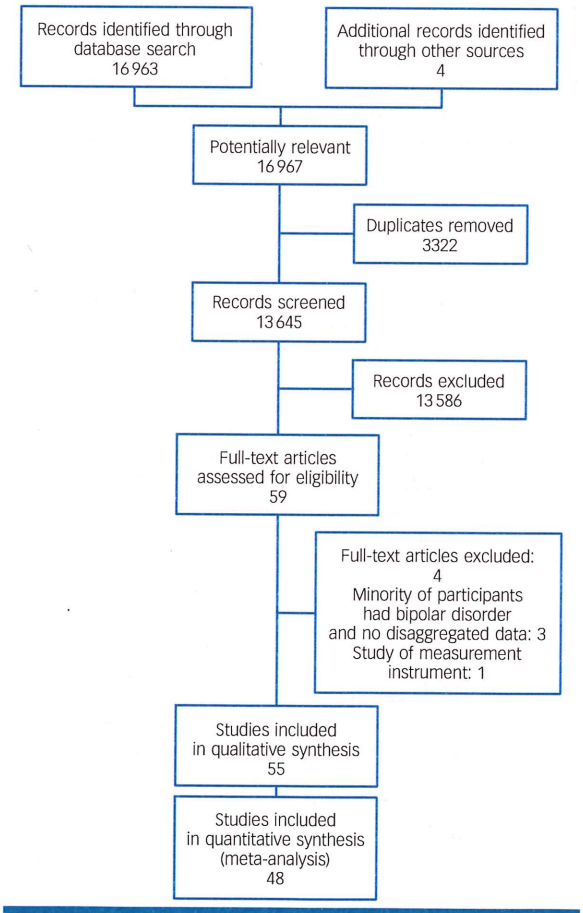


Fig. 1 Study selection.

from out-patient ($k=23$) or in-patient settings ($k=12$), primary care practices ($k=2$), community mental health teams ($k=2$) or advertising combined with (self-)referral ($k=16$). In 52 studies a diagnostic interview was used to establish the presence of bipolar disorder, in one study participants themselves reported whether they had bipolar disorder, another confirmed the diagnosis through a questionnaire, and one study reported only that bipolar disorder was an inclusion criterion. Across all trials the median of the mean ages of participants was 40 years (range 26–55); the median percentage who were female was 58% (range 9–77) and the median percentage of participants with type 1 bipolar disorder was 81% (range 42–100, apart from one study with 0%). Four studies included participants experiencing a depressive episode at baseline,[43–46] six studies included participants experiencing depressive and manic episodes,[37,38,47–50] and thirty-two studies included only euthymic participants. Twelve studies included a mix of euthymic and symptomatic cases at baseline,[35,40,41,51–59] of which only two studies provided disaggregated data.[35,59]

Interventions

Trials included a variety of interventions (online Table DS2) and comparison conditions, and were grouped in nine comparisons. The first five were interventions compared with treatment as usual (individual treatment, group treatment, family therapy, collaborative care, integrated cognitive and interpersonal therapy). Four comparisons included interventions compared with other active interventions (head-to-head trials).

Outcomes

Online Table DS3 lists the continuous measures used in the trials categorised by outcome type. Dichotomous data were also reported. Response was determined through clinical interviews, such as the Structured Clinical Interview for DSM (SCID); cut-off points on diverse scales, e.g. when scored as symptomatic at baseline and at follow-up scoring below 11 on the Young Mania Rating Scale (YMRS) for mania response or below 6 on the Bech–Rafaelsen Melancholia Scale for depression response; or a percentage of reduction on a scale, e.g. 50% on the Hamilton Rating Scale for Depression (HRSD) for a depression response. In most trials participants had to score above a cut-off score for a certain time (e.g. 2 months) to be considered responsive. Relapse in most cases was determined with clinical interviews, for example with the SCID, the Schedule for Affective Disorders and Schizophrenia, and the Mini-International Neuropsychiatric Interview. Other trials established relapse in participants with a score above a cut-off point on a depression scale (e.g. above 12 on the HRSD) or a mania scale (e.g. above 20 on the YMRS); in some, a combination of the two scales was used to evaluate the presence of mixed episodes. Five studies assumed that a relapse had occurred based on chart reviews or hospital records.

Risk of bias

Each risk of bias item is presented as a percentage across all studies in online Fig. DS1 and for each study independently in online Fig. DS2. No trial was at high risk of bias for random sequence generation; however, the method of randomisation was not reported in 15 trials. Allocation concealment was unclear in 25 trials and low risk in 30 trials. Masking of participants and providers in trials of psychological interventions is impossible, so all were at high risk of bias *per se*. Nine trials used only self-report measures and 32 trials reported masked assessor-rated outcomes; these 41 trials were at low risk of bias for allocation concealment. However, eight studies did not have masked assessment and these were considered to be at high risk of bias. In six studies it was unclear whether assessors were unaware of assignment. For incomplete outcome data, 25 trials were at low risk of bias and 24 were at high risk of bias because of the number (more than 10%) of missing cases or because missing cases were excluded from the analyses. In six studies the handling of missing data was not described.

Reporting bias

Risk of reporting bias could not be assessed indirectly (e.g. using funnel plots or statistical methods) because there were few studies for most comparisons and the studies were of similar size. We used direct methods to assess risk of reporting bias by checking trial registrations and by contacting authors. There was a high risk of reporting bias in 22 trials, including seven studies that did not report any usable data. In addition to the outcomes we analysed, several trials also reported incomplete results that could not be included in the meta-analysis. Only 11 studies were prospectively registered, but 23 others were assessed to be at low risk of bias because authors provided missing data or confirmed that all outcomes were published.

Overall evidence quality

Using the GRADE method,[27] many outcomes were downgraded because of risk of bias (e.g. inappropriate handling of missing data). Nearly all results were downgraded at least one level because of imprecision (the analyses included few participants or events). Results for relapse following individual interventions, hospital admission following collaborative care, and study discontinuation during interpersonal and social rhythm therapy (IPSRT) were of moderate quality. Most other evidence was of low or very low quality. Studies also reported controlled comparisons at follow-up, but most outcomes were of very low quality.

Quantitative data synthesis

Across nine comparisons, results of the meta-analyses suggest that psychological interventions may be associated with symptomatic improvement and with fewer relapses and hospital admissions. The majority of these low- to moderate-quality outcomes are summarised per comparison and presented in Tables 1 and 2 (post-treatment) and Tables 3 and 4 (follow-up) with reasons for downgrading; for all outcomes per comparison and subgroups we refer to online Tables DS4 and DS5.

Individual psychological interventions

The search identified 15 RCTs ($n=1580$) of face-to-face and interactive online psychoeducation,[35,59–64] cognitive therapy or CBT,[34,43,51,52,65–68] and medication adherence therapy.[69] Interventions were compared with treatment as usual. Eleven trials enrolled participants who were euthymic at baseline and four trials enrolled a mix of participants experiencing an acute episode of mania or depression and those who were euthymic.[35,51,52,59] Seven trials ($n=637$) reported low-quality evidence that individual psychological interventions were associated with a small reduction in symptoms of depression post-treatment.[35,51,59,65–68] Six trials ($n=365$) reported moderate-quality evidence that such interventions reduced the risk of relapse post-treatment.[51,64–66,68,69] However, three trials found no difference in effect on symptoms of mania.[65,67,68] One trial with few events was inconclusive regarding the risk of hospital admission.[69] Eight trials ($n=532$) reported moderate-quality evidence that individual psychological interventions were associated with a reduction in relapse at follow-up.[59,63–66,68,69] There was low-quality evidence from three trials ($n=214$) that individual psychological interventions might

Table 1 Outcomes at post-treatment assessment compared with treatment as usual

Outcome	Number of studies (*k*) and participants (*n*)	Effect size (95% CI)	Heterogeneity χ^2 (*P*), I^2	Intervention length, weeks	Quality (GRADE)
Individual psychological intervention					
Depression symptoms	*k* = 8, *n* = 683	SMD = −0.23 (−0.41 to −0.05)	8.55 (0.29), 18%	6–26	Low[a,b]
Mania symptoms	*k* = 3, *n* = 171	SMD = −0.05 (−0.35 to 0.25)	0.48 (0.79), 0%	26	Very low[a,b,c]
Hospital admission	*k* = 1, *n* = 28	RR = 0.14 (0.01 to 2.53)	NA	6	Low[b,c]
Relapse (any)	*k* = 6, *n* = 365	RR = 0.66 (0.48 to 0.92)	2.50 (0.78), 0%	6–26	Moderate[c]
Response	*k* = 1, *n* = 33	RR = 0.71 (0.46 to 1.07)	NA	26	Very low[b,c]
Group psychological intervention					
Depression symptoms	*k* = 8, *n* = 423	SMD = −0.24 (−0.64 to 0.16)	25.65 (<0.001); 73%	8–52	Very low[a,c,d]
Mania symptoms	*k* = 6, *n* = 375	SMD = −0.08 (−0.33 to 0.16)	5.60 (0.35), 11%	8–52	Very low[a,b,c]
Hospital admission	*k* = 3, *n* = 205	RR = 0.45 (0.10 to 2.09)	3.94 (0.14), 49%	14–21	Low[c]
Relapse (any)	*k* = 2, *n* = 170	RR = 0.48 (0.22 to 1.04)	2.42 (0.12), 59%	21	Low[c]
Relapse (depression)	*k* = 2, *n* = 170	RR = 0.39 (0.19 to 0.78)	0.45 (0.50), 0%	21	Low[c]
Relapse (mania)	*k* = 2, *n* = 170	RR = 0.48 (0.28 to 0.82)	0.80 (0.37), 0%	21	Low[c]
Family psychoeducation					
Depression symptoms	*k* = 1, *n* = 43	SMD = −0.73 (−1.35 to −0.10)	NA	14	Low[b,c]
Mania symptoms	*k* = 1, *n* = 43	SMD = −0.66 (−1.28 to −0.04)	NA	14	Low[b,c]
Collaborative care					
Depression symptoms	*k* = 2, *n* = 123	SMD = −0.22 (−0.63 to 0.19)	1.32 (0.25), 24%	26–30	Low[a,b,c]
Mania symptoms	*k* = 2, *n* = 123	SMD = −0.07 (−0.47 to 0.32)	1.24 (0.27), 19%	26–30	Low[a,b,c]
Hospital admission	*k* = 3, *n* = 572	RR = 0.68 (0.49 to 0.94)	0.13 (0.72), 0%	52–130	Moderate[c]
Relapse (any)	*k* = 1, *n* = 414	RR = 0.99 (0.84 to 1.17)	NA	52	Low[b,c]
Integrated cognitive and interpersonal therapy					
Depression symptoms	*k* = 1, *n* = 193	SMD = −0.64 (−1.19 to −0.09)	NA	20	Low[c]
Mania symptoms	*k* = 1, *n* = 193	SMD = −0.10 (−0.30 to 0.10)	NA	20	Low[b,c]

NA, not applicable; RR, risk ratio; SMD, standardised mean difference.
a. Risk of bias.
b. Publication/reporting bias.
c. Imprecision.
d. Inconsistency.

be associated with a reduction in admissions to hospital, but the confidence interval was compatible with both a reduction and an increase in the effect.[34,64,68,69]

Group psychological interventions

The search identified 12 RCTs ($n = 914$) of group interventions including psychoeducation,[49,70–73] CBT,[32,74,75] mindfulness therapy,[76,77] social cognition and interaction training,[78] and dialectical behaviour therapy.[44] Interventions were compared with treatment as usual except for two studies that compared psychoeducation with attention control.[70,71] In ten trials participants were euthymic at baseline,[32,70–78] one study included participants experiencing an acute episode of mania or depression,[49] and another included people with current depression. Eight trials ($n = 423$) reported very low-quality evidence of a small effect on depression outcomes at post-treatment favouring group interventions.[32,44,49,73,75–78] Six trials ($n = 375$) found no effect on

Table 2 Outcomes at post-treatment assessment compared with active controls

Outcome	Number of studies (*k*) and participants (*n*)	Effect size (95% CI)	Heterogeneity χ^2(*P*), I^2	Intervention length, weeks	Quality (GRADE)
Family-focused therapy					
Depression symptoms	*k* = 1, *n* = 79	SMD = −0.40 (−0.80 to 0.00)	NA	39	Low[a,b]
Mania symptoms	*k* = 1, *n* = 79	SMD = 0.00 (−0.40 to 0.40)	NA	39	Low[a,b]
Relapse (any)	*k* = 1, *n* = 53	RR = 0.89 (0.52 to 1.54)	NA	39	Low[b]
Hospital admission	*k* = 1, *n* = 53	RR = 0.71 (0.33 to 1.52)	NA	39	Low[b]
CBT					
Depression symptoms	*k* = 1, *n* = 76	SMD = 0.41 (0.12 to 0.70)	NA	39	Low[b,c]
Mania symptoms	*k* = 1, *n* = 76	SMD = 0.20 (−0.11 to 0.51)	NA	39	Low[b,c]
Relapse (any)	*k* = 1, *n* = 76	RR = 0.60 (0.34 to 1.05)	NA	39	Low[b,c]
IPSRT					
Depression symptoms	*k* = 1, *n* = 25	SMD = 0.44 (−0.34 to 1.22)	NA	12	Very low[a,b]
Relapse (any)	*k* = 1, *n* = 41	RR = 1.55 (0.63 to 3.84)	NA	123	Very low[a,b]
Response (any)	*k* = 1, *n* = 25	RR = 0.98 (0.60 to 1.60)	NA	12	Very low[a,b]
Integrated group therapy					
Depression symptoms	*k* = 1, *n* = 61	SMD = −0.35 (−0.85 to 0.16)	NA	12	Very low[b,c,d]
Mania symptoms	*k* = 1, *n* = 61	SMD = −0.17 (−0.68 to 0.33)	NA	12	Very low[b,c,d]

CBT, cognitive–behavioural therapy; IPSRT, Interpersonal and social rhythm therapy; NA, not applicable; RR, risk ratio; SMD, standardised mean difference.
a. Risk of bias.
b. Imprecision.
c. Publication/reporting bias.
d. Indirectness.

Table 3 Outcomes at follow-up assessment compared with treatment as usual

Outcome	Number of studies (*k*) and participants (*n*)	Effect size (95% CI)	Heterogeneity χ^2 (*P* value), I^2	Follow-up period, weeks	Quality (GRADE)
Individual psychological intervention					
Depression symptoms	*k* = 5, *n* = 534	SMD = −0.21 (−0.43 to 0.01)	6.85 (0.23), 27%	26–52	Low[a,b]
Mania symptoms	*k* = 4, *n* = 164	SMD = −0.38 (−0.71 to −0.04)	3.40 (0.33), 12%	52	Very low[a,b,c]
Hospital admission	*k* = 3, *n* = 194	RR = 0.63 (0.38 to 1.02)	2.19 (0.35), 9%	32–52	Low[b]
Relapse (any)	*k* = 8, *n* = 532	RR = 0.74 (0.63 to 0.87)	5.78 (0.57), 0%	32–78	Moderate[b]
Response	*k* = 1, *n* = 52	RR = 0.46 (0.21 to 1.02)	NA	52	Very low[a,b,c]
Group psychological intervention					
Depression symptoms	*k* = 3, *n* = 219	SMD = 0.22 (−0.05 to 0.49)	0.95 (0.62), 0%	52–61	Very low[a,b,c]
Mania symptoms	*k* = 3, *n* = 219	SMD = 0.16 (−0.10 to 0.43)	0.76 (0.68), 0%	52–61	Very low[a,b,c]
Hospital admission	*k* = 3, *n* = 200	RR = 0.48 (0.16 to 1.45)	2.30 (0.13), 56%	78–124	Very low[b,c,d]
Relapse (any)	*k* = 5, *n* = 395	RR = 0.86 (0.61 to 1.20)	21.46 (0.0003), 81%	52–124	Very low[b,c,d]
Relapse (depression)	*k* = 5, *n* = 333	RR = 0.62 (0.45 to 0.88)	7.12 (0.13), 44%	52–124	Low[b,d]
Relapse (mixed episode)	*k* = 4, *n* = 274	RR = 0.48 (0.30 to 0.77)	2.38 (0.50), 0%	52–124	Low[b,d]
Family psychoeducation					
Depression symptoms	*k* = 1, *n* = 53	SMD = -0.15 (−0.69 to 0.39)	NA	60	Very low[a,b,c]
Mania symptoms	*k* = 1, *n* = 53	SMD = -0.78 (−1.34 to −0.22)	NA	60	Very low[a,b,c]
Hospital admission	*k* = 1, *n* = 57	RR = 0.05 (0.00 to 0.83)	NA	60	Low[b]
Relapse (any)	*k* = 3, *n* = 228	RR = 0.52 (0.32 to 0.84)	2.61 (0.27), 23%	52–65	Low[b,c]
Relapse (depression)	*k* = 1, *n* = 113	RR = 0.73 (0.44 to 1.21)	NA	65	Low[b,c]
Relapse (mania)	*k* = 1, *n* = 113	RR = 0.35 (0.15 to 0.85)	NA	65	Low[b]
Response	*k* = 1, *n* = 59	RR = 0.67 (0.34 to 1.32)	NA	121	Very low[a,b,c]
Collaborative care					
Depression symptoms	*k* = 1, *n* = 65	SMD = −0.56 (−1.06 to −0.07)	NA	52	Very low[a,b]
Mania symptoms	*k* = 1, *n* = 65	SMD = −0.10 (−0.59 to 0.38)	NA	52	Very low[a,b]

NA, not applicable; RR, risk ratio; SMD, standardised mean difference.
a. Risk of bias.
b. Imprecision.
c. Publication/reporting bias.
d. Inconsistency.

mania symptoms.[32,49,73,75,76,78] Furthermore, the two studies comparing psychoeducation with attention control (*n* = 170) found low-quality evidence for a reduction in any type of relapse, but the confidence interval was compatible with both a reduction and an increase in the effect.[70,71] The two studies did find evidence for a reduction in depressive and manic relapses. Also, the two studies together with a trial comparing CBT with treatment as usual (*n* = 205) reported low-quality evidence that group interventions might be associated with a reduction in hospital admissions, but the confidence interval was compatible with both a reduction and increase in the effect.[70,71,75] Results at follow-up in five studies (*n* = 333) reported low-quality evidence of a reduction in depressive relapses.[70,71,73,74,76] Also, four studies (*n* = 274) reported a reduction of relapses into mixed episodes.[70,71,73,74] However, effects on depressive symptoms,[32,73,76] and on hospital admission,[70,71] were inconclusive.

Family psychoeducation

The search identified seven RCTs (*n* = 409) of family psychoeducation. Two trials included psychoeducation for participants and their family members,[50,79] and in five trials only family

Table 4 Outcomes at follow-up assessment compared with active controls

Outcome	Number of studies (*k*) and participants (*n*)	Effect size (95% CI)	Heterogeneity	Follow-up period (weeks)	Quality (GRADE)
Family-focused therapy					
Depression symptoms	*k* = 1, *n* = 79	SMD = −0.10 (−0.56 to 0.36)	NA	52	Very low[a,b,c]
Mania symptoms	*k* = 1, *n* = 79	SMD = −0.30 (−0.68 to 0.08)	NA	52	Very low[a,b]
Relapse (any)	*k* = 1, *n* = 101	RR = 0.67 (0.34 to 1.30)	NA	52	Very low[a,b,c]
Response (any)	*k* = 1, *n* = 62	RR = 1.15 (0.68 to 1.94)	NA	121	Very low[a,b,c]
Hospital admission	*k* = 1, *n* = 38	RR = 0.24 (0.08 to 0.74)	NA	104	Very low[a,b]
CBT					
Depression symptoms	*k* = 1, *n* = 76	SMD = 0.49 (0.04 to 0.94)	NA	143	Very low[b,c]
Relapse (any)	*k* = 1, *n* = 76	RR = 1.13 (0.81 to 1.58)	NA	143	Very low[b,c]
IPSRT					
Response (depression)	*k* = 1, *n* = 192	RR = 0.73 (0.50 to 1.07)	NA	52	Very low[a,b,c]
Integrated group therapy (*v.* group drug counselling)					
Depression symptoms	*k* = 1, *n* = 61	SMD = 0.11 (−0.39 to 0.61)	NA	26	Very low[b,c,d]
Mania symptoms	*k* = 1, *n* = 61	SMD = −0.53 (−1.05 to −0.02)	NA	26	Very low[b,c,d]

CBT, cognitive–behavioural therapy; IPSRT, interpersonal and social rhythm therapy; NA, not applicable; RR, risk ratio; SMD, standardised mean difference.
a. Risk of bias.
b. Imprecision.
c. Publication/reporting bias.
d. Indirectness.

members received psychoeducation.[57,80–83] Interventions were compared with treatment as usual. Five trials enrolled participants who were euthymic at baseline, one trial enrolled participants who were experiencing acute episode of mania or depression or were euthymic at baseline,[57] and another included only participants who were in an acute episode of mania or depression.[50] One trial ($n=43$) found low-quality evidence of medium effect in reduction of depressive and manic symptoms favouring family psychoeducation at post-treatment.[57] At follow-up, three trials ($n=228$) reported low-quality evidence of a reduction in relapse.[79,80,82] One trial ($n=113$) reported a reduction in mania relapses.[82] One study ($n=57$) reported a very large effect on reduction of the number of hospital admissions, but there were only nine events in the study.[80]

Collaborative care

The search identified five RCTs ($n=1058$) of collaborative care compared with treatment as usual. Two started with euthymic participants,[47,84] and three recruited participants experiencing an episode.[53–55] In comparison with treatment as usual, two trials ($n=123$) reported low-quality evidence of a small effect favouring collaborative care on depressive symptoms and no effect on mania symptoms at post-treatment, but the effect estimates were imprecise.[53,54] One trial ($n=234$) found no difference in reduction of relapse.[55] However, two trials ($n=572$) reported moderate-quality evidence suggesting collaborative care reduced the number of admissions to hospital at post-treatment.[55,84]

Integrated cognitive and interpersonal therapy

The search identified one RCT ($n=212$) with a group of participants who were randomised to integrated cognitive and interpersonal therapy or treatment as usual.[33] Participants in the intervention group could choose to follow individual or group integrated cognitive and interpersonal therapy. Outcome data were presented for the whole intervention group *v.* treatment as usual. The trial reported low-quality evidence at post-treatment of a medium effect favouring the intervention on depressive symptoms and no effect on mania symptoms.

Family-focused therapy

The search identified four RCTs ($n=357$) on family-focused therapy compared with psychoeducation, collaborative therapy or treatment as usual. Participants were euthymic,[85] in an episode or euthymic,[56] only depressed,[43] or in any type of episode.[50] Post-treatment data were of low quality. One study ($n=79$) found no effect of family-focused therapy compared with treatment as usual on manic symptoms and a medium effect on depressive symptoms (although the confidence interval was also compatible with no effect).[56] A small effect was found on relapse in a study ($n=53$) comparing family-focused therapy with psychoeducation, but the confidence interval was compatible with both a reduction and increase in the effect.[85] The confidence in the follow-up results were very low.

CBT *v.* supportive therapy

The search identified one RCT ($n=76$) comparing individual CBT with supportive therapy; the quality of the evidence was low.[86] At post-treatment a medium effect was found of supportive therapy on depressive symptoms. Also, a small effect was found of supportive therapy on mania symptoms, but CBT reduced the risk of relapse. However, the confidence intervals for the mania and relapse outcomes were compatible with either a reduction or an increase in the true effect.

IPSRT *v.* active control

The search identified three RCTs ($n=299$) of IPSRT compared with quetiapine therapy, intensive clinical management or treatment as usual. Participants in all three trials were in a depressive episode at baseline.[43,45,48] One study reported a small effect of quetiapine compared with IPSRT on symptoms of depression at post-treatment, but the confidence interval was compatible with both a reduction and an increase in the effect.[45] A 123-week trial ($n=41$) found effects that were in favour of intensive clinical management compared with IPSRT on a reduction in relapses, but the confidence interval was compatible with both a reduction and increase in the effect.[48] All results were of very low quality.

Integrated group therapy *v.* group counselling

The search identified one RCT ($n=61$) including people with both bipolar disorder and a comorbid substance use disorder who were either euthymic or acutely depressed at baseline. It compared integrated group therapy with group drug counselling.[58] At post-treatment there was very low-quality evidence of a small effect on depressive and mania symptoms, but confidence intervals were compatible with either a reduction or an increase in symptoms. There was very low-quality evidence of a moderate effect on mania symptoms at follow-up.

Discussion

This is the first comprehensive systematic review and meta-analysis of the full range of psychological interventions that have been evaluated for the treatment of people with bipolar disorder. The evidence suggests that some, but not all, psychological treatments reduce relapse rates and hospital admissions, and they may improve depressive symptoms. In particular, we found moderate-quality evidence that individual psychological interventions were associated with a 34% reduction in the risk of relapse at the end of treatment, sustained at 26% reduction in risk at follow-up. There was also low-quality evidence that individual psychological treatment reduced symptoms of depression, but the reduction may be small. Although the evidence was not as robust, group psychoeducation also showed beneficial effects for reducing risk of relapse, and perhaps for some symptomatic improvement. We also found a substantial reduction in relapse rates for people who received family psychoeducation, although the quality of the evidence for this finding was also low. In addition, our analysis of collaborative care showed moderate-quality evidence for a 32% reduction in admissions to hospital. We found little impact on symptoms of mania, quality of life, psychological functioning or other treatment outcomes, although in most cases the underpinning evidence was very low quality and therefore inconclusive. Moreover, we found no evidence of benefit for other types of psychological interventions such as IPSRT. These results confirm and extend the findings of previous, smaller and narrower reviews of specific psychological treatments for bipolar disorder,[14,15,17–19] and suggest that as the size of the evidence base has increased, the beneficial effects of some psychological interventions have become more apparent. Previous reviews included 10 or fewer trials and fewer than 1000 participants; in contrast, this review analysed 55 trials including data from 6010 participants. Overall, on the basis of this review, we would recommend the use of psychological interventions in the treatment of people with bipolar disorder to reduce relapse rates and to reduce depressive

symptoms. Although there is insufficient evidence to recommend one specific treatment over the others, the best evidence is for individual structured psychological interventions, and there is weaker – but still promising – evidence for group and family interventions and for collaborative care.

Our results are consistent with other recent reviews showing that psychological approaches may reduce transition to psychosis, including for people with bipolar disorder,[87] and that family psychological interventions reduce relapse rates in both early and established schizophrenia.[88,89] Additionally, psychological interventions are the most effective interventions for people with major depression.[90] The effectiveness of psychological interventions in these closely related conditions is promising for the treatment of bipolar disorder, and effective psychological strategies for people with bipolar disorder could be clinically and economically important.

Strengths and limitations

Participants in our review were similar to those in 'real world' practice in several ways. For example, the proportions of men and women and of people with type 1 and type 2 bipolar disorder in the included studies were comparable with epidemiological samples.[4,5] Most studies recruited participants from out-patient or community settings, where these psychological interventions could be carried out. Few studies were undertaken outside Europe and North America, and the effects of psychological interventions might differ in places with different healthcare systems and different levels of community support.

Although the evidence provides support for the use of psychological interventions in the treatment of people with bipolar disorder, our meta-analysis includes a number of trials with participants in different phases: sometimes euthymic, sometimes depressive, sometimes a mixture of both and sometimes a mixture of depressive and manic. Most of the trials with participants in different phases of the illness did not report disaggregated data for people in the euthymic and the depressive phases, or for people with depression and people who were experiencing mania at the start of the trial. This is likely to lead to underestimating the effects on symptoms; people who are euthymic are without symptoms, thereby diluting the mean impact of psychological intervention on depressive and manic symptoms in these mixed populations. Similarly, where data on relapse included trials in which participants were in a manic phase, this may have led to underestimating the impact on relapse rates; people who are manic are often difficult to engage in any psychological treatment, thereby diluting the effects of psychological therapy on relapse rates for those who are euthymic or depressed. In addition, the lack of disaggregated data on outcomes for people with mania makes it impossible to identify any possible harm or benefit of psychological therapies for this group. Finally, a limitation of including participants at different phases of illness is that we are not comparing like with like. Although statistical heterogeneity was minimal, summary effects should be interpreted with some caution in light of the clinical differences among participants across trials.

A further potential limitation of this analysis is the quality of the data. In some comparisons evidence for different outcomes was not consistent. For example, a psychological intervention might appear to reduce symptoms but have no effect on treatment response. Some trials were not registered, and there was evidence of selective reporting of outcomes, which could lead us to overestimate the benefits of psychological treatments in much the same way as selective publishing of drug studies has led to overestimating their true effectiveness.[91] Using GRADE to evaluate the quality of evidence underpinning each outcome, we incorporated these limitations in our evaluation of the results and restricted our conclusions to outcomes based on low- and moderate-quality evidence; importantly, evidence for key outcomes – relapse rates and symptoms – was better than evidence for most secondary outcomes. Almost all reviewed psychotherapies were given as adjuncts to pharmacotherapy (monotherapy or combinations of various medications), and they were delivered in a variety of different treatment modalities and service settings. Co-interventions and details about service settings were incompletely described in many trials and could contribute to unobserved heterogeneity. In addition, although statistical heterogeneity was minimal and there is a consensus that psychological treatments for bipolar disorder share many common elements and strategies (e.g. coping strategies for mood changes), they nevertheless differ in complexity, the skill and training required, content and duration, even when they bear the same name (e.g. CBT or psychoeducation). These problems may be addressed in further research in this rapidly expanding field.

Implications for practice

On the basis of this review, individual psychological interventions should be offered (in addition to whatever pharmacological interventions people already receive) with the aim of reducing relapse rates in people with bipolar disorder who are depressed or euthymic and for improving symptoms in people with depression. Although the evidence was limited for many outcomes in this review, there is strong evidence of the effectiveness of psychological interventions for major depression,[90] adding some support to the view that bipolar depression may be treated effectively with psychological treatment. It is also worth considering family psychological interventions, not just because the trials show some promise, but also because the benefits of family interventions for psychosis (including schizophrenia and bipolar disorder) suggest that relapse rates can be reduced in both early and later psychosis.[88,89] It seems likely, on the basis of this broader evidence as well as the evidence in this review, that family interventions could be beneficial for people with bipolar disorder and should be made available routinely to help reduce relapse rates. People with bipolar disorder may also benefit from group psychoeducation and from collaborative care. It is important to keep in mind that people with bipolar disorder are often only partially adherent to pharmacotherapy, which may contribute to the recurrence of symptoms and to relapse.[92] Group or family psychoeducational interventions and collaborative care could help these people develop skills related to medication use, stress management, recognising early symptoms and coping with symptoms. Such skills could reduce risk of relapse and improve response.

Worldwide there are few people with training and experience in delivering specific psychological interventions for individuals with bipolar depression. However, there are many therapists providing evidence-based treatments for major depressive disorder in primary care. Because the rationale and process of delivering CBT are similar for the two forms of depression, it might be sensible for therapists in primary care to provide individual CBT for people with bipolar depression if they have experience in managing people with bipolar disorder or are supervised by clinicians with that experience. Many of the skills learned through CBT for depression could also help people with bipolar disorder who are euthymic to avoid relapse. In the long term service providers and educational institutions should endeavour to increase the number of therapists trained specifically in the treatment of bipolar depression and the prevention of bipolar relapse.

Directions for future research

Although this review supports the use of individual psychological intervention for relapse reduction and symptom improvement, we do not have sufficient information to know the impact on functioning and quality of life, both key concerns for people with bipolar disorder. Further research should include sufficiently large populations to address these critical outcomes. The same is true for family interventions. Longer follow-up is needed to establish how well the effects of all of these interventions endure. Further research is needed to understand how psychological interventions compare with each other at each phase of the illness. Future studies could be improved by reporting results separately for people in different phases of the disorder (who are at risk of different outcomes), better describing treatments and comparators, pre-registering trials, completely and transparently reporting all outcomes measured, and standardising the use of outcome measurement. Moreover, including an economic (cost–benefit) analysis in trials, especially when there is a possible reduction in relapse, would add greatly to our understanding of what we can do to help people with bipolar disorder; comparing the cost-effectiveness of individual and group approaches would address common concerns about method of delivery.

There is little, if any, evidence about which psychological treatments could be beneficial for people with more severe forms of bipolar disorder. More research could address the treatment of people who have frequent episodes, people who are most severely functionally disabled, and people with persisting inter-episode symptoms. People who are admitted to hospital because of mania symptoms usually receive pharmacotherapy, and we identified no trial that examined whether a psychological intervention would be beneficial during this phase of the illness. Following this review, further research can be developed on the basis of much stronger evidence than was available only a few years ago. It is clear that psychological interventions now have an important place alongside medication in the treatment of people with bipolar disorder, and future research will elucidate the most effective ways to deliver psychotherapy.

Matthijs Oud, MSc, Department of Care Innovation, Trimbos Institute, Utrecht, The Netherlands; **Evan Mayo-Wilson**, MPA, DPhil, Center for Clinical Trials and Evidence Synthesis, Johns Hopkins Bloomberg School of Public Health, Baltimore, USA; **Ruth Braidwood**, MSc, Department of Clinical, Educational and Health Psychology, University College London, UK; **Peter Schulte**, MD, PhD, Treatment Centre for Bipolar Disorders, Mental Health Service Noord-Holland-Noord, Alkmaar, The Netherlands; **Steven H. Jones**, PhD, Department of Clinical Psychology, Spectrum Centre for Mental Health Research, Lancaster University, UK; **Richard Morriss**, MD, FRCPsych, Department of Psychiatry and Community Mental Health, Institute of Mental Health, University of Nottingham, UK; **Ralph Kupka**, MD, PhD, Department of Psychiatry, VU University Medical Centre, Amsterdam, The Netherlands; **Pim Cuijpers**, PhD, Faculty of Psychology and Education, VU University Amsterdam, The Netherlands; **Tim Kendall**, FRCPsych, National Collaborating Centre for Mental Health, London, UK

Correspondence: Matthijs Oud, Trimbos Institute, Department of Care Innovation, Da Costakade 45, 3521 VS, Utrecht, The Netherlands. Email: moud@trimbos.nl

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EXTRA CONTENT ONLINE

100 words

From Greek tragedy to a psychiatry lexicon

John H. M. Crichton

A variety of Greek terminology used in tragic drama is translated simply as 'madness': *anoia* is absence of *nous* (mental reasoning); *paranoia*, a sidestep away from *nous*; *paraphron*, movement away from *phren* (the mind); *oistros*, a fly that bites cows (irritating and persistent) and might refer to an unrelenting passion; *lussa*, a violent rage closely associated with wolves. Most commonly *mania* was used, a term related to *menos* – a violent force, perhaps originally meaning 'blood'. The terminology of the theatre has proved an enduring influence on psychiatric nomenclature, in contrast to ancient Greek clinical diagnoses such as melancholia and hysteria.

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ORIGINAL ARTICLE

WILEY BIPOLAR DISORDERS

Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder

Lakshmi N Yatham[1] | Sidney H Kennedy[2] | Sagar V Parikh[3] | Ayal Schaffer[2] | David J Bond[4] | Benicio N Frey[5] | Verinder Sharma[6] | Benjamin I Goldstein[2] | Soham Rej[7] | Serge Beaulieu[7] | Martin Alda[8] | Glenda MacQueen[9] | Roumen V Milev[10] | Arun Ravindran[2] | Claire O'Donovan[8] | Diane McIntosh[1] | Raymond W Lam[1] | Gustavo Vazquez[10] | Flavio Kapczinski[5] | Roger S McIntyre[2] | Jan Kozicky[11] | Shigenobu Kanba[12] | Beny Lafer[13] | Trisha Suppes[14] | Joseph R Calabrese[15] | Eduard Vieta[16] | Gin Malhi[17] | Robert M Post[18] | Michael Berk[19]

[1]Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada

[2]Department of Psychiatry, University of Toronto, Toronto, ON, Canada

[3]Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA

[4]Department of Psychiatry, University of Minnesota, Minneapolis, MN, USA

[5]Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON, Canada

[6]Departments of Psychiatry and Obstetrics & Gynaecology, Western University, London, ON, Canada

[7]Department of Psychiatry, McGill University, Montreal, QC, Canada

[8]Department of Psychiatry, Dalhousie University, Halifax, NS, Canada

[9]Department of Psychiatry, University of Calgary, Calgary, AB, Canada

[10]Departments of Psychiatry and Psychology, Queen's University, Kingston, ON, Canada

[11]School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada

[12]Department of Neuropsychiatry, Kyushu University, Fukuoka, Japan

[13]Department of Psychiatry, University of Sao Paulo, Sao Paulo, Brazil

[14]Bipolar and Depression Research Program, VA Palo Alto, Department of Psychiatry & Behavioral Sciences Stanford University, Stanford, CA, USA

[15]Department of Psychiatry, University Hospitals Case Medical Center, Case Western Reserve University, Cleveland, OH, USA

[16]Bipolar Unit, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain

[17]Department of Psychiatry, University of Sydney, Sydney, NSW, Australia

[18]Department of Psychiatry, George Washington University, Washington, DC, USA

[19]Deakin Univeristy, IMPACT Strategic Research Centre, School of Medicine, Barwon Health, Geelong, Vic., Australia

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Correspondence
Lakshmi N Yatham, Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada.
Email: yatham@mail.ubc.ca

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The Canadian Network for Mood and Anxiety Treatments (CANMAT) previously published treatment guidelines for bipolar disorder in 2005, along with international commentaries and subsequent updates in 2007, 2009, and 2013. The last two updates were published in collaboration with the International Society for Bipolar Disorders (ISBD). These 2018 CANMAT and ISBD Bipolar Treatment Guidelines represent the significant advances in the field since the last full edition was published in 2005, including updates to diagnosis and management as well as new research into pharmacological and psychological treatments. These advances have been translated into clear and easy to use recommendations for first, second, and third- line treatments, with consideration given to levels of evidence for efficacy, clinical support based on experience, and consensus ratings of safety, tolerability, and treatment-emergent switch risk. New to these guidelines, hierarchical rankings were created for first and second- line treatments recommended for acute mania, acute depression, and maintenance treatment in bipolar I disorder. Created by considering the impact of each treatment across all phases of illness, this hierarchy will further assist clinicians in making evidence-based treatment decisions. Lithium, quetiapine, divalproex, asenapine, aripiprazole, paliperidone, risperidone, and cariprazine alone or in combination are recommended as first-line treatments for acute mania. First-line options for bipolar I depression include quetiapine, lurasidone plus lithium or divalproex, lithium, lamotrigine, lurasidone, or adjunctive lamotrigine. While medications that have been shown to be effective for the acute phase should generally be continued for the maintenance phase in bipolar I disorder, there are some exceptions (such as with antidepressants); and available data suggest that lithium, quetiapine, divalproex, lamotrigine, asenapine, and aripiprazole monotherapy or combination treatments should be considered first-line for those initiating or switching treatment during the maintenance phase. In addition to addressing issues in bipolar I disorder, these guidelines also provide an overview of, and recommendations for, clinical management of bipolar II disorder, as well as advice on specific populations, such as women at various stages of the reproductive cycle, children and adolescents, and older adults. There are also discussions on the impact of specific psychiatric and medical comorbidities such as substance use, anxiety, and metabolic disorders. Finally, an overview of issues related to safety and monitoring is provided. The CANMAT and ISBD groups hope that these guidelines become a valuable tool for practitioners across the globe.

1 | INTRODUCTION

In the 20 years since the Canadian Network for Mood and Anxiety Treatments (CANMAT) first published guidelines on the management of BD (BD),[1] there has been an explosion of research on treatment of this illness. During this time period, CANMAT has strived to translate advances in research into international consensus on evidence-based clinical management; first by publishing 2005 guidelines accompanied by expert commentaries, then by providing updates in 2007,[2] 2009[3] and 2013[4] in collaboration with the International Society for Bipolar Disorders (ISBD). The main objective of these publications was to synthesize the wealth of evidence on the efficacy, safety, and tolerability of the range of interventions available for this complex and varied illness, with the goal of providing clear, easy to use recommendations for clinicians to improve outcomes in their patients.

Given that 13 years have elapsed since the publication of the last full edition in 2005, the objective of these 2018 CANMAT and ISBD Bipolar Disorder Management Guidelines is to provide a comprehensive, up-to-date review of research evidence on the treatment of various phases of BD, translated into clinical recommendations for evidence-based management. Updated principles related to diagnosis and management are also included, in response to significant changes made in the 5th edition of the American Psychiatric Association Diagnostic and Statistical Manual for Mental Disorders

(DSM-5).[5] With increased research into various treatments for BD, the evidence ratings have also been modified to increase rigor; for instance, minimum sample sizes are now specified for randomized controlled trials (RCTs) at each level of evidence (Table 1).

As with previous editions of CANMAT guidelines, clinical support for efficacy was an important consideration in arriving at the final treatment recommendations (Table 2). Major conflicting data are addressed in blue text boxes (figures) to clarify the rationale for arriving at a specific level of evidence for efficacy.

In the current edition, an additional distinction is made between safety and tolerability, and a consensus rating is assigned to each medication on these two measures when used in both the acute and maintenance phase. Further, a rating is also assigned to each medication for its propensity to switch patients into mania or depression (treatment-emergent switch). More information on these ratings can be found in the respective treatment sections, as well as in Section 8.

The final grading of recommendations into first, second, or third-line considers levels of evidence for efficacy, clinical support based on experience, and consensus ratings of safety, tolerability, and risk of treatment-emergent switch. In addition, hierarchical rankings were created and are listed in the tables for first and second line recommendations for acute mania, depression and maintenance treatment in bipolar I disorder (BDI). This hierarchy was created by considering the impact of each treatment across all phases of illness (Figure 1). The rationale for the hierarchical approach is that BD is a chronic lifetime condition with recurrent mood episodes and subsyndromal mood symptoms, and most if not all patients will require maintenance treatment. Since treatments that are prescribed for an acute mood episode are usually continued into maintenance treatment, maintenance efficacy should be considered when choosing acute-phase treatments. Treatments that have demonstrated efficacy across the spectrum of the illness should thus be tried first before treatments that have demonstrated efficacy for only selective phases of the disorder. As an example, if two treatments are shown to be similarly effective in acute mania, and if only one of these treatments has demonstrated efficacy for maintenance treatment, the treatment with evidence for maintenance would be placed higher in the hierarchical ranking.

Of note, when a treatment is listed as a monotherapy, that implies that it may be used on its own or in combination with other ongoing treatments, even if there are no specific studies demonstrating the efficacy of that combination. In this situation, the assumption is that the previous ongoing treatment was partially effective, and the addition of the new agent will provide benefits in either an additive or synergistic manner. In contrast, agents specifically listed as adjunctive therapy may have no evidence for efficacy as monotherapy, and/or may have safety concerns if prescribed as monotherapy (eg. antidepressants), and are only recommended for use in combination with other evidence-based agents.

As with previous editions, these guidelines also have a "not recommended" category which includes treatments that have clearly been shown to be ineffective in double-blind RCTs. Further, we have included another category called "no specific recommendation/agents that require further study" to list treatments with insufficient evidence or clinical experience to make a recommendation, or where there is a reason to believe that negative trials failed because of methodological problems-especially when the results are inconsistent with what is expected based on the pharmacological properties of treatment and clinical experience. Inclusion in this category means the efficacy of these agents is unknown at this time.

As in previous editions, these guidelines are organized into eight sections (Table 3), including the Introduction. Foundations of management (Section 2) discusses the epidemiology of BD, screening and diagnostic considerations, the importance of monitoring risk for suicide, the chronic disease management model and patient-centred care (including shared decision making), as well the importance of incorporating psychoeducation and other psychosocial treatment

TABLE 2 Definitions for line of treatment ratings

Line	Evidence level
First	Level 1 or level 2 evidence for efficacy plus clinical support for safety/tolerability and no risk of treatment-emergent switch[a]
Second	Level 3 or higher evidence for efficacy plus clinical support for safety/tolerability and low risk of treatment-emergent switch[a]
Third	Level 4 evidence or higher for efficacy plus clinical support for safety/tolerability
Not recommended	Level 1 evidence for lack of efficacy, or level 2 evidence for lack of efficacy plus expert opinion

[a]The text will specifically note when lack of clinical support for safety/tolerability or risk of treatment-emergent switch has impacted recommendations.

TABLE 1 Definitions for level of evidence ratings

Level	Evidence
1	Meta-analysis with narrow confidence interval or replicated double-blind (DB), randomized controlled trial (RCT) that includes a placebo or active control comparison (n ≥ 30 in each active treatment arm)
2	Meta-analysis with wide confidence interval or one DB RCT with placebo or active control comparison condition (n ≥ 30 in each active treatment arm)
3	At least one DB RCT with placebo or active control comparison condition (n = 10-29 in each active treatment arm) or health system administrative data
4	Uncontrolled trial, anecdotal reports, or expert opinion

What are hierarchical rankings?

Hierarchical rankings of treatment options are new to the 2018 Guidelines. They were created for first and second line treatment recommendations for acute mania, depression, and maintenance treatment of bipolar I disorder; and will further assist clinicians in making evidence based treatment decisions.

These orders were created by considering the efficacy of each treatment across all phases, as well as acute and maintenance safety and tolerability and the risk for treatment emergent switch. Thus, for example if two treatments were shown to be similarly effective in acute mania, and if only one of these treatments has demonstrated efficacy for maintenance treatment, or had better safety or tolerability, that treatment would be placed higher in the hierarchical recommendation.

When making treatment decisions, we recommend that agents listed higher in the hierarchy be tried first, unless there are patient-specific reasons for choosing an agent lower in the order (such as patient preference, prior treatment non/response, or clinical features which favor treatments lower in the ranking).

FIGURE 1 Hierarchical rankings of treatment recommendations: How were they arrived at? [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Sections

Section 1: Introduction
Section 2: Foundations of management
Section 3: Acute management of bipolar mania
Section 4: Acute management of bipolar I depression
Section 5: Maintenance therapy for bipolar I disorder
Section 6: Bipolar II disorder
Section 7: Specific populations
Section 8: Safety and monitoring

strategies into treatment. Additional information on presentation and hierarchical rankings of treatment options for acute mania (Section 3) and depression (Section 4) are reviewed, and include descriptions of clinical features that may help direct treatment choices. The importance of long-term maintenance treatment and promotion of treatment adherence for mood stability, as well as hierarchical rankings of treatment options are discussed in Section 5. An expert review of the available evidence for treatments of bipolar II disorder (BDII) and recommendations based on those findings are presented in Section 6. The management issues related to specific populations, including women at various stages of the reproductive cycle, children and adolescents, older adults, and those with psychiatric or medical comorbidity are each discussed in Section 7. Finally, the principles of medical monitoring and an overview of safety and tolerability concerns for recommended treatments are provided in Section 8.

For convenience and to avoid confusion, these guidelines also include a table of commonly used terms (with an explanation of the intended meaning) that may have overlapping definitions or criteria in the literature (Table 4).

These guidelines are intended for use by psychiatrists and primary care providers who care for patients with BD throughout the lifespan, supporting them to provide evidence-based assessment, treatment of acute symptoms, prevention of episode recurrence, and management of comorbidities. These guidelines are not meant to replace clinical judgement or define standards of care. While designed with Canadian physicians in mind, input from experts from the ISBD makes these guidelines applicable for practitioners from across the globe. As with previous publications, CANMAT will strive to publish regular updates to these guidelines, incorporating new knowledge useful for practising clinicians.

As not all medications included in these guidelines will be available in all countries, including Canada, clinicians are advised to follow the recommendations of local regulatory bodies.

2 | FOUNDATIONS OF MANAGEMENT

2.1 | Epidemiology

2.1.1 | Prevalence

Bipolar disorder is a common and disabling mental illness with significant morbidity and mortality. The estimates of prevalence of BD vary. The World Mental Health Survey Initiative reported total lifetime (and 12-month) prevalence estimates of 2.4% (1.5%) across BDI, BDII and subthreshold BD subtypes. While the prevalence rates for each subtype varied across the nine countries studied, subthreshold BD was the most common at 1.4% (0.8%), followed by BDI at 0.6% (0.4%) and BDII at 0.4% (0.3%).[6] While Canada was not included in this study, similar results were reported from the Canadian Community Health Survey-Mental Health, which found the lifetime prevalence of BDI was 0.87% and that of BDII was 0.67%.[7]

2.1.2 | Age of onset

Bipolar disorder frequently manifests in late adolescence and young adulthood, with an overall average age of onset of 25 years. Statistical models suggest the presence of three age of onset subgroups within BDI and these can be categorized into a large early-onset group (mean ± standard deviation (SD) 17.24 ± 3.20 years), and smaller middle-onset (23.93 ± 5.12 years) and late-onset (32.20 ± 11.96 years) groups, with the proportion of individuals falling into each category being 41.7%, 24.7% and 33.6% of the total sample, respectively.[8] However, the ages of onset tend to differ somewhat depending upon the origins of samples analysed. For instance, a recent study showed that the

TABLE 4 Clarifying overlapping terminology

Term	Use
Mood stabilizer	Use in the literature is inconsistent, and so this term will not be used in these guidelines
Divalproex	Encompasses valproate, valpromide, valproic acid and divalproex sodium
Conventional antipsychotics	Include first-generation antipsychotics with high affinity for dopamine D2 receptors. Note these are referred to as dopamine receptor antagonists (D2) in the new neuroscience-based nomenclature
Atypical antipsychotics	Comprise second-generation antipsychotics with affinity for dopamine D2 and serotonin 5-HT2 receptors as well as those that have partial agonist effects at D2/D3 receptors. Note these are referred to as dopamine and serotonin receptor antagonists (D2 and 5-HT2A), dopamine 2 partial agonists and serotonin receptor antagonists, and dopamine 2/3 partial agonists in the new neuroscience-based nomenclature
Recurrence	Re-emerging episode(s) of mania or depression whether it be within the previous episode or a new episode. Note that, while the literature may use "relapse" and "recurrence", respectively, inconsistencies in how they are applied and their irrelevance to treatment decisions mean we will use "recurrence" to refer to both
Maintenance	Prophylactic therapy after stabilization of acute manic or depressive episodes

mean age of onset for a USA sample was 20 years, with ages of onset of 14.5 ± 4.9 years (63%), 26.5 ± 7.6 years (28.5%), and 39.5 ± 12.5 years (8.5%) for early-, middle- and late-onset groups, respectively; while a European sample showed a later mean age of onset of 29 years and a later onset in each of the three categories, with 19 ± 2.7 years (24.8%), 27.2 ± 6.3 years (50.7%), and 41.8 ± 10.7 years (24.5%) as the ages of onset for early, middle and late-onset groups, respectively.[9] Those with an earlier age of onset tend to have a longer delay to treatment, greater depressive symptom severity, and higher levels of co-morbid anxiety and substance use.[10] While manic episodes can occur for the first time after the age of 50 years as a part of BDI, the possibility of organic mania should be considered and investigated in these cases.[11]

2.1.3 | Burden of illness

People living with BD experience substantial impairment, being symptomatic with syndromal or subsyndromal symptoms, particularly those of depression, for approximately half of their lives.[12,13] Patients are unable to maintain proper work role function approximately 30% or more of the time.[14] Quality of life is reduced in both symptomatic and non-symptomatic patients when compared to healthy controls,[15-17] and several domains of functioning have been identified by patients as being of particular importance- including physical, sleep, mood, cognition, leisure, social, spirituality, finances, household, self-esteem, independence, identity, work, and education.[18] For both psychosocial functioning and quality of life, impairments are more pronounced in patients with depressive symptoms,[19-21] in those with more previous episodes/longer duration of illness,[20,22] and in those with lower cognition.[23]

Consistent with these observations, the Global Burden of Disease Study attributed 9.9 million years lost to disability (YLD) to BD, making it the 16th leading cause of YLD worldwide.[24] The impact that BD has on young people is even greater, with being the sixth leading cause of disability-adjusted life years among people aged 10-24 years worldwide.[25] The burden of this disease was further emphasized in a systematic review addressing cost of illness studies, with findings demonstrating that the worldwide annual costs per person with BD range from US $1904 to $33 090; higher per person costs associated with BDI, delayed or misdiagnosis, frequent psychiatric interventions, use of atypical antipsychotics, treatment non-adherence, poor prognosis, relapse, and comorbidity.[26]

2.2 | Diagnostic assessment

2.2.1 | DSM-5 diagnostic criteria

Bipolar disorder encompasses a spectrum of diagnostic subgroups primarily divided according to the severity of mood elevation experienced during acute episodes[5] On this spectrum, BDI is placed at one pole due to the presence of threshold manic episodes in which features include inflated self-esteem, decreased need for sleep, pressured speech, racing thoughts, distractibility, psychomotor agitation, and risky behaviour that leads to significant functional impairment, and may include psychotic features, and/or necessitate hospitalization. At the other end of the spectrum, cyclothymia is characterized by subthreshold presentation of hypomanic and depressive symptoms that, while chronic, do not meet diagnostic criteria for a major depressive episode or manic/hypomanic episode. BDII sits between the two conditions with hypomanic episodes qualitatively like manic periods but, although distinct and observable, are not of a sufficient duration or severity to cause significant functional impairment, hospitalization, or psychosis. Individuals with BDII also experience threshold depressive episodes.

DSM-5 has replaced the BD not otherwise specified (NOS) category in DSM-IV with two new categories; other specified bipolar and related disorder and unspecified bipolar and related disorder. Also, DSM-5 includes substance/medication-induced bipolar and related disorder and bipolar and related disorder due to another medical condition. For more detailed discussion of diagnostic categories, the reader is advised to consult DSM-5 and recent Royal Australian and New Zealand College of Psychiatrists guidelines for treatment of mood disorders.[27]

2.2.2 | DSM-5 specifiers for bipolar and related disorders

DSM-5 also includes a range of specifiers that clinicians may use to further clarify the specific course, severity, and features of BDs. While a more detailed description can be found in the DSM-5 manual, the available specifiers and their use across the spectrum are listed in Table 5. Many of these specifiers may also be used to guide treatment decisions for acute mania (Section 3) and depression (Section 4). Amongst these, the mixed features specifier, which has replaced mixed episodes, warrants consideration because of the multiple and complex presentations of mixed states it can give rise to. Furthermore, the nascency of this terminology has meant that treatment data are as yet sparse. DSM-5 has added mixed features as a specifier during an episode of major depressive disorder (MDD) as well, which will probably pose some pragmatic diagnostic challenges and management dilemmas for clinicians.

2.2.3 | Staging bipolar disorder

The course of BD is heterogeneous but, on average, the risk of recurrence increases with the number of previous episodes.[28] In addition, data examining the effect of episodes on the course of illness shows that the number of previous episodes is associated with increased duration and symptomatic severity of subsequent episodes. Moreover, the number of episodes is associated with a decreased threshold for developing further episodes and with an increased risk of dementia in the long term.[28] The progressive course of illness in patients with multiple episodes is called clinical progression and the biological basis of clinical progression is defined as neuroprogression.[28,29]

The concepts of clinical progression and neuroprogression have provided the basis for the development of staging systems in BD.[30] Overall, the staging models describe three broad clinical stages: (I) individuals at increased risk for developing BD due to family history as well as certain subsyndromal symptoms predictive of conversion into full-blown BD; (II) patients with fewer episodes and optimal functioning in the interepisodic periods, and (III) patients with recurrent episodes as well as decline in functioning and cognition.[31] So far, the heterogeneity intrinsic to BD has prevented the clinical use of staging systems.[32] In addition, the field of staging is in its infancy and the ability of staging systems to guide prognosis and treatment is still to be determined. Overall, the model of staging has helped clinicians to appreciate the importance of early identification and treatment as well as illness trajectories in BD.[33]

2.2.4 | Screening and diagnosis of bipolar disorder

Due to frequent depressive onset, variable help seeking for hypomanic or manic periods, temporal instability of symptoms, and high rates of comorbidity; accurate the timely identification of BD can be difficult to achieve in many cases. Indeed, many individuals are not accurately diagnosed until up to 10 years after the onset of symptoms, with one to four alternate diagnoses typically being given prior to correct recognition and treatment[34,35] This delay has important consequences, including inadequate initial treatment and worse prognosis in terms of episode recurrence and functional outcome.[36,37]

The most frequent misdiagnosis is that of MDD, as patients are more likely to present for the treatment of depressive symptoms and may not recall periods of hypomania or mania, or may not interpret them as being pathological. Recall and insight are particularly impaired during periods of acute depression, with pronounced memory or concentration difficulties. There are several features of depression that may increase suspicion of bipolarity, and prompt more careful investigation, including earlier age of illness onset, highly recurrent depressive episodes, a family history of BD, depression with psychotic features, psychomotor agitation, atypical depressive symptoms such as hypersomnia, hyperphagia, and leaden paralysis, postpartum depression and psychosis, past suicide attempts, and antidepressant-induced manic symptoms or rapid cycling (Table 6) Given the recent change in DSM-5 to allow the possibility of depression symptoms with subthreshold simultaneous hypomanic symptoms (mixed specifier), it is also important to explore if an individual is experiencing mixed symptoms.[38,39] Schizophrenia and other psychotic disorders are the second most

TABLE 5 DSM-5 specifiers for bipolar and related disorders

Specifier	Manic episode	Depressive episode	Illness course
Anxious distress	X	X	
Mixed features	X	X	
Rapid cycling			X
Melancholic features		X	
Atypical features		X	
Psychotic features	X	X	
Catatonia	X	X	
Peripartum onset	X	X	
Seasonal pattern			X
Remission	X	X	
Current episode severity	X	X	

common misdiagnosis, occurring as the initial diagnosis in as many as 30% of patients.[40]

In addition to this under-diagnosis, there are also concerns that BD may be over-diagnosed in some circumstances.[41] For instance, the symptoms of borderline personality disorder, substance use disorder (SUD) and attention deficit hyperactivity disorder (ADHD) overlap significantly those of hypomania/mania, and some reports suggest that patients with these conditions often get misdiagnosed with BD. These conditions also are often comorbid with BD, which makes the diagnosis of this condition often challenging.[42]

Validated self-report instruments, such as the Mood Disorders Questionnaire (MDQ), may be used as a screening tool to flag patients for whom a more detailed assessment is needed. It is important to note, that such tools have poor sensitivity and specificity, especially in community or highly comorbid populations, and will thus have an elevated risk of also flagging those with borderline traits.[43] As such, tools such as the MDQ should be used only as an adjunct for screening clinical populations and not for diagnostic or treatment planning purposes.

To improve the accuracy of diagnosis, it is important that clinicians strictly adhere to diagnostic criteria rather than relying on heuristics.[44] It is important to complete a careful psychiatric history, including in first-degree relatives, with attention paid to any suspected periods of increased activity, irritability, or other change in behaviours. Collateral information from friends and family members should be included wherever possible. Ongoing monitoring of symptoms, such as mood charting, can also help to detect bipolarity that may only become apparent over time. Confirmation of the diagnosis can then be made more confidently when episodes are prospectively observed.

2.2.5 | Comorbidities and mimics

As described in Section 6, patients diagnosed with BD very commonly have one or more comorbid psychiatric diagnoses, with SUDs, impulse control disorders, anxiety disorders, and personality disorders (especially cluster B disorders) particularly common.[45] The presence of comorbidity increases the complexity of the illness and can make an accurate diagnosis even more difficult.

In addition to differentiating BD from other psychiatric diagnoses, alternative causes of mood symptoms, such as personality disorders, medical or neurological conditions, substance use, and medications must be considered in the differential diagnosis (Table 7).

2.3 | Suicide risk

It is important for clinicians to frequently monitor suicidal ideation and risk. Suicide is one of the leading causes of death in BD, with approximately 6%-7% of identified patients with BD dying by suicide; thus, suicide risk is substantially higher in BD than in the general population (10.7 per 100 000 per year).[46,47] The fatality of suicide attempts is also higher in BD than in the general population.[48,49] Worldwide, approximately 43% of patients with BD report suicidal ideation, 21% a plan, and 16% a suicide attempt within the past year.[6] Men are at a higher risk of death by suicide, with an estimated rate of 0.366 per 100 person years, compared to 0.217 for women.[47]

As reviewed in the ISBD Task Force on Suicide in Bipolar Disorder,[50] a number of sociodemographic and clinical risk factors need to be considered in determining the level of suicide risk (Table 8). Factors reported to be significantly associated with suicidal attempt include female sex, younger age of illness onset, depressive polarity of first illness episode, depressive polarity of current or more recent episode, comorbid anxiety disorder, comorbid SUD, comorbid cluster B/borderline personality disorder, first-degree family history of suicide, and previous suicide attempts. Only male sex and first-degree family history of suicide have been significantly associated with suicide deaths.[50,51] The periods during and following hospital admission further represent times of particularly high risk, with 14% of suicides occurring during an inpatient stay and another 26% within 6 weeks of discharge.[47,52]

A comprehensive assessment for suicide risk should occur during all clinical interactions. Risk stratification using assessment tools is not sufficiently accurate for prediction of suicide risk in clinical use; instead, clinical assessment should focus on modifiable risk factors that could be targeted to reduce the risk.[53] The ISBD has developed clinical tips and patient information sheets (translated into several languages) that can be useful tools for clinicians, patients and families to develop a comprehensive approach to suicide prevention (http://www.isbd.org/Files/Admin/Knowledge-Center-Documents/Suicide-Prevention-Tip-Sheet.pdf).

TABLE 6 Features of depression that may increase suspicion of a bipolar vs unipolar illness

Feature	Suggestive of bipolarity	Suggestive of unipolarity
Symptomatology and mental state signs	Hypersomnia and/or increased daytime napping Hyperphagia and/or increased weight Other "atypical" depressive symptoms such as leaden paralysis Psychomotor retardation Psychotic features and/or pathological guilt Lability of mood; irritability; psychomotor agitation; racing thoughts	Initial insomnia/reduced sleep Appetite and/or weight loss Normal or increased activity levels Somatic complaints
Course of illness	Early onset of first depression (<25 years) Multiple prior episodes (≥5 episodes)	Late onset of first depression (>25 years) Long duration of current episode (>6 months)
Family history	Positive family history of bipolar disorder	Negative family history of bipolar disorder

Adapted from Mitchell et al.[38] and Schaffer et al.[39]

TABLE 7 Differential diagnosis of bipolar disorder

Diagnosis	Distinguishing features
Major depressive disorder or persistent depressive disorder	Manic or hypomanic episodes probed for and not present
Bipolar or related disorder due to another medical condition	Episodes are judged to be a consequence of a medical condition such as traumatic brain injury, brain tumours such as frontal lobe meningiomas, multiple sclerosis, stroke, Cushing's disease or hyperthyroidism. Onset or exacerbation of mood coincides with that of the medical condition
Substance- or medication-induced mood disorder	Episodes are judged to be a consequence of a substance such as an illicit drug, or a medication (stimulants, steroids, L-dopa or antidepressants) or toxin exposure. Episodes may be related to intoxication or withdrawal
Cyclothymic disorder	Hypomanic symptoms do not meet the full criteria for a hypomanic episode, and depressive symptoms do not meet the criteria for a major depressive episode
Psychotic disorders (schizoaffective disorder, schizophrenia and delusional disorder)	Periods of psychotic symptoms in the absence of prominent mood symptoms. Consider onset, accompanying symptoms, pervious course and family history
Borderline personality disorder[a]	Instability of interpersonal relationships, self-image and mood, with marked impulsivity and a central theme of intense abandonment fears. Early onset and long-standing course. True euphoria and prolonged well-functioning intervals are extremely rare
Narcissistic personality disorder[a]	Grandiosity, need for admiration and lack of empathy of early onset. Grandiosity not associated with mood changes or functional impairments
Antisocial personality disorder[a]	Early onset of disregard for, and violation of, the rights of others, which does not occur only in the context of a manic episode

Adapted from Yatham et al. 2005[2]
[a]Can occur comorbidly with bipolar disorder.

The association between various treatments and suicide risk has been reviewed by the ISBD Task Force and others, which suggest that lithium[54] and, to a lesser extent, anticonvulsants may contribute to preventing suicide attempts and deaths; although more data are needed to determine their relative efficacies. There were limited data on both antipsychotics and antidepressant agents.[47] As the most common method of suicide in this population is self-poisoning, the potential benefits of various treatments should be considered against their risk of toxicity and lethality. One small Canadian study indicated higher rates of lethal doses of antipsychotics (32%), opioids (29%), benzodiazepines (27%), carbamazepine (21%) and diphenhydramine (15%) compared to lithium (3%) in 34 self-poisoning deaths.[55]

2.4 | Chronic disease management

Due to the chronic, relapsing and remitting nature of BD, a long-term, multidisciplinary approach to management is needed. The Chronic Disease Management Model[56] outlines several important principles to enhance long-term care for these individuals and their families (Table 9). After basic clinical management, including attention to diagnosis, comorbidity, and medical health has been established, patient health education and pharmacotherapy should be the initial and foundational steps for all patients. Ideally, the patient will be connected to a health care team which includes at least one other health care professional (typically a nurse) in addition to the psychiatrist for psychoeducation, ongoing monitoring, psychosocial support, and referral to community resources.[57] All patients should have access to a primary care provider to attend to mental and physical health needs. If the patient is stable and discharged to primary care, the mental health care system should provide support directly to the primary care provider with attention to continuity of care.[58] Additional psychosocial treatments (described below) may also be selected to fit the specific needs and preferences of the patient.

A strong therapeutic alliance is central to improve treatment adherence and outcomes.[59,60] Providers should encourage individuals to actively participate in treatment planning, using a shared decision-making approach.[61,62] Whenever possible, family members or key friends should be included as part of the care team. There is evidence that specialized, team-approach-based interventions combining pharmacotherapy and psychoeducation are more effective than standard community care.[63]

Regular, ongoing monitoring of mood symptoms and other measures related to the patient's own individual recovery, such as sleep, cognition, functioning, and quality of life is encouraged.[18] For many patients, daily recording of mood symptoms such as through a mood diary or National Institute of Mental Health (NIMH) Life Chart Method-Self Rating Scale can help identify early warning signs of relapse, as well as outline relationships between mood and treatment or lifestyle factors such as diet, exercise, or stress.[64] While many patients will agree with the value of completing a mood diary, and this strategy has been shown to improve treatment, regular completion can be a burden.[65] Online solutions such as mobile apps may improve adherence,[66] such as the Self-Monitoring and Psychoeducation In Bipolar Patients smartphone app (SIMPLE) which provides weekly and daily mood tests, with reminders to take medication or see their doctor.[67-69]

2.5 | Dealing with stigma

Stigma is an important issue that will impact individuals with BD, as well as their family members, potentially preventing individuals from seeking

TABLE 8 Summary of main factors associated with suicide attempt and suicide deaths in bipolar disorder (BD)

Variable	Increased likelihood of suicide attempts	Increased likelihood of suicide deaths
Sex	Female	Male
Age	Younger Older—higher lethality	Older—higher ratio of deaths/attempts
Race	Minorities—youth only	
Marital status	Single, divorced, single parents	
Age of onset	Younger	
First episode polarity	Depression Mixed symptoms Mania—more violent attempts	
Predominant polarity	Depressive	
Current episode polarity	Depressive Mixed	Depressive Mixed Manic with psychotic features
Other episode characteristics	Mixed features Greater number/severity of episodes Rapid cycling Anxiety Atypical features Suicidal ideation	Hopelessness Psychomotor agitation
Psychiatric comorbidity	Substance use disorder Cigarette smoking Coffee intake Anxiety disorder Eating disorder	Anxiety disorder
Personality disorders	Present—particularly borderline or cluster B	
Physical comorbidity	Obesity or high BMI	
First-degree family history	Mood disorders BD Suicide	Mood disorders BD Suicide
Prior suicide attempts	Present	Present
Early life trauma	Childhood abuse Early life stress	
Psychosocial precipitants	Interpersonal problems Occupational problems Bereavement Social isolation	Present within 1 week of death
Sexual dysfunction	Present	

Adapted from Schaffer et al.[50]
BMI, body mass index.

or engaging in treatment or causing them to conceal their illness, reducing social support, functioning and quality of life.[70] Linked to stereotypical negative attitudes that mental illness is due to personal weaknesses or decisions, or associated with violent or criminal behaviour, stigma can be perceived or experienced with interactions with others, including health care providers, or internalized (self-stigma). Specific strategies to reduce stigma, particularly self-stigma, by enhancing coping skills through improvements in self-esteem, empowerment, and help-seeking behaviour can improve outcomes in this population.[71]

2.6 | Psychosocial interventions

While pharmacotherapy is essential and forms the foundation for the successful treatment of BD, adjunctive psychosocial interventions may also be useful for acute depressive episodes, as well as in maintenance treatment to prevent relapse and to restore quality of life to the individual and family.[72,73] No evidence exists, and hence there are no recommendations, for specific psychosocial interventions in acute mania. Positive evidence has been found for psychoeducation, cognitive behavioural therapy (CBT), family-focused therapy (FFT), interpersonal and social-rhythm therapy (IPSRT), and peer support in the maintenance phase of BD and these interventions are included as recommended adjunctive treatment options. Additional studies are needed before conclusions can be drawn regarding other strategies such as family/caregiver interventions, dialectical behavioural therapy (DBT), mindfulness-based cognitive therapy (MBCT), cognitive and functional remediation, and online interventions (Table 10).

In general, provision of psychoeducation to all patients and family members is recommended for prevention of relapse, particularly at illness onset, with selection of any additional psychosocial therapies based on individual concerns/presentations or deficits.

2.6.1 | Psychoeducation

Psychoeducation broadly includes provision of information about the nature of the illness, its treatments, and key coping strategies to the patient and family.[74] Current psychoeducational models for BD teach skill development in detecting and managing prodromes of depression and mania, ongoing stress management, problem solving, how to diminish the effects of stigma and denial of the illness, and provide tips on enhancing medication adherence and developing healthy lifestyles (eg, minimizing the use of alcohol, tobacco, drugs, stimulants such as caffeine; getting regular exercise; and regulating sleep and wake times). A key goal is the creation of personalized coping strategies to prevent mood relapse.

Psychoeducation may be delivered individually or in group settings. Empirical models of psychoeducation involve face-to-face interaction with a therapist, but new models are being tested that involve online tools, smartphone apps, and workbooks.[75] Consistent with broader theories of learning, it is believed that psychoeducation is enhanced when it features active learning, with attention to monitoring the development of understanding, active skill development, and homework between sessions. Peer support and group learning are also postulated to add efficacy to psychoeducation. Regardless of the type of model and content included, priority should be given to maximize the therapeutic alliance, convey empathy, and consistently monitor symptoms.[76]

TABLE 9 The chronic disease management model

Self-management support	Empower and prepare patients to manage their health and health care
	Use effective self-management support strategies that include assessment, goal setting, action planning, problem solving, and follow-up
Decision support	Promote clinical care that is consistent with scientific evidence and patient preferences
	Embed evidence-based guidelines into daily clinical practice and share this and other information with patients to encourage their participation
	Use proven provider education materials
Community	Encourage patients to participate in effective community programs
	Form partnerships with community organizations
Delivery system design	Provide clinical care and self-management support that patients understand and that fits with their cultural background
	Ensure regular follow-up by the care team, with defined tasks for different team members
	Provide clinical case management services for complex patients
Clinical information systems	Provide timely reminders for providers and patients
	Facilitate individual patient care planning
	Share information with patients and providers to coordinate care
Health system	Measure outcomes and use information to promote effective improvement strategies aimed at comprehensive system change
	Develop agreements that facilitate care coordination within and across organizations

Adapted from Wagner.[56]

Two models of psychoeducation, both delivered in group format to individuals who are well (euthymic), have published manuals and have substantial research support. These programmes, the Barcelona BDs Program[77] (21 sessions over 6 months) and the Life Goals Program[78] (phase I is six weekly sessions), also have tools to aid implementation with workbooks and handout materials, and both are first-line psychoeducational interventions based on level 2 evidence for the prevention of relapse. Individual psychoeducation based on these manuals would probably be effective, and when individual trials utilizing several different approaches to psychoeducation are combined in a meta-analysis, individual psychoeducation of at least five sessions would still be a first-line intervention for relapse prevention, based on level 2 evidence.[75,79,80] One large study demonstrated that the six-session Life Goals Program psychoeducational intervention was equivalent in relapse prevention to 20 sessions of individual CBT, at far lower cost,[81] with probable shared mechanisms.[82] Furthermore, that study demonstrated that integration of best practices in medication and psychotherapy simultaneously produced striking overall improvement in course of illness.[83] Psychoeducation does not have any significant evidence of utility in either acute depressive or manic episodes.

2.6.2 | Cognitive behavioural therapy

CBT in BD is supported by several published manuals and typically is given in 20 individual sessions over 6 months, often with additional booster sessions. Despite evidence of efficacy for CBT for MDD and psychosis, the results of CBT trials for BD have been mixed. One large RCT supports it use for acute bipolar depression[84] in a trial that compared the efficacy of up to 30 (mean 14) CBT sessions against those of FFT, IPSRT, and a three-session control intervention, but it was not possible to identify whether the benefits came from changes in the medications prescribed or the psychosocial treatments. Efficacy of CBT in relapse prevention was observed in one RCT,[85] but not in another larger RCT, at least in patients who had multiple mood episodes.[86] From meta-analyses, effects on either depressive symptoms or on relapse remain uncertain due to important methodological problems and study selection factors.[87-89] A promising new direction in CBT has been established by a pilot study of "recovery-focused CBT" where 33 subjects received the novel CBT intervention, with evidence of reduction of relapse in the intervention group.[90] Group CBT in euthymic patients with BD is also a new direction and has shown to increase time in remission.[91]

In MDD, CBT, interpersonal psychotherapy (IPT) and behavioural activation have been explored in multiple RCTs and in general display similar efficacies.[92] Based on this and the findings of the study by Miklowitz and colleagues in acute bipolar depression,[84] CBT is still recommended as an adjunctive second-line treatment for acute bipolar depression (level 2). The recommendation is also second-line for maintenance treatment (level 2) for patients with fewer episodes and less severe form of illness. No evidence exists, and hence no recommendation is made, for CBT in mania.

TABLE 10 Strength of evidence and recommendations for adjunctive psychological treatments for bipolar disorder[a]

	Maintenance: Recommendation (Level of Evidence)	Depression: Recommendation (Level of Evidence)
Psychoeducation (PE)	First-line (Level 2)	Insufficient evidence
Cognitive behavioural therapy (CBT)	Second-line (Level 2)	Second-line (Level 2)
Family-focused therapy (FFT)	Second-line (Level 2)	Second-line (Level 2)
Interpersonal and social rhythm therapy (IPSRT)	Third-line (Level 2)	Third-line (Level 2)
Peer support	Third-line (Level 2)	Insufficient evidence
Cognitive and functional remediation	Insufficient evidence	Insufficient evidence
Dialectical behavioural therapy (DBT)	Insufficient evidence	Insufficient evidence
Family/caregiver interventions	Insufficient evidence	Insufficient evidence
Mindfulness-based cognitive therapy (MBCT)	Insufficient evidence	Insufficient evidence
Online interventions	Insufficient evidence	Insufficient evidence

[a]See text for specific definitions of type of therapy and number of sessions needed ("dose of psychosocial intervention") corresponding to this recommendation and evidence.

2.6.3 | Family-focused therapy

FFT[93] presumes that outcomes in BD may be enhanced with the support and cooperation of family or significant others, particularly in families characterized by high levels of expressed emotion. FFT focuses on communication styles between patients and their families or marital relationships, with the goal of improving relationship functioning, and is delivered to the family and patient in 21 sessions over 9 months.

For acute bipolar depression in adults, an intensive FFT (up to 30 sessions; mean 14) out-performed a three-session control condition,[94] although this study was limited by the caveats identified for CBT and IPSRT. Given that the original creation of FFT targeted factors related to depression, it may have specific antidepressant activity, which is also suggested by reduced depression relapse in maintenance studies. For relapse prevention, four significant RCTs of varying sizes have been conducted, delivered to a mixed audience of young adults and adolescents.[95] In these studies, FFT demonstrated efficacy in reducing recurrence of new episodes of depression, but not mania. Overall, FFT is recommended as adjunctive second-line treatment for acute depression (level 2) and for maintenance (level 2). No evidence exists, and hence no recommendation is made, for FFT for mania.

2.6.4 | Interpersonal and social rhythm therapy

IPSRT expands on the IPT focus on grief, interpersonal role transition, role dispute, and interpersonal deficits by including regulation of social and sleep rhythms, specifically targeted to the bipolar population. It is typically delivered in 24 individual sessions over 9 months.[96,97]

Few controlled trials of IPSRT have been conducted, with limited evidence of acute efficacy. The first, large trial[98] showed no effect of IPSRT compared to a control condition but did show benefit for reduction of relapse and improved occupational functioning. An acute bipolar depression study[84] showed intensive IPSRT (up to 30 sessions; mean 14) out-performed a three-session control condition, but it is impossible to state whether the performance was related to the intensity and number of sessions, changes in medication use, or specific attributes of IPSRT. Two small studies failed to demonstrate specific benefits of IPSRT compared to control conditions.[99,100] Other open studies have shown some pre-post benefits in very small samples.[101-103] Again, since many psychosocial treatments for bipolar disorder share common core elements that may be psychoeducational, it is possible that the relapse prevention aspects of psychoeducation may also result from IPSRT interventions, mediated by the same therapeutic processes.[104]

Overall, IPSRT is recommended as an adjunctive third-line treatment for acute depression and for maintenance, based on limited (effect size and small sample size) level 2 evidence in each phase. No evidence exists, and hence no recommendation is made, for IPSRT for mania.

2.6.5 | Peer interventions

Peer interventions, such as peer groups or one-on-one support, are an important strategy believed to reduce self-stigma and isolation in BD, and to help improve engagement in treatment.[105] Some caution is needed when applying this strategy, however, as there may be risks if the peers delivering the intervention are not adequately trained or supported, and if they promote a viewpoint that does not support treatment compliance or promotes substance use.

Reviews of peer interventions for persons with serious mental illnesses, usually incorporating a small but significant number of individuals with BD, have demonstrated modest evidence from RCTs and other controlled studies suggesting that there are important improvements in self-efficacy and reduction in self-stigma.[106-109] The largest peer intervention study involving BD allocated 153 individuals to attend 21 weekly group psychoeducation events, with another 151 assigned to attend 21 weekly group peer support events. The two programmes achieved similar outcomes in terms of time to relapse, and increased knowledge about BD, although psychoeducation was more acceptable to the subjects and worked more effectively at preventing relapse in a subset of people with fewer previous episodes.[110]

A significant source of peer support is emerging from online resources, particularly through the websites of peer advocacy organizations such as the Depression and Bipolar Support Alliance (http://www.dbsalliance.org/site/PageServer?pagename=peer_landing), the Mood Disorders Association of Ontario (https://www.mooddisorders.ca/), the research and advocacy group CREST.BD (http://www.crestbd.ca/), MoodSwings (www.moodswings.net.au/), and Revivre (http:/wwww.Revivre.org). YouTube is also emerging as an important source of peer support, along with other social media.[111,112]

Overall, peer interventions receive a third-line treatment recommendation (level 2) as an adjunctive maintenance therapy.

2.6.6 | Other psychosocial interventions

Various other approaches have been tried in BD, with a variety of aims, modalities, and outcome targets. None of the other interventions have been specifically targeted for bipolar depression or for mania. Some have been designed in part to reduce episode recurrence, but none have been successful in providing substantial evidence of efficacy. Because CANMAT recommendations are for the treatment of acute depression and mania, and maintenance treatment to prevent them, we do not make specific recommendations regarding these treatments. However, some of these approaches have been helpful in ameliorating some important symptoms in individuals with BD, (such as residual mood symptoms or anxiety) and so we will describe them briefly.

Although somewhat like FFT, family/caregiver interventions constitute a distinctly different psychosocial intervention in that the intervention is given to the family/caregiver, not the person with BD, and evidence exists that such interventions improve clinical outcomes in the patient.[75,113] Clinical wisdom and common practice, however, support the importance of family or caregivers being included in at least some sessions with the patient (particularly for psychoeducation), both to reduce symptom burden on the individual with BD and to reduce burnout and emotional burden on the caregiver. Validated caregiver resources are available online, such as www.bipolarcaregivers.org.[114]

DBT, which includes distress tolerance training, has several small studies showing its utility in the reduction of some depressive symptoms and suicidality.[75]

One RCT of MBCT involving 95 patients did not demonstrate any difference in relapse prevention compared to a treatment-as-usual group, but did reveal fewer anxiety and depressive symptoms in the MBCT arm.[115] Coupled with the findings of other smaller studies, this suggests that MBCT may have a role to play in anxiety reduction in BD.[75,116]

While not reviewed here, given that individuals with BD may have histories of childhood abuse and comorbid personality disorders, and experience various sequelae such as shame or conflict due to behaviours experienced during acute bipolar episodes, all of these may rightly be a target for psychosocial intervention in a very individualized manner.

2.6.7 | Cognitive and functional remediation

Functional impairment as well as cognitive deficits are found in many individuals with BD, not just during an acute episode but even between episodes, prompting the evaluation of various psychosocial and biological strategies to address these problems. One intervention, functional remediation (FR), involves a 21-session group intervention over 6 months. In a large RCT, FR was shown to have a substantial impact on functioning, in comparison to treatment as usual.[117] Coupled with the results of other small studies involving other interventions, these findings suggest that there is considerable hope in addressing cognitive and functional deficits in BD.[118] Computer-based cognitive remediation, though, may show positive effects on cognition but not on functioning.[119]

2.6.8 | Online and digital strategies

Modern trends to rely on the internet and apps, along with access problems in mental health, have led to the study of various online tools and mobile phone apps.[120] Such strategies also build on strong traditions of self-monitoring and self-management developed formally in traditional psychoeducational interventions. In reviews, such internet and mobile health interventions have shown good adherence to validated psychological health principles, good acceptability to patients, ease of access, and ease of use. However, research is mostly limited to pilot studies and the relatively few larger studies have not shown unequivocal benefit.[68,121]

3 | ACUTE MANAGEMENT OF BIPOLAR MANIA

3.1 | Presentations of mania

DSM-5[5] made a change to "criterion A" for mania which now requires a distinct period of abnormally and persistently elevated, expansive, or irritable mood *and* abnormally and persistently increased activity or energy present most of the day, nearly every day for at least 1 week (or less time if hospitalization is necessary). In addition, a diagnosis of a "manic episode" requires at least three (or four if the mood is only irritable) of the following symptoms: inflated self-esteem or grandiosity, decreased need for sleep, more talkative than usual or pressure of speech, flight of ideas or subjective experience that thoughts are racing, distractibility, increased goal-directed activity or psychomotor agitation, or excessive involvement in activities with a high potential for painful consequences. The mood disturbance must lead to marked impairment in functioning, require hospitalization, or be accompanied by psychotic features.

Unlike DSM-IV, DSM-5 allows a diagnosis of BDI in patients with major depression whose mania emerges during treatment (eg, during medication or electroconvulsive therapy [ECT]) and persists at a fully syndromal level beyond the physiological effect of the treatment.

DSM-5 has eliminated the categorical "mixed episode" specifier, replacing it with the more dimensional "mixed features". DSM-5 also

includes other specifiers that can accompany a manic episode: anxious distress, rapid cycling, mood-congruent or mood-incongruent psychotic features, catatonia, peripartum onset, and seasonal pattern (Table 5). The utility of several of these specifiers in selecting treatment options for mania is discussed later in this section (see "Clinical features that help direct treatment choice").

3.2 | Management of agitation

Agitation is common in mania, and is particularly frequent in patients who have mixed features.[122] Defined in DSM-5 as "excessive motor activity associated with a feeling of inner tension",[5] agitation can manifest as pacing or fidgeting in mild cases to uncooperative, threatening, or aggressive behaviours in severe cases. Severe symptoms of agitation require prompt attention in order to reduce distress, mitigate potentially dangerous behaviour, and allow for an assessment and evaluation of underlying manic symptoms.[123]

A key step in treating agitation is preventing it, or at least mitigating its severity, by rapidly treating the causative manic episode. When addressing agitation in patients with BDI, clinicians need to be aware that akathisia may present as agitation and, therefore, this must be excluded before implementing the general principles of management of acute mania described in step 1 (see "Pharmacological treatment of manic episodes"). Since agitation in this context is a manifestation of mania, it is assumed that effective interventions for treating mania that have rapid onset of efficacy would be effective in reducing agitation. Therefore, if the patient is agreeable to taking oral medications, antimanic agents with rapid onset of efficacy should be considered first.

When agitation persists despite administration of antimanic treatments, additional rapidly acting pharmacotherapy may often be needed. The evidence for specific efficacy of various agents in short-term treatment of agitation is summarized in Table 11. Some of these agents are either not available or rarely used in North America (eg, midazolam and promethazine). We further note that the dose ranges in Table 11 are based on the doses studied in the trials, and would probably be appropriate in most situations. However, a comprehensive evaluation of the agitated patient is necessary (ie, medical conditions, treatments, drugs, intoxication, etc.) to determine a safe and adequate dose.

As can be seen from Table 11, the highest level of evidence available in short-term treatment of agitation for oral formulations of any agent is level 3, and level 2 for intramuscular (IM) or inhaled formulations. In this context, it is important to remember that the absence of evidence does not constitute lack of efficacy. Indeed, clinical experience suggests that agitation in many patients with acute mania responds well to the oral medications. Thus, a loading dose of divalproex, oral formulations of atypical antipsychotics, conventional antipsychotics such as haloperidol or loxapine, and/or benzodiazepines such as lorazepam may be appropriate. If a patient indicates willingness to take oral treatment but there is a suspicion that the patient might "cheek" the medication, then either orally dispersing tablets (ODT), those that rapidly melt, oral liquid, or oral inhalation forms should be considered. In countries where inhaled loxapine is available, this could be considered if there are no contraindications.

If oral preparations are ineffective or if the agitation is severe and if the patient is refusing oral medications, or when oral therapy cannot be safely or reliably administered, then IM formulations should be considered.[124] Because of the strength of evidence for efficacy in alleviating agitation in this population, aripiprazole IM (level 2),[125,126] lorazepam IM (level 2),[125,127] loxapine inhaled (Level 1)[128,129] and olanzapine IM (level 2)[127,130-133] are recommended as the first-line option. Sublingual asenapine (level 3),[134] haloperidol IM (level 3),[131,135,136] haloperidol IM + midazolam IM (level 3),[131,137] haloperidol IM + promethazine IM (level 3),[131,137,138] risperidone ODT (level 3),[136] and ziprasidone IM (level 3)[131,137,139] are recommended as a second-line treatment. Haloperidol per os (PO) (level 4),[140,141] loxapine IM (level 4) (clinical opinion), quetiapine PO (level 4),[141] and risperidone PO (level 4)[140] are included as third-line options (Table 11).

3.3 | Pharmacological treatment of manic episodes

There are a range of strategies that have been investigated for use in mania; including lithium, divalproex, other anticonvulsants, typical and atypical antipsychotics, and other agents and therapies. These treatments have been evaluated using the criteria for strength of evidence for efficacy (Table 1) as well as safety and tolerability (Section 8). The evidence for efficacy and the recommendations for treating acute mania are summarized in Table 12.

As stated previously, the first and second-line agents are listed hierarchically taking into consideration not only their efficacy for acute mania but also their efficacy in preventing mania or depression, treating acute bipolar depression, safety/tolerability and the risk of treatment-emergent switch. The implication of this hierarchical recommendation is that those listed higher up in the table should be considered first before moving on to the next on the list, unless other factors such as history of previous non-response or patient's preferences preclude such strategy in a given patient.

Monotherapy and combination therapy are listed separately as first-line treatments for acute mania in Table 12. This does not mean that all monotherapy agents should be tried first before considering combination therapy for acute mania. We suggest that the treating clinician make a decision as to whether to treat a given patient with monotherapy or combination therapy. That decision is typically based on the rapidity of response needed (eg, combination treatments tend to work faster), whether the patient had a previous history of partial response to monotherapy, severity of mania, tolerability concerns with combination therapy, and willingness of the patient to take combination therapy. Once a decision is made whether to treat the patient with monotherapy or combination therapy, then hierarchy related to monotherapy or combination therapy could be followed. We also suggest that clinicians evaluate the efficacy and tolerability at the end of weeks 1 and 2 and modify treatment options accordingly.

TABLE 11 Level of evidence and recommendations for short-term pharmacological management of agitation[a]

Level of recommendation	Agent	Formulation	Level of evidence	Dose range of studies[b]	
				Single dose	Max/24 h
First-line	Aripiprazole	IM	2	9.75 mg	15 mg
	Lorazepam	IM	2	2 mg IM	
	Loxapine	Inhaled	1	5 mg	10 mg
	Olanzapine	IM	2	2.5 mg	10 mg[c]
Second-line	Asenapine	Sublingual	3	10 mg	
	Haloperidol	IM	3	5 mg	15 mg
	Haloperidol + midazolam	IM	3	2.5 mg (haloperidol) + 7.5 mg (midazolam)	5 mg (haloperidol) + 15mg (midazolam)
	Haloperidol + promethazine	IM[e]	3	2.5 mg (haloperidol) + 25 mg (promethazine)	5 mg (haloperidol) + 50 mg (promethazine)
	Risperidone	ODT[e]	3	2 mg	4 mg
	Ziprasidone	IM[e]	3	2 mg	20 mg
Third-line	Haloperidol	PO[d]	4	5 mg	15 mg
	Loxapine	IM	4	N/A	
	Quetiapine	PO[d]	4	Mean (SD) = 486.7 (317.2) mg/day	
	Risperidone	PO[e]	4	2 mg	

[a]See text for recommendations about use of oral antipsychotics and divalproex. IM, intramuscular; ODT, orally disintegrating tablet; PO, per os.
[b]Doses are reported as per studies.
[c]26.3% received two or three 10 mg injections.
[d]Assessed 2 h after the dose.
[e]Doses are not specifically for bipolar disorder but included schizophrenia or other diagnoses.

3.3.1 | Step 1: review general principles and assess medication status

Examination of a patient presenting in a manic state should include an immediate assessment for risk of aggressive behaviour, violence and safety threat to others, suicide risk especially in those with mixed features, degree of insight and the ability to adhere to treatment, comorbidity (including substance use that may be aggravating or contributing to clinical presentation), and availability of a psychosocial support network. A physical examination with laboratory investigations (described in Section 8) should be conducted, but may be deferred for patients who are uncooperative. Results of the overall assessment should be used to establish the most appropriate treatment setting (eg, ambulatory or inpatient).

Before initiating pharmacological treatment for a manic episode, it is imperative to rule out symptoms secondary to drugs of abuse, medications, other treatments, or a general medical or neurological condition (although, even in these cases, symptomatic treatment may be applied on a short-term basis). Steps should be taken to rule out any other factors that may be perpetuating symptoms such as prescribed medication, illicit drug use/abuse or an endocrine disorder. Any patients presenting with mania who have been taking antidepressants should have these medications discontinued. If there is a previous diagnosis of BD, it is appropriate to immediately commence antimanic agents. If this is the first emergence of manic symptoms, clinicians are advised to confirm the diagnosis of BD by monitoring patients for a period of time after antidepressant discontinuation and obtain collateral information to confirm whether symptoms remain and antimanic treatment is necessary. Patients should also be supported to discontinue stimulant use, including caffeine and alcohol. Current and prior therapies should be assessed, including appropriateness of medications, dosing, and trough serum levels (where indicated), as well as past response; and this should be used to direct subsequent therapeutic choices. Attention should be paid to managing withdrawal symptoms that may occur in manic patients with histories of substance abuse.

When the symptoms of mania have remitted, behavioural and educational strategies should be applied to promote ongoing medication adherence, reduce residual symptoms, help identify early signs of relapse, and support functional recovery (see Section 2).

3.3.2 | Step 2: initiate or optimize therapy and check adherence

It is recommended that, for all patients (including those who are untreated as well as those receiving a non-first-line treatment), therapy be initiated with one of the available first-line monotherapy or combination treatments.

First-line monotherapy

Approximately 50% of patients will respond to monotherapy with significant improvement in manic symptoms within 3-4 weeks.[142]

TABLE 12 Hierarchical rankings of first and second-line treatments recommended for management of acute mania

	Level of evidence by phase of treatment					Considerations for treatment selection				
		Maintenance				Acute		Maintenance		
	Acute mania	Prevention of any mood episode	Prevention of mania	Prevention of depression	Acute depression	Safety concerns	Tolerability concerns	Safety concerns	Tolerability concerns	Risk of depressive switch
First-line treatments: Monotherapies										
Lithium	●	●	●	●	◔	+	+	++	++	–
Quetiapine	●	●	●	●	●	+	++	++	++	–
Divalproex	●	●	◑	◔	◔	–	+	++[e]	+	–
Asenapine	●	◔	◔	◔	n.d.	–	+	–	+	–
Aripiprazole	●	◔	◔	n.d.[a]	■	–	+	–	+	–
Paliperidone (>6 mg)	●	◔	◔	n.d.[a]	n.d.	–	+	+	++	–
Risperidone	●	◔	◔	n.d.	n.d.	–	+	+	++	–
Cariprazine	●	n.d.	n.d.	n.d.	●	–	+	–	–	–
First-line treatments: Combination therapies										
Quetiapine + Li/DVP	●	●	●	●	◔[c]	+	++	+++[e]	++	–
Aripiprazole + Li/DVP	◔	◔	◔	n.d.[b]	◔	+	+	++[e]	++	–
Risperidone + Li/DVP	●	◔	◔	n.d.	◔	+	++	+++[e]	++	–
Asenapine + Li/DVP	◔	◔	◔	n.d.	◔	+	+	++[e]	+	–
Second-line treatments: Combination therapies										
Olanzapine	●	●	●	●	●[d]	+	++	+++	++	–
Carbamazepine	●	◔	◔	◔	◑	++	+	++[e]	++	–
Olanzapine + Li/DVP	●	◔	◔	◔	n.d.	+	++	+++[e]	++	–
Lithium + DVP	◑	◑	◑	n.d.	n.d.	+	++	++	++	–
Ziprasidone	●	◔	◔	n.d.	■	++	++	++	+	–
Haloperidol	●	n.d.	◔	◪	n.d.	+	++	+++	++	++
ECT	◑	◔	◔	◔	◔	+	++	+	++	–

DVP, divalproex; ECT, electroconvulsive therapy; Li, lithium.

●, level 1 evidence; ◔, level 2 evidence; ◑, level 3 evidence; ◴, level 4 evidence; ■, level 1 negative evidence; ◪, level 2 negative evidence; ◧, level 3 negative evidence; ◪, level 4 negative evidence; n.d., no data; –Limited impact on treatment selection; +, minor impact on treatment selection; ++, moderate impact on treatment selection; +++, significant impact on treatment selection.

[a]Although monotherapies are listed above combination therapies in the hierarchy, combination therapies may be indicated as the preferred choice in patients with previous history of partial response to monotherapy and in those with psychotic mania or in situations where rapid response is desirable.

[b]Did not separate from placebo in those with index mania; no studies available in index depression.

[c]No controlled trials; however, clinical experience suggests that it is a useful strategy.

[d]Did not separate from placebo on core symptoms of depression.

[e]Divalproex and carbamazepine should be used with caution in women of childbearing age.

[Colour table can be viewed at wileyonlinelibrary.com]

Lithium (level 1), quetiapine (level 1), divalproex (level 1), asenapine (level 1), aripiprazole (level 1), paliperidone (level 1 for doses >6 mg), risperidone (level 1), and cariprazine (level 1) are all recommended as first-line treatment options. Overall, these agents show comparable efficacy (Cohen's *d* 0.32-0.66; small to medium effect size).[143]

Although they have comparable efficacy for treating acute mania, we recommend that the agents listed first in the text and placed higher in Table 12 be tried first, in the order listed, unless there are patient-specific reasons for choosing an agent lower down in the order (see "Clinical features that help direct treatment choices"). For instance, lithium should be considered first for acute mania unless there are specific reasons not to, such as mixed features, comorbid substance use or previous non-response to lithium.

Carbamazepine, olanzapine, ziprasidone and haloperidol also have level 1 evidence for efficacy but they are downgraded to second-line options due to safety/tolerability risks with these agents.

First-line combination therapy

Combination therapy with the atypical antipsychotics quetiapine (level 1), aripiprazole (level 2), risperidone (level 1), or asenapine (level 2) and lithium or divalproex is also recommended as first-line treatment options with greater efficacy than monotherapy with lithium or divalproex alone, especially in those with higher index severity.[144]

In general, combination therapy is preferred to mood stabilizer monotherapy because clinical trials suggest that on average about 20% more patients will respond to combination therapy.[142,145,146] There is also some evidence to suggest the benefit of combination therapy compared to atypical antipsychotic monotherapy, although there are fewer trials. Specifically, lithium plus quetiapine showed superiority to quetiapine alone.[147] While there is also level 1 evidence for olanzapine combination therapy over olanzapine monotherapy, this is downgraded to second-line due to tolerability/safety concerns with olanzapine.

The decision to treat with one or a combination of available first-line agents should be informed by current and prior medication use, with treatment previously shown to be successful in managing symptoms preferred. Safety and tolerability factors for each medication and clinical features predictive of better response (see "Clinical features that help direct treatment choices") should also be considered. In general, combination therapy is associated with more adverse events than monotherapy. Whenever possible, options should be discussed with the patient and/or their caregiver and their preferences considered prior to treatment selection.

If symptoms are not controlled using monotherapy or combination therapy with first-line agents, dosing should be optimized, issues of non-adherence identified and addressed, and consideration given to possible substance use (Section 4) prior to adding or switching therapies (Step 3). Given that almost all antimanic agents separated from placebo within 1 week, some therapeutic response is expected with antimanic agents within 1-2 weeks. If no response is observed within 2 weeks with therapeutic doses of antimanic agents, and other contributing factors for non-response are excluded, then switch or add-on strategies should be considered.

3.3.3 | Step 3: add on or switch therapy (alternate first-line agents)

If therapy with one or a combination of the first-line agents (lithium, divalproex and/or an atypical antipsychotic) at optimal doses is inadequate or not tolerated, the next step is to switch to or add on an alternate first-line agent. An exception is that, despite level 1 evidence for monotherapy with paliperidone and ziprasidone, we do not recommend combination therapy with these agents due to lack of evidence for additional efficacy (see "No specific recommendation/agents that require further study" below). Because there are multiple first-line agents with substantial efficacy data and relative safety and tolerability, the use of second- and third-line agents is only recommended after unsuccessful trials of multiple first-line strategies.

3.3.4 | Step 4: add on or switch therapy (second-line agents)

Second-line

In patients who are inadequately responsive to first-line agents, second-line choices include monotherapy with olanzapine (level 1), carbamazepine (level 1), ziprasidone (level 1), and haloperidol (level 1)[143] or combination therapy with olanzapine plus lithium or divalproex (level 1). While each of these strategies has strong support for their efficacy, as indicated above, safety and tolerability concerns relegate them to second-line options. Although widely used in clinical practice, the combination of lithium and divalproex is also recommended as a second-line choice, as evidence supporting its efficacy is limited to uncontrolled trials (level 3).[148-151]

ECT is also recommended as a second-line option (level 3)[152] and, although the number of controlled trials is limited, there is evidence to suggest that up to 80% of patients will show marked clinical improvements.[153] Brief pulse therapy with two or three treatments per week has been used. Bifrontal electrode placement is preferred over bitemporal as it is associated with faster treatment response and fewer cognitive side effects.[154-156]

When all first-line agents have failed, the hierarchy should be applied to second-line agents as well. Hence, olanzapine, which is highest in the hierarchy amongst second-line agents, should be first choice before moving down the list in Table 12.

3.3.5 | Step 5: add on or switch therapy (third-line agents)

Third-line

Agents recommended as third-line options for treatment of acute mania include monotherapy with chlorpromazine (level 2),[157] monotherapy with clonazepam (level 2),[158] monotherapy or adjunctive therapy with clozapine (level 4),[159-162] and monotherapy with tamoxifen (level 2).[143] Tamoxifen is downgraded because of the risk of uterine cancer and the lack of clinical experience despite evidence for efficacy. Combination treatments with carbamazepine or oxcarbazepine (level 3),[163] haloperidol (level 2),[144,164] or tamoxifen (level 2)[165] plus lithium or divalproex are

TABLE 13 Additional agents evaluated for use in acute mania

	Agent	Level of evidence
Third-line	Carbamazepine/oxcarbazepine + Li/DVP	Level 3
	Chlorpromazine	Level 2
	Clonazepam	Level 2
	Clozapine	Level 4
	Haloperidol + Li/DVP	Level 2
	rTMS	Level 3
	Tamoxifen	Level 2
	Tamoxifen + Li/DVP	Level 2
Not recommended	Allopurinol	Level 1 negative
	Eslicarbazepine/licarbazepine	Level 2 negative
	Gabapentin	Level 2 negative
	Lamotrigine	Level 1 negative
	Omega-3 fatty acids	Level 1 negative
	Topiramate	Level 1 negative
	Valnoctamide	Level 2 negative
	Zonisamide	Level 2 negative

DVP, divalproex; Li, lithium; rTMS, repetitive transcranial magnetic stimulation.

also included as third-line. Repetitive transcranial magnetic stimulation (rTMS) in the right prefrontal cortex at 110% motor threshold (level 3)[166] can also be considered in combination with pharmacotherapy.

The third-line agents should only be used if a patient has not responded to adequate trials with all first and second-line agents alone and in combination. Given that the evidence is very limited for third-line agents, it was not possible to list them in any hierarchical order and they are thus listed alphabetically (Table 13).

3.3.6 | Agents not recommended for the treatment of acute mania

Antimanic efficacy has not been demonstrated for allopurinol (level 1 negative),[167] eslicarbazepine/licarbazepine (level 2 negative),[168] gabapentin (Level 2 negative), lamotrigine (level 1 negative),[143] omega-3 fatty acids (level 1 negative),[169] topiramate (level 1 negative),[143] valnoctamide (level 2 negative),[170,171] or zonisamide (level 2 negative)[172] (Table 13).

3.3.7 | No specific recommendation/agents that require further study

Trials with paliperidone (level 2 negative) and ziprasidone (level 2 negative) adjunctive therapy to lithium or divalproex showed lack of efficacy.[144] This is surprising given that all other atypical antipsychotic agents that showed efficacy in monotherapy have also been shown to offer additional benefit when combined with lithium or divalproex. It is likely that methodological problems have contributed to failure in these studies; hence, further studies are needed before specific recommendations can be made about the use of these combinations for mania.

Studies of olanzapine (level 2 negative) [173] or risperidone (level 3 negative)[174] plus carbamazepine have been negative, although this is probably due to enzyme-inducing effects of carbamazepine. While this may be overcome by dosing adjustments, because such interactions are unpredictable and effective doses have not been established, we are unable to provide a specific recommendation.

Nutraceuticals such as branched chain amino acids (level 3),[175] folic acid (level 2),[176] and L-tryptophan (level 3),[177] as well as other experimental agents such as medroxyprogesterone (level 3),[178,179] memantine (level 4),[180] mexiletine (level 4),[181] levetiracetam (level 4)[182] and phenytoin (level 3),[183] have all shown indications of efficacy when used adjunctively with other antimanic agents, as have glasses that block blue light (level 3).[184] Larger controlled trials are needed, however, before a recommendation for their use in mania can be made. While an initial small RCT did not show anti-manic efficacy for verapamil,[185] there is some evidence that it may work as an adjunctive therapy (level 4)[186] or as monotherapy in women (level 4).[187] Larger studies are needed before a conclusion can be made.

3.3.8 | Clinical features that help direct treatment choices

Clinical features, including DSM-5 specifiers, may assist in making treatment choices between first and second-line treatment options.

In general, lithium is preferred over divalproex for individuals who display classical euphoric grandiose mania (elated mood in the absence of depressive symptoms), few prior episodes of illness, a mania-depression-euthymia course,[188-190] and/or those with a family history of BD, especially with a family history of lithium response. Divalproex is equally effective in those with classical and dysphoric mania. Further, divalproex is recommended for those with multiple prior episodes, predominant irritable or dysphoric mood and/or comorbid substance abuse or those with a history of head trauma.[188,191-195] Because of its teratogenic potential, however, caution should be exercised when prescribing divalproex to women of childbearing age. Patients with specific factors such as a history of head trauma, comorbid anxiety and substance abuse, schizoaffective presentations with mood-incongruent delusions, or negative history of bipolar illness in first-degree relatives may respond to carbamazepine.[196]

Combination therapy with lithium or divalproex and an atypical antipsychotic is recommended when a response is needed faster, in patients judged at risk, who have had a previous history of partial acute or prophylactic response to monotherapy or in those with more severe manic episodes.[145]

Anxious distress

Symptoms of anxiety frequently co-occur during a manic episode, and are a predictor of poor outcome; including greater severity of manic symptoms,[197] a longer time to remission,[197,198] and more reported side effects of medication.[198] There have been no studies specifically examining the efficacy of any agents in reducing symptoms of anxiety during a manic episode, although these symptoms do tend to improve concurrently with mood disturbance. Post hoc analyses suggest that

divalproex, quetiapine, and olanzapine may have specific anxiolytic benefits[199] and carbamazepine may be useful as well.[196]

Mixed features

Depressive symptoms co-occur alongside mania in 10%-30% of cases,[200,201] with studies suggesting mixed features are indicative of a more severe and disabling course, as well as a higher rate of suicide.[201,202] Evidence supports the preferential use of atypical antipsychotics and divalproex in these cases, with combination therapy frequently required.[195,203] Atypical antipsychotics such as asenapine, aripiprazole, olanzapine and ziprasidone have been shown to be equally effective in treating manic symptoms in those with classical mania as well as in mixed mania or in manic patients with mixed features.[196,204,205]

Psychotic features (mood congruent or incongruent)

At least half of manic episodes are characterized by the presence of psychosis,[206] and theories suggest that it is a nonspecific feature which improves alongside underlying manic symptoms.[207] While the prognosis for patients experiencing mood-congruent psychotic features may not differ from those with an absence of psychotic symptoms, limited evidence does suggest that those with mood-incongruent features have a more severe illness with poorer long-term prognosis.[207-212] There is no evidence of superiority of any first-line monotherapy treatment in comparison to other monotherapy options in treating patients with psychotic features. Similarly, there is no evidence that any first-line combination therapy of lithium or divalproex plus an atypical antipsychotic is more effective than other first-line combination therapy.[174,193,213,214] However, clinical experience suggests that the combination of lithium or divalproex plus an atypical antipsychotic is more appropriate for manic patients with mood-incongruent psychotic features (ie, other than grandiose delusions). Similarly, in patients where the diagnostic possibility of schizoaffective disorder with manic symptoms is considered, either use of an atypical antipsychotic or combination of an atypical antipsychotic with a mood stabilizer is more appropriate.

Rapid cycling

Rapid cycling, or a course of illness that includes four or more mood episodes a year, affects up to one-third of patients with BDI.[215-218] Hypothyroidism, antidepressant use and substance abuse are often associated with rapid cycling; thus assessing thyroid function and discontinuation of antidepressants, stimulants, and other psychotropic agents that are contributors to cycling are imperative. Consideration should be given to gradually withdrawing substances in order to prevent withdrawal, but this needs to be balanced against the severity of mood cycling and the need for rapid mood stabilization. As there is no evidence for the superiority of any first-line treatment in addressing acute manic symptoms in patients with a rapid cycling course,[219] appropriate pharmacotherapy should be selected primarily based on effectiveness in the maintenance phase, if known (see Section 5). It is likely that combinations of mood-stabilizing drugs may be more often necessary than monotherapies when rapid cycling is present,[220] but triple mood stabilizer therapy has not demonstrated superiority to double mood stabilizer therapy in a single RCT,[221] although methodological weaknesses probably limited interpretability of the findings.

Seasonal pattern

While some individual patients may show a seasonal pattern, Canadian data are mixed as to whether episodes of mania or depression in BD follow a consistent seasonal variation.[222] There is no evidence for the superiority of any agent in patients with an observed seasonal pattern of manic episodes.

4 | ACUTE MANAGEMENT OF BIPOLAR DEPRESSION

4.1 | Presentations of bipolar depression

The DSM-5 criteria for bipolar depression are unchanged from DSM-IV. Depression is characterized by a minimum of 2 weeks of depressed mood and/or anhedonia and at least four other symptoms that include changes in sleep, appetite/weight, energy, psychomotor activity, concentration, thought content (guilt and worthlessness), and suicidal intent. For many patients with BD, the depressive polarity is often more pervasive and more debilitating than manic states, with estimates that depressed mood accounts for up to two-thirds of the time spent unwell, even with treatment.[12,223,224] Subsyndromal depressive symptoms, which persist despite treatment, are particularly common and a major source of functional impairment in these patients.[225-229] They should be treated aggressively.

DSM-5 includes several specifiers that may accompany depressive episodes: anxious distress, mixed features, rapid cycling, melancholic features, atypical features, mood-congruent or mood-incongruent psychotic features, peripartum onset, and seasonal pattern (Table 5). The utility of several of these specifiers in selecting treatment options for depression is discussed later in this section (see "Clinical features that help direct treatment choices").

4.2 | Diagnostic and treatment challenges

4.2.1 | Misdiagnosis and delayed diagnosis

Patients with depression occurring in the context of BD are frequently misdiagnosed as having MDD, since the presence of mania or hypomania (particularly mild or moderate episodes which do not require hospitalization) may be challenging to establish retrospectively. This is especially true in the absence of a comprehensive diagnostic interview or collateral information, as patients may often lack basic knowledge of what hypomania/mania is, and/or have limited insight into these symptoms; and thus may not disclose this information unless specifically asked. Alternatively, patients who will ultimately present with hypomanic or manic episodes may only have experienced episodes of depression. Thus, clinicians must be vigilant for a diagnosis of BD, and routinely ask for symptoms of a previous manic/hypomanic episode in every patient presenting

with a major depressive episode. A diagnosis of MDD should be made only after excluding the possibility of BD.

In addition to overt manic/hypomanic symptoms, there are numerous features that increase the likelihood of a diagnosis of BD in depressed individuals. These include earlier age of illness onset (before 25 years), brief, highly recurrent depressive episodes, a family history of BD, depression with psychotic features, atypical features such as reverse vegetative symptoms of hypersomnia and hyperphagia, leaden paralysis, psychomotor agitation, postpartum depression or psychosis, and antidepressant-induced irritability, manic symptoms or rapid cycling[38,39] (Table 6).

Individuals with depression who are at high risk for BD, particularly those with a strong family history of BD, should be closely monitored for emergence of manic or mixed symptoms. Consideration should also be given to applying the BD depression treatment recommendations amongst those at very high risk, rather than risk potential iatrogenic effects of antidepressant monotherapy, although this recommendation is based on clinical experience as there is a lack of sufficient research addressing this issue. As discussed in Section 2, there are also several useful psychosocial interventions, such as individual and family psychoeducation and FFT, that have been shown to have some benefit in this population.

4.2.2 | Suicide risk

Principles related to management of suicidal ideation and risk (see Section 2 and[47]) are of utmost importance during depressive episodes, as >70% of suicide deaths and suicide attempts in patients with BD occur during this phase.[230,231] Depressive episodes with mixed features are a particularly dangerous period associated with even higher short-term risks of suicide attempts or death.[232] Overall, it is imperative for clinicians to review risk factors (Table 9) and determine an appropriate treatment setting to address any safety issues. All patients at risk should be encouraged to develop and share a written safety plan listing coping strategies and sources of support which may be applied during times of crisis. As described in Section 2, the most common method of suicide in this population is self-poisoning, and so potential benefits of various treatments should be considered against their risk of toxicity and lethality. One study found that there were fewer deaths due to lethal lithium levels compared to carbamazepine, and that opioids and benzodiazepines were the most common medication classes ingested at lethal levels—noteworthy given the lack of efficacy of these agents in the disorder.[55]

4.2.3 | Cognitive and functional impairment

Part of the impact of acute and subsyndromal depressive symptoms on functional impairment is thought to be mediated through cognitive performance, which is both subjectively and objectively impaired in bipolar depression and linked to poor psychosocial function.[233-236]

Because of the important link between cognition and functioning,[237] attention should be paid to avoiding treatments that may further exacerbate cognitive difficulties[238] (see Section 8). Although evidence for their efficacy is limited, cognitive enhancement therapies can be considered experimental in this population.[72,239,240]

4.3 | Psychological interventions for acute bipolar I depression

While pharmacotherapy is essential and forms the foundation for successful treatment of BD, adjunctive psychosocial interventions may also be useful for acute depressive episodes. As described in Section 2, there are no first-line psychosocial treatment options for acute bipolar depression. Selecting between second-line options such as CBT (level 2) and FFT (level 2), as well as the third-line option IPSRT (level 3), should be based on individual strengths and needs.

4.4 | Pharmacological treatment for acute bipolar depression

Lithium, anticonvulsants, atypical antipsychotics, and other agents such as antidepressants have all been investigated for efficacy in managing bipolar depression. These treatments have been evaluated using the criteria for strength of evidence for efficacy (Table 1) as well as safety and tolerability (Section 8). Recommendations are summarized in Table 14.

4.4.1 | Step 1: review general principles and assess medication status

Examination of a patient presenting in a depressed state should include an assessment of the nature and severity of depression and associated symptoms, risk of suicide/self-harm behaviour, ability to adhere to a treatment plan, availability of a psychosocial support network, and functional impairment. Laboratory investigations (described in Section 8) should also be completed. Results of the overall assessment should be used to establish the most appropriate treatment setting (eg, ambulatory or inpatient), with consideration given to management of safety risks. Before initiating pharmacological treatment for a depressive episode, it is imperative to rule out symptoms secondary to alcohol/drug use, medications, other treatments, or a general medical condition. Patients should be supported to discontinue stimulant use and limit nicotine, caffeine, drug, and alcohol use. Course of illness and treatments used in current and prior episodes should be assessed, including past response to and tolerability of specific medications and doses, and used to direct subsequent therapeutic choices. Consideration should be given to restarting medications if their recent discontinuation appeared to coincide with a depressive relapse.

Psychoeducation and other psychosocial strategies should also be offered alongside pharmacological treatment to promote ongoing medication adherence, reduce residual symptoms and suicidal behaviour, help identify early signs of relapse, and support functional recovery (see Section 2).

TABLE 14 Hierarchical rankings of first and second-line treatments recommended for management of acute bipolar I depression

	Level of evidence by phase of treatment					Considerations for treatment selection				
		Maintenance				Acute		Maintenance		
	Acute depression	Prevention of any mood episode	Prevention of depression	Prevention of mania	Acute mania	Safety concerns	Tolerability concerns	Safety concerns	Tolerability concerns	Risk of manic/ hypomanic switch
First-line treatments										
Quetiapine	●	●	●	●	●	+	++	++	++	–
Lurasidone + Li/DVP	●	◐[a]	◐[b]	◔[c]	n.d.	+	++	++[d]	++/+	–
Lithium	◔	●	●	●	●	+	+	++	++	–
Lamotrigine	◔	●	●	◔	■	++	–	–	–	–
Lurasidone	◔	◔	◔	◔	n.d.	–	+	–	+	–
Lamotrigine (adj)	◔	◔	◔	◔	◪	++	+	++	++	–
Second-line treatments										
Divalproex	◔	●	◔	◐	●	–	+	++[d]	+	–
SSRIs/bupropion (adj)	●	n.d.	◔	n.d.	n.d.	–	+	–	+	+
ECT	◔	◔	◔	◔	◐	+	++	+	++	–
Cariprazine	●	n.d.	n.d.	n.d.	●	–	+	–	–	–
Olanzapine-fluoxetine	◔	n.d.	n.d.	n.d.	n.d.	+	++	+++	+	+

adj, adjunctive; DVP, divalproex; ECT, electroconvulsive therapy; Li, lithium, SSRIs, selective serotonin reuptake inhibitors.

●, level 1 evidence; ◔, level 2 evidence; ◐, level 3 evidence; ◴, level 4 evidence; ■, level 1 negative evidence; ◪, level 2 negative evidence; ◧, level 3 negative evidence; ◰, level 4 negative evidence; n.d., no data; –, limited impact on treatment selection; , minor impact on treatment selection; ++, moderate impact on treatment selection; +++, significant impact on treatment selection.

[a]Trend for superiority on the primary efficacy measure, hence the lower rating.

[b]Effective in those with an index episode of depression.

[c]Negative data from the trial are probably due to methodological issues; rating based on expert opinion.

[d]Divalproex and carbamazepine should be used with caution in women of child bearing age.

[Colour table can be viewed at wileyonlinelibrary.com]

Why are lithium and lamotrigine recommended as first-line agents for bipolar depression?
Reconciling conflicting data

Lithium

In the only large double blind placebo controlled trial conducted to date, lithium was not more effective than placebo for treating acute bipolar depression(254). So, how does one justify recommending lithium as a first-line agent?

The mean serum lithium levels in this study was only 0.61 mEq/L and this may account for lack of efficacy as a previous study demonstrated that lithium monotherapy was as effective as lithium plus paroxetine in those with serum lithium levels of ≥0.8 mEq/L (247).

Further, several small crossover trials demonstrated significantly higher response rates to lithium than placebo in patients with acute bipolar depression (245). As well, the STEP-BD study suggested that mood stabilizers which include lithium are as effective as mood stabilizers plus antidepressants in treating acute bipolar depression, although the durable recovery rate was modest, and there was no sub analysis focusing on lithium versus other antimanic drugs (246). Thus, the findings of these studies justify a Level 2 rating of efficacy for lithium.

Given that lithium also has clearly demonstrated efficacy in preventing mood episodes and in treating acute mania, our hierarchical ranking thus justifies lithium as an important first-line agent for bipolar depression, and based on overall evaluation of available studies, it is our opinion that a trough lithium serum level of 0.8-1.2 mEq/L would be needed for clinical effectiveness.

Lamotrigine

Lamotrigine monotherapy was not superior to placebo in four double blind placebo controlled trials of acute bipolar depression on the primary outcome (254). However, a meta-analysis conducted on the response rates from these studies as well as a BDII trial showed superiority of lamotrigine (248). Moreover, methodological issues with the trials likely led to the effect of lamotrigine being underestimated-including the relatively low final dose (200 mg in most trials, which is lower that usually used in clinical practice) (255) and short trial duration (8 weeks in most trials) which, coupled with the slow titration of lamotrigine, resulted in participants being on the final dose for only a short period (around two weeks). Further, lamotrigine was superior to placebo on Montgomery–Åsberg Depression Rating Scale (MADRS) in one of the studies (249), and changes in symptoms on this scale have since been used to demonstrate the efficacy of other agents for acute bipolar depression. Finally, the addition of lamotrigine to lithium (253) was superior to adding placebo to lithium and there was a trend for superiority of addition of lamotrigine to quetiapine vs placebo add on (252) in treating bipolar depression. It is likely that these beneficial effects are due to the direct effect of lamotrigine and not due to pharmacokinetic interaction between lamotrigine and concomitant medications. Furthermore, trial design issues, especially the fact that the six-week dose titration phase took up most of the 8 week trials, is likely to compromise efficacy signals. Lastly, the short and long-term tolerability of lamotrigine is a major benefit. Taken together, we believe these data justify at least a Level 2 rating for lamotrigine for acute bipolar depression.

In addition to this Level 2 rating for bipolar depression, lamotrigine also has demonstrated efficacy in maintenance treatment and an excellent tolerability profile-features which qualify it to be a first-line treatment for bipolar depression.

FIGURE 2 Lithium and lamotrigine as first-line agents for bipolar I depression: Summary of evidence [Colour figure can be viewed at wileyonlinelibrary.com]

4.4.2 | Step 2: initiate or optimize therapy and check adherence

It is recommended for all patients that pharmacotherapy be initiated with one or more of the available first-line agents. The choice of agent or agents to manage an acute bipolar depressive episode should be discussed with the patient and their supporters (as appropriate) and take into account current and prior medication use and response, personal preference, and the safety and tolerability of each agent, as well as clinical features that may influence prognosis (see "Clinical features that help direct treatment choices").

First-line

Quetiapine (level 1),[241-243] lithium (level 2),[244-246] lamotrigine (level 2)[242,247,248] and lurasidone (level 2)[249] are all recommended as first-line treatment options with evidence for efficacy as monotherapy.

Lurasidone (level 1)[249,250] and lamotrigine (level 2)[251,252] are also recommended as first-line adjunctive treatments (Figure 2). Although quetiapine and lithium have not been assessed for efficacy as adjunctive treatments for acute bipolar depression, clinicians may choose to apply this combination in patients who experience depression when optimized on one of either of these medications.

Recommendations as to which first-line treatment should be considered first are outlined in our hierarchy. We recommend that the agents listed first in the hierarchy be tried first, in the order listed, unless there are patient-specific reasons for choosing an agent lower down in the order, such as previous history of response/ non-response or clinical features (see Clinical features which help direct treatment choices). For instance, if a patient presents with an acute bipolar depressive episode and is not taking any treatment and has not been treated for this episode, that patient should be commenced on quetiapine monotherapy if there is no previous history of non-response or tolerability concerns with quetiapine. However, if a patient had been taking lithium and either had a breakthrough acute bipolar depressive episode or did not respond to monotherapy with lithium, then lurasidone or lamotrigine or quetiapine add-on or switch to quetiapine monotherapy or lurasidone monotherapy might be more appropriate in that order, given that lurasidone and lamotrigine adjunctive therapies have demonstrated efficacy in lithium non-responders. Similarly, in non-responders to lithium monotherapy, adjunctive lamotrigine could be another option.

Clinicians are advised to appropriately dose these medications for an adequate period of time before concluding lack of efficacy. Clinical trials have shown that there is no difference in efficacy between quetiapine 300mg and 600mg daily doses. Lower doses of quetiapine have not been studied in clinical trials for bipolar depression. Therefore, clinicians are advised to consider a target dose of 300 mg/day for quetiapine. For lithium, we suggest that serum lithium levels should be maintained between 0.8 and 1.2 meq/L, while for lamotrigine, the target should be a minimum of 200 mg/day.

4.4.3 | Step 3: add on or switch therapy (alternate first-line agents)

Across several different medications for bipolar depression, early improvement (after 2 weeks) has been found to be a reasonable predictor of overall response, whereas lack of early improvement is a more robust predictor of non-response.[255] Lamotrigine is the exception to this rule, given a necessary slow titration initiating the medication. In the case of non-response, dosing should be optimized and issues of non-adherence identified and addressed (see Section 2) prior to adjusting treatment strategies.

When determining whether an agent should be switched or another first-line agent be added on to any current treatment, the effectiveness of each of the medications needs to be understood in the context of all the goals of managing BD. It is often the case that a medication may be selected to address several goals; for instance, lithium could be added for acute depression with intent to also bolster anti-manic prophylaxis. In this scenario, if lithium is ineffective in the individual patient for an acute bipolar depression but is also being used over the long term for anti-manic prophylaxis, then an "add-on" intervention should be the next treatment for the acute bipolar depression. If, for instance, the anti-manic prophylaxis is already being fully provided by an atypical antipsychotic, then the new medication could replace lithium via a switch strategy. Decision-making must also address efficacy for comorbid conditions, as well as tolerability concerns. In principle, all things being equal, a switch is preferred over add-on to limit the degree of polypharmacy, but the clinical reality is that medications may be helpful for some but not all components of the illness, and using rational polypharmacy via add-on treatments is often required. For situations in which patients experience a depressive episode while already receiving an adequately dosed antidepressant, strong consideration should be given to discontinuing or switching the class of antidepressant, unless clear benefits are apparent in reducing the severity or frequency of depressive episodes. Switch of medications should be done in an overlap and taper manner unless there is medical necessity for abrupt discontinuation.[257]

All first-line options should be tried in adequate doses for an adequate duration of time before considering second-line options either as an add-on or switch strategy.

4.4.4 | Step 4: add on or switch therapy (second-line agents)

Second-line

In patients who are inadequately responsive to first-line agents, monotherapy with divalproex (level 2)[242,258] is included as a second-line option.

Adjunctive use of antidepressant therapy (selective serotonin reuptake inhibitors [SSRIs] or bupropion) with lithium/divalproex or an atypical antipsychotic may also be considered as a second-line add-on treatment. While some individual studies have failed to demonstrate the efficacy of adjunctive antidepressant therapy, a recent meta-analysis (level 1) supports efficacy, albeit with a small effect size.[259]

This is a key aspect of decision-making regarding antidepressants, since historically much of the focus has been on risk of manic switch or rapid cycling, with an underappreciation of the relatively weak efficacy data. This new appreciation, exemplified by the small benefit seen in the above meta-analysis, led to the change from the last CANMAT guidelines, which previously gave add-on SSRI/bupropion antidepressants a first-line recommendation. As per the ISBD Antidepressant Task Force recommendations,[260] antidepressants should ideally be avoided, or used cautiously if necessary, in patients with a history of antidepressant-induced mania or hypomania, current or predominant mixed features, or recent rapid cycling. Patients and caregivers (as appropriate) should receive education regarding early warning symptoms of mood switching or cycle acceleration, and antidepressants should be discontinued if these emerge. Antidepressant *monotherapy* should NOT be used for the treatment of BDI depression.

ECT (level 3) is also a second-line treatment, and should be considered particularly for treatment-refractory patients and those for whom a rapid treatment response is needed, such as those with severe depression with imminent suicidal risk, catatonia or psychotic depression,

Why are armodafinil and modafinil third-line treatments for bipolar I depression?

Armodafinil adjunctive therapy was assessed in three double blind randomized controlled trials. Of these, one was positive (270) but in the other two studies, it failed to separate from placebo on the primary efficacy measure (286, 287) although in one of the trials several secondary outcomes were positive (288). Furthermore, in a fourth trial, there was also suggestion of efficacy based on some secondary measures (289). Therefore, although two trials were negative on the primary efficacy measure, based on one positive trial and some positive secondary outcomes in two trials, this was given a Level 4 rating (expert opinion), and recommended as a third-line.

Although modafinil has been shown to be efficacious in the only trial (269), it was also recommended a third-line in light of the three negative trials for armodafinil.

FIGURE 3 Armodafinil and modafinil as third-line agents for bipolar I depression: Summary of evidence [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 15 Additional agents evaluated for use in acute bipolar I depression

	Agent	Level of evidence
Third-line	Aripiprazole (adj)	Level 4
	Armodafinil (adj)	Level 4
	Asenapine (adj)	Level 4
	Carbamazepine	Level 2
	Eicosapentaenoic acid (EPA) (adj)	Level 2
	Ketamine (IV) (adj)	Level 3
	Light therapy +/− total sleep deprivation (adj)	Level 3
	Levothyroxine (adj)	Level 3
	Modafinil (adj)	Level 2
	N-acetylcysteine (adj)	Level 3
	Olanzapine	Level 1
	Pramipexole (adj)	Level 3
	Repetitive transmagnetic stimulation (rTMS) (adj)	Level 2
	SNRI/MAOI (adj)	Level 2
Not recommended	Antidepressant monotherapy	Level 2 negative
	Aripiprazole	Level 1 negative
	Lamotrigine + folic acid	Level 2 negative
	Mifepristone (adj)	Level 2 negative

adj, adjunctive; MAOI, monoamine oxidase inhibitor; SNRI, serotonin and norepinephrine reuptake inhibitor.

and/or when a rapid response is important for medical stabilization. Data support efficacy for brief pulse right unilateral placement, although there are insufficient data to guide the decision of unilateral or bilateral placement for bipolar depression.[261] Additional second-line options include cariprazine, with efficacy demonstrated through a large RCT[262] and a pooled analysis of a failed RCT and a positive RCT[263] (level 2), although there is less clinical experience supporting its use. Olanzapine-fluoxetine combination (level 2)[264,265] is effective and is also recommended as a second-line option.

Similar to the approach for treatment of a manic episode, multiple first- and second-line agents and combinations should be trialled before considering initiating third-line agents in step 5.

4.4.5 | Step 5: add on or switch therapy (third-line agents)

Third-line

Third-line options are listed alphabetically in Table 15. In patients who fail to respond to multiple first- and second-line agents, third-line choices include monotherapy with carbamazepine (level 2)[242] or olanzapine (level 1).[242]

Agents that may be applied adjunctively include aripiprazole (level 4),[266,267] armodafinil (level 4)[268,269] (Figure 3), asenapine (level 4),[270] levothyroxine (level 3),[271,272] modafinil (level 2)[268] (Figure 3), and pramipexole (level 3).[273,274] rTMS targeted at the left or right dorsolateral prefrontal cortex (level 3)[275] may also be used in addition to medication. Other classes of antidepressants such as serotonin-norepinephrine reuptake inhibitors [SNRIs] and monoamine oxidase inhibitors [MAOIs] could be used adjunctively but clinicians need to ensure adequate anti-manic prophylaxis in such situations, as SNRIs and MAOIs have a higher propensity than other antidepressants to induce manic switch and cause mood destabilization (level 2).[276-278]

Ancillary treatments such as adjunctive eicosapentaenoic acid (EPA) (level 2),[169,279,280] *N*-acetylcysteine (level 3),[281] and light therapy (level 3),[282] including bright light delivered midday (level 3),[283] are also recommended as third-line treatment options to use adjunctively to other medications. There may be additional benefits to using light therapy in combination with total sleep deprivation (level 2), although there is little clinical experience with this technique. While there is evidence from several small studies that intravenous ketamine (level 3)[284] is a highly effective and fast-acting antidepressant, due to its invasive nature, short duration of effect, and lack of long-term safety data, it has been relegated to a third-line treatment, with recommendations that it be reserved for patients with severe symptoms or significant suicidal ideation for whom other treatments have been unsuccessful. In clinical situations that prioritize rapidity of response to treatment, ketamine may be considered earlier in the treatment order, although clinicians need to be aware that the data for efficacy are limited and the effects do not appear to last longer. Further, there are case reports of manic switch, but the clinical trial data have not provided any confirmatory evidence.[284] Also, clinicians need to be aware of potential abuse of ketamine, especially in domiciliary use situations.[285]

4.4.6 | Agents not recommended for the treatment of acute bipolar depression

Antidepressants should not be used as monotherapy in patients with BDI depression, as available trials do not support their efficacy and there are concerns about their safety in terms of mood switching (level 2 negative).[260,289-291]

Aripiprazole monotherapy failed to separate from placebo in two bipolar depression trials.[292] Although the pooled analysis reported separation,[293] the mean difference in Montgomery–Åsberg Depression Rating Scale (MADRS) change score was only 1.12 points, which is not clinically meaningful and it is thus not recommended (level 1 negative). Ziprasidone monotherapy or adjunctive therapy (level 1 negative),[242,294] lamotrigine in combination with folic acid (level 2 negative),[251] and mifepristone (adjunctive) (Leve 2 negative)[295] are also not recommended due to evidence for lack of antidepressant efficacy (Table 15).

4.4.7 | No specific recommendation/agents that require further study

There are insufficient data to make a recommendation regarding the use of aspirin (adjunctive) (level 3 negative),[296] celecoxib (adjunctive)

(level 3 negative),[297] gabapentin (monotherapy) (level 3 negative),[298] leviteracitam (adjunctive) (level 3 negative),[299] lisdexamfetamine (adjunctive) (level 3 negative),[300] memantine (adjunctive) (level 3),[301] pioglitazone (adjunctive) (level 3),[302,303] riluzole (level 4 negative),[304] and risperidone (adjunctive) (level 3).[305] Although adjunctive therapy with pregnenolone separated from placebo at week 6, the change in depressive symptoms was not significantly different from week 8 to week 12 between the two groups (level 2).[306]

4.5 | Clinical features that help direct treatment choices

There are limited data on predictors of treatment response in bipolar depression. However, clinical features of a depressive episode including DSM-5 specifiers may assist clinicians in choosing among recommended treatment options.

Need for rapid response

Amongst the first-line options recommended, quetiapine and lurasidone have separated from placebo in clinical trials at as early as week 1.[249,307,308] Thus, these medications may be preferable when a rapid response is required, for example in patients who are at increased risk of suicide or who have medical complications, including dehydration. While ECT is recommended as a second-line option, this may also be used earlier when a rapid response is imperative. Second-line options such as cariprazine and olanzapine-fluoxetine have also separated from placebo at as early as week 1 and may also be considered when a rapid response is desirable, but this needs to be balanced against the potential side effects. Lamotrigine administration requires slower titration due to the risk of skin rashes, Stevens-Johnson syndrome, and toxic epidermal necrolysis, and is thus not ideal for patients requiring a rapid response. Lamotrigine, however, is well tolerated, and there is some evidence that its effectiveness may be more pronounced in patients experiencing depressive cognitions and psychomotor slowing.[309]

Previous treatment response

Adjunctive antidepressant use may be appropriate in those with prior antidepressant response if there was no history of treatment-emergent switch.[310]

Anxious distress

Symptoms of anxiety are often experienced during a depressive episode, and are predictive of more persistent depressive symptoms[311] and increased suicidal ideation.[312] A pooled analysis of two double-blind RCTs demonstrated that quetiapine is more effective than placebo in relieving symptoms of anxiety co-occurring alongside bipolar depression,[313] and olanzapine-fluoxetine combination has also been shown to be effective.[314] In a post hoc analysis, lurasidone was effective in improving depressive as well as anxiety symptoms in patients with MDD who had mixed features and anxiety.[315] The anxiolytic effects of divalproex, risperidone, and lamotrigine appear to be limited.[199,316]

Mixed features

Many patients with bipolar depression will also experience at least subsyndromal hypomanic or manic features, and this presentation is associated with more severe depressive symptoms, as well as a higher rate of substance use and cardiovascular disease.[317] For many of these patients, combination therapy will be necessary to adequately address symptoms.[318] Pooled analysis indicates that atypical antipsychotics show a class effect in alleviating mixed features in bipolar depression, with olanzapine-fluoxetine combination, asenapine, and lurasidone all demonstrating efficacy.[319] Lurasidone has further been shown to have efficacy in treating both depressive and hypomanic symptoms in MDD with mixed features.[320] The ISBD Task Force recommends avoiding antidepressants in patients with mixed features[260] and the CANMAT/ISBD group concurs with this recommendation.

Melancholic features

No specific studies assessed the predictive ability of melancholic features; however, clinical experience suggests that ECT is very effective in this population.

Atypical features

There is some evidence for efficacy of tranylcypromine in patients with anergic bipolar depression.[321] However, given the risks of potential manic switch, this agent should only be used in conjunction with lithium or divalproex or an atypical antipsychotic. Clinicians also must consider adverse events of this agent related to its interactions with food and other medications.

Psychotic features (mood congruent or incongruent)

Up to 20% of inpatients experience psychosis in the context of an acute bipolar depressive episode.[322] The relative efficacy of various medications to treat these features in this phase of illness has not been examined, although clinical experience suggests that ECT and antipsychotics are highly effective for this population.

Rapid cycling

As described in Section 3, hypothyroidism, antidepressants and substance abuse may be associated with rapid cycling, thus making assessment of thyroid function and discontinuation of antidepressants, drugs of abuse, stimulants, and other psychotropic agents imperative. As there is no evidence to support any specific agent to treat acute depression during a rapid cycling phase, appropriate pharmacotherapy should be selected based on effectiveness in the acute and maintenance phases. Lithium, divalproex, olanzapine, and quetiapine all appear to have comparable maintenance efficacies in these patients.[219] In contrast, lamotrigine did not separate from placebo in maintenance treatment in patients with rapid cycling BDI.[323] Antidepressants are not recommended, as they have been shown to destabilize patients, even with concurrent mood stabilizer use.[324]

Seasonal pattern

While some individual patients may show a seasonal pattern, Canadian data are mixed as to whether episodes of mania or depression in BD

TABLE 16 Risk factors for partial adherence or non-adherence to medication

Sociodemographics	Male, younger age, low level of education, single
Psychological	Poor insight, lack of awareness of disease, negative attitude to treatment, fear of side effects, negative attitude to medication, low overall life satisfaction, low cognitive functioning
Comorbidity	Alcohol or cannabis use, obsessive compulsive disorder
Social	No social activities, work impairment
Chronology	Younger age of onset, current inpatient status, hospitalization or suicide attempt in past 12 months
Disease characteristics	Mixed episode, rapid cycling, delusions and hallucinations, greater severity of illness, BDI diagnosis, higher number of episodes
Treatment-related factors	Side effects of medications, inadequate efficacy of medication, use of antidepressants, low treatment doses

Adapted from Leclerc et al.[353]

follow a consistent seasonal variation.[222] There is no evidence for the superiority of any agent in patients with an observed seasonal pattern of manic episodes.

5 | MAINTENANCE THERAPY FOR BIPOLAR DISORDER

5.1 | Need for long-term strategies

Almost all individuals with BD require maintenance treatment to prevent subsequent episodes, reduce residual symptoms, and restore functioning and quality of life. There is increasing evidence to suggest that, for a subgroup of patients, BD may be a neuroprogressive disease in which recurrences are associated with reductions in brain grey and white matter volumes, worsening cognitive impairment, a decrease in inter-episodic recovery and functioning, a higher rate and severity of relapse, and a reduced rate of treatment response to both pharmacotherapy and psychotherapy.[325] It is therefore important that comprehensive treatment be initiated even after a first episode.[63] Effective maintenance treatment, early in the course of illness, has been shown to reverse cognitive impairment and preserve brain plasticity, particularly in those who remain episode free,[326,327] and may therefore lead to improved prognosis and minimization of illness progression.[328] There are preliminary data suggesting that, after a first episode, lithium might be superior to quetiapine in both volumetric and cognitive outcomes.[329,330]

With treatment, 19%-25% of patients will experience a recurrence every year, compared to 23%-40% of those on placebo.[331] Risk factors for recurrence include younger age of onset,[332] psychotic features,[212] rapid cycling,[331] more (and more frequent) previous episodes,[333] comorbid anxiety,[334] and comorbid SUDs.[335] Persistent subthreshold symptoms also increase risk for subsequent mood episodes,[334,336,337] and the presence of residual symptoms should therefore be an indicator of a need for further treatment optimization. Availability of psychosocial support and lower levels of stress are also protective against recurrence.[337,338]

5.2 | Treatment adherence

Concordance between clinician and patient views of illness and treatment is a crucial determinant of adherence,[339] and reinforces the need for a collaborative approach to the treatment alliance.[340] Asking about adherence behaviour and attitudes in a non-judgemental manner and exploring the reasoning behind poor adherence are important parts of treatment,[341] as up to half of patients do not take their medications as prescribed.[342-344] Unrecognized treatment non-adherence can lead physicians to believe that the patient is non-responsive, resulting in unnecessary dose increases (especially problematic for drugs with a narrow therapeutic index), medication switches, or adjunctive medications.[341] Treatment withdrawal may precipitate recurrence; 50%-90% of patients discontinuing lithium experience a recurrence within 3-5 months,[345,346] with rapid lithium discontinuation associated with greater recurrence risk than gradual discontinuation.[347] Withdrawal of other mood stabilizers also predicts recurrence.[348,349] Risks for hospitalization, suicide, and lost productivity are also increased with non-adherence or discontinuation.[350-352] A variety of patient, disorder, and treatment-related risk factors for non-adherence or partial adherence are outlined in Table 16.[353]

Meta-analyses suggest that interventions aimed at engaging patients in treatment may more than double adherence compared to treatment as usual or other control groups.[354] Brief psychoeducational interventions focusing specifically on medication adherence can be integrated into clinical practice.[354] Flexible and collaborative engagement to address individual risk factors for non-adherence is recommended to optimize acceptability of pharmacological therapies.[353,355-357]

5.3 | Psychosocial interventions for maintenance therapy

Although pharmacotherapy is the foundation of maintenance treatment in BD, it is often insufficient to prevent recurrence. Over the last two decades, several controlled trials have examined the efficacy of adjunctive psychosocial treatments in reducing recurrence. On average, adjunctive psychosocial treatments reduce recurrence rates by about 15%. Therefore, adjunctive psychosocial interventions are an important component of management of BD and should be offered for all patients.

As described in more detail in Section 2, psychoeducation is the only first-line psychosocial intervention for the maintenance phase (level 1), which should be offered to all patients. Additional second-line options such as CBT (level 2) and FFT (level 2), and third-line options such as IPSRT (level 2) and peer support (level 2) should be offered based on individual strengths and needs.

5.4 | Efficacy ratings for pharmacological agents used as maintenance therapy: importance of naturalistic and cohort studies

Evidence from RCTs is at the core of the recommendations in these guidelines. Nonetheless, RCTs are not the only source of clinically useful information, particularly when evaluating maintenance therapy. RCTs offer relatively limited follow-up time-frames while, for some patients, maintenance therapy may extend across decades. Furthermore, new medications are often assessed in studies with an enriched design (including only patients who have responded to the medication under study in the acute phase), limiting the generalizability of positive findings to patients who responded to the medication acutely.

Useful data can be obtained from large, often whole-population databases constructed from electronic medical records or electronic patient registries with large numbers of patients that would be difficult to obtain in RCTs. In some instances, they allow comparisons of multiple treatments.[358-360] These large numbers make it possible to evaluate differences in rates of rare events such as less common side effects or suicide.[361,362]

Patient cohorts followed in a specific setting provide another source of informative data. Their main advantage usually is the length of observation, in some instances reaching several decades.[363-365] This comes at the cost of generalizability, in terms of both patient selection and non-random treatment allocation.

5.5 | Pharmacological treatments for maintenance therapy

As in earlier sections, pharmacological treatments for maintenance therapy have been evaluated using the criteria for strength of evidence for efficacy (Table 1) as well as safety and tolerability (Section 8). Results are summarized in Table 17.

5.5.1 | Step 1: review general principles and assess medication status

Many agents recommended for management of acute manic or depressive episodes have prophylactic efficacy. Generally, medications that have been found to be effective in the acute phase should be continued during the maintenance phase. However, there are exceptions to this: the efficacy of adjunctive antidepressant therapy has not been examined systematically in large double-blind placebo-controlled trials; hence, long-term antidepressant use is not recommended, especially in light of the concerns about potential risk of manic/hypomanic switch and mood instability. However, in the subgroups of patients who have responded to combination treatment and are stable, preliminary evidence suggests that withdrawal of antidepressants may contribute to destabilization.[366]

Clinical trials have shown that many atypical antipsychotics are effective in preventing relapse of mood episodes; with many agents, this efficacy is related to prevention of manic episodes but not depressive episodes. However, many of these trials have been conducted in patients with an index manic episode and, given that the polarity of an index episode predicts the polarity of relapse, depressive relapse rates in placebo groups in such studies have been low- compromising the statistical power to test the efficacy of these agents in prevention of depressive relapses. Thus, the efficacy of many of these agents in preventing depressive relapses remains unknown.

For patients who are currently not receiving or responding to pharmacological treatment, a careful history including details of clinical course, response (or lack thereof) to previously used medications, and family history should be collected. Other variables to be considered include psychiatric comorbidity (including substance use), the predominant illness polarity, and the polarity of the most recent episode.

Ongoing clinical monitoring, including medication blood levels as appropriate, is also a crucial part of maintenance treatment that should be used to support enhanced medication adherence, detection of early symptoms of recurrence, and monitoring of side effects (see Section 8).

5.5.2 | Step 2: initiate or optimize therapy and check adherence

The choice of agent or agents used in maintenance treatment should be discussed with the patient and their caregivers (as appropriate) and, based on knowledge of current and prior medication use and response, safety and tolerability of each agent, predominant episode polarity, and clinical features that may influence prognosis (see "Clinical features that help direct treatment choices"). As with treatment for mania and acute depression, we recommend that treatment choices for maintenance treatment of BD should follow the hierarchy listed in Table 17 unless patient preference or other considerations such as previous response/non-response, tolerability or predominant polarity justify other choices. Similarly, as a general rule, if a patient has been treated for an acute mood episode and responded to a first-line maintenance treatment, we recommend continuing that treatment for maintenance even if lower down in the hierarchy. As an example, if a patient responded to asenapine in an acute manic episode, asenapine should be continued, even if it is lower down in the hierarchy for maintenance treatment. It may be necessary to lower the dose to some degree once in maintenance treatment as patients often experience greater side effects once out of the acute episode.

There is evidence that the risk of recurrence is reduced when an antipsychotic is combined with lithium/divalproex. When a combination therapy of an atypical antipsychotic with lithium/divalproex was used to treat acute mania, continuing the atypical antipsychotic for the first 6 months following response offered clear benefit in reducing risk of mood episode recurrence (level 2),[367] but the benefits beyond 6 months remain uncertain. Therefore, clinicians are advised to re-evaluate risks and benefits after 6 months of sustained response to determine whether maintenance combination therapy with an atypical antipsychotic is justified.

TABLE 17 Hierarchical rankings of first- and second-line treatments recommended for maintenance treatment in bipolar disorder

	Level of evidence by phase of treatment					Considerations for treatment selection			
	Maintenance			Acute		Acute		Maintenance	
	Prevention of any mood episode	Prevention of depression	Prevention of mania	Depression	Mania	Safety concerns	Tolerability concerns	Safety concerns	Tolerability concerns
First-line treatments									
Lithium	●	●	●	◔	●	+	+	++	++
Quetiapine	●	●	●	●	●	+	++	++	++
Divalproex	●	◔	◑	◔	●	–	+	++[c]	+
Lamotrigine	●	●	◔	●	■	++	–	–	–
Asenapine	◔	◔	◔	n.d	●	–	+	–	+
Quetiapine + Li/DVP	●	●	●	◕	●	+	++	+++[c]	++
Aripiprazole + Li/DVP	◔	n.d.[a]	◔	◕	◔	+	+	++[c]	++
Aripiprazole	◔	n.d.[a]	◔	■	●	–	+	–	+
Aripiprazole OM	◔	n.d.[a]	◔	n.d.	n.d.	–	+	–	+
Second-line treatments									
Olanzapine	●	●	●	●[b]	●	+	++	+++	++
Risperidone LAI	●	n.d.[a]	●	n.d.	n.d.	–	+	+	++
Risperidone LAI (adj)	◔	◕	◔	n.d.	n.d.	+	++	+++	++
Carbamazepine	◔	◔	◔	◑	●	++	++	+[c]	++
Paliperidone (>6 mg)	◔	n.d.[a]	◔	n.d.	●	–	+	+	++
Lurasidone + Li/DVP	◑[d]	◑[e]	◕	◔	n.d.	+	++	++[c]	++/–
Ziprasidone + Li/DVP	◔	n.d.[a]	◔	◧	◪	++	++	++[c]	+

DVP, divalproex; LAI, long-acting injectable; Li, lithium, OM, once monthly.

●, level 1 evidence; ◔, level 2 evidence; ◑, level 3 evidence; ◕, level 4 evidence; ■, level 1 negative evidence; ◪, level 2 negative evidence; ◧, level 3 negative evidence; ◪, level 4 negative evidence; n.d., no data; – limited impact on treatment selection; +, minor impact on treatment selection; ++, moderate impact on treatment selection; +++, significant impact on treatment selection.

[a]Did not separate from placebo in those with index mania; no studies available in index depression.

[b]Did not separate on core symptoms of depression.

[c]Divalproex and carbamazepine should be used with caution in women of child bearing age.

[d]Trend for superiority on the primary efficacy measure, hence the lower rating.

[e]Effective in those with an index episode of depression.

[Colour table can be viewed at wileyonlinelibrary.com]

Why is divalproex recommended as a first-line maintenance treatment for bipolar I disorder?

In the only large double-blind placebo controlled RCT of divalproex monotherapy (373), it was not more effective than placebo in preventing relapse of mood episodes i.e. time to any mood episode. However, in this trial, lithium which has been shown in many other studies to be effective in relapse prevention, was also found to be no more effective than placebo. Thus, these results suggest that this trial was a failed trial and not a negative trial.

Most modern studies of maintenance therapy use enriched design, meaning that those that responded in acute phase to the medication being tested are randomized to continuation of the same drug or replacement with placebo. This practice to a large extent mirrors clinical practice as clinicians are likely to continue the medication that worked in the acute phase for maintenance treatment. Interestingly, in the divalproex RCT, some but not all patients that were randomized into the double-blind phase were divalproex responders. In a post-hoc analysis of this study, in this enriched subgroup of patients that responded to divalproex during the acute phase and randomized to continuation of divalproex vs switch to placebo, divalproex was more effective in preventing relapse of mood episodes compared with placebo.

Further, divalproex was superior to placebo on a number of other secondary efficacy measures such as lower rates of discontinuation for any mood episode or a depressive episode. Surprisingly, there was also a trend for superiority of divalproex relative to lithium in time to any mood episode. Other RCTs have shown that divalproex is as effective as lithium (221) in preventing relapse of mood episodes.

As well, two meta-analysis have concluded that divalproex is effective in preventing relapse of mood episodes (370, 372), and a population based cohort study in the UK showed that there were no differences in efficacy between divalproex, quetiapine and olanzapine in the maintenance treatment of bipolar disorder (359).

Taken together, we believe these efficacy data support our rationale for a Level 1 rating. This along with clinical experience, real world cohort data, and safety, justify our recommendation of divalproex as a first-line maintenance treatment.

FIGURE 4 Divalproex as a first-line maintenance therapy for bipolar I disorder: Summary of evidence
RCT, randomized controlled trial [Colour figure can be viewed at wileyonlinelibrary.com]

First-line

Lithium (level 1),[368,369] quetiapine (level 1),[369,370] divalproex (level 1) [369,371,372] (Figure 4) and lamotrigine (level 1)[369,373] monotherapies have the best combination of clinical trials, administrative data, and clinical experience to support their use as first-line therapies for maintenance treatment of BD. Recent data suggest that asenapine (level 2)[374] is effective in preventing both manic and depressive episodes, and thus is recommended as a first-line treatment. Finally, aripiprazole oral (level 2)[375,376] or once monthly (level 2)[377] is also recommended as a first-line monotherapy in view of its efficacy in preventing any mood or manic episode as well as its safety/tolerability profile, although it has not been shown to be effective in preventing depression.

Additional combination therapies included as first- line include quetiapine adjunctive therapy with lithium/divalproex (level 1),[378,379] which has demonstrated efficacy in preventing any mood, manic or depressive episode. Aripiprazole plus lithium/divalproex (level 2)[380] should also be considered as a first-line option.

TABLE 18 Additional agents evaluated for use in maintenance treatment of bipolar I disorder

	Agent	Level of evidence
Third-line	Aripiprazole + lamotrigine	Level 2
	Clozapine (adj)	Level 4
	Gabapentin (adj)	Level 4
	Olanzapine + fluoxetine	Level 2
Not recommended	Perphenazine	Level 2 negative
	Tricyclic antidepressants	Level 2 negative

adj, adjunctive.

For patients who experience a recurrence or who remain symptomatic while on a first-line agent or a combination, dosing should be optimized and issues of non-adherence identified and addressed prior to moving to step 3.

5.5.3 | Step 3: add on or switch therapy (alternate first-line agents)

If therapy with one or a combination of the first-line agents at optimal doses is inadequate or not tolerated, the next step is to switch to or add on an alternate first-line agent. Because there are multiple first-line agents with substantial efficacy data and relative safety and tolerability, the use of second-line agents is only recommended after unsuccessful trials of multiple first-line strategies.

5.5.4 | Step 4: add on or switch therapy (second-line agents)

Second-line

Although olanzapine (level 1)[381,382] is effective in preventing any mood, manic or depressive episode, it is considered second-line treatment because of safety issues such as metabolic syndrome. Biweekly long-acting injectable risperidone monotherapy (level 1)[383] or adjunctive therapy (level 2)[384] has demonstrated efficacy in preventing any mood or manic episode, but had no clear efficacy in depressive episode prevention in these trials. Further, there was a trend for superiority of oral risperidone adjunctive therapy at 6 months in preventing any mood episode and in preventing mania but not depression.[367] Carbamazepine (level 2) has not been assessed in any large placebo-controlled trials, but active comparator trials support its efficacy.[385] Paliperidone (level 2) was more effective than placebo

in preventing any mood or manic episode but less effective than olanzapine.[386]

Ziprasidone oral adjunctive therapy (level 2)[387] has been shown to be effective in preventing any mood or manic episode, although there are conflicting (positive and negative) data for acute treatment (see Sections 3 and 4). There was a trend for superiority of lurasidone adjunctive therapy in preventing any mood episode (but not manic or depressive episodes individually) in a controlled trial with significant separation from placebo in preventing mood episodes in those with an index depressive episode.[388] Thus, lurasidone adjunctive therapy may be appropriate for those who responded to this medication during an index depressive episode.

5.5.5 | Step 5: add on or switch therapy (third-line agents)

Third-line

Third-line agents are listed alphabetically in Table 18. There was a trend for superiority of adjunctive aripiprazole with lamotrigine (level 2)[389] compared to lamotrigine monotherapy in preventing mania; thus, this combination may provide additional prophylaxis for patients on lamotrigine monotherapy in preventing manic relapses. Clozapine (level 4)[162] and gabapentin (level 4)[390] may also be useful adjunctive treatments for those who incompletely respond to first- or second-line therapies. The olanzapine/fluoxetine combination appears to maintain mood stability over a 6-month period in patients with bipolar depression who respond acutely to this combination (level 2).[391]

5.5.6 | No specific recommendation/agents that require further study

We do not provide specific recommendations for the use of cariprazine, as there is currently only evidence for efficacy in acute manic and depressive episodes[262,392] and not yet for maintenance treatment (level 4). While a small RCT suggests a lack of efficacy for flupenthixol as maintenance treatment, larger studies are needed before definite conclusions can be drawn (level 3 negative).[393] Likewise, oxcarbazepine adjunctive therapy requires further evaluation (level 4).[394-396] No recommendation is made for topiramate as there is an absence of controlled data supporting its efficacy in maintenance (level 4 negative), and a lack of efficacy in acute mania[381]; however, its use may be indicated as it has efficacy for many syndromes that are often comorbid with BD (Section 7).

5.5.7 | Agents not recommended for maintenance treatment

Perphenazine is not recommended for maintenance based on evidence that patients treated with perphenazine and a mood stabilizer following an episode are more likely to have emergent depressive symptoms or intolerable side effects, compared to those maintained on the mood stabilizer alone (level 2 negative).[397] Tricyclic antidepressant mono or adjunctive maintenance therapy is not recommended due to an increased risk of manic switch (level 2 negative)[398-400] (Table 18).

5.5.8 | Clinical features that direct treatment choices

Clinical trials tell us how efficacious one drug is in comparison with another (or placebo) in groups of patients. To determine the degree of long-term response in an individual patient requires a different evaluation and may take a considerable amount of time. Few patients manage a lifetime of BD with monotherapy—most will require short- or long-term combination therapies to address acute or subsyndromal symptoms as well as to reduce rates of recurrence. Some,[359,401,402] but not all,[403,404] reports suggest that long-term treatment becomes less effective with longer duration of untreated illness, an argument for finding an effective treatment as early as possible.

In most instances, it is difficult to differentiate nonspecific correlates of good prognosis of the illness from factors specific to the response to a particular mood stabilizer. Available data come mostly from naturalistic/cohort studies and few randomized trials.[405] Nevertheless, several tentative predictors are emerging from the available data.

Factors associated with overall good prognosis of BD include good treatment adherence, lack of early adversity, intermediate age at onset, good social support, and the absence of spontaneous rapid cycling[406,407] or features of a personality disorder.[408]

In general, lithium is the gold standard for maintenance treatment, as it is effective in preventing both manic and depressive episodes (magnitude of prophylactic efficacy greater against mania vs depression) and appears to have a degree of anti-suicidal effects.[352,369,409-413] Patients who respond well to lithium treatment usually have an episodic remitting pre-treatment clinical course, a family history of BD (especially BD responsive to lithium), low rates of comorbidity (especially anxiety and substance abuse disorders), and a pattern of mania-depression-euthymia in biphasic episodes, as well as a typical clinical presentation.[414-416] Responsiveness may also be a familial trait, with a study showing that patients who have a lithium-responsive relative have a 67% likelihood of also being lithium responsive, versus 35% of those without a responsive relative.[417] Among biological measures, lack of electroencephalogram (EEG) abnormalities, higher brain lithium concentration, increased *N*-acetyl aspartate and lower myo-inositol peaks on magnetic resonance spectroscopy, as well as several variants in candidate gene studies, may predict response,[418] but these studies require confirmation. Response to lithium in particular seems to be quite specific, as shown in a study of neurons derived from induced pluripotent stem cells. The neurons from people with BD were hyperexcitable and their activity was selectively modified by *in vitro* lithium in accordance with clinical response.[419]

Responders to lamotrigine have a predominantly depressive polarity as well as comorbid anxiety.[420,421] Lamotrigine monotherapy is not appropriate for patients with frequent manic episodes, as it has limited efficacy in preventing mania.

Quetiapine has been shown to be effective in preventing manic, depressive and mixed episodes in patients with index manic, depressive and mixed episodes, and thus may be particularly valuable in those with mixed features.[422] Asenapine appears to be effective in preventing both mania and depression, although the magnitude of prophylactic efficacy is greater for mania relative to depression. In a randomized open trial of carbamazepine versus lithium, responders to carbamazepine were more likely to have an atypical illness, BDII or schizoaffective disorder.[405]

Data to differentiate anti-psychotic medication responders from non-responders are lacking.

Overall, some of these possible predictors can have clinical utility, but not all are practical. For instance, it is difficult to evaluate a pre-treatment course in patients who started their treatment after one or two episodes (practice recommended by most treatment guidelines), and biomarkers are intriguing but lack sufficient replication and are not readily available.

In patients with a history of a rapid cycling course, as indicated in previous sections, factors associated with rapid cycling must be addressed. These include discontinuation of stimulants and antidepressants and treating hypothyroidism if present. With regard to treatment options, the evidence suggests that monotherapy with a single mood stabilizer is often ineffective and patients may require a combination of mood stabilizers to achieve mood stability.

Treatment-refractory bipolar disorder

Treatment refractoriness may be related to non-adherence to oral medications, failure to optimize evidence-based oral medication therapy/therapies, comorbidities complicating therapeutic response or true resistance to pharmacotherapy. Clinicians are advised to make a comprehensive assessment to determine factors responsible for treatment refractoriness. Adequate doses of first and second-line agents should be employed for an adequate period of time (eg, this is typically individualized based on the previous course of mood episodes in each patient) to assess prophylactic response. Comorbidities should be addressed with pharmacological or psychological strategies as appropriate. While genotyping for cytochrome P450 enzymes such as 2D6 and 3A4 which metabolize most psychotropic drugs is not routinely recommended, clinicians are advised to consider this in patients with refractory BD who have not responded to high doses of various first, second, and third-line treatments or their combinations in order to exclude the possibility of ultra rapid metabolic status contributing to poor response.

In patients who are non-adherent, psychosocial strategies such as psychoeducation should be used to improve treatment adherence. If ineffective, long-acting injectable medications should be offered. Risperidone long-acting injectable monotherapy[383] or adjunctive therapy (level 2)[384] once every 2 weeks or aripiprazole once-monthly injectable monotherapy (level 2)[377] has been shown to be effective in preventing relapse of mood episodes in patients with BD.

There is a dearth of clinical trial data to inform treatment options for management of patients with refractory BD. Clozapine adjunctive therapy has been shown to be effective in reducing symptoms and total medication use in treatment-resistant patients.[162]

TABLE 19 Strength of evidence and treatment recommendations for acute management of bipolar II depression

Recommendation	Agent	Level of evidence
First-line	Quetiapine	Level 1
Second-line	Lithium	Level 2
	Lamotrigine	Level 2
	Bupropion (adj)	Level 2
	ECT	(Level 3)
	Sertraline[a]	Level 2
	Venlafaxine[a]	Level 2
Third-line	Agomelatine (adj)	Level 4
	Bupropion (adj)	Level 4
	Divalproex	Level 4
	EPA (adj)	Level 4
	Fluoxetine[a]	Level 3
	Ketamine (IV or sublingual) (adj)[c]	Level 3
	N-acetylcysteine (adj)	Level 4
	Pramipexole (adj)	Level 3
	T3/T4 thyroid hormones (adj)	Level 4
	Tranylcypromine	Level 3
	Ziprasidone[b]	Level 3
Not recommended	Paroxetine	2 negative

adj, adjunctive; ECT, electroconvulsive therapy; EPA, eicosapentaenoic acid.
[a]For patients with pure depression (non-mixed).
[b]For patients with depression and mixed hypomania.

6 | BIPOLAR II DISORDER

6.1 | Presentation of bipolar II disorder

BDII is a distinct disorder from BDI, with a similar Canadian prevalence (0.67% compared to 0.87% for BDI).[7] The diagnosis of BDII requires one or more episodes of hypomania, one or more episodes of depression, and an absence of manic episodes. The DSM-5 criteria for hypomania are similar to those for mania, with symptoms being uncharacteristic of the individual, observable by others, and lasting at least 4 consecutive days. In contrast to mania, they cannot be severe enough to cause marked impairment or require hospitalization, and there must be an absence of psychosis. Further, DSM-5 has added a mixed feature specifier to hypomania as well. The diagnosis of BDII is generally stable over time, although there may be a higher risk of conversion to BDI early in the illness, suggesting that BDII may be a risk factor or prodrome of BDI in some patients.[423]

Why is lithium recommended as a second-line agent for bipolar II depression?

Reconciling conflicting data

In a 16-week double blind RCT, lithium was as effective as sertraline and lithium + sertraline combination (427) which qualifies lithium for Level 2 evidence. Additional supporting data come from a single-blinded trial which showed that lithium was as effective as lamotrigine in treating BDII depression over 6 weeks (445). However, neither of these studies had a placebo arm. Positive placebo-controlled data come from 4 small placebo-controlled crossover studies conducted in the 1960s and 1970s, in which lithium was effective in a mixed sample of BDI and BDII depressed patients (446-449). Results were reported separately for BDII in 2 of the studies and were identical to BDI (pooled response rate = 65% for both) (446).

In contrast, in the only modern a placebo-controlled parallel group study, lithium was not superior to placebo in BDII depression (254). Further, lithium was less effective than venlafaxine in a 12-week RCT (450).

A potential explanation might have to do with trough serum lithium levels. Lithium levels ranged from 0.8-1.3 mEq/L, and were often at the high end of that range in the older placebo-controlled RCTs while in the negative placebo-controlled RCT, the mean serum lithium level was lower (<0.61 mEq/L in the combined BDI + BDII sample, not reported separately for BDII). Thus, the optimal serum level for treating bipolar II depression is unclear. However, based on the placebo-controlled BDII trials, as well as placebo-controlled studies in BDI (247), a serum level of 0.8-1.2 mEq/L appears most likely to be beneficial.

In addition to the evidence for efficacy in acute depression, lithium also has efficacy in preventing mood episodes in BDII (400, 452-454). Therefore, in balance, we believe the evidence, though mixed, justifies recommending lithium as a second-line agent for BDII depression.

FIGURE 5 Lithium as a second-line agent for bipolar II depression: Summary of evidence.
BDI, bipolar disorder type I; BDII, bipolar disorder type II; BDNOS, bipolar disorder not otherwise specified; RCT, randomized controlled trial [Colour figure can be viewed at wileyonlinelibrary.com]

Should antidepressants be used in bipolar II depression?

Addressing the controversy

The question of whether, and if so when and how, to use antidepressants in BDII remains controversial due to concerns regarding both safety (particularly the possibility of hypomanic switch, mixed symptoms, and increased cycling) and efficacy.

With respect to safety, a meta-analysis that compared rates of antidepressant-associated mood elevations in BDII, BDI, and MDD reported that they were significantly less frequent in BDII than BDI, and occurred almost exclusively into hypomania rather than mania (454). Switch rates were low even during antidepressant monotherapy and with antidepressants associated with high switch rates in BDI (tricyclics, venlafaxine). An ISBD task force report on antidepressants also concluded that their risk-benefit ratio was more favorable in BDII (261, 449).

The issue of efficacy is less clear due to limited evidence. RCTs have shown that sertraline monotherapy was as effective as lithium and lithium+ sertraline combination, and that venlafaxine monotherapy was more effective than lithium, sufficient for level 2 evidence for these agents. In a RCT of BDI and BDII patients, bupropion was shown to be as effective as sertraline and venlafaxine (277). Open-label data also suggest efficacy for fluoxetine, and there are maintenance data for venlafaxine and fluoxetine in preventing relapses. These positive findings should be balanced against the fact that paroxetine and bupropion were not better than placebo for acute depression in patients taking concomitant mood stabilizing medications. Moreover, it is important to bear in mind that 1) there are no placebo-controlled acute-phase trials of antidepressant monotherapy in BDII, 2) many antidepressants have not been studied at all (and we do not believe it is warranted to extend positive findings from sertraline/venlafaxine -or for that matter negative findings from paroxetine/bupropion -to "antidepressants" generally), 3) the existing trials enrolled people with pure (non-mixed) depression, and their efficacy/safety in the broader spectrum of BDII patients is unclear, and 4) many of the existing trials have significant weaknesses, including one or more of: low dosing of the antidepressant; sub-therapeutic dosing of comparator medications; and lack of replication.

All of this makes it particularly difficult to make evidence based recommendations regarding antidepressants in BDII. We have restricted our recommendations to the specific agents that have been studied, and we recommend bupropion, sertraline,and venlafaxine monotherapy as second-line treatments; and fluoxetine as third-line. We further recommend that any antidepressant, especially in monotherapy, be reserved for patients with pure depression and avoided in those with mixed symptoms or a history of antidepressant-induced hypomania (261). Whether antidepressants should also be avoided in patients with rapid cycling is unclear, since some studies report poorer outcomes in rapid-cycling patients (455) while others do not (450, 456-458). Patients prescribed antidepressants must be educated regarding early-warning signs of hypomania and carefully monitored for them. Finally, there is a pressing need for further studies of other antidepressants in BDII, in both monotherapy and combination therapy.

FIGURE 6 Antidepressants for bipolar II depression: What is their role?
BDI, bipolar disorder type I; BDII, bipolar disorder type II; ISBD, International Society for Bipolar Disorders; MDD, major depressive disorder; RCT, randomized controlled trial [Colour figure can be viewed at wileyonlinelibrary.com]

Although hypomania is, by definition, less severe than mania, the disability associated with BDII is comparable to that associated with BDI,[14,424] and the economic burden of BDII is up to four times greater.[425,426] This is because patients with BDII spend as much time symptomatic as those with BDI, with mood symptoms predominantly in the depressive phase.[427,428] Rates of attempted and completed

Why is lamotrigine a second-line recommendation for bipolar II depression?
Reconciling conflicting data

Lamotrigine monotherapy was studied in two trials in BDII depression: one in which 221 BDII patients received 200 mg/day or placebo for 8 weeks, and a second in which 206 BDI or BDII patients (N = 84 with BDII) received 100–400 mg/day for 10 weeks (254). Both produced negative results. A meta-analysis confirmed that lamotrigine was not superior to placebo in BDII depression, although it did separate from placebo in BDI (248). Several methodological shortcomings likely resulted in the studies underestimating the drug's effect, including 1) a slow titration which resulted in subjects being on the target dose for a short time, 2) a target dose lower than that often used in clinical practice and in successful maintenance studies (255, 324), and 3) higher placebo response rates. In contrast, a single-blind RCT with a relatively high dose (final peak dose=300mg) and a longer duration (16 weeks) found that lamotrigine monotherapy was as effective as adequately-dosed lithium (mean final serum level=1.1 mEq/L) in N=98 BDII patients (445). Two large RCTs in BDI+BDII and a 12-week open-label trial in patients with BDI+BDII+BDNOS also reported that adjunctive lamotrigine was effective, but did not report results separately for BDII (252, 253). Finally, lamotrigine has robust efficacy in preventing depressive relapse in BDI and BDII (324, 459). Taking all of these factors into consideration we recommend lamotrigine as a second-line treatment, particularly for patients who can tolerate a slow titration and delayed effect.

FIGURE 7 Lamotrigine as a second-line agent for bipolar II depression: Summary of evidence
BDI, bipolar disorder type I; BDII, bipolar disorder type II; RCT, randomized controlled trial [Colour figure can be viewed at wileyonlinelibrary.com]

suicide are similar in BDI and BDII, with approximately one-third of patients with BDII attempting suicide over the course of their illnesses[429] and one in twenty-five completing suicide.[430]

6.2 | Pharmacological treatment of bipolar II disorder

6.2.1 | General considerations for interpreting recommendations

The treatment of BDII has been understudied relative to BDI. This is probably due to the long-standing but discredited impression of BDII as a less severe form of BD. The number of RCTs in BDII is substantially smaller than that in BDI, and those studies that do exist are frequently under-powered. It also remains common for trials to enrol patients with both BDII and BDI without reporting results separately, making it difficult to determine if there are clinically meaningful differences in treatment response between the two illnesses. This is important because, while clinical experience and the results of many studies suggest that response to mood stabilizers and antipsychotics is similar in BDII and BDI, there are enough exceptions to suggest this should not be taken for granted.[248,405,431] This is also the case for antidepressants, which may have a more favourable risk-benefit ratio in BDII (reviewed below). Therefore, in formulating our recommendations, studies that enrolled patients with both BDII and BDI but did not report results for BDII separately are assigned level 4 status (expert opinion) if the proportion of patients with BDII was less than 50%.

The relative paucity of large, methodologically sound clinical trials in BDII creates challenges in formulating evidence-based guidelines. As will be seen, there are fewer treatments with high-quality evidence in BDII compared to BDI and fewer first-line treatment recommendations. The limitations of the evidence base necessitate an awareness of the nuances of the available studies, and a greater reliance on clinical experience. We thus have endeavoured to be clear in outlining the rationale for selecting first, second, and third-line treatments for hypomania, depression, and maintenance treatment of this important illness. There is clearly a pressing need for adequately powered trials in BDII across all illness phases.

TABLE 20 Strength of evidence and treatment recommendations for maintenance treatment of bipolar II disorder

Recommendation	Agent	Evidence level
First-line	Quetiapine	Level 1
	Lithium	Level 2
	Lamotrigine	Level 2
Second-line	Venlafaxine	Level 2
Third-line	Carbamazepine	Level 3
	Divalproex	Level 3
	Escitalopram	Level 3
	Fluoxetine	Level 3
	Other antidepressants	Level 3
	Risperidone[a]	Level 4

[a]Primarily for prevention of hypomania.

6.2.2 | Acute management of hypomania

The general principles for assessing mania apply to hypomania. For some patients, hypomania causes no to minimal functional impairment and may even be associated with brief periods of above-normal functioning. However, prolonged, relatively severe, or mixed or irritable hypomania may be impairing.[423] Treatment should include discontinuing agents that can worsen or prolong symptoms, including antidepressants and stimulants, and initiating appropriate pharmacotherapy.

Unfortunately, many standard medications for mania, including lithium and most atypical antipsychotics, have not been studied in hypomania. There are four placebo-controlled trials that investigated divalproex (level 4),[432] *N*-acetylcysteine (level 4),[433] and quetiapine (level 4)[434,435]; and one open-label study of risperidone (level 4)[436] in acute hypomania. The studies generally suggested efficacy but all had significant weaknesses, including one or more of: (i) small sample sizes, (ii) mixed samples with BDI, BDII, and BD NOS; (iii) mixed samples with hypomania and mania, and (iv) positive findings on some but not all outcomes. The small numbers of patients and mixed samples mean

that even the placebo-controlled trials only met criteria for level 4 evidence (Table 1).

These methodological limitations, coupled with the lack of clinical trial evidence for many medications, make it difficult to make specific suggestions for the treatment of hypomania. Clinical experience suggests that all anti-manic medications are also efficacious in hypomania. Thus, when hypomania is frequent, severe, or impairing enough to require treatment, clinicians should consider mood stabilizers such as lithium or divalproex and/or atypical antipsychotics. *N*-acetylcysteine may also be of benefit, but further studies are needed.

6.2.3 | Acute management of bipolar II depression

The general principles for assessing depression in patients with BDI apply to those with BDII. First, second, and third-line treatment options are listed below and shown in Table 19. Specific considerations regarding each treatment are highlighted in the relevant sections.

First-line

Quetiapine is the only recommended first-line treatment for BDII depression (level 1). Pooled analyses of five identically designed trials demonstrated that quetiapine was superior to placebo, and moreover was equally effective for acute depression in BDI and BDII.[243,437] The latter finding must be reconciled with the fact that quetiapine beat placebo in only three of the five individual trials in patients with BDII, compared to all five in patients with BDI.[253,290,438-440] This is probably because the smaller sample of BDII patients—only about half as many patients with BDII as BDI were enrolled in each of the trials—provided less statistical power for BDII. Finally, open-label studies also suggest efficacy for adjunctive quetiapine (level 4).[441,442]

Second-line

Second-line treatments include lithium, ideally at a serum level of 0.8-1.2 mEq/L (level 2) (Figure 5), and the antidepressants sertraline (level 2) [426] and venlafaxine (level 2),[443,444] mainly for patients with pure (non-mixed) depression (Figure 6). Lamotrigine (level 2) is also recommended as a second-line agent despite conflicting evidence, with the rationale for this provided in Figure 7. ECT (level 3)[261] can also be considered second-line and is a good option, particularly for treatment refractory patients and those in need of rapid response.

Third-line

The third-line options include monotherapy with divalproex (level 4)[258,459,461,462-466] fluoxetine (mainly for patients with pure depression) (level 3)[467-469] tranylcypromine (level 3),[278] or ziprasidone (solely for patients with depression and mixed hypomania) (level 3).[470,471] Adjunctive agomelatine (level 4),[472] bupropion (level 4)[276] eicosapentaenoic acid (EPA) (level 4),[473-475] *N*-acetylcysteine (level 4),[476] pramipexole (level 3),[274] or thyroid hormones (level 4)[272] may also be considered.

Intravenous ketamine (level 3)[477,478] has rapid onset of efficacy and may be considered for patients who are refractory to first and second-line treatments, as well as for those in need of rapid response.

No specific recommendation/agents that require further study

A number of agents do not have sufficient data to warrant specific recommendations for BDII depression, including cranial electrotherapy stimulation (CES),[479] dextromethorphan + quinidine,[480] light therapy,[481-485] lisdexamfetamine (adjunctive),[300] olanzapine,[486] pioglitazone,[302] adjunctive pregnenolone,[306] celecoxib,[297] levetiracetam,[487] adjunctive lisdexamfetamine,[300] s-adenosylmethionine,[488-490] acetyl-L-carnitine + alpha-lipoic acid,[491] adjunctive modafinil,[268] rTMS,[275,492,493] and memantine.[494]

Not recommended

Based on negative placebo-controlled data, we do not recommend paroxetine (level 2 negative).[245]

6.2.4 | Maintenance treatment

Maintenance treatment is important to prevent relapse, reduce subsyndromal symptoms, and improve quality of life. As with BDI, selection of an agent should be informed by acute phase treatment. Recommended agents and their evidence ratings are listed in Table 20.

First-line

Monotherapy with quetiapine (level 1),[495] lithium (level 2),[399,450,452] and lamotrigine (level 2)[323] are first-line options.

Quetiapine. In two 52-week maintenance studies, patients with BDII who achieved remission from depression with quetiapine monotherapy continued it or switched to placebo.[495] A pooled analysis reported that patients treated with quetiapine had a significantly longer time to relapse into any mood episode (hazard ratio [HR] 0.33, or a 67% reduction in the risk of relapse) and into depression (HR 0.28 or a 72% risk reduction). Time to relapse into hypomania was not significantly greater (HR 0.65 or a 35% risk reduction). The latter finding may be related to the low base rate of hypomania, which occurred in only 10% of all study participants. Quetiapine was at least as effective in BDII as in BDI, for which the risk reductions were 42% for any relapse, 48% for depression, and 30% for mania. Adjunctive quetiapine was also studied in a 6-month single-blind trial which randomly assigned patients with either BDI or BDII to lithium or quetiapine added to treatment as usual. They were equally effective in preventing relapse.[453] Results were not presented separately for BDII, but BDII patients responded better to both treatments than did BDI patients.

Lithium. In three placebo-controlled RCTs conducted in the 1970s and 1980s (duration = 11-25 months), lithium decreased the frequency and/or severity of hypomanic and depressive episodes.[399,450,452] Serum lithium levels were 0.8-1.2 mEq/L. A number of active comparator studies also support lithium. As noted above, lithium was as effective as quetiapine in preventing relapse in a 6-month single-blind trial.[453] A 20-month study comparing lithium and divalproex in rapid cycling BDI

+ BDII found the two drugs to be equally effective in preventing relapses.[496] The authors noted that findings were similar for BDII and BDI, but results were otherwise not reported separately for BDII. In a 2.5-year study in BDII + BD NOS, lithium and carbamazepine were equally effective on most outcomes, although a numerical advantage favoured carbamazepine for reducing clinical plus subclinical recurrence.[405] In contrast, head-to-head comparisons with antidepressants (reviewed below) found that lithium was not as effective in preventing depressive relapse as fluoxetine or venlafaxine.[469,497] This may be explained by the mean lithium levels, which were 0.7 mEq/L in both studies, while the fluoxetine trial was also enriched for fluoxetine responders.

Long-term naturalistic data also provide strong support for lithium. In a 6-year study of patients with either BDI or BDII (39% with BDII), lithium reduced time in hypomania/mania by 61% and time in depression by 53% in the entire sample, compared with the period before lithium treatment was initiated.[498] The authors noted that the proportion of time with mood symptoms was significantly lower for BDII than for BDI.

Lamotrigine. In a 6-month placebo-controlled RCT of lamotrigine monotherapy in rapid cycling BDI + BDII, post hoc analysis showed that significantly more lamotrigine-treated than placebo-treated patients with BDII were stable without recurrence into any mood episode,[323] although lamotrigine was not superior to placebo in BDI. In a large 52-week RCT in BDI + BDII, adjunctive lamotrigine was superior to placebo for improving depression severity and remission rates. However, results were not presented separately for BDII.[251] Open-label trials and retrospective chart reviews also support lamotrigine.[248,499-502]

Second-line

Monotherapy with venlafaxine (level 2) or fluoxetine (level 3) are second-line options.

Venlafaxine. In a small 6-month RCT in patients with BDII who responded acutely to venlafaxine or lithium without hypomanic switch, there was a trend for lower rates of relapse into depression for patients treated with venlafaxine. Further, the rate of sustained response was significantly greater in those who continued venlafaxine compared to those who continued lithium.[497] No hypomanic episodes occurred in either group.

Fluoxetine. In a 50-week RCT, the mean time to relapse into depression was significantly longer for fluoxetine than for lithium or placebo. Patients had responded acutely to open-label fluoxetine, making the sample enriched for fluoxetine response. Hypomanic episodes occurred in a similarly low frequency in the three groups.[469] In a separate small 6-month placebo-controlled trial, there was a statistical trend for lower relapse rates with fluoxetine compared to placebo.[503] Finally, a post hoc analysis of a large 12-month placebo-controlled trial found that response rates to fluoxetine were similar in BDII and MDD.[468] However, it did not report whether fluoxetine was superior to placebo in BDII.

Third-line

Divalproex (level 4),[504] carbamazepine (level 3),[405] escitalopram (level 3),[505] other antidepressants (level 3),[454] and risperidone (mainly for prevention of hypomania) (level 4)[436] may be considered as third-line options.

No specific recommendation/agents that require further study

There are insufficient data to make a recommendation regarding olanzapine.[506]

7 | SPECIFIC POPULATIONS

7.1 | Management of bipolar disorder in women at various stages of the reproductive cycle

7.1.1 | Pre-conception, psychoeducation and contraceptive counselling

The importance of pre-conception counselling should be raised with all women of child bearing age. It should be provided for all patients at least 3 months prior to considering pregnancy or immediately for those already pregnant. The issues most frequently raised are fear of adverse

TABLE 21 US Food and Drug Administration (FDA) classification of teratogenicity for medications commonly used in bipolar disorder[a]

	Pregnancy risk category[b]	Lactation risk category[c]
Lithium	D	L4
Anticonvulsants		
Carbamazepine	D_m	L2
Divalproex	D_m	L4
Lamotrigine	C_m	L2
Atypical antipsychotics		
Aripiprazole	C_m	L3
Clozapine	B_m	L3
Olanzapine	C_m	L2
Quetiapine	C_m	L2
Risperidone	C_m	L2
Ziprasidone	C_m	L2
SSRI antidepressants		
Citalopram	C_m	L2
Escitalopram	C_m	L2
Fluoxetine	C_m	L2
Fluvoxamine	C_m	L2
Paroxetine	D_m	L2
Sertraline	C_m	L2
Other antidepressants		
Bupropion	B_m	L3

[a]FDA has replaced these risk categories in 2015 with Pregnancy and Lactation Labeling Final Rule (PLLR). SEE TEXT FOR DETAILS.
[b]Adapted from ACOG Committee on Practice Bulletins–Obstetrics[878]: US Food and Drug Administration Rating. A = controlled studies show no risk; B = no evidence of risk in humans; C = risk cannot be ruled out (human data lacking, animal studies positive or not done); D = positive evidence of risk (benefit may outweigh risk). The "m" subscript is for data taken from the manufacturer's package insert.
[c]Hale TW and Rowe HE.[879] Lactation risk categories are listed as follows: L1, safest; L2, safer; L3, moderately safe; L4, possibly hazardous; L5, contraindicated.

effects of medications on the fetus, fear of illness recurrence, and genetic transmission to offspring.[507] Other important topics to review include the effect of BD on risk for gestational hypertension, antepartum haemorrhage, induction of labour, caesarean section, instrumental delivery, preterm delivery, and neonatal size.[508,509] Discussion of modifiable risk factors is critical in pre-conception management of BD. For instance, pregnant women with BD are more often overweight, more often smoke tobacco during pregnancy, have poorer diet quality, and present more often with a history of drug and alcohol misuse in pregnancy.[509] Modification of these risk factors may have a significant positive impact on outcomes for both the mother and child.

Decisions should be made collaboratively on whether medications should be continued, discontinued, or switched; and whether any dosage changes are needed. Conventional antipsychotics and risperidone may need to be discontinued to increase the likelihood of conception, as these medications often increase serum prolactin levels and thus interfere with ovulation and decrease fertility.[510] For women who wish to have a medication-free pregnancy, it might be appropriate to have one or more psychotropic medications gradually tapered off prior to conception provided they have been clinically stable for a minimum of 4-6 months and are considered at low risk of relapse. Information regarding potential teratogenic effects of different psychotropic medications, as well as limitations of the scientific evidence, should be discussed and carefully considered. The decision to stop medications pre-conceptually should ideally occur only after careful individualized risk-benefit analysis for a given patient.[511-513] If pharmacotherapy is required, monotherapy at minimum effective dose is recommended whenever possible.[514,515]

Contraceptive counselling, including emphasis on its effectiveness in reducing the likelihood of unintended pregnancies, should be included as part of a comprehensive treatment plan for women with BD.

Several anticonvulsants, including carbamazepine, topiramate, and lamotrigine, can affect the pharmacokinetics of oral contraceptives and some might significantly reduce the effectiveness of oral contraceptives, and this should be considered when making treatment decisions.[516,517] Oral contraceptives might also have effects on the efficacy of lamotrigine via reduction in lamotrigine levels.[516]

While folic acid supplementation is protective against spontaneous spina bifida, there is not enough evidence to indicate that folic acid, even in high doses, protects against spina bifida following the use of anticonvulsants.[518] In addition, Health Canada recommends that "Valproate products (valproic acid, divalproex sodium) should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of its high teratogenic potential and risk of developmental disorders in infants exposed in utero to valproate." Health Canada also recommends that women of childbearing potential must use effective contraception during treatment and be informed of the risks associated with the use of valproate products during pregnancy, and in women planning to become pregnant every effort should be made to switch to appropriate alternative treatment prior to conception.[519]

Regardless of treatment decisions made prior to or following conception, it is also important to work with the patient to develop and agree upon a monitoring schedule and treatment plan to be implemented should clinically significant symptoms emerge. Education about the risks of psychotropic medications is critical, and careful discussion is needed regarding the magnitude of risks and benefits and limitations with the data. It is important to acknowledge the patient's desire to do what is right for the child and support the decision made. Whenever appropriate, involve partners in the discussion and review the decision and supporting evidence for it directly or through educational materials.[520]

7.1.2 | Screening for bipolar disorder during pregnancy and postpartum

All women with depressive symptoms should be screened for BD during pregnancy and the postpartum period.[521,522] Standardized screening tools such as the Mood Disorder Questionnaire alone or in conjunction with the Edinburgh Postnatal Depression Scale are useful.[521-524] Importantly, screening should be followed by a clinical interview to confirm or exclude a diagnosis of BD. Women should also be assessed for other psychiatric disorders that commonly co-occur with BD, such as anxiety disorders or obsessive compulsive disorder (OCD).[525]

7.1.3 | Pharmacological management of bipolar disorder during pregnancy

Given the complexity of the risks faced by women with BD in pregnancy and puerperium, it is good clinical practice to encourage liaison between the mental health and obstetrics/gynecology teams. A longitudinal study conducted in a tertiary care centre found a high risk of recurrence during pregnancy: 85% of pregnant women with BD who discontinued a mood stabilizer and 37% of those who were maintained on one or more mood stabilizers experienced a mood episode—predominately depressive or mixed—during pregnancy. For nearly half of the patients, recurrence occurred in the first trimester, with the median time for recurrence for those abruptly discontinuing treatment being 2 weeks, compared to 22 weeks for those who were gradually tapered off.[511] However, studies from primary care, as well as obstetric centres, found low rates of relapse or hospitalizations in pregnancy.[526]

The hierarchies presented throughout these guidelines should be followed for management of the various phases of BD, with consideration given to specific risks associated with the use of each medication using the most up-to-date information available from the US Food and Drug Administration (FDA) website (http://www.fda.gov/ForConsumers/ByAudience/ForWomen/WomensHealthTopics/ucm117976.htm).

Table 21 includes a brief overview of medications commonly used in BD and the risk categories. This list should not be viewed as complete or comprehensive. Further, the FDA has replaced these risk categories in 2015 with Pregnancy and Lactation Labeling Final

Rule (PLLR) with narrative sections and subsections. For instance, for pregnancy, the information for each medication is provided using the following subheadings: Pregnancy exposure registry, Risk summary, Clinical considerations, and Data. The last three subsections apply to medication risks during lactation. The FDA has not finalized and published the data for all medications as of completion date of these guidelines (February 2018), and new data appear to suggest that risks may have been overestimated for some medications such as lithium.[527] Thus clinicians are strongly advised to use all the current data, including the FDA PLLR information if available, in collaboration with patient and family members to make final treatment decisions.

Wherever possible, psychosocial strategies should be preferred over medications in the first trimester as this period holds the highest risk for teratogenicity. When medications are deemed necessary, preference should be given to monotherapy using the lowest effective dose.

Each pregnancy should be closely monitored and appropriate screening tests (eg, foetal ultrasound if lithium is used in the first trimester) should be performed.[528] Divalproex should be avoided during pregnancy due to elevated risk of neural tube defects (up to 5%), even higher incidences of other congenital abnormalities, and evidence of striking degrees of neurodevelopmental delay in children at 3 years of age and loss of an average of nine IQ points.[529-531] Because of changes in physiology in the second and early third trimesters, such as increased plasma volume, hepatic activity, and renal clearance, patients may require higher doses of medications towards the later part of the pregnancy. Prenatal vitamins, including high-dose (5 mg/day) folic acid, are also recommended, preferably even before conception and continuously through pregnancy; and preparations containing choline have recently been recommended as possibly preventive of the later development of schizophrenia.[532] While it is important to note that folic acid may reduce the effectiveness of lamotrigine,[251] the anti-teratogenic effects of folate may outweigh the potential for this loss of effectiveness. However, recent concerns have been raised regarding a potential association between very high plasma levels of maternal folate and risk of autism spectrum disorders.[533]

7.1.4 | Pharmacological management of bipolar disorder during the postpartum period

The postpartum period is a time of elevated risk for recurrence, with 66% of women who were medication free during pregnancy and 23% of those on treatment experiencing a mood episode following the delivery.[534] The risk of postpartum relapse is highest in women who also experienced a mood episode during pregnancy and those who are not on prophylactic treatment.[535] Despite the high prevalence of postpartum episodes, there is a dearth of studies investigating the efficacy of medications during this period. There is evidence of efficacy of benzodiazepines, antipsychotics, and lithium for postpartum mania,[535] and quetiapine for postpartum bipolar depression (level 4).[536] There are no studies of psychotherapy in the acute or preventative treatment of bipolar postpartum depression.[537]

Patients should be encouraged to initiate or optimize maintenance treatment as soon after giving birth as possible, with preference given to medications that have previously been shown to be successful. Near delivery, close monitoring is essential for early detection and management of symptoms that might signal onset of a mood or psychotic episode.[538] If an acute mood episode emerges in the postpartum period, the hierarchies for non-postpartum episodes should be followed, but, because most psychotropic medications are excreted in breast milk, treatment choice should take into consideration safety in breastfeeding when applicable.

The FDA website mentioned in the previous section as well as Table 21 also include information on lactation. The FDA PLLR should be consulted for further information about medication risks, as many are secreted in milk, if breastfeeding is being considered.

The potential risks and benefits of taking medications while breastfeeding should be discussed with the patient. Education about early recognition of drug toxicity and requirement for ongoing monitoring of infants is also critical.[539] A recent systematic review suggested quetiapine and olanzapine as preferred choices for breastfeeding, considering their relatively lower infant dosages.[540] The impact of medication on the infant can be reduced by scheduling medication administration after breastfeeding.[541]

Replacing or supplementing breast milk with formula can also be considered. Although there are many benefits to breastfeeding, associated sleep disruption may increase the risk of mood episodes in women with BD. If possible, bottle feeding at night by the woman's partner or a support can be beneficial to allow the woman to maintain a better sleeping schedule. In women with postpartum psychosis or mania, breastfeeding may be more risky, and therefore may not be indicated, as the mother may be too disorganized to safely breastfeed.[542]

As childbirth can be a trigger for first onset of hypomania/mania in women with MDD, antidepressants should be used cautiously, especially in women with a family history of BD.[543] Women with first onset of depression in the postpartum period or those who have recurrence of depression during the early postpartum period, may also be at a high risk of switching to BD following treatment with antidepressants.[537]

7.1.5 | Impact of the menstrual cycle on symptoms

Despite the paucity of large, well-designed research studies examining the impact of the menstrual cycle on mood symptoms in BD, accumulating evidence suggests that hormonal changes can impact the course of illness. Several case reports and prospective studies suggest that women who experience premenstrual symptom exacerbation are more likely to have a highly symptomatic and relapse prone illness.[544,545] One of the largest studies (n = 1099) found that women who met DSM-5 provisional criteria for premenstrual dysphoric disorder (PMDD) had an earlier illness onset, more comorbid Axis I disorders, a higher number of hypomanic/manic and depressive episodes, and higher rates of rapid cycling.[546] In this study, there was a closer gap between BD onset and age of menarche in women with comorbid PMDD, which suggests that sensitivity to endogenous hormones may influence the onset and the clinical

TABLE 22 Differential diagnosis of manic symptoms in children and adolescents

Symptom	Bipolar mania hypomania	Attention deficit hyperactivity disorder	Oppositional defiant disorder
Elation	Episodic, prolonged, pathological (inappropriate to context or uncharacteristic), associated with change in functioning, "travels" with ≥3 other manic symptoms	If present, not clearly episodic or pathological	If present, not clearly episodic or pathological
Irritability	Episodic, prolonged, pathological, associated with change in functioning, "travels" with ≥4 other manic symptoms	Can be an associated feature, related to stimulant rebound, or due to a comorbid illness (eg, ODD)	Diagnostic criterion, lacks distinct prolonged episodes, does not "travel" with other manic symptoms
Sleep	Reduced need for sleep (ie, significantly less sleep than usual without increased daytime fatigue or somnolence); change must be mood-related	Insomnia (ie, difficulty falling asleep); can be an associated feature or associated with stimulants, but need for sleep is unchanged	Not a symptom or common characteristic; may defy bedtime rules or routine
Grandiosity	Distinct uncharacteristic increase in confidence or self-importance; change must be mood-related	Not a symptom or common characteristic	Defiance toward authority figures is common but not necessarily mood-related
Hyperactivity and distractibility	Episodic; if comorbid ADHD is diagnosed, then distinctly "worse than usual" change must be mood-related	Diagnostic criteria, nonepisodic	Not prominent or episodic

ADHD, attention-deficit hyperactivity disorder; ODD, oppositional defiant disorder (Adapted from Goldstein and Birmaher 2012[555]).

course of BD. Premenstrual syndrome (PMS) and PMDD also occur more frequently in women with BD.[547,548] Importantly, an accurate diagnosis of comorbid PMDD in women with BD is made during euthymia, with a minimum of 2 months of prospective symptom charting.[549]

7.1.6 | Menopause

For many women, stress and hormonal changes associated with the transition to menopause may increase or trigger mood symptoms.[550-552] A post hoc analysis of the prospective Systematic Treatment Enhancement Program for Bipolar disorder (STEP-BD) study showed increased rates of depressive, but not manic episodes during menopause transition.[553] However, due to the paucity of clinical trials in this area, more data are needed before treatment recommendations can be made.[554]

7.2 | Management of bipolar disorder in children and adolescents

7.2.1 | Presentation and diagnosis

As the following section comprises only a brief overview of the epidemiology, phenomenology, and differential diagnosis of BD in children and adolescents, the reader is referred to more detailed reviews for further information.[555-560]

Between one-third (community samples) and two-thirds (clinical samples) of patients with BD experience their first mood episode during childhood or adolescence, with an earlier onset related to a more severe illness characterized by increased symptom burden and comorbidity.[561,562] In contrast to the controversies of as recently as a decade ago, there is now far greater consensus in the field that, although there are developmental differences in the manner in which symptoms manifest themselves, the actual diagnosis of BD in children and adolescents should be made based on the same set of symptoms as applied to adults.[563] When defined rigorously according to DSM-5 criteria, the course of illness in childhood and adolescence is characterized by eventual high rates of symptomatic recovery, but also high rates of recurrence, even in the context of naturalistic treatment.[564] While the concepts of "over-diagnosis" and "over-treatment" in pediatric BD have received substantial attention,[565] representative population studies demonstrate that adolescent BD is characterized by low rates of treatment, alongside high rates of suicidality and comorbidity.[566,567] Risks of incorrectly diagnosing and treating BD in a child or adolescent should thus be carefully weighed against the risk of incorrectly or not diagnosing or treating,[568] keeping in mind that the duration of treatment delay has been shown to be an independent risk factor for a poor outcome in adulthood.[569]

Distinguishing early-onset mania or hypomania from other psychiatric disorders is important as there is a high level of symptomatic overlap for multiple conditions including but not limited to ADHD, oppositional defiant disorder (ODD), disruptive mood dysregulation disorder (DMDD), substance abuse, personality disorders and generalized anxiety disorder[555,570] (Table 22). The discrete episodes of mania/hypomania and the non-overlapping symptoms can facilitate accurate diagnosis. When a comorbidity is present, such as ADHD, overlapping symptoms (eg, distractibility and hyperactivity) should only count towards a diagnosis of mania or hypomania if they intensify during intervals of elation or irritability. Notably, ADHD is an ongoing condition whereas BD is episodic, and decreased sleep, hypersexuality, hallucinations or delusions, and homicidal or suicidal thoughts and actions occur with childhood mania, but are rare or absent in uncomplicated ADHD.

It is important to note that, while chronic irritability with episodic behavioural outbursts or rages can be seen in multiple paediatric psychiatric disorders (including emerging personality disorders, substance abuse,

Reconciling the paucity of RCT data with abundant clinical experience in determining level of recommendation for treatment of pediatric bipolar depression

Aside from lurasidone, which has positive RCT data (597) alongside good tolerability, options include either treatments with substantial tolerability concerns (olanzapine-fluoxetine combination) or treatments with no RCT data (eg. lithium, lamotrigine) or without positive RCT data (eg.quetiapine). In this instance, clinical experience combined with tolerability considerations and adult data informed the ranking of recommendations. Lithium and lamotrigine have not been tested in RCTs in pediatric bipolar depression. However, there is abundant clinical experience with these agents in treating depression in the pediatric group alongside positive open trials. Further, these agents are recommended for treating acute bipolar in adult populations, and they have good tolerability. Thus, despite lack of RCT data, they are recommended as second-line agents for treating acute bipolar depression in pediatric population.

In terms of quetiapine, of the two negative RCTs (601, 602), one had a dose range of 300-600 mg/day but was limited to 32 participants and had a 67% placebo response rate. The other study was dosed at only 150-300 mg/day and had a 55% placebo response rate. One can argue that the quetiapine studies have been failed, rather than truly negative, studies. Therefore, given its demonstrated efficacy in adult bipolar depression and methodological problems in studies of pediatric bipolar depression and based on clinical experience, it is recommended as a third-line option.

Ultimately, treatment decisions in general, but particularly in the context of empirical uncertainty, should be informed by a thorough discussion of comparative risks and benefits of competing options. Risk-benefit ratios may differ across patients depending on factors such as BD subtype, comorbid anxiety, and sleep disturbance.

FIGURE 8 Treatments for pediatric bipolar depression: Summary of evidence [Colour figure can be viewed at wileyonlinelibrary.com]

ODD, pervasive developmental disorders, and major depressive episodes), such irritability and explosiveness are not sufficient to make a diagnosis, even when severe. The recent DSM-5 diagnosis DMDD—which includes chronic irritability as a defining feature—lists BD as an exclusion criterion. However, the DMDD phenotype is evident in about 25% of adolescents with episodic BD, and is associated with factors such as greater family conflict and ADHD comorbidity.[571] Classical BD and chronic irritability are therefore not mutually exclusive, the nonspecific nature of the latter notwithstanding.

A significant minority of children or youth with MDD will eventually go on to develop BD, with an average rate of 28% being reported.[572,573] Risk factors for switch to mania following a depressive episode include a family history of mood disorders, emotional and behavioural dysregulation, subthreshold manic symptoms, cyclothymia, atypical depression and psychosis.[572] A recent meta-analysis suggested that the most potent predictors were family history, an earlier age of onset and the presence of psychotic symptoms.[574] There is an increased prevalence of BD among offspring of parents with BD.[575-577] Although there is no uniform strategy for managing depression (or ADHD, anxiety, etc.) in the child of a parent with BD, increased caution is warranted when prescribing antidepressant or stimulant medications as these have the potential to precipitate mania/hypomania.[578] Patients and their parents should be informed of the potential switch risk and close monitoring for treatment-emergent manic/hypomanic switch should be instituted.

Self-report and/or parent-reported questionnaires can be informative and can raise the index of suspicion for BD.[579] However, scores on such questionnaires as the Child Behaviour Checklist (CBCL) "dysregulation phenotype", previously described as "BD phenotype", have poor capacity for differentiating BD from other complex and severe symptomatic presentations.[580] Questionnaires can be used as screeners, but do not substitute for a thorough diagnostic evaluation. Longitudinal rating by parents may be most helpful in diagnosis and assessment of treatment response. An online program for weekly parental ratings (of depression, anxiety, ADHD, oppositional behaviour, and mania) of children aged 2-12 years is available at www.bipolarnews.org, click on Child Network.[581]

7.2.2 | Pharmacological management

General principles

The general principles for managing adults with BD also apply to children and youth. In youth, themes of comorbidity and tolerability are accentuated. Comorbid ADHD is more common in children and adolescents as compared to adults with BD. Moreover, ADHD symptoms often do not improve following mood stabilization, and may require concurrent ADHD treatment. In addition, due to elevated risk for accelerated atherosclerosis and early cardiovascular disease in this population, cardiovascular risk factors should also be assessed regularly and intervention implemented. Lifestyle management including attention to diet, substance use, smoking and physical activity should be implemented alongside any psychological or pharmacological interventions.[582] Relatedly, children and adolescents are more susceptible than adults to the metabolic side effects of psychiatric medications, particularly the atypical antipsychotics that are considered first-line treatments.[583] Taken together, these distinguishing features underscore the importance of ensuring that polypharmacy, as often required, is judicious and informed by a balance of factors including mood symptom burden, global functioning, and physical health.

Acute management of mania

First-line. Lithium (level 1),[583-585] risperidone (level 1),[584,586] aripiprazole (level 2),[587] asenapine (level 2),[588] and quetiapine (level 2)[583,589] are recommended as first-line options. Risperidone may be preferable to lithium for non-obese youth, and youth with ADHD.[584]

Second-line. Due to safety and tolerability concerns, olanzapine (level 2)[590] and ziprasidone (level 2)[591] should be considered second-line options. Quetiapine adjunctive therapy (level 3)[592] is also recommended as a second-line treatment.

Third-line. Despite low response rates in two RCTs, a long history of use among adults with BD, combined with positive findings in open-label studies are grounds for considering divalproex as a third-line option for youth who do not respond to or tolerate first or second-line agents (level 4).[593]

Not recommended. Oxcarbazepine was not superior to placebo in a large RCT (level 2 negative).[594]

Acute management of bipolar depression

The data in paediatric samples are very limited, and complicated by extremely high placebo-response rates in RCTs. These recommendations are therefore to a greater extent informed by clinical experience and studies in adults than the above acute mania recommendations (see Figure 8).

First-line. A recently published RCT found that lurasidone was superior to placebo (level 2)[595] in improving depressive symptoms in children and adolescents with acute bipolar depression; however there is comparatively little clinical experience in this population. Nevertheless, given its efficacy and clinical experience in adult bipolar depression, lurasidone is recommended as a first-line treatment.

Second-line. Although lithium and lamotrigine were recommended as first-line agents for bipolar depression in adults, there are only open-label data for lithium (level 4)[596] and lamotrigine (level 4)[597] in children and youth. Despite limited RCT data, there is, however, substantial clinical experience with these agents as they are widely used in clinical practice. For this reason, together with the strength of evidence in adults, lithium and lamotrigine are recommended as second-line, rather than third-line agents (see Figure 8).

Third-line. There is a positive RCT of olanzapine-fluoxetine combination among youth with bipolar depression (level 1)[598]; however, metabolic concerns regarding olanzapine, and limited clinical experience with olanzapine-fluoxetine combination in youth lead to the positioning of this option as third-line. Despite negative findings in paediatric samples, quetiapine (level 2 negative)[599,600] is also recommended as third-line for this population due to the abundance of evidence from adult studies combined with substantial clinical experience. There are also several methodological concerns with the studies done in pediatric samples (see Figure 8).

Despite limited knowledge regarding the precise risks of antidepressant-induced mania in youth with BD, observational pharmaco-epidemiology studies support the conclusion that antidepressants should be used with caution in BDI and BDII, and in combination with mood-stabilizing medication (level 4).[578,601]

Not recommended. A large RCT found that oxcarbazepine was not superior to placebo (level 2 negative)[594] although it was effective in the youngest group of patients but not the older adolescents.

Maintenance treatment

The data in paediatric samples are very limited. These recommendations are therefore informed by clinical experience and studies in adults to a greater extent than the above acute mania recommendations.

First-line. Preferred maintenance treatment options for this population are aripiprazole (level 2),[602,603] lithium (level 2)[604] and divalproex (level 2).[604,605] However, it should be noted that follow-up duration for the aripiprazole study was only 30 weeks, and the sample size in the 18-month maintenance study of lithium vs divalproex was only 30 participants. It is important to note that few patients continued to do well upon the switch to either lithium or divalproex monotherapy and the majority re-responded when the combination was reinstated. Further, other studies have also suggested the efficacy of combination therapy (eg, risperidone plus lithium or divalproex[584] and lithium plus divalproex or carbamazepine[606]) to achieve and maintain remission. Adjunctive lamotrigine may also be considered for those aged ≥ 13 years (level 2).[607]

Second-line. No treatments with level 3 or higher evidence are available to recommend as second-line options for maintenance.

Third-line. Although there has been far less experience with asenapine than with other medications discussed in this section, a recent open-label extension study suggests continual reduction in manic symptoms over 50 weeks (level 4).[608] Further, a recent RCT in adults confirmed its efficacy in preventing relapse of mood episodes.[374] Although there have not been maintenance studies for quetiapine, risperidone, or ziprasidone in this population, clinical experience and open-label studies indicate that continuation and maintenance treatment with these medications is another option, particularly for those patients who have responded well to acute treatment (level 4).[591,609,610] Further, there is evidence that oral quetiapine and long-acting injectable risperidone monotherapy and adjunctive therapy and oral ziprasidone adjunctive therapy are effective in preventing mood episodes in adults with BD.[369,370,383,384,387]

Treatment of comorbid conditions

ADHD. Stimulants may also be used for comorbid ADHD in stable/euthymic youth taking optimal doses of anti-manic medications. Adjunctive mixed amphetamine salts (level 3)[611] and methylphenidate (level 3)[612] have both been shown to be effective in addressing attention symptoms and have been well tolerated overall within the RCTs completed to date, theoretical and epidemiological data regarding risks of induction of mood elevation notwithstanding.[613] Although open trials suggest potential benefits of atomoxetine (level 4),[614,615] the possibility of inducing mania or hypomania remains,[616] suggesting the need for RCTs before clinical recommendations can be made.

Substance use. Comorbid substance use should be treated concurrently to mood symptoms, with inpatient hospital or community residential treatment employed as clinically indicated. A small study suggests that lithium may be effective for reducing substance use in this population (level 3),[617] and FFT should also be considered (Section 2). Positive trials of *N*-acetylcysteine for cannabis use disorders among adolescents,[618] smoking,[619] and bipolar depression among adults [281] suggest that *N*-acetylcysteine may benefit adolescents with comorbid bipolar and SUDs; however, studies examining this hypothesis have not yet been completed (level 4).

7.3 | Management of bipolar disorder in older age

7.3.1 | Presentation and course

Because of the aging population in Canada and many countries around the world, knowledge of pertinent issues related to the management of older adults is becoming increasingly important. Approximately 6% of geriatric psychiatry outpatients and 10% of inpatients have BD,[620] and proportionally this population is one of the highest users of psychiatric and physical health services.[621] Approximately 25% of the patients with BD in the USA in 2005 were over the age of 60 years,[622] and by 2030 >50% of patients with BD are expected to be aged >60 years.[623]

The lifetime prevalence of late-life BD is about 1%-2% with a 1-year prevalence of 0.1%-0.7% in the general population. About 90%-95% of older adults with bipolar disorder have their initial episode prior to age 50 years, although there is a minority who will have a later onset.[624,625] Late onset is often related to neurological or physical comorbidity,[626] and may carry a negative prognosis,[627] although this is not a consistent finding.[628]

While symptoms of mania or hypomania are generally less prominent in older adults, depressive and cognitive symptoms are more often observed, and hyperactivity, aggression, insomnia, impulsivity, and self-neglect may pose a significant risk to the patient and others.[629,630] Psychiatric comorbidity is also generally lower than in younger patients, with anxiety and substance use being the most common.[631] Compared to younger patients, older adults are less likely to utilize inpatient, outpatient, and emergency room services and more likely to use case-management and conservator services.[632]

Cognitive dysfunction is a significant concern for this population, with >30% showing significant deficits across all mood states, including euthymia.[633] This cognitive dysfunction is relatively stable, related to the number of mood episodes earlier in life, and does not appear to exceed normal aging in 2-5-year follow-up.[634-636] Lithium use has been associated with lower rates of cognitive disorders in BD,[637] and higher lithium levels in drinking water may be associated with lower dementia risks,[638,639] although prospective trials are required to definitively assess this. Standardized instruments, such as the Montreal Cognitive Assessment (MoCA), should be used to quantify cognitive dysfunction. Because of the link between cognition and functioning in BD,[634,640] the impact of medications (particularly those with a high anticholinergic burden) on cognition should be considered when making treatment decisions. Furthermore, improvement of modifiable risk factors such as diet, exercise, and mental stimulation should also be promoted in order to further diminish the risk of cognitive decline.

7.3.2 | Medical comorbidity

Older adults with BD have an average of three to four medical comorbidities, with metabolic syndrome, hypertension, diabetes, cardiovascular disease, arthritis, and endocrine abnormalities being the most common.[631,641] Together, these contribute to a reduction in life expectancy of 10-15 years in BD compared to non-psychiatric populations.[642] Because of these high rates of comorbidities, assessment of an older adult with BD should include a thorough physical and neurological examination, including clinical laboratory tests. Neuroimaging should also be applied as indicated, particularly in the presence of focal neurological signs and symptoms or abrupt late onset, or if the presentation is different from prior episodes. Coordination with other health care providers is also imperative, as this can optimize physical health,[643] as can smoking cessation.

7.3.3 | Pharmacological treatment

The data supporting efficacy of medications in various mood states in this population are limited, with only a single RCT exclusively in geriatric patients completed to date, comparing lithium vs divalproex for the treatment of mania/hypomania.[644] Despite this, open-label trials, naturalistic studies, and post hoc analyses of mixed aged RCTs suggest that medications efficacious in adults overall will also be effective in older adults, although additional considerations regarding medication tolerability and age-related changes in pharmacokinetics and pharmacodynamics must be taken into account. Because of the high number of medical comorbidities as well as physical changes related to the aging process, strict attention must be paid in these patients to potential pharmacokinetic issues, drug-drug interactions, side effects, and the need for ongoing monitoring (see Section 8).

Amongst other effects, lithium has been associated with adverse neurological effects[645] and renal disease.[646] Divalproex has been associated with motor side effects[645] and metabolic effects (weight gain and diabetes mellitus).[647] Carbamazepine induces cytochrome P450 enzymes and can reduce the levels of divalproex and other medications.[648] Regarding antipsychotics, which are now very commonly used for BD in older adults, dose reduction may be beneficial in some aging patients to lower the risk of motor, sedation, metabolic syndrome, and cognitive effects.[649] There is an association between mortality and antipsychotics in patients with dementia[650] but it is unclear how this should be managed for patients with BD. Recently there have also been data linking antipsychotics with acute kidney injury.[651]

In particular, when lithium is used in this population, lithium level and renal monitoring should occur at least every 3-6 months, as well as 5-7 days following a lithium dose adjustment or adjustment of nonsteroidal anti-inflammatory drugs (NSAIDs), antiontensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), or thiazide diuretic dosing.[652] Special consideration also needs to be given to dose selection. A post hoc analysis of the STEP-BD study found that while, on average, older patients required a similar number of medications to younger patients to achieve recovery, lower doses were used. In that sample, over twice as many older patients as younger ones recovered using lithium alone (42% vs 21%, respectively).[653] In general, starting at a lower dose (eg, 150 mg nightly for lithium) is recommended, with gradual adjustments to reach the lowest end of the therapeutic range for adults, with subsequent titration based on tolerability and effectiveness; keeping in mind that some older patients will require similar blood levels as the general adult population in order to achieve remission. Further discussion, including clinical guidance and

more detailed treatment recommendations, can be found in the ISBD Task Force report.[654] In light of very limited international guidelines for maintenance treatment of older adults with BD, an ISBD Task Force is currently undertaking a Delphi survey of international experts, and clinicians are advised to consult this as results become available in the future (Shulman K, personal communication).

Pharmacological treatments have been evaluated using the criteria for strength of evidence for efficacy (Table 1) in older adults as well as safety and tolerability (Section 8). Unfortunately, there is a dearth of literature for efficacy of treatments in older adults. However, clinical experience supports the notion that treatments known to work in general adult populations are also effective in older adults. Tolerability may be different and this is an important consideration in treatment selection in older adults. General principles for management of acute episodes described in Sections 3 and 4 also apply to this population.

Acute mania

Monotherapy with lithium (level 2)[644] or divalproex (level 2)[644] is recommended as a first-line treatment. Quetiapine (level 2)[655] can be considered as second-line. Asenapine (level 4),[656,657] aripiprazole (level 4),[658] risperidone (level 4),[659] or carbamazepine (level 4)[654] may be applied as third-line treatments. For treatment-resistant episodes, clozapine (level 4)[660] and ECT (level 4)[654] should also be considered.

Bipolar depression

There are no RCTs of any agents in older adults with acute bipolar depression. Post hoc analyses of RCTs suggest efficacy of quetiapine (level 2)[661] and lurasidone (level 2)[662] monotherapy and hence these are recommended as first-line options. However, in older adults, given the concerns about side effects of atypical antipsychotics, clinicians may wish to try lithium or lamotrigine first based on their efficacy in adult populations, although the evidence of efficacy is limited in older adults (lithium, level 4; lamotrigine, level 4).[663,664] Divalproex (level 4), aripiprazole (level 4),[658] and carbamazepine (level 4)[665] are third-line options. ECT (level 4)[654] is an important option that should be considered in treatment-resistant cases, for suicidal patients, or for patients with inadequate food or fluid intake.

While the use of antidepressants in BD remains controversial[260,426] and there have been no studies in older age BD; antidepressants are frequently used in this population (>40% of patients).[666] Antidepressants with lower manic switch potential (eg, SSRIs and bupropion)[260] used in combination with mood stabilizers may be beneficial in selected patients who cannot tolerate/do not respond to other agents with a stronger geriatric evidence base. Possible medication interactions with ongoing medications for non-psychiatric conditions must always be considered.

Maintenance

Choice of agents should be based on what has been effective in the acute phase, with recommended options with geriatric efficacy data being lithium (level 2),[667,668] lamotrigine (level 2),[668] and divalproex (level 3).[667]

7.4 | Management of comorbid conditions in bipolar disorder

7.4.1 | Comorbid psychiatric disorders

Epidemiology

Most patients diagnosed with BD will also have at least one comorbid psychiatric diagnosis. The most common comorbid conditions are substance use disorder, anxiety disorder, personality disorder, and impulse control disorder (such as ADHD, ODD, and CD).[45] Comorbidity impacts the course of BDs by increasing the likelihood of treatment resistance and suicide risk, and also by increasing the time spent with impairing symptoms.[34,50,669,670]

When treating comorbid conditions, determining which disorder to address first requires careful consideration. Some comorbid disorders may be managed with the same treatment employed to manage bipolar symptoms (eg, quetiapine for comorbid anxiety and BD), while other comorbid disorders (eg, ADHD) may require distinct treatments. Importantly, some treatments for comorbid disorders may lead to bipolar symptom destabilization; for instance, an antidepressant employed to treat an anxiety disorder may provoke mood elevation.

Safely and effectively managing comorbid conditions often necessitates the implementation of a hierarchical approach, depending on each patient's individual needs and preferences. In general, the disorder or symptom associated with the greatest morbidity and mortality—such as acute mania, psychosis, or suicidal ideation—should be managed first. Substance use disorders may be addressed concurrently or sequentially, depending on severity and contribution to mood instability. Once mood stability is established, the treatment of additional comorbid conditions, such as ADHD or metabolic disorders, should follow based on their impact and the patient's preference.

There is a dearth of research to guide the best management of BD in the context of comorbid conditions. There have been few trials designed with comorbid symptoms as the primary target for mood-stabilizing treatments—evidence is mainly derived from secondary analysis of published data. Thus, the limited research informing the treatment of comorbidities constrains our ability to make definitive recommendations. However, because comorbidity is so common and burdensome for patients, appropriate management is a challenging daily reality in clinical practice. Therefore, CANMAT decided to provide a brief overview of relevant clinical issues and the evidence base for pharmacological treatments for treating comorbid populations. The reader is advised to consult the following references for the role of psychological treatments in managing comorbidity.[671-673]

Substance use disorders

Two recent reviews indicated that the prevalence rate of comorbid SUD in BD is about 33% in general population surveys[674] and approximately 45% in clinical settings.[675] SUD can negatively impact the course of BD, resulting in lower rates of remission,[407] a higher number of hospitalizations,[676,677] and an increased risk of suicide attempts[429] and perhaps suicide deaths.[678]

Substance use should be addressed as early as possible, as it is likely to interfere with treatment for BD. However, the presence of a SUD should not preclude an attempt to treat BD, which might result in an individual being more amenable to treatment. As the directionality of the interaction between SUD and BD is rarely clear in the reality of clinical practice, it is recommended that the two conditions be treated simultaneously.

A more detailed discussion on the impact of and the general principles of the treatment of substance use comorbidity can be found in a CANMAT Task Force publication,[679] and other reviews[673,681] and a meta-analysis[680] published on the topic since 2012. Here we provide a brief update on the pharmacological treatments identified in the CANMAT Task Force publication. It is important to note that the criteria for level of evidence used here are more stringent than those applied to the Task Force report.

The levels of evidence for treatment of comorbid SUD are low. This is because of (i) the paucity of data, (ii) complexity of study designs (given the fact that many patients will be using more than one substance), and, most importantly (iii) inconsistency of the outcome variables used in these studies; hindering direct comparison of results. Nevertheless, some evidence-based recommendations are available for clinicians, starting with general principles of treatment: if at all possible, avoid medications that could increase the risk of destabilizing the BD, and choose treatments that could help both conditions.

Alcohol use disorder

A combination of divalproex and lithium is the only treatment for alcohol use disorder comorbid with BD that meets criteria for level 2 evidence.[682,683] In a small RCT, there was a significant reduction in the number of drinks per drinking day, as well as per heavy drinking day, in the combination group compared to the group with lithium alone when adherence to treatment was added as a covariate. There is only level 3 evidence for lamotrigine,[684] and divalproex monotherapy or add-on.[685-687] While lithium may also show some benefits (level 3),[617] it has to be used with caution in heavy drinkers because of potential electrolyte imbalance; and anticonvulsants warrant liver function tests and lipase levels before initiating treatment. Agents for primary alcohol use disorder may also show benefits in BD, such as disulfiram (level 3),[688-691] naltrexone (level 3)[692-695] and gabapentin (level 4).[696,697] Furthermore, guidelines for pharmacotherapy in alcohol dependence alone can offer some guidance in the absence of comorbidity-specific trials.[698]

Quetiapine is not recommended for the treatment of alcohol use disorder comorbid to BD because of lack of efficacy. Quetiapine add-on therapy was not more effective than placebo add-on in reducing the number of drinks per day or other alcohol-related measures in patients with BDI[699] or BDI and BDII with alcohol dependence (level 1 negative).[700] In another RCT, quetiapine monotherapy or add-on therapy to mood stabilizers was compared with placebo monotherapy or add-on therapy in patients with bipolar depression with comorbid anxiety and substance use disorders.[701] No significant improvement was found in depressive or anxiety symptoms but alcohol or substance use-related outcomes were not reported separately.

No specific recommendations are given regarding acamprosate at this time. In a smaller RCT, acamprosate add-on was ineffective in improving drinking-related outcomes in BDI/BDII patients with alcohol dependence (level 3 negative)[702] but a post hoc analysis showed a small decrease of the Clinical Global Impression scores for substance use severity towards the end of the trial. Further studies are needed.

Cannabis use disorder

About 20% of patients with BD have cannabis use disorder at some point in their life.[675] Cannabis use disorder is associated with younger age, manic/mixed episode polarity, presence of psychotic features, and comorbid nicotine dependence, alcohol use disorder, and other SUDs.[703] Cannabis use is also associated with more time in affective episodes and rapid cycling.[704]

There is limited research into treatment options for this frequent SUD. Lithium and/or divalproex have level 3 evidence.[617,682,685-687] Quetiapine failed to provide any benefit in terms of mood and anxiety symptoms in a small subsample of highly comorbid patients with BD. generalized anxiety disorder (GAD) and cannabis use disorder[701] (level 3 negative). The effect of quetiapine on specific cannabis use-related outcomes was not reported.

Stimulants: cocaine, amphetamine, and methamphetamine use disorders

Citicoline adjunctive therapy had a positive outcome in two RCTs in patients with BD with comorbid cocaine use disorder, although the benefits of citicoline decreased over time in the more recent study (level 2).[705,706]

Lithium or divalproex, either alone or in combination, were proven useful in small studies addressing cocaine use disorder[682,685-687,707,708] (level 4). Quetiapine in monotherapy or in combination with the ongoing treatment shows evidence of efficacy for cocaine, amphetamine and methamphetamine use disorder[709-711] (level 3). Risperidone has been studied alone and as an add-on agent for cocaine and for methamphetamine use disorders with level 3 evidence for efficacy.[711,712]

Bupropion has anecdotal reports favouring efficacy in cocaine use disorders (level 4).[713] Citicoline improved depressive symptoms in patients with methamphetamine use disorder and bipolar depression.[714]

Lamotrigine has been studied in a 10-week RCT of lamotrigine vs placebo added to ongoing medication. While results were negative for the *a priori* outcome variable (positive urine drug screens), they were positive on the secondary outcome of the amount of dollars spent per week on cocaine purchases (level 2 negative).[715]

Opioid use disorder

While methadone has the most evidence of efficacy in comorbid BD and opioid use disorder (level 3),[716,717] because of the lack of research in this area and increasing concern related to risk of overdose, clinicians should consult the Canadian Research Initiative in Substance Misuse (CRISM) national treatment guidelines on primary opioid use disorder when available (anticipated 2018) for further advice on managing opioid use disorders in their patients.

Primary treatments for anxiety disorders: Should they be used to treat co-morbid anxiety in bipolar disorder?

There are no large RCTs that examined the efficacy of SSRIs, SNRIs, pregabalin or lorazepam in treating anxiety symptoms in BD patients with co-morbid GAD. However, several RCTs assessed the efficacy of these agents in patients with primary GAD and have been found to be effective (723). So,should clinicians employ these treatments in treating co-morbid anxiety symptoms in GAD? As with any clinical decision, CANMAT recommends assessing risk-benefit ratio.

Pregabalin is effective and is not associated with risk of mood destabilization and is well tolerated. Hence, pregabalin would be considered an appropriate option although this has not been tested in BD population with co-morbid anxiety. Lorazepam also does not cause mood instability but given the potential dependence with longer-term use, only short-term use of lorazepam may be appropriate. In the case of antidepressants, especially with SNRIs, the risk of manic/hypomanic switch is likely higher. Therefore, if antidepressants are being considered for treating anxiety symptoms, it is recommended to primarily use SSRIs. Further, if SSRIs are used, it is important to ensure adequate mood stabilization with one or more prophylactic antimanic agents (eg. lithium or divalproex or an atypical antipsychotic).

Lorazepam and clonazepam do not provoke mood instability, they are rapidly effective for the acute management of anxiety and they may address early warning signs of mania by inducing sleep. While inappropriate prescribing may result in misuse and dependence and caution must be exercised when prescribing benzodiazepines to elderly patients in particular, the use of benzodiazepines may be appropriate for treating anxiety associated with bipolar disorder. Short-term use is desirable but some patients are unable to tolerate other anxiety treatments and experience significant symptomatic relief and functional improvement due to the judicious use of benzodiazepines.

FIGURE 9 What is the role of primary treatments for anxiety disorders in treating co-morbid anxiety in bipolar disorder? RCT, randomized controlled trial [Colour figure can be viewed at wileyonlinelibrary.com]

Others

Olanzapine add-on therapy was effective in decreasing manic symptoms and measures of substance use such as reduction in cravings in hospitalized inpatients (level 2).[718] Aripiprazole has level 4 evidence to decrease craving of alcohol, but not consumption, and level 4 evidence to decrease cocaine use in polysubstance users.[719]

Anxiety disorders

Patients with BD frequently experience symptoms of anxiety and co-morbid anxiety disorders (GAD, panic disorder, post-traumatic stress disorder and others). Clinical samples indicate that 24%-56% of patients with BD meet criteria for one or more anxiety disorders, with the highest rates in women.[720] Comorbid anxiety symptoms and anxiety disorders are associated with a higher number of mood episodes and depressive symptoms, including suicidality and sleep disturbance, and greater impairment of psychosocial functioning and quality of life.[721] The presence of a comorbid anxiety disorder is also associated with high rates of use of antidepressants,[722] which should be employed with caution due to their potential for mood destabilization (Section 4).

While the CANMAT Task Force report[720] described key studies and treatment recommendations in length, those recommendations have been updated below. However, it remains the case that there are few studies that have focused exclusively on anxiety symptoms or disorders comorbid with BD, whether for treatment efficacy or safety. While there are treatment options, the limitations resulting from a paucity of data prevent the development of clear guidelines or treatment algorithms.

A "step-wise" approach was recommended in the 2012 CANMAT recommendations for managing comorbid anxiety. In general, mood stabilization is the priority before specific anxiety treatments are considered (Figure 9). Despite clinical experience, antidepressants, particularly serotoninergic agents, should be employed with caution due to their potential to provoke mood destabilization. While benzodiazepines are an important clinical tool because they can rapidly alleviate anxiety, clinicians should strive to prescribe them at the lowest possible dose for the shortest period possible, given the concerns about suicide risk, abuse and dependence. CBT continues to be an appropriate first-line treatment for anxiety.

Generalized anxiety disorder and panic disorder

Quetiapine was superior to placebo and divalproex in improving anxiety symptoms in patients with comorbid GAD and/or panic disorder (level 2).[724] Further, secondary analyses from several RCTs indicate that quetiapine monotherapy significantly reduces symptoms of GAD and panic disorder in patients with bipolar depression.[290,313,725] Negative trials include risperidone versus placebo in patients with BD and comorbid GAD and/or panic disorder[726] and ziprasidone versus placebo in a similar trial.[727]

For patients who are euthymic and treated with lithium, the addition of lamotrigine or olanzapine has demonstrated similar anxiolytic effects (level 3).[728] In a secondary post hoc analysis, combinations of olanzapine and fluoxetine (level 3), and to a lesser extent olanzapine monotherapy, were effective in reducing anxiety in patients with bipolar depression.[314]

Gabapentin employed as an adjunctive therapy in open-label studies reduced anxiety symptoms in patients with BD (level 4).[696,729] Given its relatively benign side effect profile and efficacy in other primary anxiety disorders, gabapentin is an appropriate strategy.

Obsessive compulsive disorder

Obsessive compulsive disorder was re-categorized in DSM-5 and is no longer characterized as an anxiety disorder; however, anxiety is a cardinal feature. OCD is a comorbid condition in 10%-20% of patients with BD[730-733] compared with 2%-3% in the general population.[734] However, the prevalence appears to vary widely, depending on the clinical setting and bipolar subtype.[731] Comorbid OCD may be more common in children and adolescents with BD than in adults[731] and has

been reported to co-occur more commonly with BD than other anxiety disorders,[735] although other studies have not found that association.[736]

When diagnosed comorbidly with BD, OCD has been associated with an earlier onset of BD, a higher number of previous mood episodes, rapid cycling, seasonality, substance misuse, and lower overall functioning.[732,737-742] Jeon et al recently conducted a comprehensive review of patients diagnosed with BD and comorbid OCD and found twice the rate of pharmacological switch to mania or hypomania, but suggested this could be due to the more frequent use of antidepressants in that population.[732] Other authors have raised similar concerns.[743]

Symptoms of OCD may precede or follow mood symptoms and the severity of OCD symptoms tends to fluctuate with mood changes.[744] The high rate of co-occurrence and the many shared clinical features of OCD and BD suggest a shared neurobiology. Some researchers have posited that the high rate of co-occurrence might reflect a distinct bipolar phenotype rather than separate disorders.[736,745]

OCD symptoms may remit during effective treatment of BD; mood stabilizers alone or with atypical antipsychotics may be adequate to resolve comorbid symptoms of OCD and antidepressants might not be necessary for the majority of patients.[730,736] If antidepressants are used, clinical experience suggests that SSRIs are preferred, but because of the potential risk of manic switch clinicians need to optimize prophylactic antimanic agents before initiation. The CANMAT Task Force 2012 report included several small case reports indicating the potential benefit of lithium,[743] anticonvulsants,[743,746] olanzapine,[747,748] risperidone,[749,750] quetiapine[751] and aripiprazole [752] for the treatment of comorbid OCD (all level 4 evidence).

Since the 2012 CANMAT publication, there has been very limited new evidence regarding the treatment of comorbid BD and OCD. Two published case reports described successfully employing aripiprazole once monthly[753] and orally[754] for patients with intractable bipolar and OCD symptoms. Another case report described benefits of ECT,[755] and a small trial also found benefits with adjunctive topiramate (level 3).[756]

Personality disorders

A meta-analysis indicates that 42% of patients with BD also have a comorbid personality disorder, and this feature can be both a diagnostic confound and predictor of poorer treatment response. The most prevalent was obsessive compulsive personality disorder (18%), followed by borderline (16%), avoidant (12%) paranoid (11%), and histrionic (10%) personality disorders.[757] Despite the high prevalence of these comorbidities, research assessing the effectiveness of treatments is sparse. The CANMAT Task Force recommendations describe key issues in the management of personality disorders, including the relationship between personality and mood disorders, accurate diagnosis, and the effect on treatment response and clinical course.[758]

The 2012 CANMAT Task Force recommendations for comorbid personality disorder concluded that divalproex (level 3)[466] and lamotrigine (level 4)[759] may provide some symptomatic relief for comorbid borderline personality disorder. Psychoeducation might be of value, as one small RCT that included patients with any comorbid personality disorder (level 3)[760] demonstrated. That study, along with another small trial that combined psychoeducation and skills training for patients with a mood disorder plus a personality disorder and suicidal ideation (level 3),[761] showed a modest long-term benefit. Larger, more specific studies are needed. There are also data to support the utility of DBT for the treatment of BD, which has robust data for efficacy in the treatment of borderline personality disorder.[75,762,763]

Since those CANMAT recommendations were published in 2012, few new studies have significantly contributed to our understanding of the appropriate treatment of these highly comorbid disorders. Alesiani and colleagues assessed the value of the Systems Training for Emotional Predictability and Problem Solving (STEPPS) program for 32 subjects with personality disorder and mood disorder (half MDD and half BD, mostly BDII), and a history of suicide attempts or self-harm and emotional and behavioural dysregulation. Although results are preliminary due to small sample size and high drop-out rate, findings suggest that such group treatment may improve symptoms, as well as reduce suicide attempts and hospitalizations.[761]

ADHD

ADHD and BD co-occur far more commonly than would be expected based on their individual prevalences in the general population. Approximately 10%-20% of patients with BD meet the criteria for adult ADHD and up to 20% of adults with ADHD also meet the criteria for BD.[764] BD and ADHD have a high degree of symptom overlap, making the comorbid diagnosis difficult and requiring careful attention to childhood history and lifetime course of illness. Patients with comorbid ADHD often experience a more treatment-refractory course, more mood episodes, greater functional impairment and a heightened risk of suicide.[765]

The treatment of ADHD presenting comorbidity with BD is discussed in detail in a previous CANMAT Task Force Recommendation paper.[765] Recommendations were to treat bipolar symptoms first with mood stabilizers and/or atypical antipsychotics to stabilize mood before considering treatment for ADHD symptoms. Mixed amphetamine salts (level 3),[611] methylphenidate (level 3),[612] atomoxetine (level 4),[615] bupropion (level 4),[766] or lisdexamfetamine (level 4)[767] add-ons to mood-stabilizing treatments have been reported to be efficacious in improving ADHD symptoms.

In a s Swedish national patient registry study of patients with BD and ADHD, methylphenidate monotherapy significantly increased the risk of mania, while those patients treated concurrently with a mood stabilizer experienced a significantly reduced risk of mania when methylphenidate was employed.[289]

7.4.2 | Comorbid metabolic disorders

Epidemiology

While there is consistent evidence showing the high prevalence of comorbid medical conditions in BD[768-774] and the negative impact these diagnoses have on longevity,[775,776] these conditions frequently go undiagnosed or undertreated. In a large UK cross-sectional analysis of electronic data sets involving 1.7 million patients in primary care, those diagnosed with BD, when compared with healthy controls, had lower rates of diagnoses

(odds ratio [OR] 0.59, 95% confidence interval [CI] 0.54-0.63) and treatment of medical conditions, despite higher rates of one (OR 1.2, 95% CI 1.16-1.39) or multiple illnesses (OR 1.44, 95% CI 1.3-1.64).[769]

Metabolic syndrome in particular is a highly prevalent comorbidity, present in 20-65% of patients with BD.[777] Defined as a cluster of clinical and biochemical features, including abdominal adiposity, hypertension, impaired fasting glucose, diabetes mellitus, and atherogenic dyslipidaemia,[778] metabolic syndrome not only greatly increases an individual's risk for cardiovascular disease, diabetes mellitus, and premature mortality[779] but also worsens bipolar clinical outcomes.[780,781] Increased body mass index (BMI) is an important contributor to metabolic syndrome, although metabolic dysfunction is not always accompanied by overweight/obesity, and so patients with normal BMI should also receive regular monitoring (Section 8).

It has been hypothesized that BD and metabolic syndrome share a set of common risk factors and overlapping pathophysiology.[782-784] While medications used to treat BD, particularly atypical antipsychotics, can also lead to metabolic dysfunction and weight problems (Section 8), insufficient access to primary and preventative health care, low socioeconomic status, habitual inactivity, insulin dysfunction, peripheral inflammation and neuroinflammation, oxidative stress, and childhood adversity are also important contributors.[785]

Principles of management

As noted in previously in these guidelines, older adults commonly have three or more medical comorbidities that contribute to the 10-15 year lower life expectancy compared to non-psychiatric populations.[642] The most common medical comorbidities are metabolic syndrome, hypertension, diabetes, cardiovascular disease, arthritis, and endocrine disorders.[631,641] This highlights the necessity for vigilance when treating all patients with BD, including regular assessments of their metabolic parameters.

Working collaboratively with other members of a patient's health care team is as essential aspect of good clinical care. Comprehensive management of comorbid medical conditions should include a multidisciplinary team-based approach, including primary care, medical specialists, nurses, psychologists, and social workers as appropriate, with patients taking an active role in their care. Treatment strategies should focus both on the psychiatric symptoms and medical issues and risk factors.

A promising strategy for improving the medical care of people with BD is through "primary care-based medical homes" where those with a serious mental illness and at least one other chronic condition receive integrated care. While most studies do not separate BD from other major mental illnesses in analyses, matched samples in the North Carolina Medical Homes programme indicate that patients with BD (n = 13 406) in primary care medical homes had greater use of primary care and specialty mental health care compared with propensity-matched controls, and marginally lower use of emergency services. However, of three diagnostic groups studied (depression, schizophrenia and BD), use of preventative services such as lipid screening and cancer screening was only greater in the subgroup with depression.[786] At the same time, a cross-sectional Canadian study examining patient-centred medical homes in naturalistic practice found that, where rostering was elective, individuals with BD and psychosis were differentially excluded (relative risk [RR] 0.92, 95% CI 0.90-0.93),[787] suggesting that concentrated efforts should be made to ensure appropriate access to these services.

TABLE 23 Baseline laboratory investigations in patients with bipolar disorder

CBC
Fasting glucose
Fasting lipid profile (TC, vLDL, LDL, HDL, TG)
Platelets
Electrolytes and calcium
Liver enzymes
Serum bilirubin
Prothrombin time and partial thromboplastin time
Urinalysis
Urine toxicology for substance use
Serum creatinine
eGFR
24h creatinine clearance (if history of renal disease)
Thyroid-stimulating hormone
Electrocardiogram (>40 years or if indicated)
Pregnancy test (if relevant)
Prolactin

CBC, complete blood count; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride; vLDL, very low density lipoprotein (Adapted from Yatham et al. 2006[2]).

Treatment recommendations

Treatment strategies that target metabolic disorders should include non-pharmacological lifestyle interventions. Replacing "high metabolic risk" psychiatric medications with medications that have a more favourable profile is highly recommended if the therapeutic advantage of the high-risk agent over the alternative is minimal and metabolic/weight issues persist. Bariatric surgery should be considered following unsuccessful attempts at the aforementioned strategies if the individual has a BMI ≥27 with weight-related morbidity or a BMI ≥30 without significant metabolic morbidity. Readers are referred to the CANMAT Task Force report[785] for further detailed discussion on foundational principles for managing metabolic conditions in patients with BD.

While there is no evidence specifically regarding treatment of comorbid dyslipidaemia or hypertension in BD, it is noteworthy that many of the medications used to manage these comorbid medical disorders have epidemiological or even clinical trial evidence that they may benefit mood. Examples include statins, aspirin and angiotensin antagonists.[788-793] The implications are that clinicians should be actively engaged in the management of these disorders, and should select therapies from those agents that may have benefit in mood symptoms. This again is concordant with the notion of shared risk pathways for these non-communicable disorders.

7.4.3 | Other comorbid medical conditions

Two studies from a random sample of 1 million people, taken from a large population-based retrospective cohort in Taiwan, demonstrated a reduced risk of both stroke and cancer associated with lithium treatment for BD. The lithium group was compared with propensity-matched controls.

The first study reported hazard ratio for stroke over 11 years of 0.39 (95% CI 0.22-0.68) for those prescribed lithium, even when adjusting for the risks associated with typical and atypical antipsychotics. The reduced risk was also correlated with a higher dose, longer treatment duration and a higher rate of exposure to lithium.[794] In the second study, in a sample of 4729 patients diagnosed with BD, lithium exposure was associated with a reduced risk of cancer, compared to a group prescribed anticonvulsant medications. (Lithium with or without anticonvulsant HR = 0.735, 95% CI 0.55-0.97). The study also demonstrated a dose-response relationship.[795] In a subsequent large BD cohort study (n = 9651) focusing on genitourinary cancer, however, lithium was not associated with any change in risk.[796]

A recent meta-analysis suggests increased risk of dementia in BD.[797] There is some evidence that lithium in drinking water reduces the risk of dementia in the general population[638] as does the use of lithium in patients with BD.[798]

8 | SAFETY AND MONITORING

8.1 | Medical evaluation and laboratory investigations

A complete medical history including assessment of BMI and baseline laboratory investigations (Table 23) should be performed prior to initiating pharmacological treatment for BD or, in the case of an acute clinical situation, as soon as the patient is cooperative. For more detail, readers are referred to comprehensive guidelines for safety monitoring in BD.[652] In women of childbearing age, pregnancy should be ruled out, and they should be counselled about the possibility of lamotrigine and carbamazepine affecting the efficacy of oral contraceptives before initiating pharmacotherapy.

For those on maintenance therapy with lithium, thyroid and renal function as well as plasma calcium[799] should be assessed at 6 months and at least annually thereafter or as clinically indicated. Menstrual history (to assess for polycystic ovary syndrome), haematology profile, and liver function tests should be obtained at 3-6 month intervals during the first year, and yearly thereafter and as clinically indicated, in patients on maintenance treatment with divalproex. Patients initiated on lamotrigine or carbamazepine should be routinely educated about the risks of skin rashes and the potential for Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). They should be advised to contact the treating physician if they observe any type of skin rashes or mucosal ulcers as they require urgent medical evaluation to determine the nature of rashes/ulcers and implementation of most appropriate treatment options which might include discontinuation of these medications and instituting other therapeutic strategies to treat serious rashes and prevent destabilization of BD. Further, prior to commencing carbamazepine, patients with ancestry in genetically at-risk populations such as Han Chinese and other Asian patients should have genotyping performed to ensure that they do not have the human leucocyte antigen (HLA)-B*1502 allele, which confers a high risk for SJS/TEN with carbamazepine.[800] In addition, those on carbamazepine therapy should have serum sodium levels measured at least annually and as clinically indicated given the risk of hyponatraemia with this compound. Patients on atypical antipsychotics should have their weight monitored monthly in the first 3 months and every 3 months thereafter. Blood pressure, fasting glucose and lipid profile should be assessed at 3 and 6 months, and yearly thereafter. Children under 10 years of age, seniors, medically ill patients, and patients on combination treatments should receive more frequent monitoring. Re-emergence of clinical symptoms, as well as signs of haematological, hepatic, cardiovascular, and neurological dysfunction, should also signal the need for additional investigations.

Patients receiving treatment should be regularly monitored for side effects, including weight changes and other adverse events such as extrapyramidal symptoms (EPS).

8.2 | Monitoring medication serum levels

Patients on lithium, divalproex, or carbamazepine need to have their serum medication levels monitored regularly. This is particularly important for those who may be non-adherent to treatment. Measurement of serum levels should be repeated at the trough point, which is approximately 12 h after the last dose. It is recommended that two consecutive serum levels be established in the therapeutic range during the acute phase for lithium and divalproex, and then measurement be repeated every 3-6 months or more frequently if clinically indicated. For carbamazepine, serum level monitoring is mainly done to ensure that the levels are not in the toxic range and to check for treatment adherence as there is no established relationship between efficacy and serum level; thus, monitoring for serum carbamazepine levels may be done at 6-12 monthly intervals and as clinically indicated.

The target serum level for lithium in acute treatment is 0.8-1.2 mEq/L (0.4-0.8 mEq/L in older adults) while in maintenance treatment, serum levels of 0.6-1 mEq/L may be sufficient[801,802]; serum levels should be obtained about 5 days after the most recent dose titration. Clinicians may wish to consult the "lithiumeter" schematic for further guidance.[803] It is important to avoid toxic levels as these are associated with an increased risk of kidney damage in the long term.[804] The target serum level for divalproex is 350-700 mM/L (50-100 ug/mL) in the acute phase and should be obtained 3-5 days after the most recent dose titration. There is some evidence for a linear relationship between serum divalproex level and therapeutic efficacy in acute mania, with higher levels associated with greater efficacy.[805] It is currently unknown what levels of divalproex offer optimum efficacy in maintenance treatment as no study to date has systematically assessed the relationship between serum divalproex level and the maintenance

TABLE 24 Safety/tolerability concerns and risks of treatment-emergent switch with pharmacological agents indicated for use in bipolar disorder

	Safety concerns		Tolerability concerns		Risk of treatment emergent switch	
	Acute	Maintenance	Acute	Maintenance	Mania/hypomania	Depression
Lithium	+	++	+	++	–	–
Anticonvulsants						
Carbamazepine	++	++[a]	+	++	–	–
Divalproex	–	++[a]	+	+	–	–
Gabapentin	–	–	+	+	–	–
Oxcarbazepine	+	+	+	+	–	–
Lamotrigine	++	–	–	–	–	–
Atypical antipsychotics						
Aripiprazole	–	–	+	+	–	–
Asenapine	–	–	+	+	–	–
Cariprazine	–	–	+	–	–	–
Clozapine	++	+++	++	+++	–	–
Lurasidone	–	–	+	+	–	–
Olanzapine	+	+++	++	++	–	–
Paliperidone	–	+	+	++	–	–
Quetiapine	+	++	++	++	–	–
Risperidone	–	+	+	++	–	–
Ziprasidone	++	++	++	+	–	–
Conventional antipsychotics						
Haloperidol	+	+++	++	++	–	++
Loxapine	+	+	+	+	–	nk
Antidepressants (adjunctive[b])						
Agomelatine	+	–	–	–	+	–
Bupropion	+	–	+	–	+	–
Ketamine IV	++	nk	++	nk	nk	nk
MAOIs	++	++	+	++	++	–
SNRIs	–	+	+	–	++	–
SSRIs	–	–	+	+	+	–
TCAs	++	++	++	++	+++	–
Stimulants						
Amphetamines	–	++	+	–	+++	–
Modafinil	–	–	–	–	++	nk
Dopamine agonists						
Pramipexole	–	+	–	–	++	nk

MAOIs, monoamine oxidase inhibitors; SNRIs, serotonin norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

–, limited impact on treatment selection; +, minor impact on treatment selection; ++, moderate impact on treatment selection; +++, significant impact on treatment selection; nk, not known.

[a]divalproex and carbamazepine should be used cautiously in women of child bearing age (Section 7).

[b]Antidepressant monotherapy is not recommended in bipolar I disorder; for more information on bipolar II disorder, see Section 6.

efficacy. Therefore, clinician are advised to maintain serum divalproex levels within the accepted laboratory range values during maintenance treatment and carefully monitor patients for emerging mood symptoms and tolerability and adjust the dose of divalproex as needed in order to achieve optimum efficacy and tolerability.

Patients who are treated with concurrent carbamazepine or other hepatic enzyme-inducing agents should have serum levels of all psychotropic medications monitored, particularly in cases of inadequate response or non-response, to determine whether efficacy has been compromised because of reduced serum levels.

8.3 | Safety and tolerability of pharmacotherapy

Safety and tolerability issues, in addition to efficacy data, have been considered when determining recommendations for each phase of illness. The most notable concerns are described below and a summary of their potential impact on treatment selection is included in Table 24, as well as in treatment hierarchy tables in Sections 2-4. As medication side effects are an important contributor to medication non-adherence, these potential concerns should be discussed with patients receiving or considering treatment with various agents to help inform decision making.

8.3.1 | Weight gain

As described in Section 6, despite normal weight at illness onset,[806] it is common for patients with BD to become overweight or obese, and several medications used to treat the illness may also exacerbate this effect. The likelihood of medications to cause weight gain should be carefully considered, as this is one of the most frequent treatment-related factors of non-adherence; contributing to upwards of 60% of cases.[807] The medications most commonly associated with weight gain are olanzapine, clozapine, risperidone, quetiapine, gabapentin, divalproex and lithium; with carbamazepine, lamotrigine, and ziprasidone being the safer or options associated with less weight gain.[808] Recent reviews further suggest that asenapine and aripiprazole (longer term use) [809] also may lead to weight gain, but the impact of lurasidone on weight is minimal.[810] All patients should be regularly monitored for weight changes.

8.3.2 | Gastrointestinal symptoms

Both lithium and divalproex are commonly associated with nausea, vomiting, and diarrhoea, with 35%-45% of patient experiencing these side effects.[372,811] For lithium, this is particularly pronounced during treatment initiation, or rapid dose increases.[812] Gradual dose titration, taking the medication at bedtime, taking medications with food, and slow release preparations may reduce nausea and other side effects.[813]

8.3.3 | Renal toxicity

Lithium has a well-recognized potential for renal toxicity, including nephrogenic diabetes insipidus (NDI), chronic tubulointerstitial nephropathy, and acute tubular necrosis, with NDI reported in 20%-40% of patients.[814-816] Upwards of 70% of patients on chronic lithium treatment will experience polyuria, which can cause impairment in work and daily functioning. This side effect is commonly underreported, unless it is directly inquired about.[817] Long-term administration (ie, 10-20+ years) is further associated with decreased glomerular filtration rate and chronic kidney disease.[818] While long-term lithium administration is probably an important risk factor for developing chronic kidney disease, factors that may increase susceptibility include higher plasma lithium levels, multiple daily lithium doses (vs once daily), concurrent medications (eg NSAIDs, ARBs, ACEIs and diuretics), somatic illnesses (eg, hypertension, diabetes mellitus and coronary artery disease) and older age.[819,820] Instances of lithium toxicity will also greatly increase risk of renal dysfunction.[821] Lithium use is associated with a two-fold higher risk of chronic kidney disease in older adults (>66 years).[822] While the overall risk for progressive renal failure is low, plasma creatinine concentrations and ideally estimated glomerular filtration rate (eGFR) for these patients should be measured at least every 3-6 months.[652] Since 37% of patients aged >70 years have an eGFR <60 mL/min per 1.73 m^2,[823] a strict eGFR cut-off for lithium discontinuation is difficult. The UK National Institute for Healthcare and Excellence (NICE) guidelines for chronic kidney disease (CKD) recommend nephrologist consultation if there is rapidly declining eGFR (>5 mL/min per 1.73 m^2 in 1 year, or >10 mL/min per 1.73 m^2 within 5 years), if the eGFR falls below 45 in two consecutive readings, or if the clinician is concerned.[646,824]

Because of its narrow therapeutic window, acute lithium intoxication is also a complication, which, though reversible, can lead to reductions in glomerular filtration rate.[825,826] Drugs that alter renal function and general medical conditions characterized by decreased circulating volume all contribute to increased risk.[827]

8.3.4 | Haematological effects

Carbamazepine may be a risk factor for leucopenia,[828-830] although this finding is not robust.[831] This side effect is generally reversible with dose reduction or discontinuation. There is also some concern about rapidly developing bone marrow suppression resulting from hypersensitivity, particularly in older patients.[831,832]

Clozapine carries the greatest risk for drug-induced changes in white blood cell counts, with approximately 0.18% of patients experiencing changes rated as probably or definitely drug induced.[828] All patients started on clozapine should have a baseline haematological profile established and be enrolled in the clozapine monitoring programme which requires regular monitoring of haematological parameters: weekly at first and then every 2-4 weeks later in the course of treatment.[833]

8.3.5 | Cardiovascular effects

Lithium can increase the risk of abnormal QT prolongation or T-wave abnormalities,[834] an impact more pronounced with age, as almost 60% of older patients on lithium maintenance therapy have ECG abnormalities.[835] Several antipsychotics, including risperidone, olanzapine, ziprasidone and asenapine, are also associated with arrhythmias, QTc prolongation, and other cardiovascular adverse events. Clozapine may increase the risk of several rare but serious events such as dilated cardiomyopathy, myocarditis, and pericarditis. Of the antipsychotics, lurasidone and aripiprazole are considered safe from a cardiac perspective, although aripiprazole may increase the risk for hypotension.[810]

8.3.6 | Endocrine effects

There is also a strong link between lithium maintenance treatment and hypothyroidism, which is also associated with increased risk of affective episodes, rapid cycling, and more severe depression.[836,837] Routine screening of thyroid function is therefore recommended for all patients on lithium treatment. Since lithium can also cause hyperparathyroidism, routine monitoring for serum calcium is recommended, and, if elevated, further investigations should be performed to evaluate for hyperparathyroidism.[838] Hypothyroidism is ordinarily not an indication for lithium cessation in a patient with a good response; rather, thyroid supplementation is recommended.

New onset oligomenorrhoea or hyperandronism is more common in divalproex users.[839] While there are reports of an increased incidence of polycystic ovary syndrome (PCOS) in divalproex treatment, a recent meta-analysis did not support this.[840] In those who develop PCOS on divalproex, there is evidence from a small sample that discontinuing divalproex results in remission of some of the aspects of PCOS.[841]

Hyperprolactinaemia is common with some antipsychotics, and can have short-term and long-term adverse effects. Risperidone, amisulpride and paliperidone are more likely than other compounds to cause it.[842] Hyperprolactinaemia can induce amenorrhoea, sexual dysfunction, and galactorrhoea, amongst other effects. In the long term, it can cause gynaecomastia and osteoporosis.[843] When such effects are seen, it may advisable to reduce the dose or switch to a different medication.[844]

8.3.7 | Cognition

While many patients experience cognitive impairment, these deficits may be attributable to the disease itself, with more pronounced effects in those with more severe or chronic illness.[845] While a small study has led to suggestions that medicated patients who are euthymic do perform similarly to those not receiving treatment,[846] other naturalistic trials point towards the potential negative impact of several medications, with the effects of antipsychotics being the most significant.[845] Lithium can also lead to impairment in processing speed and memory, which patients may find distressing,[847] although recent randomized controlled data suggest lithium is superior to quetiapine in this regard.[329] Indeed, the effects of lithium on neurocognition are complex and further research is needed to fully elucidate its neurocognitive impact.[848] Anticonvulsants, except for lamotrigine, are also linked to subjective cognitive impairment.[847] Given the importance of cognition on a patient's function and quality of life, further studies are needed in this area.

8.3.8 | Sedation

Sedation is a concern for many, and is reported by over half of patients as a reason for treatment non-adherence.[807] Divalproex and atypical antipsychotics are most likely to lead to these effects, with 30%-50% of patients on atypical antipsychotics experiencing sedation, compared to 8%-13% with placebo[164,214,849-851] and 21%-29% of patients on divalproex.[852,853] This is not a concern with all antipsychotics, however; quetiapine, clozapine, and olanzapine will generally have higher rates of sedation compared to ziprasidone, risperidone, and aripiprazole.[810] Lamotrigine and lithium have both been found to be less likely to cause sedation than divalproex.[854,855]

8.3.9 | Neurological effects, including EPS

Tremor can be a significant cause of frustration for many patients, and is experienced by up to 10% of those treated with lithium or divalproex.[668,856,857] New onset neurological symptoms in patients on divalproex should raise suspicion of hyperammonaemic encephalopathy, which, while rare, can be potentially fatal, and hence early detection and discontinuation of divalproex is critical to prevent morbidity and mortality[858] Sustained release formulations and dose reductions may limit symptoms.[802,859,860] While conventional antipsychotics such as haloperidol are often associated with EPS (including pseudoparkinsonism, akathisia, acute dystonia, and tardive dyskinesia),[861] this risk is either absent or low with atypical antipsychotic agents.[862,863] Among the atypical agents, risperidone, aripiprazole, cariprazine, ziprasidone and lurasidone are more likely to cause EPS, particularly at higher doses.[810] In older patients, impaired swallowing function and dysphagia have also been linked to atypical agents, particularly at higher doses.[864,865]

Although rare, neuroleptic malignant syndrome (NMS) is a potentially life-threatening adverse event associated with antipsychotic agents. The risk with atypical agents was considered negligible initially; however, while the risk is very low, several atypical agents have nevertheless been associated with NMS.[866] While generally unpredictable, the risk is greatest during the initial phase of treatment or change of dosage, with intravenous or intramuscular administration, with high dosages or polypharmacy, when the patient is physically restrained or dehydrated, in high ambient temperatures, in older patients and in patients with medical or psychiatric comorbidities. Patients with a previous history of NMS and/or a personal or family history of catatonia are also at higher risk.[867] Antipsychotics may also impact thermoregulation, with case studies indicating the potential for both heat-related illnesses[868] and hypothermia[869]; thus, patients should be made aware and monitored for these risks during periods of extreme temperatures.

8.3.10 | Dermatological reactions

Approximately 10% of patients being treated with lamotrigine will experience a non-serious rash, with 0.3%-1% developing a serious rash such as toxic epidermal necrolysis and SJS,[870] although for those initiated on a dose of 25 mg with a gradual titration increasing the dose by 25 mg biweekly, the risk of developing serious rash may be as low as 0.02% or 1 in 5000.[871] In some cases, an even lower rate of titration may be used (ie 12.5 mg/day and then gradually increase as per instructions. Carbamazepine is also associated with increased risk of rash and SJS, especially in the first 8 weeks of therapy,[872] although the baseline risk is extremely low. Similarly, while these can also occur with divalproex, the risk is extremely low. Nevertheless, it is important that patients be

informed of these risks and told to report any rash immediately, and these treatments should be discontinued if a serious rash is suspected.

Lithium is also linked with a variety of potentially distressing skin conditions, including acne, psoriasis, eczema, hair loss, hidradenitis suppurativa, nail dystrophy and mucosal lesions, with overall estimates ranging from 3% to 45% depending on the criteria applied. Most cases can be managed without treatment discontinuation.[873]

8.3.11 | Metabolic syndrome, hyperglycaemia, type 2 diabetes and dyslipidaemia

As described in Section 6, patients with BD are already at elevated risk for these physical illnesses and this risk is further exacerbated by some atypical antipsychotic agents and mood stabilizers. Clozapine and olanzapine are associated with the greatest level of risk, followed by quetiapine (particularly in higher doses) and risperidone, with a more minimal impact of aripiprazole, ziprasidone, asenapine, and lurasidone.[810] Lithium and divalproex are also associated with weight gain.[791] All patients on atypical antipsychotics should be monitored for changes in blood glucose and lipid profiles as indicated previously in this section, and if disturbances are detected, the atypical antipsychotic should be discontinued if possible and appropriate treatment initiated if necessary.

8.3.12 | Fracture risk and osteoporosis

Some anticonvulsants, antidepressants, and antipsychotics may decrease bone mineral density and increase the risk of fracture in high-risk patients.[874,875] This risk is increased by the presence of mood disorders, as well as known risks for mood disorders such as physical inactivity, smoking and poor diet quality.[876] Thus, screening for this population may be indicated.[877]

9 | CONCLUDING REMARKS

The diagnosis and management of BD is complex, and effective, evidence-based care requires knowledge of current research as well as lessons gained from years of clinical experience. Members of the CANMAT guidelines committee hope this document does an effective job at providing an easy to understand narrative of both, thus aiding both specialists and primary care providers in delivering evidence-based care to their patients. As with previous editions of these guidelines, CANMAT will strive to provide regular updates capturing emerging trends and evaluating new evidence; and readers are encouraged to consult those as they become available to stay up to date in the field.

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ORCID

Sidney H Kennedy http://orcid.org/0000-0001-5339-7185
Ayal Schaffer http://orcid.org/0000-0001-6220-5042
Benjamin I Goldstein http://orcid.org/0000-0003-0340-349X
Soham Rej http://orcid.org/0000-0002-3908-9124

Martin Alda http://orcid.org/0000-0001-9544-3944
Glenda MacQueen http://orcid.org/0000-0003-3352-6781
Roumen V Milev http://orcid.org/0000-0001-6884-171X
Raymond W Lam http://orcid.org/0000-0001-7142-4669
Roger S McIntyre http://orcid.org/0000-0003-4733-2523
Jan Kozicky http://orcid.org/0000-0003-0697-0342
Beny Lafer http://orcid.org/0000-0002-6132-9999
Eduard Vieta http://orcid.org/0000-0002-0548-0053
Robert M Post http://orcid.org/0000-0002-4246-524X
Michael Berk http://orcid.org/0000-0002-5554-6946

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GUIDELINES

The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2012 on the long-term treatment of bipolar disorder

HEINZ GRUNZE[1,2], EDUARD VIETA[3], GUY M. GOODWIN[4], CHARLES BOWDEN[5], RASMUS W. LICHT[6], HANS-JÜRGEN MÖLLER[2], SIEGFRIED KASPER[7] on behalf of the WFSBP Task Force on Treatment Guidelines for Bipolar Disorders*

[1]*Newcastle University, Institute of Neuroscience, Newcastle upon Tyne, UK,* [2]*Ludwig-Maximilians-University, Department of Psychiatry, Munich, Germany,* [3]*Bipolar Disorders Programme, Institute of Neuroscience, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain,* [4]*University of Oxford, Department of Psychiatry, Warneford Hospital, Oxford, UK,* [5]*University of Texas Health Science Center, Department of Psychiatry, San Antonio, TX, USA,* [6]*Mood Disorders Research Unit, Aarhus University Hospital, Risskov, Denmark,* [7]*Medical University of Vienna, Department of Psychiatry and Psychotherapy, Vienna, Austria*

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Abstract

Objectives. These guidelines are based on a first edition that was published in 2004, and have been edited and updated with the available scientific evidence up to October 2012. Their purpose is to supply a systematic overview of all scientific evidence pertaining to the long-term treatment of bipolar disorder in adults. *Methods*. Material used for these guidelines are based on a systematic literature search using various data bases. Their scientific rigor was categorised into six levels of evidence (A–F) and different grades of recommendation to ensure practicability were assigned. *Results*. Maintenance trial designs are complex and changed fundamentally over time; thus, it is not possible to give an overall recommendation for long-term treatment. Different scenarios have to be examined separately: Prevention of mania, depression, or an episode of any polarity, both in acute responders and in patients treated de novo. Treatment might differ in Bipolar II patients or Rapid cyclers, as well as in special subpopulations. We identified several medications preventive against new manic episodes, whereas the current state of research into the prevention of new depressive episodes is less satisfactory. Lithium continues to be the substance with the broadest base of evidence across treatment scenarios. *Conclusions*. Although major advances have been made since the first edition of this guideline in 2004, there are still areas of uncertainty, especially the prevention of depressive episodes and optimal long-term treatment of Bipolar II patients.

Key words: *Bipolar disorder; Maintenance; Prophylaxis; Pharmacotherapy; Antipsychotics*

*WFSBP Task Force on Treatment Guidelines for Bipolar Disorders: Siegfried Kasper (Chairman, Austria), Guy Goodwin (Co-Chairman, UK), Charles Bowden (Co-Chairman, USA), Heinz Grunze (Secretary, UK), Hans-Jürgen Möller (WFSBP Past-President, Germany), Rasmus W. Licht (Denmark), Eduard Vieta (Spain), Hagop Akiskal (USA), José Luis Ayuso-Gutierrez (Spain), Michael Bauer (Germany), Per Bech (Denmark), Michael Berk (Australia), Istvan Bitter (Hungary), Graham Burrows (Australia), Joseph R. Calabrese (USA), Giovanni Cassano (Italy), Marcelo Cetkovich-Bakmas (Argentina), John C. Cookson (UK), Nicol I. Ferrier (UK), Maria Luisa Figueira (Portugal), Wagner F. Gattaz (Brazil), Frederik K. Goodwin (USA), Gerhard Heinze (Mexico), Chantal Henry (France), Teruhiko Higuchi (Japan), Robert M. Hirschfeld (USA), Cyril Hoeschl (Czech Republic), Edith Holsboer-Trachsler (Switzerland), Kay Redfield Jamison (USA), Cornelius Katona (UK), Martin Keller (USA), Lars Vedel Kessing (Denmark), E. Kostukova (Russia), Hever Kruger (Peru), Parmanand Kulhara (India), Veronica Larach (Chile), Odd Lingjaerde (Norway), Henrik Lublin (Denmark), Mario Maj (Italy), Julien Mendlewicz (Belgium), Roberto Miranda Camacho (Mexico), Philip B. Mitchell (Australia), Sergey Mosolov (Russia), Stuart Montgomery (UK), Charles Nemeroff (USA), Willem Nolen (The Netherlands), Timucin Oral (Turkey), Eugene S. Paykel (UK), Robert M. Post (USA), Stanislaw Puzynski (Poland), Zoltan Rihmer (Hungary), Janusz K. Rybakowski (Poland), Simavi Vahip (Turkey), Per Vestergaard (Denmark), Peter C. Whybrow (USA), Kazuo Yamada (Japan).

Correspondence: Prof. Dr. Heinz Grunze, Institute of Neuroscience, Department of Psychiatry, RVI, Newcastle University, Newcastle upon Tyne, NE1 4LP, UK. Tel: +44 191 282 5765. Fax: +44 191 222 6162. E-mail: Heinz.Grunze@ncl.ac.uk

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Abbreviations: AE, adverse event; AED, antiepileptic drug; AIMS, Abnormal Involuntary Movement Scale; BARS, Barnes Akathisia Rating Scale; CANMAT, Canadian Network for Mood and Anxiety Treatments, CBT, cognitive behavioural therapy; CE, category of evidence; CGI-BP, Clinical Global Impression – Bipolar; CI, confidence interval; DBS, deep brain stimulation; DDD, defined daily dose; DSM, Diagnostic and Statistical Manual; DSS, Depressive Symptom Scale; ECT, electroconvulsive therapy; EPS, extrapyramidal motor symptoms; ER, extended release; ESRS, Extrapyramidal Symptoms Rating Scale; FE, further evidence; FEW, free and easy wanderer; FDA, US Food and Drug administration; GAS, Global Assessment Scale; HAM-D, Hamilton Rating Scale for Depression; HR, hazard ratio; ICD, International Classification of Diseases; IDS, Inventory of Depressive Symptoms; ISBD, International Society for Bipolar Disorder; KM, Kaplan–Meier; LAI, long acting injectable; LOCF, last observation carried forward; MADRS, Montgomery–Asberg Depression Rating Scale; MDE, major depressive episode; MOAT-BD, Multistate Outcome Analysis of Treatments in Bipolar Disorder; MRS, Mania Rating Scale; NNT, numbers needed to treat; OFC, olanzapine–fluoxetine combination; OR, odds ratio; PA, preventive agent; PES, prevention of TEE in enriched samples; PR, practicability; PRC, prevention of TEE in rapid cyclers; PSu, prevention of suicide; RC, rapid cycling; RCT, randomized controlled trial; RG, recommendation grade; RR, relative risk; rTMS, repetitive transcranial magnetic stimulation; SAS, Simpson–Angus Extrapyramidal Side Effect Scale; SD, standard deviation; SFBN, Stanley Foundation Bipolar Network; ST, safety and tolerability; STEP-BD, Systematic Treatment Enhancement Program for Bipolar Disorder; TAU, Treatment as usual; TEAS, treatment emergent affective switch; TEE, treatment emergent episode; VNS, vagus nerve stimulation; WFSBP, World Federation of Societies of Biological Psychiatry; YMRS, Young Mania Rating Scale.

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Preface and disclosure statement

This practice guideline for the biological, mainly pharmacological maintenance treatment of bipolar disorder was developed by an international Task Force of the World Federation of Societies of Biological Psychiatry (WFSBP) and is part of a series covering the acute treatment of mania, bipolar depression and maintenance treatment of bipolar disorder. The preparation of these guidelines has not been financially supported by any commercial organization.

This guideline has mainly been developed by psychiatrists and psychotherapists who are in active clinical practice. Experts of the task force were selected according to their expertise and with the aim to cover a multitude of different cultures.

In addition, some contributors are primarily involved in research or other academic endeavours. It is possible that through such activities some contributors have received income related to medicines discussed in this guideline. A number of mechanisms are in place to minimize the potential for producing biased recommendations due to conflicts of interest.

Some drugs recommended in the present guideline may not be available in all countries, and approved doses may vary.

Introduction

Parts I and II of the World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders (Grunze et al. 2009, 2010) concerned the acute treatment of mania and bipolar depression. The authors are aware that acute and long-term treatment are and must be closely linked together in terms of treatment planning and evaluation. However, in interest of reducing complexity, this guideline series deals with acute and long-term treatment separately.

Although it is of great importance to control the acute manifestations of the illness as rapidly and effectively as possible, the real key issue is successful maintenance treatment, i.e., the prevention of new episodes and all kinds of complications and disablement. In fact, bipolar disorder ranks worldwide among the top ten of the most disabling disorders in working age adults (The World Health Organisation 2002), and the socioeconomic impact is considerable (Hakkaart-van Roijen et al. 2004; Runge and Grunze 2004; Young et al. 2011).

Starting with Kraepelin (1921), several long-term observational studies have demonstrated that the duration of the symptom-free interval is inversely linked to the number of previous episodes (Zis et al. 1980; Angst 1981; Roy-Byrne et al. 1985; Kessing 1998a). Likewise, aspects of cognitive impairment are associated with increasing episode frequency (Kessing 1998b; Lebowitz et al. 2001; Lopez-Jaramillo et al. 2010a) leading to lasting psychosocial and work impairment (Dickerson et al. 2004; Wingo et al. 2009). Subsyndromal symptoms may also contribute significantly to long-term disability in individual patients (Coryell et al. 1993; Angst and Preisig 1995; Altshuler et al. 2006; Bonnin et al. 2010) and are a risk factor for the emergence of new mood episodes (Frye et al. 2006). Finally, bipolar disorder is associated with an excess mortality including an increased risk of suicide (Angst et al. 2002; Licht et al. 2008). Independent of the number of episodes, cognitive deficits and subsyndromal symptoms are causally related to a progressive course of this illness, goals of long-term treatment should be not only the prevention of new clinically significant episodes and suicide, but also minimization of subsyndromal symptoms and cognitive decline.

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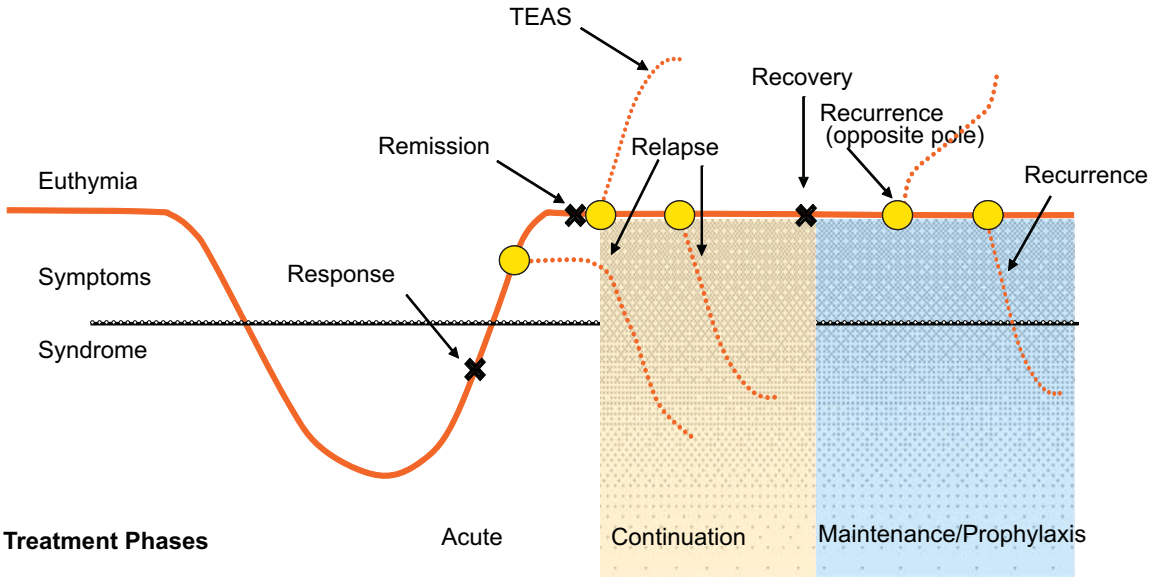


Figure 1. The different phases of treatment in bipolar disorder (modified from Frank et al. (1991)).

The different phases of long-term treatment

Long-term treatment in this article refers to the post-acute biological treatment of bipolar patients. Such treatment will in almost all cases be a psychopharmacological approach; in rare instances, physical treatments as maintenance electroconvulsive therapy (ECT) might be needed.

Long-term treatment in mood disorders has been traditionally divided into continuation and maintenance (or prophylactic) treatment, which are, in turn, associated with the starting points "remission" and "recovery", respectively (Figure 1). In the original proposal by Frank et al. (1991), developed for major depression, recovery was achieved when there was remission even in the absence of any treatment. Re-emergence of symptoms after that point was labelled "recurrence" in contrast to re-emerging symptoms as being part of the index-episode, labelled "relapse". Transferring this model to bipolar disorder, the primary goal of acute treatment is to improve symptoms to the point of remission. Once remission is achieved, the goals of the continuation treatment are to protect the patients from re-emergence of symptoms, i.e., relapses, and from treatment emergent affective switches (TEAS), defined as an episode of opposite polarity within the continuation phase. However, since we cannot identify the exact time point of recovery in treated patients, we do not know for sure when we move from relapse prevention to recurrence prevention, i.e., from continuation to maintenance treatment.

Even though these concepts of recurrence and relapse (and the corresponding treatment phases) are theoretically meaningful, they can only be identified under certain circumstances. Therefore, a wholly pragmatic set of definitions has been adopted by the DSM-IV and ICD-10 (World Health Organization 1992; American Psychiatric Association 1994), separating two episodes by an interval of at least 8 weeks of remission, regardless of treatment. This definition implies that the continuation phase ends after 8 weeks of continuous absence of symptoms (remission). The International Society of Bipolar Disorder (ISBD) suggested different time criteria for the continuation therapy phase, namely 4 weeks for recently manic and 8 weeks for recently depressed patients (Tohen et al. 2009a), taking into account the different time lines for recovery from mania and depression (Solomon et al. 2010). A more conservative estimate proposed by Calabrese et al. (2006) set a cut-off point of 90 and 180 days in patients with an index episode of mania/hypomania and bipolar depression, respectively.

Given the unclear boundary between continuation and prophylactic treatment due to the different approaches and definitions, there are also other pragmatic partitions in use. Instead of separating between continuation phase and maintenance phase, separating between "After-Care" (or "Medium-Term Treatment") lasting for up to 1 year after remission has been achieved for the first time, and long-term prophylaxis may make more sense clinically (R. Licht, personal communication). In line with this, the general term treatment emergent episodes (TEE) may be more useful than relapse and recurrence. Likewise, all post-acute treatment can be considered (and labelled) preventive treatment. However, when appropriate this review will stick to the concepts of relapse and recurrence and the corresponding treatment phases.

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Methodological issues in long-term trials

What do we want to measure?

Primary outcome measures in randomized, controlled long-term trials (RCT) in bipolar disorder vary considerably, and this wide variation of outcome criteria makes it quite difficult to compare efficacy of medication across studies.

Most long-term studies use as primary outcome the result of Kaplan–Meier (KM) survival analyses based on time to intervention. However, some studies use as study endpoint "any reason of failure" (inefficacy as indicated by new mood episodes or need for additional treatments or hospitalization, adverse events, withdrawal of consent, lost to follow-up) as primary outcome, and some use dropout for emerging new mood episodes defined either by symptomatic DSM-IV criteria or/and by clinical rating scale thresholds. An intrinsic problem with KM survival analytic techniques is that they measure the occurrence of a predefined event, e.g., TEE, intervention, discontinuation, only at two time points, at baseline (absence of the event) and endpoint (occurrence of event). This might be suitable if in between these time points there is only one state possible, e.g., "absolutely healthy". Clearly, this is not the case in bipolar disorder, where subsyndromal fluctuations of mood, impairing functionality and quality of life, are rather the rule than exception. In addition, other clinical valuable information as tolerability and impact of medication on physical health will not be fully captured. Another issue in survival analysis is that the risk of censoring should be independent of the risk of the event in question, which most often is not the case. One reason why survival analyses have gained popularity in pivotal trials is that they are more sensitive for measuring differences than the more traditional counting of failures.

To address the limitations of KM techniques, a multi-state statistical technique has recently been developed and tested in data sets of published maintenance studies which allows clinical episodes to be entered multiple times and which can incorporate weightings for adverse effects and functional status. This procedure, Multistate Outcome Analysis of Treatments in Bipolar Disorder (MOAT-BD), provides statistical significance from bootstrapping estimates of the variance for the estimated times spent in each clinical states, including subsyndromal states of depression or mania (Singh et al. 2012). However, for the present, regulatory agencies are likely to require KM analytic techniques. The statistical procedures to conduct MOAT-BD analyses are now available from a URL site, with several studies in progress set to apply these approaches. Therefore, within the next several years prospects are promising that a priori application of this methodology will begin to provide analyses particularly pertinent to effectiveness considerations. Such novel analyses should strengthen the generalizability of maintenance study results for clinical practice and recommendations of guidelines such as this.

As an alternative to KM survival analyses mean change over time of symptomatic rating scales, e.g., the Young Mania Rating Scale (YMRS, Young et al. 1978) and the Montgomery–Asberg Depression Rating Scale (MADRS, Montgomery and Asberg 1979), has been used mainly in extension studies of acute efficacy studies, e.g., the olanzapine versus valproate study (Tohen et al. 2003a) or the asenapine 40-week extension study (McIntyre et al. 2010).

However, this appears unsatisfactory as it does not allow identification of the occurrence of clinically meaningful TEE in individual patients but only minor shifts of statistical means derived from all patients. The true value of rating scales in long-term studies lies in allowing an estimate of meaningful improvement (not just prevention of TEE) versus persistence of subsyndromal symptoms.

On the other hand, rating scales used in studies are not uniform which creates the "Tower of Babel" problem. The content overlap with the MADRS and the YMRS, for instance, might in themselves be a source of bias. To increase the content validity of different scales, e.g., MADRS and HAM-D some acute studies have focussed on the pure depression subscales in order to exclude secondary symptoms such as sleep and appetite. Furthermore, clinicians opinion may well differ from patients' experience. Zimmerman et al. (2012) have demonstrated that remission of depression as defined by a score HAM-D_{17} of <8 was discordant with the patient's own opinion in 25–50% of instances. Thus, in addition to clinician rating scales, brief patient-rated quality of life scales might be of special importance for an overall assessment of long-term treatment of bipolar disorder.

A general limitation in all current outcome evaluations is that the further outcome after a major TEE is not captured, making it impossible to assess relative response including gradual mood stabilization over time. Hopefully, future studies will give a priori more consideration to clinically more meaningful analyses of data.

Remission or recovery as study entrance criteria

Remission is, in most clinical studies, defined as achieving syndromal recovery to a degree that symptom severity scores are below a predefined threshold in established clinician rating scales, e.g., a MADRS score of ≤ 10 in patients with a recent depressive episode (Hawley et al. 2002), or a YMRS score

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of ≤ 12 in recently manic patients (Tohen et al. 2009a).

Recently, the focus appears to be moving towards increasingly stringent definitions of remission (Chengappa et al. 2005; Martinez-Aran et al. 2008) with some incorporating criteria that require low scores on mood scales for both the total scores and scores for specific items (Ketter et al. 2007). A study with olanzapine operationally defined symptomatic remission in patients with bipolar I disorder using a combination of rating scales, including the YMRS (score ≤ 7), the Hamilton Depression Rating Scale (HAM-D) (score ≤ 7), and the Clinical Global Impression Bipolar Version (CGI-BP) (score ≤ 2) (Chengappa et al. 2005). Even these criteria might still be too broad for clinically meaningful remission, as a CGI-BP score of 1, not 2, corresponds to a symptom-free patient. Based on trials that used both CGI-BP and YMRS and MADRS, it appears that a cut-off score of < 5 on the MADRS and < 4 on the YMRS approximates a CGI-BP of 1 for a meaningful definition of remission (Berk et al. 2008b). Clinical meaningful remission is rarely achieved in published controlled trials; e.g., in the lamotrigine long-term studies, remission as entry criterion for the double-blind phase was defined as having a CGI-S score of ≤ 3 for four consecutive weeks (Goodwin et al. 2004)

A more general definition of remission has recently been proposed by the afore-mentioned ISBD task force. Specifically the group recommended that remission implies that the signs and symptoms of a specified clinical state (e.g., depression) be absent or nearly absent, and that no concomitant increase in symptoms of another bipolar clinical state (e.g., mania or hypomania) has occurred. Such a stringent definition could be operationalized in clinical studies by the absence of minimum DSM-IV criteria (excluding duration of symptoms) for depression or mania, respectively, and the CGI-BP score (Tohen et al. 2009a).

Recovery has been even less clearly defined and depends on the scales used to measure outcome, and the patient population studied (Martinez-Aran et al. 2007). In some instances, recovery is defined as a minimum number of weeks with sustained remission, e.g., 8 weeks (Sachs et al. 2007). In the mentioned open study by Chengappa et al. (2005) clinical recovery was defined as meeting the more operationalized remission criteria for ≥ 8 weeks as a proxy for a patient's ability to function (minimum symptomatology). In that open-label study, clinically meaningful symptomatic remission was achieved slowly and maintained for ≥ 8 weeks by only a few patients within an average of 7 months of continuous treatment.

In a broader, clinically relevant sense, recovery is a multidimensional concept in bipolar disorder which includes both symptomatic and functional recovery. Symptomatic recovery is the sustained resolution of the symptoms of the disorder. Functional recovery is the ability to return to an adequate level of functioning and includes an assessment of occupational status and living situation (Tohen et al. 2000, 2003c; Harvey 2006). Previous studies have indicated that the majority of patients achieve symptomatic recovery but less than half achieve functional recovery within 24 months of a first manic/mixed episode (Tohen et al. 2003c).

The study population and the research conditions

An important issue is patient selection. The vast majority of recent long-term studies have used enriched discontinuation designs wherein the patient's acute symptoms had to respond to the given medication during open label treatment to the point of syndromal remission before randomisation, which results in sample "enrichment" for acute responders (see Figure 2). In a few studies, e.g., in the pivotal lamotrigine studies, the criterion for selection was

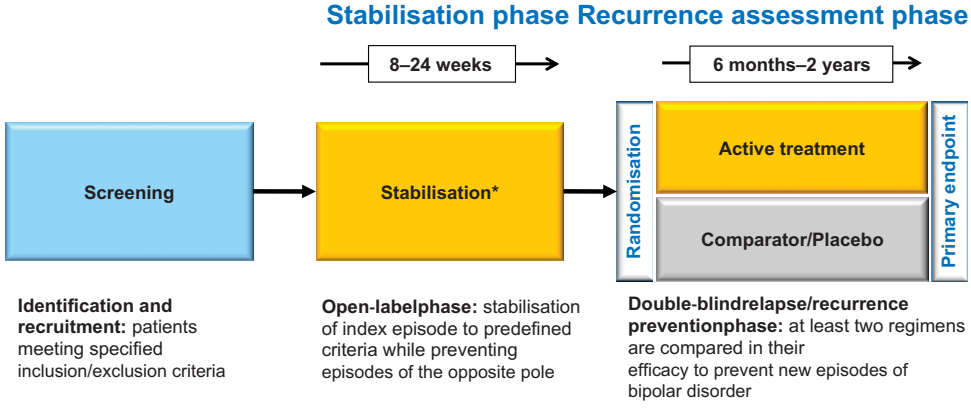


Figure 2. Design commonly used in bipolar long-term maintenance studies in enriched samples. *Period of 8–12 weeks recommended by the US Food and Drug Administration (FDA) for maintenance studies unless otherwise specified. Adapted from Gitlin et al. (2010).

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not acute response, but tolerability and mood stability, e.g., for a minimum of 4 weeks on lamotrigine including 1 week of monotherapy, thus constituting a moderate degree of enrichment for lamotrigine tolerability and response, in contrast to no enrichment for lithium (Goodwin et al. 2004). An enriched design not only limits the generalizability of study results to patients treated under similar conditions, but also favours the test drug with respect to an active comparator if introduced at randomisation and not during the open phase. Also, a possible discontinuation effect of the drug under investigation might lead to a higher frequency of early relapses in the placebo and comparator arms of a study. On the positive side, though, discontinuation designs address the pragmatic clinical question of whether the drug that was used for an acute episode should be maintained beyond the achievement of remission.

Extrapolation of results from such a study to bipolar patients in general might also be limited for an additional reason. Predominance of polarity in bipolar disorder, defined as at least twice as many episodes of one pole of the disorder over the other, is a valid long-term prognostic parameter with important clinical and therapeutic implications (Vieta et al. 2009a). According to Colom et al. (2006), about one-half of bipolar disorder patients qualify for a specific predominant polarity. In a long-term study enriched for acute response to study drug, e.g., in mania, chances are increased that the study population has recurrent mania as the predominant polarity in the long-term course. Vieta et al. (2009b) showed that in a RCT in acute bipolar depression, predominant polarity of mood episodes could be demonstrated in 46.6% of patients by retrospective life-charting indicating a 2.7-fold excess of depressive over manic past episodes (34.1 vs. 12.4%). The implication of this finding for maintenance studies is that results will be biased toward the subgroup of patients who were enrolled with respective particular polarity, rather than be applicable to bipolar patients in general. Also if the duration of the maintenance phase of a study is short, it may not provide any indication of the efficacy of the drug for all kind of episodes. For example, a 6-month discontinuation study that includes manic patients with predominant manic polarity is unlikely to provide a sufficient number of depressive episodes to allow a meaningful analysis of the drug's utility for recently depressed patients. This has been clearly demonstrated by the two pivotal lamotrigine maintenance studies, which followed identical designs, except that one (Bowden et al. 2003) included subjects with a manic or hypomanic index episode, whereas the other (Calabrese et al. 2003) included acutely depressed bipolar patients. In both studies, interventions for an episode of identical polarity as the index episode outnumbered those for an episode of opposite polarity approximately by 3:1 in the lamotrigine arm. This effect is probably more prominent in studies with a relatively short stabilization phase and potential discontinuation effects, and thus an increased probability of early relapses.

Figure 3 illustrates a hypothetical long-term course for a bipolar patient with depressive polarity and an index episode of depression, and the treatment objectives during the different phases.

Time lines of studies

The duration of what is usually called the stabilisation phase of the study is a critical design issue for all long-term studies. By and large it corresponds to the post-acute continuation treatment phase (or part of it) in clinical practice. This becomes critical if we want to distinguish relapse-preventive from recurrence-preventive (prophylactic) properties of a drug. As detailed above, there is no consensus on the duration of continuation treatment before it should be considered maintenance (prophylactic) therapy. The FDA nowadays recommends 8–12 weeks in RCTs for the duration of the stabilization phase of (see Figure 2). However, in recent monotherapy studies with a stabilisation phase, the duration varied from only 6 days to 6 consecutive weeks. Looking into TEE rates with placebo in different RCTs, longer stabilization phases are clearly associated with longer time to TEE in the placebo-arm after discontinuation of medication (Gitlin et al. 2010). It was instructive to compare one study with a 2-week stabilization period (olanzapine) (Tohen et al. 2006), one with a 4-week stabilization period (lamotrigine) (Bowden et al. 2003) and one with a 6-week stabilization period (aripiprazole) (Keck et al. 2007). The 2-week stabilization period used in the olanzapine pivotal study resulted in a precipitous drop in probability of maintaining in remission; the median time to TEE on placebo was 22 days. In the lamotrigine study, in which the stabilization phase was 4 weeks the median time was 85 days. In the aripiprazole study which included a 6-week stabilization phase the median time to TEE on placebo was 203 days. Although some of these differences in time to relapse on placebo likely reflect other variables that differ across studies, e.g., a differential propensity of a medication to induce discontinuation syndromes when switched to placebo, thus resulting in early destabilization, the pattern is compelling. Unfortunately, we do not have a systematic examination of a single medicine with different stabilization times.

Thus, the length of the stabilization phase in modern long-term studies using a discontinuation design after enriching the study population for acute

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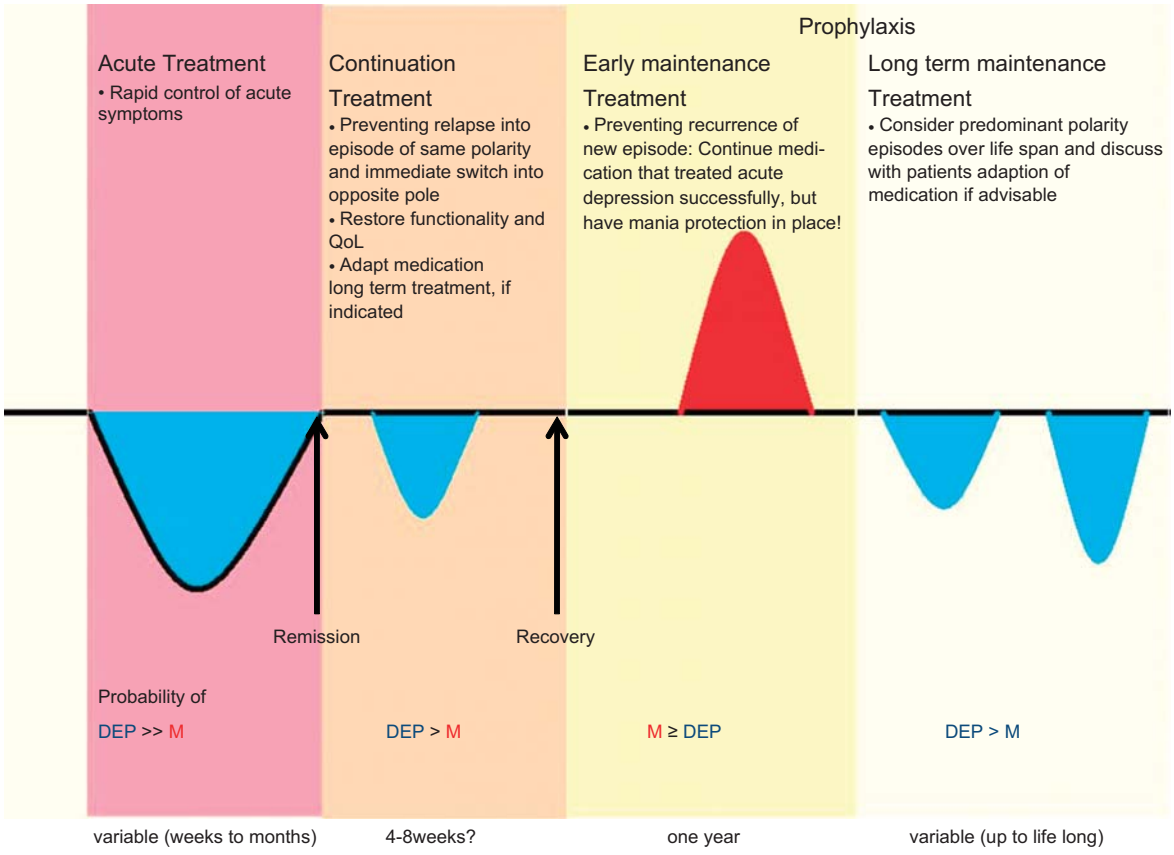


Figure 3. Hypothetical long-term course of a bipolar patient with depressive polarity and an index episode of depression, and treatment objectives during the different phases. DEP: Depressive episode, M: Manic (or mixed) episode.

response to the drug under investigation is critical for assessing whether a medication has only a relapse preventive effect or rather a recurrence preventive effect. Few studies have analysed potential recurrences separate from relapses and thus allowed separate analyses of their time of appearance after discontinuation, i.e., late versus early appearance, respectively. In the few studies where such additional information is available, we detail it in the section of the respective medication as it may allow clinicians a better estimate of the medications' various values in long-term treatment.

It can be argued that genuine prophylactic efficacy might exist independent of acute efficacy, but proof requires studies not to be enriched for responders to the drug being tested and that discontinuation effects also to be excluded, e.g., by a drug-free run in period. In practice, the closest we have come to such designs are studies in which a drug has been introduced as an internal active control under non-enriched conditions and with the discontinuation effect impacting this control and placebo equally (e.g., the lamotrigine maintenance studies, Bowden et al. 2003; Calabrese et al. 2003, or the paliperidone maintenance study, Berwaerts et al. 2012).

A final note of caution concerns the duration of clinical trials in regard to long-term safety. Whereas acceptable relapse/recurrence prevention studies can be as short as 26 weeks (Keck et al. 2006a), adequate pharmaco-vigilance of safety data requires longer term use (5 years or longer). Such evidence, admittedly expensive and impractical in blinded trials, can be derived from national registry studies (Kessing et al. 2011a), cohort and observational studies (Gitlin et al. 1995) or pragmatic trials (Licht et al. 2010).

Why elaborate so extensively on methodology?

In summary, study designs are heterogeneous as they have evolved over the past 20 years. Primary outcome criteria in long-term studies vary considerably, as do the samples enrolled and time lines. Each of these issues can critically impact the validity and informative value of long-term studies in bipolar disorder. In contrast to studies of acute mania (and acute depression), a core design for long-term therapy for bipolar disorder has not yet been agreed upon by researchers in the field. Therefore, disparate results observed may be the product of an

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interaction between agents with different prophylactic potentials and different study designs (Gitlin et al. 2010).

Additionally, results from acute treatment studies are often relevant to maintenance issues of treatment choices, strategies of application and expectation of tolerability. This is particularly so in areas such as evidence regarding impact of a particular group of antidepressants on affective instability, including development of mania/hypomania and adverse effect profiles that are generally evident in acute treatment paradigms, e.g., weight gain.

Although it would be useful to see more non- or equally enriched, prospective head-to-head studies, to date these have been rare in this field. Although a few pragmatic head-to-head comparisons of lithium and different anticonvulsants have been conducted (Greil et al. 1997b; Hartong et al. 2003; Geddes et al. 2010; Licht et al. 2010), to date we have extremely limited reliable information comparing, e.g., different atypical antipsychotics in bipolar maintenance treatment. The reasons for this small number of comparative trials may be the fear of sponsors to fail in a superiority design, and the limitations of non-inferiority designs (Vieta and Cruz 2012).

As distinct from the guidelines on the treatment of acute episodes (Grunze et al. 2009, 2010), where we dealt with largely similar study designs, the heterogeneity of long-term study design leaves greater uncertainty when comparing different treatments.

- We therefore want to make the reader aware that both the recommendations and the assigned efficacy ratings may be to a greater degree subject to individual judgment in the absence of uniform measures.
- Therefore, it is crucial that the reader also inform his own perspective by referring to the original publications before implementing these recommendations into his clinical practice.

How to choose among the various episode preventive agents (PA)

The range of medication covered in this guideline needs some explanation. No single agent shows equally good efficacy for all mood deflections throughout the bipolar spectrum and would thus qualify as the "ideal" mood stabilizer (Grunze 2002). Following the suggestions of Ketter and Calabrese (2002), we have here included medicines that preferentially act on and prevent emergence of only one pole of the illness (mania or depression), without detrimental effect on the other. The modalities under consideration in this review include lithium, several anticonvulsants and antipsychotics, selected experimental treatments and physical therapies. We also briefly review the evidence for antidepressants as a group in long-term treatment of bipolar disorder since they are frequently used in clinical practice (Ghaemi et al. 2006), especially in complex treatment regimens (Goldberg et al. 2009a). An additional practical limitation of this international guideline is the fact that not all medicines are licensed and marketed in every country. The reader should consider such factors when applying them in clinical practice.

In accordance with the principle of evidence based medicine, when finally choosing among the graded mood stabilisers as outlined in this review, individual patient's characteristics such as the following should also be considered:

- Previous and current treatment history, in particular if the patients has responded acutely to a given drug (given the data supporting long-term efficacy from enriched discontinuation trials). On the other hand, in case of uncertainty about what made a patient respond acutely, data from non-enriched conditions should be consulted.
- Potential predictors of differential response, e.g., predominance of mania or hypomanic episodes versus depressive episodes over the course of illness, and/or selection for likelihood of medication response, e.g., lithium (Grof 2010).
- Severity of episodes including presence/absence of psychotic symptoms; this may argue in favour (or against) a combination treatment (including an antipsychotic) right from the beginning.
- Whether previous episodes were or were not related to concurrent treatment with antidepressants or use or misuse of psychostimulants.
- Special vulnerability to specific long-term adverse drug effects.
- History of suicide attempts or current suicidal ideation.
- Patient preferences as this will directly impact on adherence.

Monotherapy or combination treatment?

In routine practice, combination treatments in BBD are regularly employed to enhance efficacy of maintenance treatment and to address subsyndromal symptoms or functional impairment. For example, prospective data of the Stanley Foundation Bipolar

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Network confirmed the complex medication regimens in 429 naturalistically treated bipolar disorder patients, with lithium (51%) and valproate (42%) being the most frequently prescribed medications at the time of clinical improvement: 96.5% of the patients who responded at 6 months were on one to five medications, with over 55% of patients being on two or three medications, 31.8% requiring four or more drugs and 13.8% requiring five or more medications, but still it took a mean time of 1.5 years to achieve such sustained remission (Post et al. 2010a). The treatment of bipolar disorder patients may also change frequently in response to side effects, emerging comorbities including physical health issues, and other needs to be specifically tailored for each patient. These needs in real world patients are virtually impossible to capture in a guideline whose focus is the efficacy of a given combination treatment over a limited time period and in a fair proportion of patients.

These limitations should be kept in mind when interpreting data of randomized controlled combination maintenance studies. For this reason, this guideline does not make a special note or recommendation for specific combination treatments as other guidelines, e.g., CANMAT (Yatham et al. 2009) did, unless there is clear evidence for a special synergistic action of medication – which, as far as we can tell, has not been proven for any of the most researched and prescribed combination regimens. Positive placebo-controlled RCTs exist for combination treatments of mood stabilizers, usually valproate or lithium, with all atypical antipsychotics that have a licence for bipolar maintenance treatment – aripiprazole (Marcus et al. 2011), quetiapine (Vieta et al. 2008c; Suppes et al. 2009), risperidone (Yatham et al. 2003) and ziprasidone (Bowden et al. 2010). The 18-month RCT of olanzapine + mood stabiliser vs. placebo + mood stabilizer is the exception as it was underpowered at end point due to a high attrition rate, contributing to olanzapine's separation from placebo only on secondary, post-hoc outcomes (Tohen et al. 2004). In this review, we will count evidence derived from combination treatments the same way as we do for monotherapy with the respective drug, and discuss the respective studies under the same header.

When should preventive treatment be initiated?

There is no doubt that all patients need some period of aftercare with continuation treatment after the acute symptoms have resolved. This period could last from a few months to a year. However, we have no controlled prospective study to indicate when long-term prophylaxis (beyond this after care) becomes compulsory. Retrospective chart analyses suggest that with every episode the length of the subsequent symptom-free interval decreases (Zis et al. 1980; Angst 1981; Roy-Byrne et al. 1985; Kessing 1998a), but the causality here is unknown. In addition, the duration of the untreated interval after a first episode seems to be predictive for poor long-term outcome (Post et al. 2010b). For lithium, there is also evidence that prophylactic efficacy may decrease with a longer delay between onset of illness and initiation of treatment (Franchini et al. 1999; Garcia-Lopez et al. 2001), but there are also contradictory data on this (Baldessarini et al. 1999b). These findings, together with all the literature on neurocognitive impairment associated with illness progression (Goodwin et al. 2008) might justify starting maintenance treatment as soon as possible after the diagnosis has been established. However, not all patients would suffer from an additional episode (Goodwin 2002), and the number needed to treat (NNT) will increase, the lower the risk is at the beginning of treatment. Also, the acceptance of long-term treatment by many patients is low at this early stage. Sudden discontinuation, especially of lithium, may harm patients more than having never been on prophylactic treatment (Goodwin 1994; Baldessarini et al. 1999c) and increase suicide risk (Baldessarini et al. 1999a).

Most recent guidelines, e.g., CANMAT (Yatham et al. 2009) or the British Association for Psychopharmcology Guidelines (Goodwin 2009) do not specify when long-term prophylactic treatment becomes necessary. Clinical practice in some countries seems to involve waiting for at least a second episode of illness, and only recommend maintenance treatment if these episodes occur within a rather short time interval (e.g., 5 years, Licht et al. 2003). More radically, US guidelines favour commencement of maintenance treatment with the first manic episode (Sachs et al. 2000). Compromising between these recommendations, the Dutch guideline considers the number of episodes and variables such as severity and positive family history of bipolar disorder suggestive of an increased genetic risk (Nolen et al. 2008). Thus, if the first episode is manic, of disruptive severity, and there is a family history, they recommend considering seriously the start of maintenance treatment. Otherwise, with two episodes (one of them manic), maintenance treatment should be initiated if at least one is of particular severity or the patient has a positive family history. With the third episode, prophylaxis should always be recommended to patients (Figure 4). But whatever the advice from doctors, the limiting consideration at this stage is often the attitude of patient and family, underlining the necessity of psychoeducation (Colom et al. 2009; Reinares

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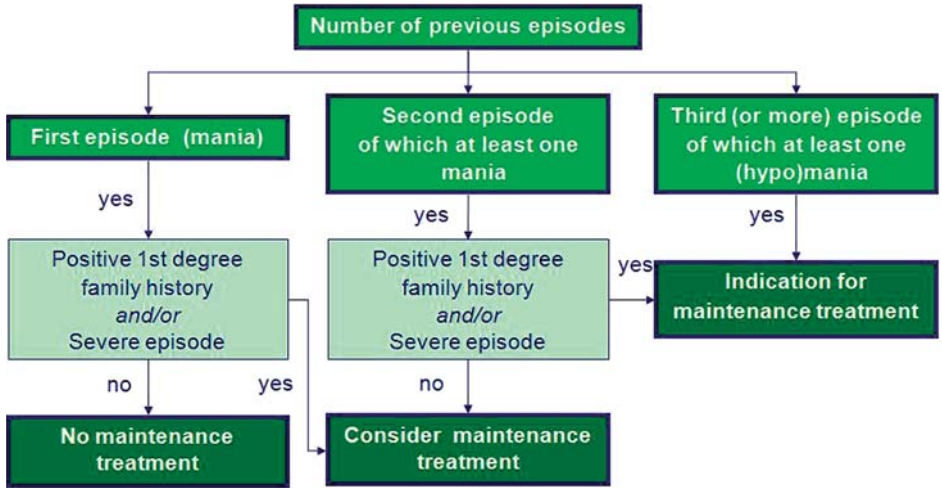


Figure 4. Algorithm for indication for maintenance treatment (Dutch guidelines (Nolen et al. 2008)).

et al. 2009). As to the attitude of the patients, the concept of "aftercare" may be useful: when conferring to the patient that he or she in any case needs pharmacological aftercare up to 1 year after remission has been achieved, this will give time for the clinician to discuss the future perspective and also to assess the tolerability of the current treatment.

When to amend preventive treatments and how long should preventive treatment last?

The proportion of bipolar treated with monotherapy is generally very small, as no drug seems to address all aspects of the disease. The consistently low completion rates in published maintenance trials, most around 10%, make a strong case for evidence informed combination regimens. Combination of mood stabilizers, such as lithium and valproate, are supported by a strong rationale from preclinical science (Kramer et al. 2001; Ryves and Harwood 2001; Perova et al. 2010). However, a superiority of combination treatments versus monotherapy has not consistently be established in pragmatic studies such as the BALANCE study (Geddes et al. 2010).

Therefore, it is usual practice to try patients on monotherapy with a preventive agent (PA) and only amend or switch treatments when ineffective. However, the important question little supported by data from research is the question, when and based on what criteria a PA should be considered as only partially beneficial or ineffective and treatment needs to be changed, either by adding or switching medication.

Current RCTs do not answer the problem, since patients are usually withdrawn from a trial at the first worsening, no matter potential benefits of the drug in question beyond this point. Only few studies, e.g., the valproate maintenance study (Bowden et al. 2000) allowed addition of medication in case of a manic or depressive break-through episode. A PA or combination of PAs may need time beyond a first treatment emergent episode to develop full prophylactic efficacy. In some patients this might not mean a total absence of recurrences, but a marked reduction in number and intensity of new episodes (Vieta and Cruz 2012). A longitudinal evaluation of the patient's history of illness before and after the onset of treatment seems crucial to understand whether a medication is properly acting as a PA.

For lithium, Serretti and Artioli (2003) proposed that recurrence rates should be evaluated by considering the number of recurrences prior to the introduction of lithium (pre-lithium treatment recurrence index = number of episodes/month duration of illness before lithium treatment × 100) and during actual lithium treatment (on-lithium treatment recurrence index = number of recurrences/ month duration of lithium treatment × 100). Starting from this proposal, Murru et al. (2011) generalised it from lithium to the wider concept of PA. They suggested a scheme which may help clinicians evaluating whether a PA is being useful or not in improving a patient's course of illness. Namely, after having obtained a pre PA recurrence index (PrePAri) – with PrePAri being defined as number of episodes/month duration of illness before PA × 100 – and a post PA recurrence index – with PostPAri being defined as number of episodes/month duration of illness during PA × 100 – they propose to classify the percentage reduction from PrePAri to PostPAri ranging from excellent to lack of response (see Table I). However, this is a very formal equation and does not take into account other important variables such as the PA's impact on physical health issues and suicidality.

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Table I. Classifying maintenance treatment success and therapeutic consequences derived from it (modified from Murru et al. 2011).

Reduction pre/post number of episodes	Response	Category description	Subsequent therapeutic step
100%	Excellent	No relapse/ recurrences, no residual symptoms	Continue therapy with PA
>50%	Good	Objective improvement in terms of number of new episodes/ severity of symptoms. Excellent improvement in a cluster of symptoms (i.e., sleep, anxiety, impulsivity)	Continue therapy. Consider combination therapy
<50%	Partial	Less clear improvement in the patient's course, partial or no improvement in a cluster of symptoms	Consider combination therapy Consider switch to new PA
<10%	Lack	No appreciable changes in the course of illness with respect to previous history	Switch to new PA

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Less formalistic, but probably more informative is an approach introduced by Grof et al. (2002), the so called Alda scale. It is used to retrospectively identify quantity and quality of lithium response, but theoretically can also be applied to other PA.

Given the high disposition for recurrences in bipolar disorder, it appears to be common clinical sense that maintenance treatment should be continued lifelong whenever possible. Discontinuation studies, e.g., after 2 years of successful prophylaxis, targeting this question are non-existing and may raise ethical concerns. Limiting factors of prophylactic treatment, besides lack of efficacy, could be side effects, safety issues, newly emerging medical comorbidities or special circumstances, e.g., pregnancy. In clinical practice, however, the limiting factor is quite often the wish of the patient to try a life without medication, and if this request is not addressed in a satisfactory way, he or she may discontinue medication without medical supervision. Reported non-adherence rates for long-term prophylaxis in BD range from 20 to 66% (Bech et al. 1976; Adams and Scott 2000). This implies that clinicians often have to compromise between what they consider in the patients best interest and self-determination of the patient.

Scope of this review

Due to the quality and quantity of evidence, this guideline has its primary focus on bipolar I disorder. However, despite belonging to the same spectrum, the longitudinal course of bipolar I and II disorder is distinct enough to allow separation as separate subcategories (Judd et al. 2003; Vieta and Suppes 2008) and while it is becoming apparent that to define rapid cycling in a separate category is to some degree artificial (Kupka et al. 2003, 2005) it is still consistently applied in prophylactic treatment trials. Therefore, when evidence is available, we will also refer to bipolar II disorder and rapid cycling patients. As the evidence has been derived by and large from studies in adults aged 18–65, this guideline is primarily only applicable to this patient group. In the few cases where additional information for efficacy or safety in children or old age was retrieved, we also cited it in the body of text but did not include it for primary efficacy ratings, but as additional supportive/non-supportive evidence (category "Further evidence (FE)").

Different from the previous edition of this guideline (Grunze et al. 2004) we did not include schizoaffective disorders despite their wide similarities with bipolar disorder (Marneros 2001) as it was felt that such a broad spectrum view would go beyond the scope of this paper. In addition, the positioning of schizoaffective disorder as a separate disorder between affective disorders and schizophrenia remains debatable, and future classification systems (like Diagnostic and Statistical Manual 5th edition, DSM-5) might substantially change this diagnosis (Lake and Hurwitz 2007).

When considering efficacy in preventive treatment, we will focus on the prevention of manic and depressive episodes. There is a virtual absence on separately extractable information regarding the prevention of hypomania or mixed states as separate entities; when fulfilling threshold criteria – which can differ from trial to trial – they were usually counted as "manic" relapse. In addition, there is the expectation that future classification systems as DSM-5 will no longer consider mixed states as an episode subtype but rather as a specifier.

When information is available, we will distinguish between a medication's efficacy in preventing manic and depressive relapses. "Prevention of any episode" refers to the aggregated outcome measure in studies and does not imply, e.g., that a drug literally has an effect in prevention of any distinct type of episode, i.e., for the prevention of mania as well as the prevention of depression. The reader should be aware that a category of evidence (CE) for "any relapse" could mean three different scenarios: Either (especially in older studies) manic and depressive relapses have not been reported

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separately, or a drug is effective in preventing both mania and depression (e.g., quetiapine), or the effect size in preventing one pole is so strong that it drives the overall signal to be positive. For example, aripiprazole has a CE "A" for manic relapses and a CE"E" for depressive relapse. However, the CE for "any relapse", the reported primary study outcome, is still "A" as the strong antimanic efficacy compensates for the lack of prevention of depressive TEE. In this case, "any relapse" has to be understood as a technical term (primary efficacy measure) rather than indication that a medication prevents both poles in clinical practice. These apparent short-comings when reporting on CE for "any relapse" also underlines the importance of studying the same compound in populations of patients who present both recently depressed and/or recently manic/hypomanic/or mixed to improve the generalizability of the data. Unfortunately, for most more modern compounds we lack this data.

Besides efficacy, we will also give close consideration to safety and tolerability issues, although all practical details regarding the management of these issues will not be covered. Physical health issues in bipolar patients, related and unrelated to medication, have also increasingly become a major focus. Finally, given the high rate of death by suicide in bipolar patients, considering suicide-preventive properties of individual medications should be self-evident when making the best informed treatment decision. Unfortunately, these important issues are not uniformly captured across studies and seldom measured as rigorously as efficacy; thus, any in-depth grading of these important aspects is difficult and subject to bias.

Biological treatments, i.e., pharmacological or physical treatments of bipolar disorder, are generally tailored towards the needs of the current stage of the disorder, and may change from acute phase treatment to long-term prophylactic treatment (see also Figure 3). Ideally, combinations of different medication needed for control of a range of acute symptoms will be slimmed down over time to a lean and simple (mono-) therapy regimen. Clinical reality, however, shows that there is not much of a difference in the use of combinations between acute treatment and long-term treatment (Goldberg et al. 2009b), especially in patients with a high burden of depressive illness in the past. Unfortunately, controlled data on different combination strategies are still limited. Combination treatments in clinical practice therefore often rest on choices of medicines, which properties have being established, in many cases, only as monotherapies. The rational for combinations are often to combine medicines with differential preventive efficacy on mania and depression. In the review presented here we will focus both on the published evidence for individual medicines, as confirmed by controlled trials or large-scale naturalistic studies, as well as on evidence from combination treatment strategies when making an efficacy rating and recommendation for a specific drug. This is done with the – potentially wrong and unproven – assumption that medication effects in these studies are additive, and, unless proven otherwise, that there is no unique, efficacy multiplying effect of a specific combination.

At the end, this guideline aims to supply the reader with the following information on a specific medication:

- Evidence for efficacy in preventing treatment emergent episodes of any polarity, and separately manic/mixed and depressive episodes in study samples enriched for acute response and/or acute tolerability of this medication ***("Prevention of TEE in enriched samples (PES)")***
- Evidence for efficacy in preventing treatment emergent episodes of any polarity, and separately manic/mixed and depressive episodes in non-enriched study samples ***("Prevention of TEE in non-enriched samples (PNES)")***
- Evidence for efficacy in frequently relapsing patients (rapid cycling) ***("Prevention of TEE in rapid cyclers (PRC)")***
- Further important supportive/unsupportive evidence, e.g., from large scale naturalistic studies, extension studies, post-hoc analyses of small numbers from RCTs, or in specific subgroups, e.g., children, adolescents, old age ***("Further evidence (FE)")***
- Long-term safety and tolerability of the medication ***("Safety and tolerability (ST)")***
- Antisuicidal properties if documented ***("Prevention of suicide (PSu)")***
- Practicability of the use of this medication, including variety of application forms, dosing strategies, need of routine monitoring examinations, potential discontinuation symptoms***("Practicability (PR)")***
- Overall grade of recommendation, taking all the information above into account ***(" Recommendation grade (RG)")***

Although this guideline is focussing on biological treatment modalities, the authors clearly recognize the importance of and evidence for psychotherapies and psychoeducation as additional therapies (Beynon et al. 2008; Miklowitz 2008; Vieta et al. 2009c). Various psychological approaches are not only tools for optimizing the outcome in individual patients

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and for the substantial proportion of patients not benefiting from any biological treatment, but may be of benefit to all patients, at least to increase to understand the importance of and the adherence to biological treatments.

Methods of this review

The methods of retrieving and reviewing the evidence base, and deriving a recommendation are by large identical to those described in the WFSBP guideline for acute mania and bipolar depression (Grunze et al. 2009, 2010). For those readers who are not familiar with these guidelines, we will summarize the methods in brief.

The data used for these guidelines have been extracted from a MEDLINE and EMBASE search, the Science Citation Index at Web of Science (ISI) and a check of the Cochrane library for recent meta analyses (all until February 2012), and from recent proceedings of key conferences. To ensure comprehensiveness of data, we also consulted various national and international treatment guidelines, review papers and consensus statements (Nolen et al. 2008; Goodwin 2009; Vieta et al. 2010a, 2011). A few additional trials were found by handsearching in text books. In addition, www.clinicaltrials.gov was accessed to check for unpublished studies. All searches cover the time span from 1967 to April 2012.

Given the large heterogeneity of study designs, we did not use the results of meta-analyses as evidence of the same level as results from single RCTs fulfilling inclusion criteria. In addition to the methodological problems inherent to bipolar disorder maintenance studies (see section on Methodology), meta-analyses may have a number of methodological shortcomings of their own, which can make their conclusions less reliable than those of the original studies (Anderson 2000; Bandelow et al. 2008; Möller and Maier 2010; Maier and Möller 2010).

In order to achieve uniform and, in the opinion of this taskforce, appropriate ranking of evidence we adopted the same hierarchy of evidence based rigor and level of recommendation as was published in the WFSBP Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders (Bandelow et al. 2008) (see Table II). In brief, a drug must have shown its efficacy in double-blind placebo-controlled studies in order to be recommended with substantial confidence (Categories of evidence (CE) A or B, corresponding to RGs 1–3). Lower level evidence from open studies (CE "C") or conflicting results (CE "D") were accepted for a low RG 4 or 5, respectively. Substantial concerns about long-term safety and tolerability of a drug could also result in a downgrading of the RG, especially when making a distinction between RG 1 and 2.[1]

Different from other disease areas, studies in bipolar disorder are frequently subject to post-hoc analyses. Many of these analyses were done on data sets that have been not informative in their primary outcome, were not hypothesis generated, and therefore have been counted as CE "C" (similar to open studies). However, when a post-hoc analysis has been included a priori in the analyses plan and is sufficiently powered, a CE "B" could be considered.

Depending on the number of positive trials and the absence or presence of negative evidence, different CEs for efficacy were assigned. A distinction was also made between "lack of evidence" (i.e., studies proving efficacy or non-efficacy do not exist, CE "F") and "negative evidence" (i.e., the majority of controlled studies shows non-superiority to placebo or inferiority to a comparator drug (CE "E"). When there is lack of evidence, a drug could still reasonably be tried in a patient unresponsive to standard treatment, while such an attempt should not be undertaken with a drug that showed negative evidence.

We set a minimum of 25 participants for a placebo-controlled study to be considered as evidence for the categories of evidence A or B, as we found a multitude of small studies with low methodological standard and thus a high probability of error. However, those studies could still be considered for the category "Further evidence (FE)". Further evidence (FE), safety and tolerability (ST), practicability (PR) and evidence for suicide preventive effects (PSu) were graded with a simplified system ranging from "++" for most supportive

[1]A point of discussion within the task force, raised by JRC, was applying more restrictive criteria for a drug to meet the highest category of evidence (CE) criteria "A". It was proposed that the optimal bipolar drug development maintenance therapy design should be one in which data are obtained on both recently manic patients and recently depressed patients. This should be considered as the "gold standard" and all of the maintenance studies that limited study entry to just mania or just depression be defined as being at its best Category B – as being less methodologically rigorous and less valid. However, it would have meant creating a CE category content different from the one used in the other WFSBP guidelines. In addition, it was felt that this categorization might give too much weight to discontinuation (enriched) studies and undervalues pure prophylactic studies randomizing euthymic patients, but neither patients in mania nor in depression. Nevertheless, although not applied in this update, the feasibility of this proposal should be tested in parallel in future updates of this guideline.

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Table II. Categories of evidence (CE) and recommendation grades (RG).

Category of Evidence		Description
A		**Full evidence from controlled studies is based on:** Two or more double-blind, parallel-group, randomized controlled studies (RCTs) showing superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo" in a study with adequate blinding) *and* One or more positive RCT showing superiority to or equivalent efficacy compared with established comparator treatment in a three-arm study with placebo control or in a well-powered non-inferiority trial (only required if such a standard treatment exists) In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least two more positive studies or a meta-analysis of all available studies showing superiority to placebo and non-inferiority to an established comparator treatment. Studies must fulfil established methodological standards. The decision is based on the primary efficacy measure.
B		**Limited positive evidence from controlled studies is based on:** one or more RCTs showing superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo") *or* a randomized controlled comparison with a standard treatment without placebo control with a sample size sufficient for a non-inferiority trial *and* In the case of existing negative studies (studies showing non-superiority to placebo or inferiority to comparator treatment), these must be outweighed by at least one more positive study or a meta-analysis of all available studies showing superiority to placebo or at least one more randomized controlled comparison showing non-inferiority to an established comparator treatment.
C		**Evidence from uncontrolled studies or case reports/expert opinion**
	C1	**Uncontrolled studies is based on:** One or more positive naturalistic open studies (with a minimum of five evaluable patients) *or* a comparison with a reference drug with a sample size insufficient for a non-inferiority trial *and* no negative controlled studies exist
	C2	**Case reports** is based on: one or more positive case reports *and* no negative controlled studies exist
	C3	Based on the opinion of experts in the field or clinical experience
D		**Inconsistent results** Positive RCTs are outweighed by an approximately equal number of negative studies
E		**Negative evidence** The majority of RCTs studies or exploratory studies shows non-superiority to placebo (or in the case of psychotherapy studies, superiority to a "psychological placebo") or inferiority to comparator treatment
? F		**Lack of evidence** Adequate studies proving efficacy or non-efficacy are lacking.
Recommendation grade (RG)		**Based on:**
1		Category A evidence *and* good risk–benefit ratio
2		Category A evidence *and* moderate risk–benefit ratio
3		Category B evidence
4		Category C evidence
5		Category D evidence

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evidence to "–" for strong negative or most concerning evidence (see Tables III and IV).

A profound difference from the acute treatment guidelines is how the final recommendation grades (RG) were derived. In the mania and bipolar depression guidelines the recommendation is based on acute efficacy against the specific pole of the disorder, safety and tolerability, and practicability. This long-term treatment guideline, however, has to consider multiple areas of efficacy (in enriched samples, in non-enriched samples, prevention of mania, prevention of depression, prevention of rapid cycling) and the vast majority of medications have data only in some, but not all areas of efficacy. Simply using a mean value of all categories would not be useful given the rapidly changing landscape of regulatory advice. Older medications, e.g., lithium or carbamazepine, were subject to study designs

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Table III. Grading of categories FE, ST, PSu and PR.

	Further evidence (FE)	Safety and tolerability (ST)	Prevention of suicide (PSu)	Practicability (PR)
++	Several supportive FE, e.g., metaanalysis or positive studies which, however, fall short of criteria to be considered as evidence for CE "A" or "B" for enriched or non-enriched samples	Very good	Good evidence	Easy to use, several formulations, likely to support adherence
+	Some (or more) supportive FE, e.g., limited evidence from open studies in samples where enrichment is unclear	Good	Some supportive evidence	Choice between different formulations, simple titration, no discontinuation effects
0	Conflicting data or unknown	Equally advantages and disadvantages, or Unknown	Conflicting data or unknown	Equally advantages and disadvantages
−	Some (or more) non-supportive FE, e.g., limited negative evidence from open studies in samples where enrichment is unclear	Some concerns	May enhance suicidal ideation	Aspects that make the use difficult in clinical practice
−	Several non-supportive FE, e.g., negative metaanalysis or negative studies which, however, fall short of criteria to be considered as evidence for CE "A" or "B" for enriched or non-enriched sample.	Major concerns	May enhance suicide attempts and/or suicides	Virtually impossible to use in clinical practice

considered as truly prophylactic, and they were only seldom tested in a design enriched for acute response; whereas the opposite is true for medications developed more recently.

- Thus, the RG given to medication by the taskforce values not necessarily its efficacy and usefulness in all areas, but gives special consideration and weight to its strength in only one (or more) efficacy area.
- Only medications with any positive CE rating (A–D) in the areas of "Prevention in enriched samples" (see Table V), "Prevention in non-enriched samples" (Table VI) or "Prevention of TEE in rapid-cycling patients" (Table VII) no matter prevention of any episode, mania or depression, were given an RG.

Table IV. Ratings for Further evidence (FE), Safety and tolerability (ST) and Practicability (PR).

Agent	FE	ST	PR
Amisulpride	−	−	+
Antidepressants	0	0	+
Aripiprazole	+	+	+
Asenapine	0	+	−
Carbamazepine	++	−	−
Clozapine	+	−	−
Gabapentin	+	+	−
Lamotrigine	+	+	0
Lithium	++	−	−
Olanzapine	++	−	+
Oxcarbazepine	0	0	0
Paliperidone	0	0	0
Phenytoin	0	−	0
Quetiapine	+	−	0
Risperidone	+	−	+
Topiramate	+	+	+
Typical AP (all)	0	−	+
Valproate	+	0	+
Ziprasidone	0	0	+
Omega 3 fatty acids	−	+	−
ECT	+	−	−

Table V. CE in enriched samples.

Agent	Prevention of mania	Prevention of depression	Prevention of any mood episode*
Amisulpride	F	F	F
Antidepressants	D	C	D
Aripiprazole	A	E	A
Asenapine	C	F	F
Carbamazepine	F	F	F
Clozapine	F	F	F
Gabapentin	F	F	F
Lamotrigine	D	A	A
Lithium	B	B	B
Olanzapine	A	B	A
Oxcarbazepine	F	F	F
Paliperidone	B	E	B
Phenytoin	F	F	F
Quetiapine	A	A	A
Risperidone	A	E	D
Topiramate	F	F	F
Typical AP (perphenazine)	E	E	E
Valproate	F	F	C
Ziprasidone	B	E	B
Omega 3 fatty acids	F	F	F
ECT	F	F	C

*In this and the following tables, "Prevention of any episode" refers to the aggregated outcome measure in studies and does not imply, e.g., that a drug literally has an effect in prevention of any distinct type of episode, i.e., for the prevention of mania as well as the prevention of depression.

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Table VI. CE in non-enriched samples.

Agent	Prevention of mania	Prevention of depression	Prevention of any mood episodes
Amisulpride	C	F	C
Antidepressants	E	B	E
Aripiprazole	F	F	F
Asenapine	F	F	F
Carbamazepine	F	F	C
Clozapine	F	F	C
Gabapentin	F	F	C
Lamotrigine	F	F	F
Lithium	A	D	A
Olanzapine	B	B	B
Oxcarbazepine	F	C	C
Paliperidone	F	F	F
Phenytoin	F	F	C
Quetiapine	F	F	F
Risperidone	F	F	F
Topiramate	F	F	F
Typical AP (all)	F	F	F
Valproate	F	B	F
Ziprasidone	F	F	F
Omega 3 fatty acids	F	F	C
ECT	F	F	F

- However, we detailed in the text and tables if we found other studies suitable for the category "Further evidence" or supporting effects on suicidality as we feel that these information are valuable for treatment decisions.

This use of RGs which differs from the previous mania and bipolar depression guideline implies that

Table VII. Ratings for PRC and effects on suicide prevention (PSu).

Agent	Rapid cyclers/frequently relapsing patients	Prevention of suicide
Amisulpride	F	0
Antidepressants	E	+
Aripiprazole	C	0
Asenapine	F	0
Carbamazepine	F	0
Clozapine	C	+†
Gabapentin	F	0
Lamotrigine	E	0
Lithium	F	++
Olanzapine	C	0
Oxcarbazepine	F	0
Paliperidone	F	0
Phenytoin	F	0
Quetiapine	C	0
Risperidone	B	0
Topiramate	C	–
Typical AP (all)	F	0
Valproate	F	0
Ziprasidone	F	0
Omega 3 fatty acids	F	0
ECT	C	0

†so far only demonstrated in patients with schizophrenia

- the RG in this guideline is clearly more subject to arbitrary judgement then in the depression and mania guideline. It is largely derived from the highest score in those areas where CE ratings are given (see Table VIII).
- Thus, use of any given medication should never be uncritically based on the RG without an understanding on which strengths or weaknesses the recommendation is based upon.

We have not considered the direct or indirect costs of treatments as these vary substantially across different health care systems. It may be worth noting that medication costs are usually a minor (if measurable) component of direct costs, especially in the long term. Some of the drugs recommended in this guideline may not (or not yet) have received approval for the long-term treatment of bipolar disorder in every country. As the approval by national regulatory authorities is also dependent on a variety of factors, including the sponsor's commercial interest (or lack thereof) this guideline is exclusively based on the available evidence.

The task force is aware of several inherent limitations of these guidelines. When taking negative evidence into consideration, we rely on their publication or their presentation or the willingness of study sponsors to supply this information. This information may not always be complete and may inflate evidence of efficacy in favour of a drug where access to such complete information is limited. This potential bias has been minimized as much as possible by checking the www.clinicaltrials.gov database. Another methodological limitation is sponsor bias (Lexchin et al. 2003; Perlis et al. 2005; Heres et al. 2006; Lexchin and Light 2006) inherent in most single studies on which the guidelines are based. Although all recommendations are formulated by experts trying their best to be objective, they are still subject to their individual pre-determined attitudes and views for or against particular choices. Therefore, no review of evidence and guideline can in itself be an absolutely balanced and conclusive piece of evidence, but should direct readers to the original publications and, by this, enhance their own knowledge base.

Finally, the major limitation of any guideline is defined by the limitations of the evidence. One of the most important clinical questions that cannot be sufficiently answered in an evidence based way is what to do when any first step treatment fails, which happens in a significant number of cases. Therefore, with the current level of knowledge we cannot provide rigorous algorithms for long-term treatment.

Once a draft of this guideline had been prepared by the Secretary and co-authors it was sent out to the 53 members of the WFSBP Task Force on Treatment

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Table VIII. Overall Recommendation Grades for long-term treatment.

Agent	RG	Mainly based on:
Amisulpride	**4**	CE "C" in PNES for "mania" and "any episode"
Antidepressants	**3**	CE "B" in PNES for "depression"
Aripiprazole	**1**	CE "A" in PES for "mania" and "any episode"
Asenapine	**4**	CE "C" in PES for"mania"
Carbamazepine	**4**	CE "C" in PNES for "any episode"
Clozapine	**4**	CE "C" in PRC for "any episode" CE "C" in PNES for "any episode"
Gabapentin	**4**	CE "C" in PNES for"any episode"
Lamotrigine	**1**	CE "A" in PES for "depression" and "any episode"
Lithium	**1**	CE "A" in PNES for "mania" and "any episode" CE "B" in PES for "any episode, "mania" and "depression"
Olanzapine	**2**	CE "A" in PES for "mania" and "any episode" CE "B" in PES for "depression" and in PNES for "depression" , "mania" and "any episode" Downgraded because of safety issues (weight gain and metabolic issues)
Oxcarbazepine	**4**	CE "C" in PNES for "any episode" and "depression"
Paliperidone	**3**	CE "B" in PES for "mania" and "any episode"
Phenytoin	**4**	CE "C" in PNES for "any episode"
Quetiapine	**1**	CE "A" in PES for "mania" , "depression" and "any episode" CE "C" in PRC
Risperidone	**2**	CE "A" in PES for "mania" CE "B" in PRC for "any episode" Downgraded because of safety issues (weight gain and prolactin related AE)
Topiramate	**4**	CE "C" in PRC for "any episode"
Typical AP	**Ø**	Insufficient (negative) evidence, Issues with long-term safety
Valproate	**3**	CE "B" in PNES for "depression"
Ziprasidone	**3**	CE "B" for combination treatment in PES for "mania" and any episode"
Omega 3 fatty acids	**4**	CE of "C" for PNES
ECT	**4**	CE "C" in PES and PRC for "any episode"

Guidelines for Bipolar Disorders for critical review and addition of remarks about specific treatment peculiarities in their respective countries. A second draft, revised according to the respective recommendations, was then distributed for final approval.

These guidelines were established without any financial support from pharmaceutical companies. Experts of the task force were selected according to their expertise and with the aim to cover a multitude of different cultures.

Medications commonly used as preventive agents and their ranking by evidence

In the following sections, we will highlight pivotal studies supporting (or speaking against) efficacy of a PA, amended by other supportive evidence if clinically relevant, key findings referring safety, tolerability and antisuicidal effects, and an estimate of its practicability to use. We assigned ratings for efficacy as detailed in the section on "Methods of this review", and graded the other categories in a more simplified system (ranging from ++ to −/−, see Table III). As this guideline should useful for the practicing clinician, PA under consideration are not exclusively those where data of randomized controlled long-term studies are available, but those which are either used with some trust and frequency by clinicians in bipolar patients, e.g., antidepressants as a group, or in specific subgroups, e.g., clozapine in otherwise treatment refractory patients. This explains, for example, why we consider and list from the frequently used antiepileptic drugs gabapentin, but, e.g., not ethosuximide. Given the large heterogeneity of what has been grouped as "atypical antipsychotics" and "mood stabilizer", we will consider the evidence for each of these substances individually, mentioning them in alphabetical order. "Antidepressants" and "typical antipsychotics", however, will be dealt with as a group of medication, given the relative lack of evidence for single drugs of these groups.

Amisulpride: see "Other atypical antipsychotics used in bipolar disorder"

Antidepressants

With the exception of imipramine, antidepressants have hardly been studied as maintenance treatment of bipolar disorder, and their use is highly controversial, not only in short-term treatment, but even more so in the long term (Frye 2011; Vieta and Grunze 2011). Given that rigorous evidence is limited, we

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have considered antidepressants as a group. We are aware that this is a simplification as we see differences at least in the side effect profile and in the potential risk of inducing Treatment emergent switches (TEAS) and RC; given the multitude of licensed antidepressants, looking into each individually would be unprofitable. However, the reader should be aware that there are subtle differences in the rate of TEAS, and SSRI, bupropion and MAO inhibitors may have a lower intrinsic risk to induce TEAS than other antidepressants (Leverich et al. 2006; Nolen et al. 2007).

When discussing antidepressants, we also have to be aware of the caveat that the vast majority of studies look into combination treatment of an antidepressant and a mood stabilizer; thus, drawing conclusions about antidepressant monotherapy is misleading as the mood stabilizer will impact on side effects and TEAS in these studies.

Despite the lack of evidence from RCTs, antidepressants play an important role in daily clinical practice. A recent large study looking into prescribing habit in both academic and non-academic centres in Spain (SIN-DEPRES) found that almost 40% of patients were on a long-term combination treatment including at least one antidepressant. Factors associated with the use of an antidepressant were bipolar disorder II diagnosis (Odds ratio (OR) = 2.278, $P = 0.008$) and depressive polarity of the most recent episode (OR = 2.567, $P = 0.003$) (Grande et al. 2012b). It can be assumed that in most cases the use of antidepressants in long-term treatment of bipolar disorder is not de novo as a pure prophylactic treatment, but a continuation in acute antidepressant responders.

Univariate factor analysis in large cohorts revealed that antidepressant use in bipolar patients is associated with lifetime depressive morbidity (including first-episode depression, more depressive episodes, and melancholic features at index episode), more years ill, and less affective illness in first-degree relatives (Undurraga et al. 2012). Especially the presence of anxiety symptoms are a strong indicator for antidepressant use, but the causality remains unclear (Pacchiarotti et al. 2011). It has been suggested that antidepressants may provoke increased irritability and dysphoria (El-Mallakh et al. 2008) and also mixed states, which might be more common with SNRIs (Valenti et al. 2011). The risk of TEAS and consequently of cycle acceleration with antidepressant use may be especially prominent in patients having distinct manic symptoms while depressed, namely increased motor activity, speech, and language-thought disorder (Frye et al. 2009).

The British Association for Psychopharmacology suggests that there is not sufficient evidence to recommend the discontinuation of antidepressant as a general principle (Goodwin 2009), but an individual decision rests with the clinician considering factors such as previous or current mood instability with manic features, tolerability and safety, special comorbidities, e.g., panic disorder, and the existence/non-existence of more promising treatment options for the individual patient. A Bayesian approach to the use of antidepressants in long-term treatment might be currently the most practical and patient-centred way of treatment (Belmaker et al. 2010).

Prevention of TEE in Enriched samples (PES)

We identified one randomized and blinded study testing the efficacy of imipramine as bipolar disorder maintenance treatment against placebo and lithium. In this study by Prien and co workers, labeled as "study 2" in the accompanying paper (Prien et al. 1974), hospitalized patients with an index episode of depression were treated openly with imipramine and lithium, and at the time of discharge randomized to continuing on lithium, imipramine or placebo. Similar to the study of Prien et al. in patients with a manic index episode (Prien et al. 1973a), see section on "Lithium", patients and raters, but not treating clinicians were blinded to medication. Of the 122 patients, 44 were bipolar. Of the 44 bipolar patients, 18 were randomized to lithium, and 13 each to imipramine or placebo. Imipramine was statistically significant less effective than lithium in preventing any relapse. The difference between the lithium and imipramine groups was due almost entirely to the higher incidence of manic episodes in the group receiving imipramine ($P < 0.05$), whereas there was no significant difference between the lithium and imipramine groups in the incidence of depressive episodes ($P > 0.05$). Compared to placebo, the article reports for imipramine only numbers and percentages, but no tests for significance. Of the 13 subjects randomized to placebo, five (38%) relapsed into depression, and eight (62%) into mania. Of the 13 subjects randomized to imipramine, seven (54%) had a manic and four (31%) a depressive relapse. Overall, 77% of patients in both groups had at least one recurrence of a mood episode over the 2 years of observation: three subjects in the placebo group and one subject on imipramine had more than one recurrence. Thus, in this study imipramine was not better than placebo; a slight advantage in protecting against depression was gained on the expenses of more new manic episodes.

Two large open studies have addressed antidepressant continuation versus discontinuation after acute response to treatment. Antidepressants were not

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restricted to specific drug, and subjects also received mood stabilizer treatment in addition. One study (Ghaemi et al. 2010) which was part of the STEP-BD program used a randomized discontinuation design; the other (Altshuler et al. 2003), part of the Stanley Foundation Bipolar Network (SFBN) portfolio, used a naturalistic design leaving the decision to continue versus discontinue antidepressants to patients and clinicians. In the STEP-BD study, the primary outcome was change of depression scores in the STEP-BD Clinical Monitoring Form (CMF). The CMF grades DSM IV manic and depressive symptoms on a severity scale ranging from −2 (severe depressive symptom) to +2 (severe manic symptom) with 0 meaning absence of the specific symptom. Antidepressant continuation had a marginal effect trending toward less severe depressive symptoms after 1 year (mean difference in CMF depression score = −1.32 [95% CI, −0.30 to 3.16] and, as a secondary outcome, mildly delayed depressive episode relapse (HR = 2.13 [1.00–4.56]), without increased manic symptoms. The subgroup of patients with RC, however, had three times more depressive episodes with antidepressant continuation (RC = 1.29 vs. non-RC = 0.42 episodes/year, $P = 0.04$) which was not observed in the antidepressant discontinuation group and clearly questions the utility of antidepressants in this subgroup (Ghaemi et al. 2010).

The Stanley Foundation study examined the effect of antidepressant discontinuation versus continuation in 84 subjects with bipolar disorder who achieved remission from a depressive episode with the addition of an antidepressant to an on-going mood stabilizer regimen, prospectively followed for 1 year. One year after successful antidepressant response, 70% of the antidepressant discontinuation group experienced a depressive relapse compared with 36% of the continuation group. By the 1-year follow-up evaluation, 15 (18%) of the 84 subjects had experienced a manic relapse; only six of these subjects were taking an antidepressant at the time of manic relapse (Altshuler et al. 2003).

A 1-year double-blind follow-up of a 10-week acute study compared sertraline, bupropione and venlafaxine in addition to on-going mood stabilizers in acute bipolar depression (Leverich et al. 2006), among patients acutely responsive to antidepressant treatment. At the study endpoint 69% of the 61 acute positive responders maintained positive response and 53% achieved remission. Compared to the acute positive responders, six (27%) of the 22 acute partial responders had achieved positive treatment response at study endpoint ($P < 0.001$). Only eight acute positive responders (13%) and five acute partial responders (22%) developed mania (Altshuler et al. 2009).

Overall, the few studies conducted are neither persuasive in supporting nor refuting mania protective effects of antidepressants; results remain ambiguous whether antidepressants are protective or neutral as far as TEAS are concerned.

In summary, we conclude that the effect of antidepressants for PES has not been sufficiently studied in placebo-controlled designs; however, evidence from open studies indicate that antidepressants may be beneficial in non-rapid cycling patients who showed acute response to this treatment. This holds true for the prevention of new depression, whereas for any episode and mania results are equivocal (Prien et al. 1974; Altshuler et al. 2003, 2009; Ghaemi et al. 2008). ***CE for PES for depression: "C"; for any mood episode and for mania: "D".***

Prevention of TEE in non-enriched samples (PNES)

We identified only one study in bipolar I patients where a antidepressant was used a priori as preventive treatment in euthymic patients (Prien et al. 1973b). Subjects received lithium ($n = 18$), imipramine ($n = 13$) or placebo ($n = 13$) for time periods between 5 and 24 months. Thus, with 26 patients either on imipramine or placebo, the study just meets our inclusion criteria for potential CoE "A" or "B". No difference in overall recurrence rates between imipramine and placebo has been reported. However, imipramine had a significant advantage over placebo in preventing new depression (RR, 95% CI : 0.40 [0.17–0.95], whereas there were not statistically significantly more manic episodes with imipramine compared to placebo (RR,95% CI1.60 [0.71–3.60] (Ghaemi et al. 2008). However, because of the small samples there is a risk of a type 2 error occurring; another flaw of the study is that the incidence of hypomania was not stated. ***CE for PNES for depression "B", for mania and any mood episode: "E".***

Prevention of TEE in rapid cyclers (PRC)

Although there are no blinded RCTs of antidepressants in RC patients, all available evidence from uncontrolled studies and charts reviews suggest that at least older TCAs and SNRI are more likely to induce RC than to prevent new episodes in RC patients (Ghaemi 2008; Grunze 2008). This may be also true for SSRI; 52% of subjects in the study of Ghaemi et al. (2010) had an SSRI. However, the paper does not supply a breakdown of new episodes

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in RC patients by medication. Clinical wisdom would suggest avoiding antidepressants in RC patients. We therefore consider the CE for antidepressants as preventive agent in RC patients as "E". ***CE for PRC: "E"***

Further evidence (FE)

We found a few older studies with tricyclic antidepressants or fluoxetine in usually small numbers of patients and mixed unipolar/ bipolar study populations.

When investigating bipolar II patients, Kane at al. (1982) found no advantage of imipramine over placebo. In combination with lithium, imipramine was also not more effective than lithium monotherapy (Quitkin et al. 1978, 1981).

Johnstone et al. (1990) reported that in a randomized study, lithium alone versus amitriptyline + lithium showed no advantage in 13 bipolar patients for the combination treatments in reducing depressive relapses.

Amsterdam et al. (1998) compared fluoxetine in unipolar depressed with fluoxetine in bipolar II depressed patients in acute and long-term treatment (up to 1 year). During long-term relapse-prevention therapy, relapse rates were similar in bipolar II and unipolar patients. One bipolar II and two unmatched unipolar patients taking fluoxetine had a TEAS. Two more studies by the same group (Amsterdam and Shults 2005, 2010) also support the efficacy and low switch risk of fluoxetine in bipolar II patients. It appears that fluoxetine monotherapy is relatively safe in bipolar II patients which is in line with other analyses of rates of short-term TEAS (Parker et al. 2006; Bond et al. 2008). ***Rating of FE: "0"***

Safety and tolerability (ST)

Given the very heterogeneous group of antidepressants, ranging from usually well tolerated and safe SSRI to older tricyclics and MAO-I associated both with safety and tolerability problems we cannot make a uniform statement applicable to all antidepressants. A comprehensive review of the safety and tolerability of antidepressants has been recently published by the Collegium Internationale Neuro-Psychopharmacologicum (CINP) (Sartorius et al. 2007). ***Rating of ST: "0"***

Prevention of suicide (PSu)

There had been much discussion of the possibility that antidepressants, mainly SSRI and the SNRI venlafaxine, induce suicidal behaviours in depressed patients. This is sometimes further linked to undiagnosed bipolar spectrum disorder in depressed populations. Careful reanalysis of the randomized controlled data (Simon et al. 2006; Stone et al. 2009) as well as pharmaco-epidemiological and large observational studies (Gibbons et al. 2007; Leon et al. 2011) refute the hypothesis that antidepressants induce suicidality. Specifically for bipolar patients, the STEP-BD study did not observe an increase of new onset suicidality in response to initiation, dosage increase or decrease of antidepressants (Bauer et al. 2006).

On the other hand, there is compelling evidence for a reduction of suicides in bipolar patients treated with antidepressants (Angst et al. 2005). Data derived from the large Zurich cohort study showed a significant long-term protective effect of treatment with antidepressants (and also with lithium and antipsychotics) against completed suicide. ***Rating of PSu: "+"***

Practicability (PR)

Most antidepressants are available in a variety of formulations allowing also once daily administration and graded dosage steps to enable easy tapering. ***Rating of PR: "+"***

Recommendation grade (RG)

Based on CE "B" evidence for PNES, we assigned antidepressants a ***RG "3".*** Otherwise, evidence for PES is "C" to prevent new depression which may be considered as too weak to make a general recommendation for the long-term use of antidepressants in bipolar disorder. Readers should be aware that more than in the case of any other medication, this CE and subsequent RG ratings are based on data derived from combination treatments. It cannot be excluded with certainty that synergistic effects between the antidepressants and antimanic agents or mood stabilizers occur, which might influence efficacy, tolerability or suicidality. Clearly, further conclusive research is needed.

Aripiprazole

Prevention of TEE in Enriched samples (PES)

One monotherapy study (with a first endpoint after 26 weeks, Keck et al. 2006a, and a second endpoint after 100 weeks, Keck et al. 2007) and one combination treatment study (aripiprazole add on to lithium or valproate, Marcus et al. 2011) support the efficacy of aripiprazole in preventing new manic and mixed

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episodes in samples enriched for acute response to aripiprazole in acute mania. These studies appear adequately powered, and given the extended and rigorously controlled stabilization phase of 6 and 12 weeks, respectively, they measure rather recurrence of mood episodes but relapse (see section on "Time lines in studies", Gitlin et al. 2010). However, when the stabilization criteria become too strict, a study might end up with a population of "super-stable" patients, independent from treatment intervention. A further combination treatment study comparing lamotrigine + aripiprazole versus lamotrigine + placebo in patients recently manic or mixed and being stabilized for 9–24 weeks showed a numerical, but not statistical significant advantage of the combination treatment (Carlson et al. 2012). Given the implications and uncertainties associated with such an extended stabilization phase and selection of patients, the task force decided to consider this study as "failed" study rather than "negative". Thus, the ***CE for the prevention of any episode and mania in ES would remain "A"*** with two positive and one failed (not "negative") study.

All these studies did not find a positive signal for the prevention of depressive episodes. It remains unclear whether this is a signal that also holds true in a population not selected for mania as index episode, or resembles a design artefact. In addition, as there is a greater likelihood that a subsequent episode is of the same polarity as the index episode, depressive relapses are much less likely during short observation periods and "time to episode" being the study endpoint (see section "What is the population under examination?" Calabrese et al. 2004). Larger study populations and longer observation periods might clarify this issue, but as it stands now the ***CE to prevent new depressive episodes in ES is "E".*** However, as the overall outcome of the pivotal studies was still significantly in favour of aripiprazole, the ***CE to prevent any episode and mania in ES is "A".***

Prevention of TEE in non-enriched samples (PNES)

We could not identify any long–term aripiprazole study in non-enriched samples satisfying inclusion criteria for this review. ***CE for PNES: "F"***

Prevention of TEE in rapid cyclers (PRC)

A post-hoc analysis of the 26- and 100-week monotherapy studies (Keck et al. 2006a, 2007) showed that time to any mood relapse in RC was significantly longer with aripiprazole monotherapy compared with placebo at week 26 ($P = 0.033$) and at week 100 ($P = 0.017$), despite the small sample size of 28 patients (Muzina et al. 2008). The combination treatment study of Marcus et al. (2011) included only 9.5% rapid cycler (defined as patient having four to six episodes in the past 12 months), a number too small allowing a meaningful separate analysis. ***CE for PRC: "C"***

Further evidence (FE)

The efficacy of aripiprazole as maintenance treatment to prevent new manic episodes has also been supported by a recent metaanalysis (Vieta et al. 2011). Also quite recently, a double blind add-on study from Korea has been published comparing valproate + aripiprazole vs. valproate + placebo for 6 months in patients acutely responsive to open combination treatment in mania (Woo et al. 2011). During the 6-month double-blind treatment, the time to relapse of any mood episode in the aripiprazole group was longer than the placebo group, but the difference did not reach statistical significance ($P = 0.098$). Numerically fewer patients in the aripiprazole group experienced TEEs (15.0%) than in the placebo group (32.6%) ($P = 0.076$). Aripiprazole combination treatment was also associated with a lower severity of inter-episode mania and depression symptoms during the period of remission than placebo combination treatment, as measured by YMRS, MADRS, and CGI-BP-S. The proportion of patients relapsing into mania was minimal and only around 10% under both treatments. After controlling for mean valproate level, the time to depressive episode relapse in the aripiprazole group was longer than those in the placebo group ($P = 0.029$).

This study raised some discussion within the task force whether it should be counted as negative evidence thus leading to a downgrading of aripiprazole. However, it was decided to rather consider it as failed, but with some supportive evidence in secondary outcomes. The main reasons are insufficient power and design issues. With only 83 patients included (43 on valproate + placebo and 40 on valproate + aripiprazole, with 25 and 23 patients, respectively, staying in the study for 6 months) it is unlikely to see separation in combination studies comparing one versus two active and effective treatments. Both treatments have also demonstrated reliable antimanic properties (Grunze et al. 2009), and are tested in a population with a manic index episode where depressive recurrence is less likely than manic relapse (Calabrese et al. 2004). The generally low relapse rate into mania is suggestive of a lack of assay sensitivity. Given the small number of patients included and low likelihood of a depressive recurrence, separation for depressive

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relapses, although significant, is unlikely to drive the overall result.

A 46-week, open-label extension of an acute mania combination treatment study (Vieta et al. 2008d) also supports continuous antimanic efficacy of aripiprazole. In total, 283 (aripiprazole + lithium, $n = 108$; aripiprazole + valproate, $n = 175$) completers of the acute study entered and 146 (aripiprazole + lithium, $n = 55$; aripiprazole + valproate, $n = 91$) completed the 46-week, open-label extension. Over the 46-week extension, aripiprazole provided continued YMRS improvement showing an YMRS reduction of 2.9 with aripiprazole + lithium, and 3.3 with aripiprazole + valproate (Vieta et al. 2010b).

Findling et al. (2012) conducted a 6-month, placebo-controlled study in children where, after acute response in mania, 30 patients (mean age = 7.1 years) were randomly assigned to continue aripiprazole and 30 patients (mean age = 6.7 years) were randomly assigned to placebo. The study was inconclusive as both aripiprazole and placebo groups showed substantial rates of withdrawal from maintenance treatment over the initial 4 weeks (15/30 [50%] for aripiprazole; 27/30 [90%] for placebo), suggesting a possible nocebo effect (i.e., knowledge of possibly switching from active medication to placebo increasing concern about relapse). ***Rating of FE: "+"***

Safety and tolerability (ST)

Common side effects during aripiprazole treatment are akathisia, tremor, headache, dizziness, somnolence, sedation fatigue, nausea, vomiting, dyspepsia, constipation, light-headedness, insomnia, restlessness, sleepiness, anxiety, hypersalivation and blurred vision. Rarely described side effects, whose frequency is not precisely known, include uncontrollable twitching or jerking movements, seizures, weight gain, orthostatic hypotension or tachycardia, allergic reactions, speech disorder, agitation, fainting, transaminasaemia, pancreatitis, muscle pain, stiffness, or cramps and very rarely neuroleptic malignant syndrome and tardive dyskinaesia (Fountoulakis and Vieta 2009). However, side effects are still relatively rare and do not necessarily lead to treatment discontinuation in RCTs. This is different in clinical settings where the principal causes of discontinuation for any drug should be vigilantly addressed by the psychiatrist, and, given the array of alternative drugs, discontinued unless the adverse reaction ceases. The principle should be *primum nos nocere*, especially for what would interfere with adherence or social comfort.

Safety analyses were performed on LOCF data from the combined 26- and 100-week double-blind studies. Rates of discontinuation due to treatment emergent adverse events (TEAEs) were 16% in the aripiprazole group and 28% in the placebo group. The most common adverse event (AE) leading to discontinuation was labelled as manic reaction (7% for aripiprazole and 11% for placebo). During the 100-week study, 60 patients (78%) in the aripiprazole group and 60 patients (72%) in the placebo group reported ≥ 1 TEAE. Extrapyramidal motor symptoms (EPS) associated TEAEs were more frequently reported with aripiprazole than with placebo (22 vs. 15%); the most common of these were tremor (9 vs. 1%), akathisia (8 vs. 1%), and hypertonia (4 vs. 2%). The applied scales measuring EPS – the Simpson–Angus extrapyramidal side effect scale (SAS), Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS) – showed no significant differences between aripiprazole and placebo. Only two patients discontinued the study due to akathisia.

The metabolic profile of aripiprazole appears rather benign. At week 100, no significant differences between groups in terms of combined fasting and non-fasting glucose, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglycerides were observed. There was no increase of prolactin associated with aripiprazole treatment. The mean (± standard deviation, SD) weight change was + 0.4 (0.8) kg in the aripiprazole group and –1.9 (0.8) kg in the placebo group, a non-significant finding. However, a clinically significant (≥ 7%) weight increase occurred in 12 patients (20%) in the aripiprazole group but only in three patients (5%) in the placebo group ($P = 0.01$) (McIntyre 2010), indicating, against some common belief, that aripiprazole is not free of significant weight gain.

Aripiprazole is in the US Food and Drug administration (FDA) "C" pregnancy category, meaning that risk cannot be ruled out as human studies are lacking, and animal studies are either positive for foetal risk or lacking as well (Nguyen et al. 2009). ***Rating of ST: "+"***

Prevention of suicide (PSu)

Fortunately, suicide is still a too rare event to be sufficiently captured and analysed from controlled studies with a limited number of participants. As aripiprazole is rather activating than sedative, there has been some worries that it may increase suicide risk. An epidemiological study, using administrative data from three US sources, assessed study endpoints of suicide attempts and death by suicide in patients aged ≥ 18 and being enrolled

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continuously for ≥3 months in their health plans before receiving their first ever antipsychotic (November 2002–December 2005, 20,489 antipsychotic users, 8985 patient-years). It found that compared with other SGA combined, aripiprazole is not associated with an increased risk of suicide events in this naturalistic cohort of patients with schizophrenia or bipolar disorder (Ulcickas et al. 2010). On the other hand, we do not know whether aripiprazole has a specific preventive effect against suicide. ***Rating of PSu: "0"***

Practicability (PR)

Aripiprazole is in most countries available as tablets of different strength, orodispersable tablets, oral solution and as intramuscular injectable solution. Thus, there is a very reasonable choice of applications. The recommended treatment dose for recurrence prevention of mania is 15 mg once daily, if necessary; maximal 30 mg once daily. This is the dose that had been used in the pivotal monotherapy studies; lower doses may work but have not been tested in controlled studies. In the combination treatment study, dosages from 10–30 mg have been employed (Marcus et al. 2011).

An injectable depot formulation has already been tested in schizophrenia (ClinicalTrials.gov Identifier: NCT00705783) but results have not been published yet. It has been communicated that the study was positive for relapse prevention (Park et al. 2011). Aripiprazole injectable depot is currently under investigation as Bipolar I maintenance treatment (ClinicalTrials.gov Identifier: NCT01567527). ***Rating of PR: "+"***

Recommendation grade (RG)

Aripiprazole has well proven efficacy in the recurrence prevention of mania in enriched samples (CE: "A") with additional evidence for rapid cycling patients (CE: "C"). The CE to prevent new depressive episodes is "E". In non-enriched samples, the CE is "F" as no informative studies have been conducted. Further evidence, the safety and tolerability profile and practicability of use (all rated "+") also support the use of aripiprazole. ***Thus, for patients with a index episode of mania and acute response to aripiprazole, the RG is "1".*** For all other groups of patients, the long-term use of aripiprazole is not supported by solid evidence, but should not be excluded in specific clinical scenarios as non-response, tolerability or safety problems with other long-term treatments.

Asenapine: see "Other atypical antipsychotics used in bipolar disorder"

Carbamazepine

Prevention of TEE in enriched samples (PES)

We could not identify any randomized, controlled, long-term study of carbamazepine in enriched samples which satisfied our inclusion criteria. The study by Lusznat et al. (1988) (see section on "Further evidence") was insufficiently powered to allow reliable statistics for non-inferiority. Additionally, we found a 26-week study comparing carbamazepine + placebo vs. carbamazepine + the herbal remedy "Free and easy Wanderer (FEW)" which was conducted in bipolar patients acutely responsive either to carbamazepine or the combination with FEW. However, as this study lacks a placebo control for carbamazepine or an established comparator, it can only supply safety and tolerability data for carbamazepine. Thus, the ***CE for the prevention of manic episodes in ES is "F". CE for the prevention of new depressive episodes in ES is "F". CE to prevent any episode in ES is "F".***

Prevention of TEE in non-enriched samples (PNES)

Greil and co-orkers (Greil et al. 1997b; Greil and Kleindienst 1999a,b) compared carbamazepine and lithium in an open-label, but randomized parallel group study, lasting for 2.5 years and involving 144 patients with bipolar I, bipolar II and not otherwise specified bipolar disorders. No significant difference was observed between both treatments based on survival analysis with time to hospitalization or episode recurrence (hospitalization: 22% for lithium and 35% for carbamazepine, recurrence: 28% for lithium and 47% for carbamazepine, both *P* values. These results hold true both in bipolar I and II patients (Greil and Kleindienst 1999a,b). However, when combining different outcome-measures giving a more complete picture of clinical usefulness (recurrence and need for additional medication and/or adverse events) lithium was significantly better than carbamazepine.

The relative frequency of recurrences with a depressive versus manic or mixed symptomatology was numerically higher under carbamazepine (Kleindienst and Greil, personal communication). Although not statistically significant ($P = 0.1002$), these data provide a first indication, that under carbamazepine bipolar disorder patients might be more prone towards relapse to the depressive pole than under lithium.

Despite being the probably most informative study on carbamazepine, it falls short of satisfying criteria for

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a CE "B" evidence. In the absence of a placebo arm, the sample size is insufficient for a non- inferiority trial, and although randomized, it was not blinded (see "Table III. Check list for Quality of Controlled Studies" in Bandelow et al. (2008) which outlines the CE criteria of WFSBP guidelines)

Based on this study, the ***CE for the prevention of manic episodes in NES "F"; CE to prevent new depressive episodes in NES is "F";*** and the ***CE to prevent any episode in NES is "C".***

Prevention of TEE in rapid cyclers (PRC)

The study of Denicoff et al. (1997b) comparing lithium, carbamazepine and the combination of both showed a poor response to both lithium and carbamazepine in RC patients compared to non-RC patients (for carbamazepine: 19 vs. 31.4% for CGI improvement). An open study (Joyce 1988) and a case report (Riemann et al. 1993) are suggestive of some positive effects of carbamazepine in RC patients, but controlled evidence is missing. ***CE for RC: "C"***

Further evidence (FE)

The only placebo-controlled published study for carbamazepine (Okuma et al. 1981) felt short of satisfying criteria to be counted for CE "A" or "B" evidence, as it included only 22 subjects (12 randomized to carbamazepine, 10 to placebo). It was a true prophylactic study investigating bipolar I patients who were euthymic at study entry, however previous exposure or response to carbamazepine was not an exclusion criterion; thus, the degree of potential enrichment is unknown. Primary efficacy variable was the proportion of patients with no recurrence or less frequent recurrences over one year when compared to the year prior to study. Carbamazepine was found to be effective in 60% of the cases and placebo in 22.2% (U-test, $P < 0.10$). Approximately the same percentages were reported for manic versus depressive relapses; however, numbers were too small and thus power too low to reach significance.

Six studies compared carbamazepine with lithium (Placidi et al. 1986; Watkins et al. 1987; Lusznat et al. 1988; Coxhead et al. 1992; Denicoff et al. 1997b; Hartong et al. 2003), but all in sample sized insufficient for non-inferiority studies, as requested for CE "B" evidence.

Hartong et al. (2003) compared 94 patients in a randomized, 2-year double-blind design. Only patients who had not been previously been treated with lithium or carbamazepine, or had less than 6 months lifetime exposure, were included. The study was designed and powered as a superiority trial for carbamazepine over lithium. Out of 44 patients on lithium, 12 patients developed a new episode compared with 21/50 on carbamazepine treatment (P = n.s.). Interestingly, relapse with lithium occurred almost exclusively within the first 3 months of the trial, while carbamazepine patients carried a constant risk of a new episode of about 40% per study year. Unfortunately, the publication does not supply statistics of (hypo)manic versus depressive recurrences with lithium and carbamazepine; in absolute numbers, four patients on lithium developed a new (hypo)manic episode vs. 10 on carbamazepine, and eight on lithium a new depressed episode vs. 11 on carbamazepine.

Coxhead et al. (1992) carried out a 1-year prophylaxis study in 31 patients enriched for lithium, not carbamazepine. All were previously stable on lithium; 15 were switched over to carbamazepine and 16 remained on lithium. The overall relapse rate was similar in the two groups (six on carbamazepine, eight on lithium). The authors concluded that carbamazepine is as effective as lithium in the prophylaxis of bipolar affective disorder, but change over from lithium to carbamazepine should be done slowly to avoid relapse due to lithium discontinuation.

The study by Lusznat et al. (1988) was enriched both for acute lithium and carbamazepine response. Of the 54 subjects entering the acute study while manic or hypomanic, 40 (20 in each arm) continued for 1 year in a rater-blind design. No statistically significant differences were found, but carbamazepine appeared slightly less effective as a treatment for acute mania and more effective as a prophylactic treatment in this group of patients.

The studies by Placidi et al. (1986) and Watkins et al. (1987) included mixed populations with bipolar, schizoaffective und schizophreniform disorder (Placidi et al. 1986) or unipolar and bipolar patients (Watkins et al. 1987), respectively, not allowing a differentiation of response depending on diagnosis. Whereas Watkins et al. (1987) found lithium superior to carbamazepine, Placidi et al. (1986) did not report significant differences.

Denicoff et al. (1997b) compared carbamazepine, lithium and the combination of both in 52 bipolar I patients in an open, randomized study. Patients were randomized either to carbamazepine or lithium treatment for the first year, then switched over to the alternative treatment for the second year and finally to combination treatment for the third year. Whereas the prophylactic efficacy of both monotherapies was statistically not different and overall disappointing, combination treatment with both lithium and carbamazepine was clearly superior to each monotherapy.

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Looking across studies into specific sub-groups of patients where carbamazepine may be especially helpful, it seems to have clinical value in patients with incomplete response to lithium or rapid cycling (Denicoff et al. 1997b), patients with co-morbid organic (neurological) disorders (Schneck 2002) and schizoaffective patients (Elphick 1985; Goncalves and Stoll 1985; Greil et al. 1997a). ***Rating of FE: "++"***

Safety and tolerability (ST)

Tolerability problems with carbamazepine are not infrequent, and the therapeutic index is relatively low. Most frequent side effects include ataxia, nausea, dizziness, drowsiness, vomiting, blurred vision and diplopia. Less frequent are hair loss, light sensitivity, polyuria, erectile dysfunction, headaches, tinnitus, dry mouth and constipation. Severe and potentially life threatening adverse events include allergic reactions (Steven–Johnson Syndrome), hyponatraemia, liver failure, agranulocytosis and other blood dyscrasias with increased risk of bleeding.

Carbamazepine is teratogenic with an estimated risk of neural tube defects of 0.5–1%, and should be avoided during pregnancy (FDA pregnancy category "D") (Ernst and Goldberg 2002). ***Rating of ST: "–"***

Prevention of suicide (PSu)

There are only sparse data about effects of carbamazepine on suicide prevention. Data from the MAP study (Thies-Flechtner et al. 1996; Greil et al. 1997b) and from the SFBN (Born et al. 2005) suggest that it is less effective than lithium in preventing suicide and suicidal ideation; on the other hand, there is no evidence that carbamazepine may enhance suicide risk. ***Rating of PSu: "0"***

Practicability (PR)

Carbamazepine is in most countries available as tablets and oral solutions. Thus, there is a choice of applications. The recommended plasma concentrations for recurrence prevention are 4–12 mg/l (with slight variations depending on laboratories), though this recommendation is extrapolated from data in epileptic patients. When used purely for prophylactic reasons in euthymic patients it should be tapered in slowly; when initiated in acute mania, faster loading strategies can be applied (Weisler et al. 2006).

When used in combination treatment, a major disadvantage of carbamazepine is the induction of different members of the cytochrome P450 family (Spina et al. 1996). This may cause an increased metabolism of different antidepressants and antipsychotics, including olanzapine (Tohen et al. 2008), quetiapine (Fitzgerald and Okos 2002) and risperidone (Yatham et al. 2003) leading to reduced effectiveness. In addition, carbamazepine shows significant interactions both with valproate and lamotrigine. Carbamazepine also interacts with contraceptives potentially causing unwanted pregnancy. ***Rating of PR: "–"***

Recommendation grade (RG)

Carbamazepine has CE "B" evidence for preventing any mood episode in non-enriched samples, preventing mania in one study more effective than lithium, resulting in a ***Recommendation grade for PNES: RG "3".*** Otherwise, evidence for long-term efficacy in other patient populations only comes from either underpowered or open studies which would result in a lower recommendation grade. The clinical usefulness is also clearly limited given problems with tolerability and a high interaction potential.

Cariprazine: see "Other atypical antipsychotics used in bipolar disorder"
Clozapine: see "Other atypical antipsychotics used in bipolar disorder"
Gabapentin: see "Other anticonvulsants used in bipolar disorder"

Lamotrigine

Prevention of TEE in enriched samples (PES)

Two RCTs provided proof of lamotrigine' s efficacy in preventing TEE in patients who had been treated openly with lamotrigine for a minimum of 8 weeks before randomization to double-blind continuation on lamotrigine, or switch to lithium or placebo (Bowden et al. 2003; Calabrese et al. 2003). Enrichment for lamotrigine in these studies was primarily for tolerability; patients could be stabilized during open treatment with any other treatment in parallel with titrating lamotrigine. However, they needed to maintain stability for at least 4 weeks before randomization, being on lamotrigine monotherapy for at least 1 week. Both studies were conducted in bipolar I patients only, with not more than six episodes in the year prior to study, and having an index episode of either mania or hypomania (Bowden et al. 2003) or depression (Calabrese et al. 2003). Both studies showed significant separation in time to intervention for a mood episode, the primary outcome, for lamotrigine and lithium from placebo. Lamotrigine was also superior to placebo in both studies for time to

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intervention for depression, but not for mania or hypomania, whereas lithium outperformed placebo for hypomania/mania prevention, but not for depression. However, the studies were not primarily powered to show such a difference for lithium. In a pooled analysis of the two studies (Goodwin et al. 2004), lamotrigine was superior to placebo in all three outcomes, time for intervention for any mood episode, (hypo)mania and depression. The hazard ratio for a manic/hypomanic recurrence in the pooled data analysis was 0.642 (95% CI 0.427–0.966, $P = 0.033$). Of special interest is also a secondary analysis of these studies by Calabrese et al. (2006) trying to separate relapses from recurrences. The studies had a reasonable requirement for stabilization (at least 4 weeks with multiple checks), and both lamotrigine and lithium were more effective than placebo in delaying the time to intervention for any mood episode (depression, mania, hypomania, or mixed) when relapses that occurred in the first 90 days were excluded from the analyses ($P = 0.002$, lamotrigine vs. placebo; $P = 0.010$, lithium vs. placebo).

However, when applying a MOAT-BD analysis (see subsection "What do we want to measure?") to the two lamotrigine maintenance studies, the clinical utility of lamotrigine appears less favourable. The MOAT-BD analyses indicate no benefits from lamotrigine for mania, no differences in groups for time in remission in the recently depressed study, and partial benefit for lamotrigine solely for subsyndromal depression in the recently depressed study (C. Bowden, personal communication, 30.5.2012).

In clinical practice, lamotrigine appears to be prescribed mostly in patients with predominant depressive polarity and in bipolar II patients (Grande et al. 2012a). For clinicians, a crucial question is whether they can predict response to guide their treatment choice. A Canadian research group looked into 164 patients with either good lamotrigine or lithium response (Passmore et al. 2003). The course of illness in lamotrigine responders was rapid cycling or chronic, while episodic in responders to lithium, and lamotrigine-responders had a higher comorbidity with panic disorder and substance abuse compared to lithium responders. The relatives of lithium responders had a significantly higher risk of bipolar disorder, while relatives of lamotrigine responders had a higher prevalence of schizoaffective disorder, major disorder and panic attacks.

Thus, we would consider a ***CE for the prevention of manic episodes in ES "D"*** with single studies (and MOAT-BD analyses) failing, but combined analysis supporting it. The ***CE to prevent any episode and depressive episodes in ES is "A".***

Prevention of TEE in non-enriched samples (PNES)

We could not identify any RCT with a blinded and/or placebo-controlled design testing lamotrigine in non-enriched samples. ***CE: "F"***

Prevention of TEE in rapid cyclers (PRC)

Two studies have focused on lamotrigine's efficacy in rapid cycling bipolar disorder, of which one has been published. In this double-blind study (SCAA2012) lamotrigine was added to current therapy of rapid cycling bipolar I and II disorder patients. Lamotrigine was slowly titrated and psychotropic drugs other than lithium or valproate were tapered over a 6–8-week open period. Patients with HAM-D scores ≤ 14 and MRS ≤ 12 entered a 26-week blinded phase with immediate discontinuation of lamotrigine if randomized to placebo. Fifty-six percent of placebo-treated and 50% of lamotrigine-treated patients continued to receive additional lithium or divalproex during the blinded, randomized phase (Calabrese et al. 2000).

Time to additional pharmacotherapy for emerging symptoms was the primary outcome measure. Interestingly, 80% of additional pharmacotherapy was commenced for depressive symptom, but the specific drugs added were not reported. Overall and in bipolar I subjects, lamotrigine was not more effective than placebo over 6 months. On a secondary measure, stability without relapse on monotherapy for 6 months, bipolar II patients, but not bipolar I patients, had significantly better outcomes on lamotrigine than placebo. However, the positive effect of lamotrigine in bipolar II disorder was a post-hoc finding and related to reduction of depression only. Further post-hoc analyses revealed that subjects taking lamotrigine were also 1.8 times more likely than those taking placebo to achieve euthymia, as measured by the Life chart method (Denicoff et al. 2002), for at least once per week over 6 months (95% CI = 1.03–3.13). Subjects taking lamotrigine also had an increase of 0.69 more days per week being euthymic as compared with those taking placebo ($P = 0.014$) (Goldberg et al. 2008).

A second, negative study in rapid cycling bipolar II patients (SCAB2005) was not published separately but is reported on the GSK web site (www.gsk-clinicalstudyregister.com/result_detail.jsp?protocolId = SCAB2005&studyId = 8462FC12-9812-4B49-8DF4-B095BAAC08BA&compound=lamotrigine) and mentioned in a review (Goldsmith et al. 2003). With two negative studies in rapid cycling patients – despite a few positive secondary outcomes, mainly in Bipolar II patients – the ***CE for PRC would be "E".***

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Further evidence (FE)

van der Loos et al. (2009) conducted a RCT for the combination treatment of lithium + lamotrigine vs. lithium + placebo in patients with acute bipolar depression and insufficient response to lithium monotherapy (see also Grunze et al. 2010). Patients stabilized after 8 weeks or after 16 weeks following addition of paroxetine were then included in a 1-year, double-blind follow-up study. Fifty-five subjects (30 on lamotrigine + lithium, with four subjects on additional paroxetine, 25 on lithium + placebo, with six subjects on additional paroxetine) were included. During follow-up the efficacy of lamotrigine was maintained: time to relapse or recurrence was longer for the lamotrigine group (median time 10.0 months (CI: 1.1–18.8)) vs. the placebo group (3.5 months (CI: 0.7–7.0)), but no formal statistical test was performed as numbers of subjects were low and thus the probability of statistical error high (van der Loos et al. 2011). The unequally distributed use of paroxetine between groups to achieve remission in the first place also makes an interpretation of results difficult. However, the study adds to evidence for the usefulness of lamotrigine combination treatment in enriched samples (in this case for tolerability and response in acute depression).

Licht et al. (2010) compared lamotrigine to lithium under conditions more similar to clinical routine conditions than in ordinary RCTs. Adult bipolar I disorder patients with an index episode requiring treatment were openly randomized to lithium ($n = 78$) or to lamotrigine ($n = 77$; up-titrated to 400 mg/day. Patients could continue up to 6 months after randomization with additional psychotropics and monotherapy failures (primary end-point) were not recorded until after that point in time. Thus, this study deals with a reasonably mood- stable population. The non-restrictive design also allowed that a subgroup of patients could be followed for more than 5 years. The primary outcome measure was time to any of the predefined endpoints indicating insufficient maintenance treatment. This included psychotropic treatment in addition to study drugs and benzodiazepines still required at month 6 (after randomization), hospitalization still required at month 6 (after randomization), psychotropic treatment for at least 1 week (in addition to study drugs and benzodiazepines) required after month 6 (after randomization) or hospitalization lasting at least 1 week required after month 6 (after randomization). For the primary outcome measure, any recurrence independent of polarity, the relative risk (RR) for lamotrigine relative to lithium was 0.92 (95% CI: 0.60–1.40). When the primary endpoints were broken down by polarity, the RR (lamotrigine relative to lithium) for mania and depression were, respectively, 1.91 (95% CI: 0.73–5.04) and 0.69 (95% CI: 0.41–1.22). There was no between-group difference in terms of staying in study (RR: 0.85 (95% CI: 0.61–1.19)). Most treatment failures occurred within the first 1.5 years of treatment, and, among patients followed for at least 5 years, practically no patients were maintained successfully on monotherapy with either of the drugs. In summary, no differences in maintenance effectiveness between lithium and lamotrigine were demonstrated, but numbers might still have been too low to find such a difference. Overall, the study can be seen as supportive of the use of lamotrigine.

In potential contrast to this finding, the Danish registry study by Kessing et al. (2011a) noted that lithium might still be more effective than lamotrigine over long observation periods, although this finding may be influenced by selection bias (see section on "Lithium – Further evidence") .

Finally, three recent meta-analyses of the placebo-controlled studies support the findings for lamotrigine in enriched samples (Smith et al. 2007; Beynon et al. 2009; Vieta et al. 2011). ***Rating of FE: "+"***

Safety and tolerability (ST)

Lamotrigine is usually very well tolerated which additionally makes it an attractive choice for long-term treatment. The combined analysis of the two RCT's by Goodwin et al. (2004) showed that during the open label run-in phase a skin rash occurred in 11% of patients. During double-blind treatment, side effects with lamotrigine were not more frequent than with placebo: headache (19% lamotrigine and placebo, 15% lithium), nausea (11% placebo, 14% lamotrigine, 20% lithium) and diarrhoea (8% placebo, 7% lamotrigine, 19% lithium).

During double-blind treatment the incidence of benign rash was similar in all treatment groups. There were two cases of a more severe skin reaction. A case of a maculopapular facial rash required hospitalization, and one case of a mild Stevens–Johnson syndrome occurred 31 days after initiating lamotrigine, but hospitalization was not required. Overall, the incidence of a serious rash appears low with the recommended slow titration scheme. An analysis of placebo-controlled studies with lamotrigine in different indications demonstrated that the incidence of serious rashes, including Stevens–Johnson syndrome, in clinical trials of bipolar and other mood disorders is approximately 0.08% (0.8/1000) in adult patients on lamotrigine monotherapy and 0.13% (1.3/1000) in adult patients receiving lamotrigine as adjunctive therapy (Seo et al. 2011).

A major advantage of lamotrigine for long-term treatment is the benign metabolic profile and the lack of weight gain.

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Major congenital defects have been described with lamotrigine in 1.0–5.6% of pregnancies. Despite an FDA pregnancy category "C" rating, a teratogenic risk with lamotrigine treatment is suggested at doses exceeding 200 mg/day (Morrow et al. 2006). Case registers also indicate that lamotrigine is associated with a 10–24 times increased risk of oral cleft versus the general population (Viguera et al. 2007), and folic acid supplementation is recommended as with other antiepileptic drugs.

In summary, the tolerability and long-term impact on weight and metabolic parameters of lamotrigine is good, but there are concerns with birth defects and allergic reactions. ***Rating of ST: "+"***

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Prevention of suicide (PSu)

The FDA report on the relationship between antiepileptics and suicidal behaviour (US Food & Drug Administration 2008) included 199 RCTs concerning 11 drugs: carbamazepine; divalproex; felbamate; gabapentin; lamotrigine; levetiracetam; oxcarbazepine; pregabalin; tiagabine; topiramate; zonisamide. For all agents, the 95% CI includes an odds ratio of 1, except that for topiramate (95% CI 1.21– 5.85) and lamotrigine (95% CI 1.03– 4.40), suggesting that, beyond reasonable doubt, only these two might put patients at a higher risk to experience a suicide-related event, a composite outcome for what was considered as suicidal ideation or behaviour.

The FDA analysis does not account for a number of methodological problems that limit its suitability for bipolar disorder patients (Fountoulakis et al. 2012). Adverse event outcome data from RCTs were used, instead of systematically collected data, the sample sizes were small and the number of events was limited. In most of the epilepsy trials (92%) included in the final analysis, the study drug was add-on therapy and although 11 antiepileptics were included in the conclusion, only two of the drugs showed a statistically significant increase in risk of suicidal ideation. Most important, the potentially modifying effect of comorbid mental disorders was not taken into account, and, e.g., the comorbid presence of a depressive syndrome with suicidality might have aided the use of lamotrigine.

As a matter of fact, Gibbons et al. (2009) could not corroborate the FDA warning when examining data on patients with bipolar disorder receiving antiepileptic drugs (AED). They looked for suicide attempts in a cohort of 47,918 patients with bipolar disorder with a minimum 1-year window of information before and after the index date of their illness. There was no significant difference in suicide attempt rates for patients treated with an AED (13 per 1000 person-years, PY) vs. patients not treated with an AED or lithium (13 per 1000 PY). Treatment with AED appeared suicide protective as in AED-treated subjects, the rate of suicide attempts was significantly higher before treatment (72 per 1000 PY) than after (13 per 1000 PY). For lamotrigine, the figures were 39 suicide attempts per 1000 PY before and 13 per 1000 PY after treatment initiation. The authors concluded that, as a class, AEDs do not increase risk of suicide attempts in patients with bipolar disorder relative to patients not treated with an AED or lithium.

Also in contrast to the FDA findings in predominantly epileptic patients, Born et al. (2005) found that compared to lithium, the relative risk of suicidal ideation in a cohort of 128 bipolar patients was numerically slightly higher for valproate and carbamazepine, but lower in patients treated with lamotrigine, without reaching statistical significance. ***Rating of PSu: "0"***

Practicability (PR)

Lamotrigine is in most countries available as tablets (ranging from 2 to 200 mg) and as water-soluble tablets. The recommended plasma levels for safety (not efficacy) in epilepsy are 3–14 mg/l (11.7–56.4 μmol/l), with slight variations depending on laboratories (Neels et al. 2004), and there is a linear relationship between dose and plasma concentration. Titration to the recommended dosage in bipolar maintenance of 200 mg/day takes 6 weeks. Lamotrigine has significant plasma level interactions with carbamazepine, valproate and with the ethinyl estradiol contained in oral contraceptives, which means that the lamotrigine dosage should be doubled (in the presence of carbamazepine), increased (with oral contraceptives) and halved (with valproate) (Johannessen and Landmark 2010). On the other hand, lamotrigine might increase the levonorgestrel clearance and, by this, change FSH and LH serum levels which might make contraception unreliable. ***Rating of PR: "0"***

Recommendation grade (RG)

Lamotrigine has efficacy in the recurrence prevention of any episode in enriched samples (CE:A) as proven by two RCTs, clearly more pronounced for prevention of depression (CE:A), with additional weaker evidence for mania (CE:D). However, the study by Kessing et al. (2011a), the MOAT analyses and the lamotrigine–valproate combination study (Bowden et al. 2012) all soften the evidence even for depressive prevention. Lamotrigine provides partial,

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i.e., subsyndromal depression benefit in both MOAT analyses of the RCTs. There is CE "C" evidence for rapid cycling patients. In non-enriched samples, the CE is "F" as no informative studies have been conducted. Further evidence rated "+", and good tolerability also support the use of lamotrigine. However, there are minor concerns with safety in pregnancy and practicability (slow titration scheme).

Thus, for patients tolerating lamotrigine where the predominant treatment goal is to prevent depressive recurrences or any episode, the task force decided to assign a RG of "1". However, some doubts about lamotrigine's clinical utility remain as explained above. For all other groups of patients, the long-term use of lamotrigine is not supported by solid evidence, but should not be excluded in specific clinical scenarios such as non-response, or tolerability or safety problems with other long-term treatments.

Lithium

Following Baastrup and Schou's (1967) observation in 1967 of lithium decreasing the frequency of episodes in bipolar disorder (and in recurrent unipolar depression), a number of early placebo-controlled RCTs (1970–1978) preliminary established the long-term efficacy of lithium in bipolar disorder. These studies have been extensively reviewed, e.g., by Goodwin and Jamison (2007) or Maj (2000), and more recently by Licht (2012). These studies built the foundation of the widespread clinical use of lithium in bipolar disorder for decades, despite some evidence that they may have overestimated the clinical utility of the drug (Maj et al. 1998) and its restrictions by long-term physical health issues (Gitlin 1999). However, the vast majority of these early prophylaxis studies would nowadays not fulfil methodological criteria to be considered as sufficient scientific proof of evidence. Thus, we will not give them extensive consideration. The only exception is the study by Prien et al. (1973a); the majority of good evidence now stems from studies published from 2000 onwards, which used lithium as an established standard comparator in placebo-controlled RCTs of other drugs of interest. This should not derogate the merits of the early pioneers in lithium research as, in the end, modern studies confirmed what had been suggested before.

However, the treasure trove of experience to which also older studies contribute is of great clinical value as it allows predicting potential response to lithium. Putative predictors of favourable response to lithium (family history of bipolar disorder, Mania-Depression-Free interval course, no rapid cycling, no alcohol or drug abuse and, especially, good adherence) should also be considered when recommending treatment with lithium (Grof 1979).

Prevention of TEE in enriched samples (PES)

In 1970, Baastrup et al. (1970) conducted a placebo-controlled maintenance discontinuation study with lithium in stable female outpatients who had suffered in the past from recurrent unipolar depression or bipolar disorder. In that way the sample was enriched on stabilization, albeit not necessarily on acute response to lithium. Questionable applying today's ethical standards, patients were not made aware that they participated in a study and that their lithium might be substituted with placebo. For this reason, investigators decided to keep observation time to an absolute minimum and stopped the study after 5 months when the predetermined significance level ($P < 0.001$) conducting sequential analysis of pairs matched for number of previous episodes was achieved. The mean duration on trial medication for patients without relapse was 19.7 weeks for placebo and 20.3 weeks on lithium. None of the 45 lithium continuation patients relapsed, but 21 out of 39 who were switched to placebo. Secondary subanalysis of the bipolar patients revealed that 12 of the 22 patients on placebo relapsed (35%), seven of them into a manic, and five into a depressive episode, whereas all 28 lithium continuation patients remained well. As by trial design, the overall relapse rate was significantly lower with lithium ($P > 0.001$); the authors did not supply statistical analyses of manic and depressive relapses separately. The clear limitations of the study are the short observation period under double blind conditions, and inclusion of females only.

Soon afterwards, Prien et al. (1973a) conducted a maintenance study in 205 patients (101 on lithium, 104 on placebo) who had been post-acutely stabilized on lithium (serum levels 0.5–1.5 mmol/l) after a manic episode treated with lithium and/or other drugs. Thus, the study sample was enriched at least for post-acute stabilization. Prien used a composite outcome distinguishing between "severe relapse" (requiring hospitalization) and "moderate relapse" (requiring additional medication). For clarification, a distinction between relapse and recurrence was not made in this paper; any new mood episode was termed "relapse". Over 2 years, 67% of patients on placebo had at least one relapse compared to 31% on lithium ($P < 0.001$), 29% in the placebo group and 12% in the lithium group had two or more severe recurrences of mood episodes, which was non-significant. When combining severe and moderate relapses the proportion of patients remaining relapse-free was significantly

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higher in the lithium group (57 vs. 19%, $P<0.001$). Given a high pre-existing manic polarity in the study subjects (Prien et al. 1974) and that the index episode was mania, it is not surprising that 64% of relapses with lithium were manic and 24% depressive, the rest was clustered as mixed or schizo-affective. Distribution between polarity of relapse was similar for placebo; however, statistical significance for a superiority of lithium was only achieved for manic, not depressive relapses (Prien et al. 1974). A problem with the study is that it is, strictly speaking, not entirely double-blind, although rater and patients were blinded to medication. However, the treating physicians, responsible for managing any relapse, were aware of the identity of subjects' medication. They were also instructed to increase the dose of lithium when a patient on lithium started to show symptoms. The importance of this issue is that it means that the treatment conditions of the two groups were not entirely comparable, and lithium was dosed not only in response to plasma levels, but also treatment success.

In a second study by Prien et al. (1974), already described in the section on "Antidepressants", lithium was significantly better than placebo and imipramine in preventing new affective episodes ($P<0.01$, using Fisher's exact probability test). The difference between the lithium and imipramine groups was due almost entirely to the higher incidence of manic episodes in the group receiving imipramine ($P<0.05$) whereas the incidence of depressive episodes was not statistically different ($P>0.05$). The difference between the lithium and placebo groups was due to both manic and depressive episodes: both, types of episodes were about three times as prevalent in the placebo group. However, the difference between the lithium and placebo groups reached statistical significance only for depressive episodes ($P<0.05$). The lack of statistical significant separation for new manic episodes can be explained by the lack of power and the characteristics of patients included. New depressive episodes clearly prevailed in the lithium and placebo group (but not in the imipramine group), reflecting a pre-existing depressive polarity in the participants.

Further lithium discontinuation studies were conducted in the 1970s (Melia 1970; Cundall et al. 1972; Hullin et al. 1972; Stallone et al. 1973; Fieve et al. 1976), but each of them has methodological shortcomings, e.g., mixed patient populations, crossover designs, small numbers and observation period, unclear enrichment, or incomplete or mixed outcome reporting which disqualifies them from being utilized as higher ranked evidence. Nevertheless, they can be seen as supportive further evidence (FE) for the use of lithium.

In summary, we identified several placebo-controlled studies supporting the efficacy of lithium for PES. Three of them (Baastrup et al. 1970; Prien et al. 1973a, 1974) appear reasonably informative, but still have not the same rigor in methods and reporting as other more recent studies to which we assigned top CE ratings. Thus, the task force felt that a CE rating of "A" would be not adequate, but, considering the combined bulk of evidence, the ***CE to prevent manic, depressive and any episode in PES should be "B".***

Prevention of TEE in non-enriched samples (PNES)

A total of four large RCTs in which lithium was used as an internal comparator for assay sensitivity has been conducted since the 1990s. Different from the substances under investigation in three out of the four studies (two with lamotrigine, one with quetiapine) the lithium arm was incorporated in a non-enriched way, meaning that lithium (in contrast to the others) was tested independently of showing any mood-stabilizing effect and tolerability during the index episode prior to randomization. Also, lithium was not favoured by any discontinuation effect since this influenced the lithium and placebo group equally. The first study comparing valproate, lithium and placebo failed for both valproate and lithium (Bowden et al. 2000), most likely due to methodological shortcomings (Bowden et al. 1997). However, all subsequent studies confirmed lithium's efficacy. On a significant level, lithium separated from placebo in time to intervention for any recurrence, manic and depressive recurrences in the quetiapine study (Weisler et al. 2011), and for any recurrence and for manic recurrence in the two lamotrigine studies (Bowden et al. 2003; Calabrese et al. 2003), as well as in a combined analysis of these studies (Goodwin et al. 2004). Lithium did not separate from placebo for prolonging time to a depressive episode in neither lamotrigine study, nor in the combined analysis ($P=0.325$). Whereas lithium's efficacy in preventing new manic episodes in non-enriched samples is confirmed in three of four studies, the evidence for preventing new depressive episodes is, at the moment, at odds.

What are, besides enrichment, likely reasons for the diverging results for lithium preventing new depressive symptoms between the study of Prien et al. (1974), mentioned in the previous paragraph, the quetiapine study and the lamotrigine studies? Prien et al.'s study probably also separated because they limited enrolment to severely ill hospitalized patients with bipolar I depression. In the lamotrigine study, lithium might have not separated because patients entering the study were less seriously ill outpatients.

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The patients in the quetiapine study, which included a mixture of in- and outpatients, might have been less severely ill, too. However, this study recruited more than twice as many patients on lithium and placebo than the two lamotrigine studies together, favouring the detection of a significant difference.

Thus, given this evidence from three positive studies, the ***CE to prevent any episode and manic episodes in PNES is "A".*** With conflicting results, the ***CE to prevent depressive episodes in PNES is "D".***

Prevention of TEE in rapid cyclers (PRC)

The prophylactic use of lithium in rapid cycling patients has been discouraged for a long time based on the observation of insufficient acute and prophylactic efficacy in these patients (Dunner and Fieve 1974; Dunner 1998). Based on case series in rapid cyclers, valproate has been preferred over lithium for a long time. However, the direct head-to-head comparison of lithium and valproate in a double-blind, randomized design did not reveal a statistical significant advantage of valproate over lithium (Calabrese et al. 2005). Unfortunately, attrition in this trial was high (76% premature discontinuations) as even with open combined lithium + valproate treatment the fast majority of patients did not meet stability criteria sufficient for randomization. So, in the end, this study is inconclusive.

Other than this study, we found only one further double-blind RCT for lithium in rapid cycling patients, comparing over 6 months lithium monotherapy with combined lithium/valproate treatment in bipolar patients with comorbid substance abuse or dependence (Kemp et al. 2009). Patients had been stabilized on the combination treatment, and then valproate was withdrawn and replaced by placebo in half of the subjects. Again, attrition during open-label stabilization was high with 79% drop outs, so that only 31 patients could be randomized. In all outcome parameters (any relapse, manic or depressive relapse), the authors found no advantage of the combination versus lithium monotherapy.

A positive interpretation of these two studies would be that lithium is at least as good as the "standard" valproate; a more realistic interpretation would be that neither treatment is particularly efficacious in preventing new mood episodes in rapid cycling patients. However, as these studies lack a placebo arm and there is no clear proof for efficacy of the comparator valproate in RC patients, a CE of "E", meaning negative evidence, would not be justified, also keeping in mind that there have been no RCTs demonstrating a drug–placebo difference for any compound in rapid-cycling patients. Therefore, the appropriate ranking would be a ***CE: "F" for PRC.***

Further evidence (FE)

Several meta-analyses confirm the prophylactic efficacy for lithium in preventing any relapse and manic relapses (Geddes et al. 2004; Smith et al. 2007; Beynon et al. 2009; Vieta et al. 2011). However, as all were published too early to include the latest study of Weisler et al. (2011), and since they primarily were based on the other studies reviewed here above, they do not yet support the efficacy of lithium in preventing bipolar depression. It can be assumed that this will change in future metaanalysis using today's base of knowledge.

In the MAP study (Greil et al. 1997b) (see section on "Carbamazepine") differences in TEE in non-enriched samples were not different between lithium and carbamazepine on a statistically significant level (Kleindienst and Greil, personal communication 26.4.2012), but composite outcomes were in favour of lithium. Similarly, in the study by Hartong et al. (2003) lithium was numerically more effective than carbamazepine but just missing significance.

In a head-to-head comparison, olanzapine ($n = 217$) was compared to lithium ($n = 214$, target blood level: 0.6–1.2 mmol/l) in a double-blind, 1-year study in patients that were stabilized for 6–12 weeks on the combination of both agents given while manic, and then randomized to continuation on either substance (Tohen et al. 2005). The primary outcome was testing non-inferiority of olanzapine against lithium for the occurrence of a TEE. Symptomatic relapse/recurrence (score $>$ or $= 15$ on either the YMRS or HAM-D scale) occurred in 30.0% of olanzapine-treated and 38.8% of lithium-treated patients, and non-inferiority of olanzapine relative to lithium was established. Secondary results showed that compared with lithium, olanzapine had significantly lower risks of manic episode and mixed episode relapse/recurrence, but no difference was observed for depressive recurrences. Both agents were comparable in preventing recurrence of depression. As the primary hypothesis of this study was non-inferiority of olanzapine versus lithium (and not vice versa), and statistical assumptions were made accordingly, we cannot use it as level "B" evidence for lithium (but for olanzapine). Nevertheless, this company sponsored study also supports the usefulness of lithium in long-term treatment relative to olanzapine.

In the multinational BALANCE study (Geddes et al. 2010) lithium was tested against valproate and the combination of both for 2 years. A total of 330 bipolar I patients were randomly allocated to

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open-label lithium monotherapy (plasma concentration 0.4–1.0 mmol/l, $n = 110$), valproate monotherapy (750–1250 mg, $n = 110$), or both agents in combination ($n = 110$), after an active run-in of 4–8 weeks on the combination. Thus, the study was enriched for tolerability of both lithium and valproate. The primary outcome was initiation of new intervention for a TEE. Fifty-nine (54%) of 110 subjects in the combination therapy group, 65 (59%) of 110 in the lithium group, and 76 (69%) of 110 in the valproate group needed intervention for a new mood episode during follow-up. Lithium was significantly more effective than valproate, whereas there was no significant difference between lithium monotherapy and the combination treatment. Hazard ratios (HR) for the primary outcome were 0.59 (95% CI 0.42–0.83, $P = 0.0023$) for combination therapy versus valproate, 0.82 (0.58–1.17, $P = 0.27$) for combination therapy versus lithium, and 0.71 (0.51–1.00, $P = 0.0472$) for lithium versus valproate. This study clearly supports the use of lithium, however, it felt short of being counted towards higher evidence (large non-inferiority study against an established comparator) as, strictly speaking, valproate cannot be considered as established comparator for maintenance treatment based on its lack of positive controlled evidence from single RCTs (see section on "Valproate").

Two studies compared lamotrigine with lithium. The already cited study by Licht et al. (2010) found no difference in effectiveness for observation periods up to 5 years (see section on "Lamotrigine").

Kessing et al. (2011a) compared rates of switch to, or add on of, another psychotropic, and rates of psychiatric hospitalization for patients treated with lamotrigine or lithium in clinical practice. From the Danish registers they identified 730 patients who received lamotrigine and 3518 patients received lithium between 1995 and 2006. The overall rate of switch to or add on of another psychotropic was higher for lamotrigine compared with lithium (HR = 2.60, 95% CI: 2.23–3.04), regardless of whether the index episode was depressive, manic, mixed or remission. In addition, the overall rate of psychiatric hospitalization was increased for lamotrigine compared with lithium (HR = 1.45, 95% CI: 1.28–1.65), as were the rates for patients with a depressive (HR = 1.31, 95% CI: 1.01–1.70) and patients with a manic (HR = 1.65, 95% CI: 1.31–2.09) index episode. Rates did not differ significantly between the drugs for patients with a mixed index episode and for patients in remission. Kessing et al. concluded that, in daily practice, lithium is still superior to lamotrigine in long-term treatment. However, when interpreting these data, the risk of selection bias should be taken into account.

A recent NIMH funded multisite comparative effectiveness study was conducted to address whether tolerable doses of lithium either alone or added to other medications improved 6-month outcomes of clinically symptomatic (CGI-S ≥ 3) bipolar I and II patients (Nierenberg et al. 2009). The LiTMUS project compared lithium plus optimized treatment (OPT) with OPT without lithium. The study retained over 80% of subjects for the full 6-month trial. All planned outcomes found no significant differences between the two regimens despite assessing outcomes in the patients on a broad range of measure. The study, not yet published, may have enrolled patients with more depression weighted illnesses, which, given the mixed evidence of lithium prophylaxis for depression could have contributed to the negative result for low dose lithium. Another issue might be that a 6-month study duration is too brief for lithium to establish its full effectiveness.

To some degree unique, lithium seems to enable a fair proportion of bipolar patients to achieve and maintain full (also functional) remission. Paul Grof proposed the term "excellent lithium responders" for patients in whom lithium monotherapy has dramatically changed their lives by the total prevention of further episodes. He found that the best response to lithium is associated with clinical features of an episodic clinical course, complete remission, bipolar family history and low psychiatric comorbidity similar to those described by Kraepelin as *manisch-depressives Irresein* (Grof 2010). Rybakowski et al. (2001) demonstrated that patients on lithium monotherapy who do not experience affective episodes for 10 or more years (excellent lithium responders) make up one-third of lithium-treated patients. Important for full functional recovery, excellent lithium responders seem to preserve their cognitive function similar to control subjects (Rybakowski and Suwalska 2010). ***Rating for FE: "++"***

Safety and tolerability (ST)

Lithium has a low therapeutic index, with serum levels not more than double the therapeutic levels occasionally leading to serious CNS toxicity, potentially lethal. Dehydration may put patients under such risk. Benign side effects of lithium are also well known and in their majority dependent on plasma level. Up to 75% of patients on lithium experience some side effects, but most are minor (transient metallic taste in mouth, polyuria, polydipsia, weight gain, mild oedema, concentration difficulties, sedation) and can be reduced or eliminated by dose adjustment or dosage schedule. Mild CNS symptoms with higher plasma levels of lithium are frequent. Tremor affects up to 65% of patients treated

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with lithium and a severe tremor may be a sign of toxicity. Nausea, diarrhoea or blurred vision may also be signs of toxicity (Freeman and Freeman 2006). These side effects might be more exaggerated in combination treatments with increased risk of neurotoxicity, e.g., typical antipsychotics (Sachdev 1986) or carbamazepine (Shukla et al. 1984), or in patients with pre-existing neurological conditions (Moskowitz and Altshuler 1991).

From the patient perspective, in addition to the just mentioned adverse effects, the risk of weight gain and the risk of mental side effects (cognitive impairment and/or reduced intensity of perceptions and emotions) may be most crucial (Licht 2012). The discussion whether lithium (in non-toxic plasma levels) can cause cognitive impairment is controversial; patients report feeling less creative and emotionally blunted; however, psychological testing in lithium patients is not conclusive (Lopez-Jaramillo et al. 2010b). On the other hand, there is some evidence from animal research that lithium might delay Alzheimer's disease (Young 2011; Zhang et al. 2011).

Long-term lithium treatment affects kidney function (Tredget et al. 2010), and after many years of treatment, renal impairment may occur (Bendz et al. 2010). Close monitoring of the eGRF is essential part of lithium safety measures (Jefferson 2010). Hypothyroidism is frequent with lithium treatment, and substitution treatment is often indicated. Especially women seem to be on increased risk (women 14% vs. men 4.5%) (Johnston and Eagles 1999).

Lithium's teratogenic effect rarely gives rise to not initiating lithium treatment, possibly due to the fact that the risk is well characterized and relatively low in absolute terms (Yonkers et al. 2004; Nguyen et al. 2009). Potential heart dysplasias can nowadays be detected early by routine sonography and be corrected in utero. Discontinuing lithium during pregnancy might not be justified balancing risks and benefits (Baldessarini et al. 1999c).

Lithium also has a significant, albeit infrequent, impact on parathyroid function (leading to hyperparathyroidism) and calcium levels, which is widely unappreciated (McKnight et al. 2012). ***Rating for ST: "–"***

Prevention of suicide (PSu)

Much evidence has been accumulated for a specific, suicide preventive effect of lithium, which might be independent from improvement of an affective disorder. Lithium has anti-agressive and anti-impulsive properties which might link it to anti-suicidal effects (Kovacsics et al. 2009) as shown in a metaanalysis of RCTs conducted by Cipriani et al. (2005). They found that patients who received lithium compared to other treatments were less likely to die by suicide (odds ratio (OR) = 0.26; 95% CI = 0.09–0.77). The composite measure of suicide plus deliberate self-harm was also lower in patients who received lithium (OR = 0.21; 95% CI = 0.08–0.50). There were fewer deaths overall in patients who received lithium (OR = 0.42, 95% CI = 0.21–0.87) which is in line with large observational studies as the Zurich cohort study, finding a decreased mortality from all causes with lithium (Angst et al. 2002). For more in depth information on this clinically highly relevant topic we refer the reader to the pertinent literature (e.g., Baldessarini et al. 2006; Gonzalez-Pinto et al. 2006; Müller-Oerlinghausen et al. 2006; Wasserman et al. 2012). ***Rating for Psu: "++"***

Practicability (PR)

For use in bipolar disorder, lithium is available in different salt preparations, as lithium carbonate, lithium citrate, lithium hydrogenaspartate and lithium sulfate. It is available as tablets, including extended release formulations, or droplets and syrup (lithium citrate only). There is no evidence for differences in efficacy between lithium salts; the choice of preparation is based on slight differences in tolerability and ease of administration.

In most cases, lithium is up titrated in small steps guided by individual experience and plasma level monitoring; however, it is also possible to predict the target dose by calculating the lithium clearance (Abou-Auda et al. 2008).

Due to its relatively small safety margin, plasma concentrations need to be checked on a frequent and regular basis until equilibrium in the therapeutic range has been achieved and thereafter. It is recommended to check every 3–6 months in patients with stable lithium levels and whenever the clinical status changes, physical health issues appear or co-medication that might affect lithium levels (e.g., furosemide) is introduced (Zarin et al. 2002). Renal and thyroid function should also be checked regularly, every 6–12 months depending on risks.

Plasma levels for successful prevention of mania are likely to be different from those for preventing depression. Lithium concentrations ≤ 0.6 mmol/l seemed to be ineffective preventing new manic episodes in RCTs , but may be still sufficient to prevent depression (Severus et al. 2010). Higher lithium concentrations may not necessarily protect better against depression; a post-hoc analysis of the MAP study found that lithium concentrations preceding

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reappearance of depressive symptoms were significantly higher than those preceding new manic episodes (Kleindienst et al. 2007; Severus et al. 2009). A meta-review by Severus et al. concluded that "the minimum efficacious serum lithium concentration in the long-term treatment of bipolar disorder was 0.4 mmol/l with optimal response achieved at serum concentrations between 0.6 and 0.75 mmol/l. Lithium concentrations >0.75 mmol/l may not confer additional protection against overall morbidity but may further improve control of inter-episode manic symptoms. Abrupt reduction of serum concentrations of more than 0.2 mmol/l was associated with increased risk of relapse" (Severus et al. 2010). Despite the recommendations outlined here above, it should be born in mind that the optimal concentration is highly individual.

Any need to discontinue lithium often poses a problem. Especially for lithium, an increased relapse risk after its sudden discontinuation has been described (Mander and Loudon 1988) and reinstituting lithium may not always be effective (Post et al. 1992; Goodwin 1994). If necessary, it is strongly recommended that lithium maintenance is always tailed off slowly over some weeks or even months (Suppes et al. 1993).

Before lithium is initiated the patient should always be instructed carefully regarding signs of toxicity and risk situations (Licht 2012). ***Rating for PR: "–"***

Recommendation grade (RG)

Unique in comparison to the other PAs, lithium does not only score with the highest CE in the category PNES for "any relapse" and "mania", but also receives a good score (CE: "B") for PNES "depression", PES "any episode" and substantial support from ratings for FE and PSu. Undoubtedly, lithium is more difficult to use than other PAs and has safety and tolerability issues; however, these are outweighed by its overall effectiveness, so clearly the ***RG is "1"***.

Olanzapine

Prevention of TEE in enriched samples (PES)

All pivotal maintenance studies with olanzapine have been conducted in samples enriched for acute response in mania, except of one follow-up study with olanzapine, olanzapine/fluoxetine combination or placebo where the index episode was bipolar depression (Shelton 2006).

Focussing on studies which recruited patients with a manic index episode, there are four randomized, double-blind trials investigating the efficacy of olanzapine compared to placebo or lithium monotherapy as well as augmentation in maintenance therapy for prevention of relapse of affective episodes in bipolar I disorder. Enrichment for olanzapine response in these studies varied; in the olanzapine versus placebo study, all patients were previously stabilized on olanzapine monotherapy. In the olanzapine versus lithium study, enrichment was for response to combined olanzapine and lithium. Finally, in the combination treatment studies, manic patients had previously participated in an acute trial (Tohen et al. 2002b) and had responded to the combination of olanzapine and either lithium or valproate acutely.

One study compared olanzapine with placebo in bipolar I patients with a manic or mixed index episode who have responded to open olanzapine treatment (Tohen et al. 2006). The criteria for stabilization prior to randomization were quite liberal and required only two consecutive weekly visits fulfilling criteria for symptomatic remission. As pointed out by Gitlin et al. (2010) this will favour early relapse in the placebo arm due to a still on-going underlying acute episode and withdrawal of effective medication. Two hundred and twenty-five patients were randomly assigned to double-blind maintenance treatment with olanzapine or placebo ($N=136$) for up to 48 weeks. The primary measure of efficacy was time to symptomatic relapse into any mood episode. Time to symptomatic relapse into any mood episode, defined as YMRS score ≥ 15, HAM-D score ≥ 15, or hospitalization, was significantly longer among patients receiving olanzapine (a median of 174 days, compared with a median of 22 days in patients receiving placebo). Times to symptomatic relapse into manic, depressive, and mixed episodes were also all significantly longer among patients receiving olanzapine than among patients receiving placebo. The overall relapse rate was significantly lower in the olanzapine group (46.7%) than in the placebo group (80.1%); however, the RR of relapse compared to placebo was only significant for any relapse and manic or mixed relapses, but not for depression (Vieta et al. 2011). This may be due to the relatively higher risk of manic relapses in patients with a manic index episode, but could also suggest a weaker prophylactic effect of olanzapine against depressive recurrences.

A post-hoc analysis of this study also revealed similar efficacy of olanzapine in mixed patients versus placebo as with pure manic patients (Tohen et al. 2009b).

More recently, olanzapine was also used as a comparator in two placebo-controlled long-term studies involving paliperidone extended release (ER; Berwaerts et al. 2012) and risperidone long-term injectable (LAI; Vieta et al. 2012a). These studies are

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especially remarkable as they support olanzapine's efficacy in RCTs which were not sponsored by the producer of olanzapine. The study of Vieta et al. was conducted in a sample of patients with a manic index episode without enrichment for olanzapine response and will therefore be considered in the next paragraph on PNES.

The study by Berwaerts et al. (2012) compared paliperidone ER, placebo and olanzapine as internal comparator for assay sensitivity for up to 24 months (for more details see section on "Paliperidone"). Post-hoc pairwise comparisons of olanzapine with placebo, and olanzapine with paliperidone ER showed that time to recurrence of any mood symptoms (the primary outcome) was significantly longer with olanzapine ($P \leq 0.001$ vs. either treatment group). The NNT for olanzapine at 12 and 24 months of treatment in the maintenance phase was 3 (95% CI: 2–5), which is one of the lowest ever reported for a maintenance study. Post-hoc pairwise comparisons of olanzapine with placebo, and olanzapine with paliperidone ER also showed that time to recurrence of manic symptoms was significantly longer in the olanzapine group compared with the placebo ($P \leq 0.001$), or paliperidone ER groups ($P = 0.014$). Recurrence of depression occurred in 18% ($n = 26$) of those on placebo and 24% ($n = 35$) on paliperidone ER, and 12% ($n = 10$) on olanzapine; testing for significance has not been reported, but due to the small number of depressive recurrences such testing is unlikely to demonstrate a significant difference.

Two studies compared olanzapine head-to-head to other PAs without a placebo control. The study comparing olanzapine with lithium has been described in the section on lithium. It supports the long-term use of olanzapine to prevent any episode, mania and depression in patients with a manic or mixed index episode. The sample used in this study is as much enriched for tolerability to olanzapine as it is for lithium, and partly for acute efficacy as we cannot make a distinction who responded to olanzapine, lithium or both during acute treatment.

The other study (Tohen et al. 2003a) is an extension study of an acute double-blind head-to-head comparison of olanzapine and valproate (Tohen et al. 2002a). Patients remitting during the acute 3-week study were followed up for another 44 weeks without re-randomization. As valproate cannot be considered as a well-established comparator for prophylactic treatment (see section on "Valproate") this study is listed in the category "Further evidence".

The combination of olanzapine + lithium or valproate versus lithium or valproate + placebo was tested in an 18-month RCT (Tohen et al. 2004). Ninety-nine patients who received combination treatment during a preceding acute phase trial (Tohen et al. 2002b) and had achieved syndromic remission of both mania and depression were randomly re-assigned at visit 8 (week 6 of the acute phase) in a 1:1 ratio to receive an additional 18 months of double-blind therapy, consisting of either olanzapine (flexible dosage range of 5–20 mg/day) in combination with lithium or valproate (combination therapy), or placebo added to lithium or valproate (monotherapy). Forty-one of the 99 subjects had a rapid cycling course and 26 exhibited psychotic features in their index episode of mania which may have contributed to a high rate of premature discontinuation. Due to the high attrition rate with 78 of 99 subjects discontinuing before study end, the results are inconclusive. The treatment difference in time to relapse into either mania or depression was not significant for syndromic relapse (median time to relapse: combination therapy 94 days, monotherapy 40.5 days; $P = 0.742$), but was significant for symptomatic relapse (combination therapy 163 days, monotherapy 42 days; $P = 0.023$).

This, we would consider a ***CE for the prevention of manic episodes in ES of "A"***, and also the ***CE to prevent any episode in ES is "A".***

The CE to prevent new depressive episodes in ES is "B" based on the placebo-controlled study by Tohen et al. (2006). We felt that the lack of a statistical significant signal in the other RCTs is rather a methodological artefact than contradicting efficacy of olanzapine in preventing depression. These studies were not designed to show such a separation, neither from the patients included, nor from the numbers assigned to the respective olanzapine arms.

Prevention of TEE in non-enriched samples (PNES)

A RCT by Vieta et al. (2012a) compared risperidone long acting injectable (LAI), placebo and olanzapine as internal comparator for assay sensitivity. After a 12-week open-label period with risperidone LAI ($n = 560$), patients who did not experience a recurrence entered an 18-month randomized, double-blind period with risperidone LAI ($n = 132$) or placebo ($n = 135$); a third treatment arm ($n = 131$) was randomized to oral olanzapine (10 mg/day + placebo injections) for reference and exploratory comparisons. Thus, different from the other studies, this study did not enrich for acute olanzapine response as patients were stabilized on risperidone. The primary efficacy endpoint was time to recurrence of any mood episode. For a detailed description of the outcome for risperidone LAI the reader should refer to the section on risperidone. Time to recurrence of any

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mood episode was significantly longer with oral olanzapine than with placebo in both the prespecified analysis and analysis stratified for region ($P < 0.0001$ and $P < 0.001$, respectively). An additional exploratory post-hoc analysis showed that the time to recurrence of any mood episode was also significantly longer with oral olanzapine compared with risperidone LAI ($P = 0.001$, stratified by region). Times to recurrence of an elevated mood episode ($P < 0.0001$) or depressive episode ($P = 0.011$) were also significantly longer with olanzapine compared with placebo. Importantly, this study also adds to the body of evidence of olanzapine's ability to prevent depressive recurrences in patients with a manic index episode. Based on this study, the ***CE for PNES is "B" for any TEE, manic and depressive recurrences***

Prevention of TEE in rapid cyclers (PRC)

Post-hoc analysis of the 47-week olanzapine versus valproate study revealed that rapid cycling patients did less well over long-term treatment than non-rapid cycling patients. Among rapid cycling patients, olanzapine and valproate appear similarly effective against manic symptoms; however, among non-rapid cycling patients, olanzapine-treated patients experienced superior mania improvement. Olanzapine-treated, non-rapid cyclers experienced greater mania improvement than rapid cyclers (Suppes et al. 2005).

Although the observation is interesting, the equal efficacy on manic symptoms of olanzapine and valproate cannot count as solid CE "B" evidence, as the evidence of efficacy of valproate in rapid cycling patients is weak. We therefore decided on a ***CE for PRC "C".***

Further evidence (FE)

Tohen et al. (2003a) report a 47-week comparison of olanzapine (5–20 mg/day) and valproate (500–2500 mg/day). The study had two endpoints which have been reported separately, the first one after 3 weeks (Tohen et al. 2002a) and the second one at week 47. Two hundred and fifty-one manic or mixed patients were included. The primary efficacy instrument was the YMRS. Over 47 weeks, the mean improvement in the YMRS score was significantly greater for the olanzapine group, but there was only a numerical, but not significant advantage for olanzapine in the rates of subsequent relapse into mania or depression (42.3 and 56.5%).

Olanzapine was also used as internal comparator in a double-blind 12-week (McIntyre et al. 2009) and an additional 40-week extension study (McIntyre et al. 2010) of two acute studies testing asenapine against olanzapine and placebo (which was discontinued after 3 weeks). Changes in the YMRS ratings were numerically not different between asenapine and olanzapine in observed cases; however, attrition over 1 year was high.

Whereas the previous studies used subjects with a manic or mixed episode at entry, one study included patients who recovered from bipolar depression while taking olanzapine. Responders and remitters of the acute bipolar depression study comparing olanzapine, olanzapine–fluoxetine combination and placebo (Tohen et al. 2003b) had the option to continue treatment for another 24 weeks. The study was not randomized, but patients could choose between olanzapine monotherapy and the combination treatment. Patients were started on open-label olanzapine alone for 1 week, and then they were offered the option of assignment to the combination treatment if wanted. Approximately two-thirds of patients who had responder status at study entry achieved remission over 24 weeks. The rates of relapse, however, even in patients who achieved remission, were high (more than 37% of remitters within 24 weeks), suggesting that continuation of olanzapine alone was not very efficacious. However, rates of TEAS to mania were low and did not differ between patients treated with olanzapine or the combination (both $< 7\%$) (Corya et al. 2006; Shelton 2006).

The positive results of RCTs for long-term olanzapine treatment are reflected in the outcome of the large naturalistic study EMBLEM (Goetz et al. 2007). This open-label, non-randomized study compared the 2-year outcomes of patients with a manic/mixed episode of bipolar disorder taking olanzapine monotherapy or olanzapine in combination with other agents. The study consisted of two phases: acute (12 weeks) and maintenance (follow-up over 2 years). The longitudinal outcome measure was the CGI-BP scale. Cox regression models compared outcomes of both therapy groups using intention-to-treat and switching medication analysis. 1076 patients were included in this analysis. A total of 29% took olanzapine as monotherapy ($n = 313$) and 71% as combination ($n = 763$) at 12 weeks post-baseline (end of study acute phase). After adjusting for patient characteristics using switching medication analysis, relapse rates differed ($P = 0.01$) in favour of monotherapy-treated patients (Gonzalez-Pinto et al. 2011). This might indicate that olanzapine alone is already an effective treatment in patients improving on olanzapine, and additional medication does not necessarily add additional benefits. However, there is a caveat: due to the non-randomized design of the study, the findings could also be interpreted as indicating that the patients

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who were treated with the combination had more severe illness that was not able to be controlled with olanzapine monotherapy. ***Rating of FE: "++"***

Safety and tolerability (ST)

The olanzapine monotherapy study versus placebo (Tohen et al. 2006) is probably most informative for assessing tolerability and safety aspects.

The most common adverse events reported during the open-label phase were weight gain, dry mouth, increased appetite, and somnolence. During the double-blind phase, adverse events reported by patients who received olanzapine were weight gain and fatigue.

The prevalence rate of a metabolic syndrome in bipolar disorder ranges from 30 to 42%, a proportion much higher than the general population but similar to that observed in schizophrenia (Fagiolini et al. 2005). Metabolic changes and weight gain are those side effects which may limit the usefulness of olanzapine in many patients. The most common emergent event in this study was weight gain. During the open-label phase which lasted 8–14 weeks, patients who received olanzapine gained a mean of 3.1 kg (SD = 3.4). During double-blind treatment, placebo patients lost a mean of 2.0 kg (SD = 4.4) and patients who continued to take olanzapine gained an additional 1.0 kg (SD = 5.2).

Thirty-five percent of patients experienced an increase in baseline weight of ≥ 7% during the open-label phase while treated with olanzapine. Among these 125 patients, 14 (17.7%) of 79 patients who received olanzapine and one (2.2%) of 46 patients who received placebo experienced an additional increase in weight of ≥7% from the point of randomization in the double-blind phase.

Weight gain is closely linked to metabolic abnormalities. Increases in non-fasting glucose (mean = 5.3 mg/dl, SD = 34.4) and cholesterol (mean = 10.7 mg/dl, SD = 29.6) levels were reported during the open-label phase. Three patients in the olanzapine group and two in the placebo group had treatment-emergent elevations in glucose level during the double-blind phase. Two patients in the olanzapine group had treatment-emergent elevations in cholesterol level; maximum cholesterol values for those patients were 283.2 and 248.2 mg/dl, respectively. No patient in the placebo group had an elevation in cholesterol level.

Considering all olanzapine exposures, regardless of study phase, treatment-emergent elevation in prolactin level occurred in 134 (27.0%) of 496 patients.

Incidence rates of extrapyramidal symptoms were low in both the open-label and double-blind phases. No differences were found between the olanzapine and placebo groups in rates of treatment-emergent parkinsonism, akathisia and dyskinesia.

QTc prolongations were found in eight (4.5%) of 179 patients who received olanzapine and one (0.9%) of 117 patients who received placebo.

For a more extensive review of olanzapine-associated metabolic risks we refer the reader to the pertinent literature (e.g., Kantrowitz and Citrome 2008; Rummel-Kluge et al. 2010).

Olanzapine has a FDA pregnancy "C" category rating. Cases of cleft lip, encephalocele, and aqueductal stenosis associated with the use of olanzapine have been reported, and the incidence of major congenital malformations associated with olanzapine has been estimated as 1% (Nguyen et al. 2009) which largely corresponds to the expected population figure.

Given the issues with weight gain and metabolic changes which might result in increased susceptibility to relapse (Fagiolini et al. 2003) and increased morbidity and mortality from physical illness (Staiano et al. 2012; Newcomer 2007), the ***Rating of ST is "–".***

Prevention of suicide (PSu)

It has been suggested by Angst et al. (2005) that antipsychotics in general have an ameliorating effect upon suicide rates in affective disorders, similar to antidepressants and lithium. However, we could not retrieve any information more specific to olanzapine. In schizophrenic patients it appears that olanzapine has no comparable benefits as does clozapine on suicidality and suicidal behaviour (Meltzer and Baldessarini 2003). ***Rating of PSu: "0"***

Practicability (PR)

Olanzapine is available as tablets, oral soluble tablets and a soluble powder for short-acting injection as well as long-action injection. Thus a fair selection of application forms is available. The recommended doses for olanzapine for long-term treatment range from 5 to 20 mg/day depending on monotherapy versus combination treatment and other modifying factors such as age and comorbidities. When re-analysing the lithium versus olanzapine maintenance study Tohen et al. (2005) and Severus et al. (2010) found that patients with less than 10 mg olanzapine/day had a significantly increased risk of depressive (HR = 2.24, $P = 0.025$) TEE compared to patients with higher olanzapine dosages (10–20 mg/day). However, there was no statistically significant difference in risk for

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manic/mixed episodes between the two groups (HR = 0.94, $P = 0.895$). This appears in contrast to lithium dosing where higher lithium levels were associated with a greater risk of depressive recurrences. ***Rating of PR: "+"***

Recommendation grade (RG)

Olanzapine has a solid body of evidence for the prevention of TEE with a CE "A" in PES for "mania" and "any episode" and a CE "B" in PES for "depression" and in PNES for "depression", "mania" and "any episode". However, weight gain accompanied by metabolic changes puts a significant burden on patients and their physical health, and may lead to non-adherence or increased morbidity and mortality from cardiovascular disease. Balancing risks and benefits, the task force decided to downgrade the ***RG to "2".***

Oxcarbazepine: see "Other anticonvulsants used in bipolar disorder"

Paliperidone

Paliperidone is the major active metabolite of risperidone. There is no a priori reason to expect very different properties from the parent compound.

Prevention of TEE in enriched samples (PES)

In the study by Berwaerts et al. (2012), manic patients were randomized to a 15-week, double-blind acute treatment phase with either paliperidone extended release (ER; 3–12 mg/day) or olanzapine (5–20 mg/day). Olanzapine patients who fulfilled remission criteria at the end of week 15 were continued on olanzapine ($n = 83$) whereas the group of paliperidone remitters was split into those continuing on paliperidone ($n = 152$) or being switched to placebo ($n = 148$). The primary efficacy endpoint was time to first recurrence of any mood symptoms (i.e., manic or depressive) during the maintenance phase. The key secondary efficacy endpoint was the time to the first recurrence of manic symptoms. Time to recurrence of mood symptoms was significantly longer with paliperidone ER versus placebo ($P = 0.017$). The median time to recurrence was 558 days on paliperidone ER and 283 days on placebo; but could not be calculated with olanzapine, as less than 50% of patients (23%) reported recurrence of any mood symptoms. During the first year of treatment in the maintenance phase, the NNT was 8 (95% CI: 4; 885); however, this advantage was not seen at the end of the second-year of treatment.

The time to recurrence of manic symptoms was significantly longer in the paliperidone ER group versus placebo ($P < 0.001$). The HR (placebo: paliperidone ER) was 2.06 (95% CI: 1.32; 3.22) indicating that patients on placebo were twice as likely as patients on paliperidone ER to report recurrence of manic symptoms. A depressive recurrence occurred in 18% ($n = 26$) on placebo and 24% ($n = 35$) on paliperidone ER, but testing for statistical significance has not been performed.

In summary, we identified one study that supplied evidence for efficacy of paliperidone in preventing TEE in a sample enriched for a manic index episode and acute response to paliperdone. Thus, we would consider a ***CE for the prevention of any episode and of manic episodes in ES "B"***. The ***CE to prevent new depressive episodes in ES is "E"*** for similar reasons as seen with the ziprasidone maintenance study (see section on "Ziprasidone").

Prevention of TEE in non-enriched samples (PNES)

We could not identify any relevant trials of paliperidone for the category PNES. ***CE for PNES: "F"***

Prevention of TEE in rapid cyclers (PRC)

We could not identify any relevant information on effects of paliperidone on PRC. ***CE for PRC: "F"***

Further evidence (FE)

We could not identify any other relevant evidence for the use of paliperidone for recurrence prevention in bipolar patients. ***Rating of FE: "0"***

Safety and tolerability (ST)

The study by Berwaerts et al. (2012) is probably most informative as it contains not only information on TEAS compared to placebo, but also in relation to olanzapine as a standard treatment. In summary, slightly more EPS-related AEs and a moderate, but transient prolactin increase was observed. The proportion of patients reporting EPS-related AEs during the 15 weeks of acute and continuation treatment was higher in the paliperidone ER ($n = 207$, 34%) than olanzapine ($n = 23$, 16%) group, but during the maintenance phase this changed and reported EPS-related AEs were higher in the olanzapine group ($n = 8$, 10%) than paliperidone ER ($n = 6$, 4%) or placebo ($n = 4$, 3%) groups. EPS-related AEs in the paliperidone ER group during the maintenance phase were dyskinesia,

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akathisia, hypokinesia, tremor ($n = 1$, 1% each) and extrapyramidal disorder ($n = 2$, 1%); the event of dyskinesia resulted in study discontinuation. Median change from baseline to endpoint in the SAS and AIMS scores during the maintenance phase was 0 in all treatment groups. Based on BARS scores, the proportion of patients with mild or moderate akathisia was similar at baseline and endpoint for all groups during the maintenance phase. Parkinsonism (defined as SAS total score > 0.3) and akathisia (defined as BARS global clinical rating ≥ 2) occurred in a similar proportion of patients on paliperidone ER ($n = 9$ (6%) and $n = 1$ (1%), respectively) and olanzapine ($n = 5$ (6%) and $n = 1$ (1%), respectively) during the maintenance phase (vs. placebo: $n = 4$ (3%) and $n = 2$ (1%), respectively). However, the use of anti-EPS medications was higher in the paliperidone ER group than other groups during the 15-week acute and continuation phases ($n = 151$, 25% vs. olanzapine: $n = 13$, 9%) and maintenance phase ($n = 29$, 19% vs. placebo: $n = 24$, 16% and olanzapine: $n = 7$, 8%) which might have obscured true EPS rates. Glucose-related AEs were generally low, also with olanzapine. The mean ($\pm$ SD) prolactin levels increased from acute treatment baseline to acute/continuation treatment endpoint in both sexes in the paliperidone ER group (men: $+22.37 \pm 24.26$; women: $+72.23 \pm 93.19$ ng/mL) but decreased from maintenance phase baseline to endpoint in both sexes with paliperidone ER (men: -7.19 ± 20.83; women: -5.55 ± 52.88 ng/ml). Potentially prolactin-related AEs occurred in 32 (5%) patients on paliperidone ER and 5 (3%) on olanzapine during the 15 week acute and continuation phases. During the maintenance phase, potentially prolactin-related AEs occurred in 8 patients on paliperidone ER (galactorrhea ($n = 3$), decreased libido and amenorrhea ($n = 2$, each), irregular menstruation and erectile dysfunction ($n = 1$, each)) and one patient on placebo (breast pain).

So far, there is little known about risks of paliperidone in pregnancy. It can be assumed that they may be similar to the parent substance, risperidone. ***Rating of ST: "0"***

Prevention of suicide (PSu)

We could not identify any relevant information on effects of paliperidone on suicide or suicide related behaviours. ***Rating of PSu: "0"***

Practicability (PR)

Paliperidone is not available in all countries. Formulations include oral extended release tablets and a long-acting injectable suspension. Thus, the choice of available formulations is limited, but may be sufficient for the purpose of long-term treatment. The recommended treatment dose ranges from 3 to 12 mg/day, depending on tolerability, as tested in the study by Berwaerts et al. (2012). ***Rating of PR: "0"***

Recommendation grade (RG)

Paliperidone has ***CE "B" evidence for the prevention of treatment emergent mania and any episode in PES*** which relates to a ***RG of "3"***. However, it is of note that it has no evidence in any other category, not even for "Further evidence". And it is one of the few compounds in which a maintenance placebo-controlled RCT showed numerically better results for placebo in preventing depression. In addition, it seems to be clearly less effective than olanzapine in all outcome parameters tested. On the other hand, there is little reason to treat it separately from risperidone and clinicians are referred to the data also extant for risperidone.

Phenytoin: see "Other anticonvulsants used in bipolar disorder"
Pregabaline: see "Other anticonvulsants used in bipolar disorder"

Quetiapine

Prevention of TEE in enriched samples (PES)

The evidence for quetiapine to prevent TEE in patient populations enriched for acute response to the drug (both with an index episode of mania and depression) is quite convincing. Two monotherapy RCT's and two add-on studies support the efficacy of quetiapine in this population.

The study by Weisler et al. (2011) (see also the section on "Lithium") investigated the efficacy and safety of quetiapine monotherapy (330–800 mg) as maintenance treatment in bipolar I disorder compared with switching to placebo or lithium in patients with a manic/mixed or depressive index episode stabilized on quetiapine for 4–25 weeks. To be eligible for the double-blind randomized phase, patients had to achieve stabilization at the latest by week 20 and to maintain stability for at least four subsequent weeks. Patients achieving stabilization were randomized to continue quetiapine or to switch to placebo or lithium (0.6–1.2 mmol/l) for up to 2 years in a double-blind trial. The primary outcome measure was time to recurrence of any mood event; secondary measures were times to manic or depressive events. Recurrence was defined as at least one of the following: initiation of an antipsychotic, antidepressant, anxiolytic (other than lorazepam), or other

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medication to treat a mood event; hospitalization for a mood event; YMRS score ≥ 20 or MADRS score ≥ 20 at two consecutive assessments or final assessment if the patient discontinued or discontinuation from the study if, according to the investigator, discontinuation was due to a mood event. Approximately 50% of those receiving open label quetiapine were successfully stabilized and randomized ($n = 1226$). Time to recurrence of any mood event was significantly longer for both quetiapine versus placebo (HR = 0.29; 95% CI, 0.23–0.38; $P < 0.0001$) and for lithium vs. placebo (HR = 0.46; 95% CI, 0.36–0.59; $P < 0.0001$). Quetiapine and lithium significantly increased time to recurrence of both manic events (quetiapine: HR = 0.29; 95% CI, 0.21–0.40; $P < 0.0001$; lithium: HR = 0.37; 95% CI, 0.27–0.53; $P < 0.0001$) and depressive events (quetiapine: HR = 0.30; 95% CI, 0.20–0.44; $P < 0.0001$; lithium: HR = 0.59; 95% CI, 0.42–0.84; $P < 0.004$) compared with placebo. When data were censored to exclude events in the first 4 weeks after randomization, the HR for the time to recurrence of any mood event was 0.27 ($P < 0.0001$) for quetiapine versus placebo, 0.41 ($P < 0.0001$) for lithium versus placebo, and 0.70 ($P = 0.041$) for quetiapine vs. lithium in the intend-to treat (ITT) population pointing towards a true effect of quetiapine in preventing recurrences rather than just relapses.

Different from the first study, in the study by Young et al. (2012), all patients had a depressive index episode, and, before entering the 1-year, double-blind maintenance phase, they participated in two acute bipolar depression RCTs (McElroy et al. 2010; Young et al. 2010) comparing quetiapine, placebo and an internal comparator (lithium in one, paroxetine in the other trial). Patients ($N = 584$) with bipolar I or II disorder who achieved remission after 8 weeks of treatment with quetiapine (300 or 600 mg/day) in these RCTs were randomised to the same quetiapine dose or placebo for up to 52 weeks or until mood event recurrence. As a result, the risk for a TEE was significantly lower with quetiapine than placebo (HR 0.51 (95% CI: 0.38–0.69); $P < 0.001$). Quetiapine was associated with a lower risk for recurrence of depressive events (HR 0.43 (95% CI: 0.30–0.62); $P < 0.001$) but recurrence of manic/hypomanic events was not significantly reduced (HR 0.75 (95% CI: 0.45–1.24; $P = 0.263$). This might be related to the selection of patients with an index episode of depression (see section on "Population under examination"). There was a lower risk of recurrence of mood events both in bipolar I (HR 0.58 (95% CI: 0.41–0.82), $P = 0.002$) and bipolar II patients (HR 0.33 (95% CI: 0.18–0.60), $P < 0.001$).

Finally, two identically designed combination treatment studies comparing lithium or valproate + quetiapine versus lithium or valproate + placebo (Vieta et al. 2008c; Suppes et al. 2009) add further to the evidence. Patients had manic/mixed or depressive episodes, and were stabilized with open label quetiapine (400–800 mg/day) for up to 36 weeks until they fulfilled stability criteria for at least 12 weeks. After randomization to either treatment arm they were followed-up double-blind for up to 2 years. Results in both studies are virtually identical: the combination treatment of quetiapine + lithium or valproate was significantly superior to lithium or valproate + placebo for all primary and secondary outcome parameters: In the study by Vieta et al. (2008c), a multinational study, the proportion of patients having a mood event was markedly lower in the quetiapine than in the placebo group (18.5 vs. 49.0%). The HR for time to recurrence of any mood event was 0.28 ($P < 0.001$), a mania event 0.30 ($P < 0.001$), and a depression event 0.26 ($P < 0.001$) corresponding to risk reductions of 72, 70 and 74%, respectively. In the study by Suppes et al. (2009), conducted in North America, also significantly fewer patients in the quetiapine group experienced a TEE compared with the placebo group (20.3 vs. 52.1%). The HR for time to recurrence of a mood event was 0.32. HRs were similar for mania and depression events (0.30 and 0.33, respectively, all significant at $P < 0.001$). A pooled analysis of both studies (Vieta et al. 2008c; Suppes et al. 2009) showed that quetiapine was effective in preventing TEE in patients with mixed index episodes (Vieta et al. 2012b).

In summary, based on two monotherapy and two combination treatment studies, quetiapine has solid evidence for the prevention of TEE in enriched samples. The ***CE for PES is "A" for any mood episode, mania and depression.***

Prevention of TEE in non-enriched samples (PNES)

Our literature search could not identify any studies of quetiapine in NES that would satisfy CE criteria "A–D". Thus, the ***CE for PNES is "F" for any mood episode, mania and depression.***

Prevention of TEE in rapid cyclers (PRC)

About 15% of patients in the monotherapy study by Weisler et al. (2011), and up to 30% in the combination treatment studies had a rapid cycling course, but a separate subanalysis of this group has not been published yet. An open explorative study by Vieta et al. (2002) in 14 patients, treated with quetiapine add on to on-going medication for a mean of 112 ± 3 days, suggested benefits for acute manic, but not

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depressive symptom remission and relapse prevention. Accordingly, the ***CE for PRC is "C" for any mood episode and mania.***

Further evidence (FE)

Prior to the pivotal RCTs, several open studies on quetiapine as bipolar maintenance treatment have been published (Altamura et al. 2003; Suppes et al. 2004, 2007; Duffy et al. 2009) contributing to a ***Rating for FE: "+"***

Safety and tolerability (ST)

The safety and tolerability data of the study of Weisler et al. (2011) are probably most informative as they are generated in monotherapy and also allow comparison to lithium. During the open-label quetiapine stabilization phase of 4–25 weeks, 170 patients (7.0%) experienced adverse events leading to discontinuation, most commonly sedation ($n = 40$, 1.6%) and somnolence ($n = 26$, 1.1%).

16.8% of patients had an increase of body weight $>7\%$ during open quetiapine treatment. After randomization, 10.6% of those randomized to quetiapine, 5.4% of those on lithium and 2.6% of those receiving placebo had a $>7\%$ increase of body weight. Clinically important elevations in blood glucose (i.e., ≥ 7.0 mmol/l) at any time after randomization in subgroups with documented fasting glucose concentrations were recorded in 30 patients (8.5%) in the quetiapine, 17 (4.4%) in the lithium, and 13 (3.5%) in the placebo group. Quetiapine treatment during the randomized phase was also associated with a greater increase of triglycerides, total cholesterol and LDL cholesterol than treatment with lithium or placebo.

Adverse events potentially associated with EPS during randomized treatment were reported by 16 (4.0%), 38 (9.1%), and 18 (4.5%) patients receiving quetiapine, lithium, and placebo, respectively, with no apparent differences in mean SAS, BARS, or AIMS scores.

Data on safety in pregnancy with quetiapine are sparse. Animal studies suggested that quetiapine may delay skeletal ossification as well as reduce birth weight (Nguyen et al. 2009) and as a consequence it is listed by the FDA as a category "C" medication for safety in pregnancy.

In summary, and in line with other observations, safety and tolerability problems associated with quetiapine are sedation after treatment initiation, and later weight gain and metabolic changes. Weight gain and metabolic changes appear not of the magnitude as observed with, e.g., clozapine or olanzapine, but nonetheless might constitute a physical health problem in the long run. ***Rating of ST: " −"***

Prevention of suicide (PSu)

There are no reliable data available specific to an antisuicidal effect of quetiapine. On the other hand, there is no evidence that quetiapine might enhance suicide risks. ***Rating of PSu: "0"***

Practicability (PR)

Quetiapine is only available in tablets, both for immediate and extended release. Thus, the portfolio of available formulations is rather restricted. Dosages of quetiapine used in maintenance studies range from 300 to 800 mg. In the monotherapy study by Weisler et al. (2011) the mean (SD) median quetiapine dose was 546 (± 173) mg in stable patients during the randomized phase. ***Rating of PR: "0"***

Recommendation grade (RG)

The evidence for quetiapine, both in monotherapy and combination treatment, to prevent TEE in enriched samples is quite outstanding and merits a ***RG "1".*** There are issues with weight gain and metabolic changes that need to be carefully monitored; however, the task force felt that balancing risks and benefits, these issues are still outweighed by the bulk of evidence for efficacy.

Risperidone

Prevention of TEE in enriched samples (PES)

There are no published RCTs on bipolar maintenance treatment with oral risperidone. Two RCTs (Quiroz et al. 2010; Vieta et al. 2012a) investigated the efficacy of risperidone LAI monotherapy for the prevention of TEE in patients with a manic/mixed index episode after successful stabilization on oral risperidone and switch to LAI.

The study by Quiroz et al. (2010) compared risperidone LAI monotherapy against placebo injections in 303 patients, stabilized for 6 months on risperidone LAI after a manic/mixed index episode, for 2 years. Most (77%) of the patients in the risperidone LAI group remained on the minimum dose of 25 mg every 2 weeks. The primary efficacy variable was the time to recurrence of a mood episode during double-blind treatment, with "recurrence" being defined as a composite outcome of fulfilling DSM-IV criteria and severity criteria. Time to recurrence was significantly longer in the risperidone LAI

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group than the placebo group (log-rank $\chi^2 = 23.5$, df = 1, $P < 0.001$). In the risperidone LAI group, 42 (30%) of 140 patients experienced recurrence during double-blind treatment versus 76 (56%) of 135 in the placebo group. Patients in the risperidone LAI group were less than half as likely to experience a recurrence than patients in the placebo group (estimated HR, 95% CI): 0.40, 0.27–0.59). Time to recurrence was significantly longer in the risperidone LAI group than the placebo group for time to recurrence of elevated mood episodes ($P < 0.001$; HR,95% CI: 0.25, 0.15–0.41) but not for depressive episodes ($P = 0.805$; HR, 95% CI: 1.09, 0.55– 2.17). However, the overall number of depressive recurrences was small ($n = 20$ for risperidone LAI and $n = 14$ for placebo) as this population with a manic index episode was possibly not at high risk for depression anyway.

The second study in an enriched population was conducted by Vieta et al. (2012a), and included besides risperidone LAI and placebo also an olanzapine arm for assay sensitivity (see section on "Olanzapine"). Patients first entered a 2-week screening period (Period I) in which non-acute patients continued to receive their current medication, while acute patients were treated at the investigator's discretion. At the end of the screening period, eligible patients entered a 12-week open-label period (Period II) in which all patients received risperidone LAI (25, 37.5 or 50 mg every 2 weeks; initiated at 25 mg or, if deemed by the investigator to be clinically appropriate, 37.5 mg). During Period II, patients were assessed for recurrence events, defined as the occurrence of a new episode or need for change of treatment. At the end of Period II, patients ($n = 398$) who had responded to treatment (i.e., had not experienced a recurrence event) were randomized to double-blind treatment (Period III) with risperidone LAI (25, 37.5 or 50 mg) + oral placebo or oral and injectable placebo or oral olanzapine 10 mg/day + placebo injection. In Period III, patients randomized to risperidone LAI received a fixed dose throughout, according to their final dose in Period II (25 mg, 64%; 37.5 mg, 32%; 50 mg, 4%). So, at the beginning of Period III, we deal with a patient population that is enriched both for tolerability and continuation treatment efficacy of risperidone LAI. The primary efficacy evaluation was the time to recurrence of any TEE (as defined above) in Period III.

In the pre-specified analysis (log-rank test stratified by patient type and region), time to recurrence of any mood episode in Period III did not differ significantly between the risperidone LAI and placebo arms ($P = 0.057$). Time to recurrence of an elevated (hypomanic, manic or mixed) mood episode was significantly longer with risperidone LAI compared with placebo ($P = 0.005$). There was no significant difference in time to recurrence of a depressive episode between risperidone LAI and placebo ($P = 0.655$). As detailed in the olanzapine section, olanzapine was not only significantly superior to placebo in all primary outcome variables, but also to risperidone LAI.

In summary, we have to consider the following data basis: One positive and one negative study for ***PES any episode, which relates to a CE of "D".*** Two positive subanalyses support the prevention of manic TEE which relates to a ***CE for PES manic episode of "A".*** And, finally, two subanalyses showing no benefit of risperidone LAI compared to placebo in preventing new depressive episodes, with the additional information that olanzapine did so (in other words, it would have been possible to show depression preventive effects in the Vieta et al. (2012a) study if a medication is efficacious.) Thus the ***CE for PES depressive episode is "E".***

Prevention of TEE in non-enriched samples (PNES)

We could not identify any studies satisfying CE "A–D" criteria testing risperidone long-term treatment in samples not previously enriched for acute response or tolerability. ***CE for PNES for any TEE, mania or depression: "F"***

Prevention of TEE in rapid cyclers (PRC)

One RCT (Macfadden et al. 2009) investigated risperidone LAI in combination with on-going medication (treatment as usual = TAU) in bipolar patients with frequent relapses. Eligible patients were between 18 and 70 years of age and had experienced four or more mood episodes (defined as an event requiring psychiatric intervention) in the past 12 months. Different from the monotherapy studies in non-RC patients, there was no requirement for a manic or mixed index episode. Patients in any phase of bipolar illness (manic, hypomanic, depressed, mixed or euthymic) at study entry were included. TAU consisted of any number or combinations of antidepressants, mood stabilizers or anxiolytics, determined for each patient by his or her investigator. Risperidone LAI and TAU could be changed or adjusted at any time during the first 12 weeks of the stabilization phase but to be eligible for the double-blind phase, risperidone LAI and TAU medications and dosages had to be stable for at least 4 weeks prior to randomization. This design implies that patients have been selected for tolerability of risperidone LAI, but not

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necessarily for efficacy in an acute episode. In the stabilization phase, the risperidone LAI modal dose was 25 mg in 79.2% of patients, 37.5 mg in 19.6% of patients, and 50 mg in 1.3% of patients. A total of 183 of 240 subjects completed the stabilization phase (76.3%), and 124/240 (51.7%) fulfilled stabilization criteria and were randomised to either continue double-blind risperidone LAI or switch to placebo injections. The primary endpoint was time to relapse from randomization in the double-blind relapse-prevention phase that lasted 12 months. "Relapse" was a composite outcome defined as fulfilling DSM-IV criteria of an acute episode and, additionally, showed a marked worsening according to predefined YMRS, MADRS and CGI-BP criteria, or being either hospitalized for worsening of symptoms according to predefined criteria and suicidal ideation.

Adjunctive risperidone LAI treatment was associated with a significant delay in the time to relapse of any mood episode compared with adjunctive placebo treatment ($P = 0.010$). Relapse rates were 23.1% ($n = 15$) with adjunctive risperidone LAI treatment and 45.8% ($n = 27$) with adjunctive placebo. The relative risk of relapse was 2.3-fold higher with adjunctive placebo compared with adjunctive risperidone LAI ($P = 0.011$, chi-square (Cox regression). The study was not powered to conclusively demonstrate prevention of particular types of mood episodes (mania, depression, mixed states). Numerically, 19 patients in the total double-blind study population relapsed to a depressive episode (adjunctive risperidone LAI, $n = 8$ (12.3%); adjunctive placebo, $n = 11$ (18.6%)), 17 patients relapsed to a manic episode (adjunctive risperidone LAI, $n = 5$ (7.7%); adjunctive placebo, $n = 12$ (20.3%)), and six relapsed to a mixed episode (adjunctive risperidone LAI, $n = 2$ (3.1%); adjunctive placebo, $n = 4$ (6.8%)). A post-hoc calculation of the RR for relapse by Vieta et al. (2011) showed a RR of 0.40 (0.18–0.90, $P = 0.026$) for manic relapses, whereas there was no significance for depressive relapses which might be attributable to the lack of power.

Based on this double-blind RCT, the ***CE for PRC is "B" for any episode, and "C" for manic/mixed and "F" for depressive TEE.***

Further evidence (FE)

Earlier case series also support the use of risperidone LAI to prevent new mood episodes (Han et al. 2007; Malempati et al. 2008; Vieta et al. 2008b; Benabarre et al. 2009). Some case series also support the use of risperidone given as an oral tablet in preventing new mood episodes (Ghaemi and Sachs 1997; Fountoulakis et al. 2004; Ghaemi et al. 2004; Yoshimura et al. 2006). ***Rating of FE: "+"***

Safety and tolerability (ST)

The best evidence for the safety and tolerability of risperidone LAI can be derived from the study by Vieta et al. (2012a) as it is monotherapy and allows not only comparison against placebo, but also olanzapine. The most common AEs in Period II during open-label risperidone LAI treatment were insomnia (16%), akathisia (7%) and headache (6%). Adverse events considered to be potentially prolactin related (such as galactorrhoea or libido decreased), as reported by the investigator, occurred in 33 patients (6%). Clinically significant increase in body weight ($\geq 7\%$) was reported in 14% of patients.

During Period III (double-blind maintenance phase), the most common AES occurring in patients receiving risperidone LAI were weight increase (24%), insomnia (17%) and amenorrhoea (8%). Placebo rates were for weight increase 9%, insomnia 18%, amenorrhoea 2%. The most common adverse events in the olanzapine arm were weight increase (27%), somnolence (12%) and insomnia (10%). Discontinuations because of adverse events occurred in five patients (4%) receiving risperidone LAI, five patients (4%) receiving olanzapine and two patients (2%) receiving placebo. Extrapyramidal Symptoms Rating Scale (ESRS) score from Period III baseline to endpoint were low and remained low in all three arms.

Hyperprolactinaemia was reported during Period III in two patients (1%) receiving risperidone LAI, with potentially prolactin-related adverse events reported in 14% of patients receiving risperidone LAI and 3% receiving placebo. Two patients receiving risperidone LAI (1%) reported diabetes mellitus as an adverse event. Clinically significant weight increase (defined as $>7\%$ increase) was seen at the end of Period III in 18% of patients receiving risperidone LAI, 28% of patients receiving olanzapine and 5% of patients receiving placebo.

McKenna et al. (2005) in a prospective study reported eight cases of major congenital malformations associated with risperidone exposure including a case of corpus callosum agenesis, the FDA safety-in-pregnancy category rating for risperidone is "C".

In summary, risperidone LAI was well tolerated, and the rate of extrapyramidal side effects and prolactin elevation is clearly less from that has been reported in acute studies with oral risperidone. Still, issues with prolactin are not trivial given the increased risk of breast cancer (Harvey et al. 2008).

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Weight gain, however, is also of some concern, both with risperidone LAI and olanzapine. ***Rating of ST: "–"***

Prevention of suicide (PSu)

We could not identify any relevant literature that gives evidence for effects of risperidone on suicidality, other than the general observation that antipsychotics as a group might prevent suicide (Angst et al. 2005). ***Rating of PSu: "0"***

Practicability (PR)

Risperidone is available as tablets, oral soluble tablets, solutions and as long acting injectable. Risperidone LAI was also used in the pivotal studies cited in this section. Both in monotherapy and combination treatment with TAU, the majority of patients were on 25 mg risperidone LAI every second week which would be the recommended dose. A dosage increase to 37.5 or 50 mg biweekly can be considered in partial responders, but it may increase the rate of adverse events. ***Rating of PR: "+"***

Recommendation grade (RG)

A uniform finding of all studies is that risperidone LAI delays manic relapses in enriched samples (CE "A"). It is also effective in preventing any relapse in RC patients (CE "B"). However, its overall efficacy in non-rapid cycling patients to prevent any relapse remains controversial (CE "D"). This makes it different from other medications that do prevent mania, e.g., aripiprazole, but also still differ from placebo for any relapse due to their very powerful mania-protective effect as expressed in their polarity index (Popovic et al. 2011). In addition, weight gain and prolactin-associated side effects are of some concern. Therefore, the task force feels that it would appropriate to assign risperidone an ***RG "2".***

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Typical antipsychotics (first-generation antipsychotics)

The long-term use of typical antipsychotics has always been complicated by the high risk of extrapyramidal side effects and, as a consequence, non-adherence. More recently, there is also increasing evidence that their long-term use can be neurotoxic in schizophrenia and lead to loss of grey matter volume (Lieberman et al. 2005; Ho et al. 2011; Vernon et al. 2012). Thus, not only peripheral motor side effects can complicate treatment, but much more cognitive decline in addition to the one caused by the disorder itself.

Prevention of TEE in enriched samples (PES)

We could only identify one study (Zarate and Tohen 2004) with a sufficient number of patients investigating the continuous use of a typical antipsychotic (perphenazine) in addition to lithium, carbamazepine or valproate versus lithium, carbamazepine or valproate + placebo. Following remission of a manic episode treated with the combination of perphenazine and either lithium, carbamazepine, or valproate, 37 patients were randomly assigned to 6 months of double-blind treatment with continuation of this treatment regimen or exchange of perphenazine against placebo. Patients receiving placebo were more likely than those who continued receiving perphenazine to complete the study (83.3 vs. 47.4%, respectively), have a longer time to depressive relapse ($P < 0.03$), remain in the study for a longer duration of time ($P < 0.03$), and experience less frequently akinesia, dysphoria (both $P < 0.05$), and parkinsonism ($P < 0.01$). There were no differences in manic relapses between the groups. YMRS total scores at endpoint did not differ between the groups. ***CE for PES for any episode, mania and depression: "E"***

Prevention of TEE in non-enriched samples (PNES)

We could not identify any long-term treatment trials with typical antipsychotics in non-enriched samples of bipolar disorder patients. ***CE for PNES for any episode, mania and depression: "F"***

Prevention of TEE in rapid cyclers (PRC)

We could not identify any long-term treatment trials with typical antipsychotics in RC samples of bipolar disorder patients. ***CE for PRC for any episode, mania and depression: "F"***

Further evidence (FE)

A small randomized, open comparison of flupenthixol and lithium (Ahlfors et al. 1981) showed no advantage of either substance compared to the previous course of illness. A second study in a larger group of 93 patients showed that flupenthixol decanoate was associated with significant decrease of the frequency of manic episodes and percentage of time ill in mania, but also with a significant rise of the frequency of depressive episodes and percent time ill in depression. Increase of depressive morbidity was

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seen only in patients who had been given lithium during the pre-trial period and could presumably be a result of the discontinuation of lithium. However, the exact modalities of pre-treatment in this group are not described in the paper, so it is unclear whether and to which degree the group was enriched to acute flupenthixol response. In summary, it appears that flupenthixol may have some mania-protective properties. On the other hand, Esparon et al. (1986) conducted a double-blind cross-over trial of depot flupenthixol in bipolar patients. All patients continued on lithium, and 11 patients completed the 2-year trial. The authors report that flupenthixol appeared to have no prophylactic effect. In addition, some case reports have been published suggestive of flupenthixol-induced mania (Szabo 1993; Becker et al. 2002). ***Rating for FE: "0"***

Safety and tolerability (ST)

Similar to antidepressants, anticonvulsants or atypical antipsychotics we are not likely to be dealing with a homogenous group of medications for the typical antipsychotics. The safety and tolerability profile varies, but any member of the group has at least one safety and tolerability issue which might compromise its use. Frequency and severity of side effects with typical antipsychotics is dose and time dependent, and clearly in the past there has been a tendency of overdosing them, at least in acute mania treatment. The use of all typical antipsychotics is associated with extrapyramidal motor symptoms both in the short and long term, with tardive dyskinesias and probably CNS neurotoxic effects in the long run, as well as with differing degrees of prolactin elevation and weight gain. As far as weight gain is concerned, some typical AP are by large weight neutral, such as molindone, fluphenanzine, perphenazine, pimozide or haloperidol, others may cause significant weight gain, e.g., chlorpromazine. Finally, typical antipsychotics put patients at greater risk of a malignant neuroleptic syndrome than atypical antipsychotics (Tural and Onder 2010).

The risk of major congenital malformations in pregnancy might differ between agents. Haloperidol is generally considered as a relatively safe option (FDA safety in pregnancy rating "C") (Diav-Citrin et al. 2005); perphenazine has not been formally assigned to a FDA pregnancy category as animal studies have not been reported and there are no controlled data in human pregnancy. ***Rating for ST: "–"***

Prevention of suicide (PSu)

We could not identify any relevant literature that gives evidence for effects of typical antipsychotics on suicidality in bipolar patients, other than the general observation that antipsychotics as a group might prevent suicide (Angst et al. 2005). ***Rating of PSu: "0"***

Practicability (PR)

Typical antipsychotics are offered in a wide range of preparations, including tablets, solution, and short- and long-acting injectables. This is true for the most frequently used typical neuroleptic, haloperidol, but not for every single substance all options are necessarily available. Titration of most typical antipsychotics is usually straight forward, and plasma concentration checks or extensive pathology tests are not necessary. More recent, some concerns have been voiced over QTc prolongation with pimozide and haloperidol, especially when given intravenously (FDA alert 9/2007); routine ECG has been recommended. However, this might not affect the routine use of oral haloperidol preparations. ***Rating of PR: "+"***

Recommendation grade (RG)

Given the absence of reliable evidence and the more unfavourable side effects profile, the long-term use of typical antipsychotics in bipolar patients cannot be recommended. ***RG: "Ø"***

Valproate (incl. divalproate, divalproex, valpromide)

The different formulations of sodium 2-propylpentanoate, or sodium valproate, are summarized here as "valproate". The reason for this is that the active compound that penetrates the brain–blood barrier is always valproic acid; the different preparations may show differences in gastric tolerability, but not CNS activity (Grunze and Walden 2004). Valproate has a widespread use as a prophylactic medication in bipolar disorder which developed at a time where alternatives to lithium were scarce but urgently needed. The unequivocal scientific evidence for long-term beneficial effects, however, is rather poor, and licensing in some countries, e.g., Germany, for prevention of new mood episodes has been based on its established clinical use rather than evidence. However, it has to be said in favour of valproate that it has not received the benefit of having been prospectively examined in modern discontinuation design following prior enrichment for response, as most atypical antipsychotics have been. There is only one RCT versus placebo (and lithium as internal comparator) published which, however, failed in its

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primary outcome measure. Thus, the data for the primary outcome (time to recurrence of any mood episode) for valproate in maintenance treatment are rather inconclusive than negative, but it is unlikely that valproate will be subject to further pivotal studies given the lack of incentives for a potential sponsor. However, there were several secondary outcome measures that were established a priori, including time to a manic episode, time to a depressive episode, average change from baseline in scores on the Mania Rating Scale (MRS), Depressive Syndrome Scale (DSS) score (derived from SADS-C) and GAS during maintenance treatment, rate of early discontinuation for depression, proportion of patients with depressive relapses, mean change in DSS from baseline, proportion of patients receiving adjunctive antidepressants, and time in the study (Bowden et al. 2000; Gyulai et al. 2003). The analyses of these outcome measures appear of good scientific reliability as they were not decided post hoc, but as part of the protocol. Thus, the task force decided to consider them for CE "B" evidence if adequately powered and reported.

This sole placebo-controlled RCT for valproate is actually also difficult to classify as to its degree of enrichment. During the up to 3-month run-in phase the index manic episode was treated at the discretion of the investigator, and 117 patients had been treated with valproate only (31.5%), 124 with lithium only (33.3%), 50 with both drugs (usually sequentially) (13.4%), and 81 with neither drug (21.8%). Considering that 187 subjects were subsequently randomised to valproate, 91 to lithium, and 94 to placebo (a 2:1:1 randomisation scheme) and that patients taking valproate or lithium on the day of randomisation had the drug gradually withdrawn over 2 weeks, this design might slightly have favoured valproate over placebo and lithium. On the other hand, the frequency of use of valproate and lithium as antimanic treatment largely reflects clinical practice in the 1990s, at least in those patients who were not too ill to be considered as eligible for an RCT. Excluding or limiting the number of patients on valproate would rather have created a bias against valproate and not reflect actual treatment habits. Thus, the task force feels that the enrichment was not artificial per study protocol, but resembled clinical practice, and thus the study should be considered in this section on non-enriched study populations. However, post-hoc analysis of the subjects in this study who were treated with valproate during the open phase supplies some information which we value with a lower CE in the PES section. The same applies for the adjunctive maintenance studies with aripiprazole (Marcus et al. 2011) and ziprasidone (Bowden et al. 2010) where subsets of data for patients receiving valproate as mood stabilizer were available.

Prevention of TEE in enriched samples (PES)

We identified one long-term study with valproate following a systematic prior enrichment for acute efficacy and/or tolerability (Bowden et al. 2012). In this underpowered study, recently depressed Bipolar I and II patients were stabilized with lamotrigine + valproate combination treatment, and then randomized to 8 months of maintenance treatment with either lamotrigine + placebo or lamotrigine + valproate. While the primary outcome (time to a new depressive episode) was not significantly different, several secondary outcomes were supportive of additional benefits by adding valproate to lamotrigine. Furthermore, a post-hoc analysis of the randomized, double-blind, placebo- and lithium-controlled valproate maintenance study (Bowden et al. 2000) showed that the 148 patients treated with open phase valproate and then randomized to valproate achieved longer times to any mood episode than did patients randomized to placebo ($P = 0.05$) (McElroy et al. 2008).

Valproate or lithium was used as primary mood stabilisers in two maintenance studies with aripiprazole or ziprasidone. In the aripiprazole study, patients who achieved predefined stability criteria for 12 consecutive weeks were randomized to double-blind aripiprazole (ARI, 10–30 mg/day) or PLC + LiI/VPA. Relapse was monitored for 52 weeks (see also section on "Aripiprazole"). In the ziprasidone study, patients achieving at least eight consecutive weeks of stability with open-label ziprasidone and lithium or valproate were randomly assigned in the 6-month, double-blind maintenance period to ziprasidone plus mood stabilizer or placebo plus mood stabilizer (see also section on "Ziprasidone"). In the adjunctive aripiprazole maintenance study the time to a relapse to any episode was in favour of adjunctive aripiprazole therapy versus lithium alone (16% ARI + LI vs. 45% PLC + LI; $P = 0.002$). Among the subgroup of patients treated with valproate, the time to a relapse to any episode was not significantly different between the ARI + VAL and PLC + VAL groups (18 vs. 19%, respectively; $P = 0.824$) (Marcus et al. 2011). Numerically similar findings were published for the ziprasidone maintenance study, although not statistical tests were made (Bowden et al. 2010). These results indicate equivalence of valproate to aripiprazole plus valproate, or ziprasidone plus valproate on time to any episode, despite the studies being enriched for ziprasidone and aripiprazole response. No study analysed mania or depression separately, and both studies enrolled only manic and mixed patients.

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CE for PES any episode: "C", for mania and depression "F".

Prevention of TEE in non-enriched samples (PNES)

Almost all of the controlled evidence about valproate's ability to prevent TEE stems from one pivotal study, comparing valproate, lithium and placebo in a 1-year, double-blind RCT (Bowden et al. 2000). Patients had recovered from a manic index episode, which could be treated with any suitable medication, including valproate or lithium.

The primary outcome measure was time to recurrence of any mood episode. As mentioned, the study failed in this primary outcome. The valproate group did not differ significantly from the placebo group in time to any mood episode. However, valproate was statistical significantly superior in a number of a priory determined secondary analyses:

Valproate was superior to placebo in terms of lower rates of discontinuation for any reason ($P = 0.05$) and depression ($P = 0.02$); in addition, it outperformed lithium on several other outcomes: discontinuation for any reason ($P = 0.03$), time to intervention for emerging depressive symptoms with an SSRI ($P = 0.03$), and worsening of depression (Change of Depressive Symptom Scale from baseline, $P = 0.04$).

Although not defined a priori, a clinically very relevant additional analysis of the study was conducted by Keck et al. (2005). It showed that with valproate plasma levels between 75 and 99.9 mg/l valproate were significantly better than placebo for discontinuation for any reason ($P < 0.05$), mania and depression (both $P = 0.03$).

In summary, the evidence for valproate maintenance in PNES is difficult to grade and was subject to diverging opinions in the task force. Valid secondary, but a priori defined analysis supports a ***CE of "B" for the prevention of depression***. The fact that valproate was also better than lithium in depression related outcomes appears to some degree at odds with the data from the BALANCE study which are in line with mania-protective, but not depression-protective effects. In this study, the advantage of lithium compared to valproate was most apparent for depressive relapses ($P = 0.0331$). On the other hand, meta-analysis of acute studies is suggestive of acute antidepressant effects of valproate (Grunze et al. 2010), which makes a prophylactic efficacy to some degree likely. Neither primary nor secondary analysis of the Bowden et al. (2000) study, however, supply clear evidence for prevention of mania or any episode; such a prophylactic effect may hold true with optimal plasma levels as demonstrated post hoc by Keck et al. (2005), but they have not been demonstrated in the whole study sample. As lithium also failed in this study, probably for reasons as outlined by Bowden et al. (2000), we consider this study rather a failed but negative one. Therefore, the ***CE for any relapse and mania would be "F".***

Prevention of TEE in rapid cyclers (PRC)

Only one substantial RCT has been conducted comparing valproate to lithium. The outcome was that neither both substances by themselves nor their combination during the open run-in phase were very effective in preventing new episodes (see paragraph on lithium). However, this study had no placebo control, so the ***CE for PRC is "F"***

Further evidence (FE)

In a 47-week, double-blind extension phase of a RCT comparing olanzapine and valproate in patients with a manic index episode (Tohen et al. 2003a), the mean improvement in the YMRS score was significantly greater for the olanzapine group. However, as far as TEE are concerned there was no significant difference between valproate and olanzapine in the rates of subsequent relapse into mania or depression (see also section on "Olanzapine").

Previous to this more recent study, several open, but in part, randomised studies (Lambert 1984; Puzynski and Klosiewicz 1984a,b; Vencovsky et al. 1984; Hayes 1989; Emrich and Wolf 1992; Denicoff et al. 1997a; Hirschfeld et al. 1999; Solomon et al. 1998) have been conducted, and their overall outcome supports some prophylactic efficacy of valproate against TEE.

However, this seems to be not fully reflected in daily clinical practice, at least not when it comes to comparison with lithium. A large open-label, randomized study (BALANCE) (Geddes et al. 2010) demonstrated that valproate monotherapy is significantly less effective than lithium in preventing TEE over 2 years: 69% of patients on valproate needed an intervention compared to 59% on lithium (for more details of this study, see section on "Lithium").

In line with the results from BALANCE are those of a large Danish registry review conducted by Kessing et al. (2011b). These authors reviewed data on all people with a diagnosis of bipolar disorder in psychiatric hospital settings who were prescribed valproate or lithium in Denmark during a period from 1995 to 2006. A total of 719 subjects received valproate and 3549 received lithium subsequent to the diagnosis of bipolar disorder. Lithium significantly outperformed valproate in all outcomes: rate of switch/add on to the opposite drug (lithium or

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valproate), antidepressants, antipsychotics or anticonvulsants (other than valproate), rate of psychiatric hospital admissions regardless of the type of episode leading to a hospital admission (depressive or manic/mixed). Similarly, for participants with a depressive index episode, a manic index episode or a mixed index episode the overall rate of hospital admissions was significantly increased for valproate compared with lithium.

Although less effective than lithium, the other cited studies are suggestive of some evidence that valproate has a recurrence preventive effect. ***Rating of FE: "+"***

Safety and tolerability (ST)

Usually valproate is well tolerated. More frequent dose-dependent side effects include gastrointestinal side effects, neurological symptoms such as tremor and mild sedation, thrombopenia or leukopenia and asymptomatic increase of liver transaminases which attenuates with dose reduction. Thrombocytopenia and leucopenia is usually benign and fully reversible after discontinuation of valproate. Hair loss or change of hair texture may occur. Of the severe and potentially life threatening adverse events, idiosyncratic hepatic failure occurs in approximately 1 in 50,000 patients with valproate and is not dose dependent. Retrospective analysis of patient charts identified potential risk factors as age under 2 years, combination treatment with several anti-epileptics, family history of severe liver disease, genetically determined carnitine deficiency or disturbances of the urea metabolism. Acute haemorrhagic pancreatitis with valproate has been observed in a few cases and occurs most likely in the first 3 months of treatment. Identified risk factors are a young age and polypharmacy. Valproate- induced encephalopathies caused by hyperammonemia are described in epilepsy treatment. A genetically determined deficiency of carnitine or ornithine transaminase as well as a combination with several antiepileptic medications, especially phenobarbital is a risk factor. Symptoms usually develop within 3–4 days and reverse with instant discontinuation of valproate (Grunze and Walden 2004).

Weight gain is probably the most prominent side effect in long-term treatment and may impact medication adherence. At endpoint (LOCF) of the olanzapine versus valproate study (Tohen et al. 2003a), 23.6% ($N = 29$) of 123 olanzapine patients and 17.9% ($N = 22$) of 123 valproate patients had gained at least 7% of their baseline weight (Fisher's exact test, $P = 0.35$). Polycystic ovary syndrome (PCOS) in valproate treated female patients is also an important issue, and together with valproate's terotogenicity (FDA pregnancy category "D") makes it use not suitable in young women of child-bearing age. Valproate is associated with the highest rate of major congenital malformations (6.2–16%) (Nguyen et al. 2009). In addition, lasting developmental delays of children of mothers who had taken valproate during pregnancy has been described (Meador et al. 2009). As a consequence, the FDA assigned valproate a safety in pregnancy "D" rating which means that "there is positive evidence of human foetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks" (US Food & Drug Administration 1975)

The interaction potential of valproate with other medications frequently used in bipolar disorder is low. When combined with barbiturates, neuroleptics, benzodiazapines and MAO inhibitors or other antidepressants valproate may increase their sedative effects. Valproate inhibits the metabolism of lamotrigine, meaning that doses have to be adapted in combination treatment. As carbamazapine and valproate show interaction, this combination needs special monitoring when clinically used (see section on "Carbamazepine"). ***Rating of ST: "0"***

Prevention of suicide (PSu)

In contrast to the FDA warning about increased suicide risk with antiepileptic drugs (US Food & Drug Administration 2008), Gibbons et al. (2009) demonstrated that most antiepileptic drugs, including valproate, are not associated with increased suicide risk. On the other hand, valproate did not show similar protective effects as lithium as demonstrated by Goodwin et al. (2003). However, more recent randomized controlled data suggest that, if at all, the risk of suicidal behaviours including suicide attempts, and suicide seems to be not substantially different between lithium and valproate, although subtle differences cannot be excluded (Oquendo et al. 2011). Thus, we would consider the ***Rating of PSu as "0"***

Practicability (PR)

There is a wide range of preparations for valproate available, including immediate and slow release tablets, mini tablets, oral solutions and solutions for intravenous injections. Whereas plasma levels for acute mania treatment have been quite firmly established (Allen et al. 2006), the optimal serum levels for maintenance are less clear. A plasma concentration range of 45–100 mg/l (315–700 µmol/l) provided superior results than lower or higher concentrations in the 1-year maintenance trial by Bowden et al. (Keck et al. 2005). ***Rating of PR: "+"***

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Recommendation grade (RG)

In summary, valproate has CE evidence "B" for depression in PNES, and further supportive evidence from a CE "C" for PES any relapse. Thus, ***the RG is "3".*** However, the safety and tolerability profile is not without issues, and therefore ***it should not be routinely used as long-term treatment in women of child-bearing age.*** However, if a woman of child-bearing age unambiguously achieves better mood stabilization with a regimen including valproate, understands the risks and their cause, and reliably practices birth control, risks should be balanced against benefits in the individual case.

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Ziprasidone

Prevention of TEE in enriched samples (PES)

We identified one placebo-controlled add-on study to lithium or valproate (Bowden et al. 2010). Patients were included with a manic or mixed index episode, stabilized on ziprasidone and either lithium or valproate, and after fulfilling stabilization criteria for eight consecutive weeks, randomized to continuation on combination treatment ($n = 127$) or lithium/valproate + placebo ($n = 113$) for 6 months. Combined ziprasidone + lithium/valproate was significantly superior to lithium/valproate + placebo for PES for any TEE ($P = 0.027$) (CE "B") and manic/mixed TEE ($P = 0.014$) (CE "B"), but not for depressive TEE ($P = 0.682$) (CE "E"). The lack of preventive effects against depressive recurrences is likely due to similar reasons as assumed in the aripiprazole add-on study (Marcus et al. 2011), and different study designs might be needed to detect depression protective effects of ziprasidone if existing. ***CE for the prevention of manic episodes in ES "B"; CE to prevent new depressive episodes in ES is "E";*** and the ***CE to prevent any episode in ES is "B".***

Prevention of TEE in non-enriched samples (PNES)

We could not identify any long-term study with ziprasidone for PNES which would satisfy CE "A", "B" or "C" criteria. ***CE to prevent a manic, depressed or any episode in NES is "F".***

Prevention of TEE in rapid cyclers (PRC)

The only bipolar disorder maintenance RCT (Bowden et al. 2010) allowed patients with less than eight episodes in the previous year into the trial, but a separate analysis of subjects with four to seven episodes in the year preceding the study has not been published. We also could not identify any other evidence such as case series supporting the use of ziprasidone in preventing new episodes in RC patients. ***CE for RC: "F"***

Further evidence (FE)

One-year open-label extension of the first two pivotal 3-week acute mania studies (Keck et al. 2003; Potkin et al. 2005) gave evidence for a maintenance of antimanic effectiveness, together with a good safety and tolerability profile (Dubovsky and Dubovsky 2011). ***Rating for FE: "+"***

Safety and tolerability (ST)

The safety and tolerability profile of ziprasidone is generally good; of note is the negligible impact on metabolic parameters, prolactin and the fact that ziprasidone is relatively weight neutral (Kemp et al. 2012). Some sedation, although less than with several other APs, and EPS, especially tremor and akathisia, are more frequent side effects (Seemuller et al. 2005). The most frequent side effects (≥5% incidence) in the long-term add-on study were sedation (22.9%), somnolence (17%), tremor (12.5%), insomnia (10.1%), dizziness (8.4%), akathisia (8%), fatigue (7.5%), nausea (7.2%) and headache (5.5%).

QTc prolongation has been a major concern with the use of ziprasidone in the past. An analysis of the acute mania study by Keck et al. (2003) described a mean QTc prolongation of 11 ms, but no prolongation of greater than 500 ms (Seemuller et al. 2005). In the add-on maintenance study no critical QTc prolongation was observed. At the end of the 16-week stabilization phase the mean QTc time was 390.3 ms (range 308–73 ms) with no subject exceeding 500 ms. ECG monitoring is recommended with the use of ziprasidone; however, the risk of QTc prolongations resulting in torsades de pointe appear minimal in otherwise healthy subjects.

Ziprasidone is in the FDA "C" pregnancy category meaning that risk cannot be ruled out as there are no controlled data in human pregnancy, but animal studies have revealed evidence of developmental toxicity including possible teratogenic effects, an increase in the number of offspring born dead, and a decrease in postnatal survival. However, a developmental delay after in utero exposure has been observed for ziprasidone in a preliminary report so, for now, ziprasidone should be used even more cautiously in pregnancy than other antipsychotics (Nguyen et al. 2009).

In summary, the favourable metabolic profile on the one hand, and possible minor QTc prolongation and some concerns in pregnancy on the

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other hand balance each other, so the ***Rating of ST: "0"***

Prevention of suicide (PSu)

Karayal et al. (2011)conducted a pooled analysis to identify possibly suicide-related adverse events in sponsored placebo-controlled, double-blind, adult and paediatric randomized controlled trials of ziprasidone. No cases of completed suicide occurred in this analysis. Suicidality events (suicidality and suicidal behaviour) were identified in 52 among 5123 subjects treated with either ziprasidone or placebo in 22 trials. There were no statistically significant differences between ziprasidone and placebo in any of the individual classification categories derived from the Columbia Classification Algorithm of Suicide Assessment. ***Rating of PSu: "0"***

Practicability (PR)

Ziprasidone is available as an i.m. injectable or oral solution and as tablets in different strengths. Thus, there is a reasonable choice of forms of applications. The recommended dose for maintenance treatment in combination with lithium or valproate is 80–160 mg which is identical to the recommended monotherapy dosage in acute mania. If there is a need, e.g., in break-through mania, ziprasidone can be titrated quickly to achieve a rapid response. ***Rating of PR: "+"***

Recommendation grade (RG)

Based on a CE "B" for combination treatment in PES for "mania" and any episode", the ***RG is "3".***

Zotepine: see "Other atypical antipsychotics used in bipolar disorder"

Other atypical antipsychotics used in bipolar disorder

Amisulpride is a frequently used medication in bipolar disorder in some countries, also beyond acute treatment. The only published evidence we found was an open-label amisulpride add-on study by Carta et al. (2006). The study enrolled 14 bipolar I outpatients not responding to on-going standard therapy: 11 were followed-up for 11.7 ± 8.2 months before and 5.2 ± 2.7 months after the introduction of amisulpride. Relapse rates before and during treatment with amisulpride were calculated in accordance to an increase of 1 or more in the CGI-BP score that was at the same time accompanied by a change in therapy or to an exacerbation of the symptoms that required hospitalization. The authors found a statistically significant decrease in overall relapse rate during the period of added amisulpride. The relative risk of relapse in the absence of amisulpride therapy was 3.1 ($P < 0.05$). Similarly, the rates of manic/mixed and depressive relapse were decreased but only manic episodes reached statistical significance (RR = 5.3, $P < 0.02$). These data give amisulpride a CE of "C" for any relapse and manic relapses in PNES. If used in long term, the metabolic profile appears quite acceptable, but prolactin elevation and extrapyramidal motor symptoms might limit its usefulness (Rummel-Kluge et al. 2010). Similar to risperidone, the rating for ST would be "–".

Asenapine has proven antimanic efficacy in two RCTs in monotherapy (CE "A" for mania (Grunze et al. 2009)) and in one more recent combination therapy study (Szegedi et al. 2012). The monotherapy studies included a 1-year double-blind extension comparing asenapine against olanzapine. Maintenance of efficacy as measured with regular YMRS assessments appeared similar between medications; however, it was only a secondary outcome with predefined wide non-inferiority criteria. Also the combination treatment study included a 1-year extension; however, due to a very high attrition rate results are not conclusive. Thus, asenapine can be assigned a ***CE of "C" for prevention of mania in ES,*** whereas the other efficacy categories are CE "F". There is also no published further supportive evidence (FE "0"). The available long-term data raise only minor concerns when it comes to weight gain and mild sedation (ST "+"), but practicability (only as sublingual formulation available) may be a problem in some patients (PR "–").

Cariprazine has recently demonstrated antimanic efficacy in a RCT (Yildiz et al. 2011); however, long-term data still need to be generated.

Albeit there are no placebo-controlled RCTs with **clozapine** in bipolar disorder, it is frequently used in otherwise treatment-refractory bipolar patients.

A pharmaco-epidemiological database study using a 2-year mirror-image design was carried out in Denmark, investigating the effectiveness of clozapine in 326 BD patients (Nielsen et al. 2012). The mean follow-up time was 544 ± 280 days. During clozapine treatment, the mean number of bed-days decreased from 177.8 to 34.6 ($P < 0.001$), the mean number of admissions from 3.2 to 2.0 ($P < 0.001$), and the number of psychotropic co-medications from 4.5 defined daily doses (DDD) to 3.9 DDD ($P = 0.045$). There is also more evidence based on

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case reports (Puri et al. 1995; Zarate et al. 1995; Hummel et al. 2002) ***(CE "C" for any episode in PNES)*** but issues exist with safety (especially agranulocytosis) and, consequently, practicability making frequent blood check mandatory (ST and PR "–").

Case series support the use of clozapine in rapid cycling patients not responsive to standard treatments (Calabrese et al. 1991; Suppes et al. 1994; Frye et al. 1996; Lancon and Llorca 1996) that merit a ***CE of "C" for PRC and a RG "3" for prevention of TEE in RC (PRC).***

Also of note are the suicide preventive effects of clozapine in schizophrenic patients, which, however, still need replication in bipolar subjects (PSu "+"). However, the mentioned study by Nielsen et al. (2012) also found that somatic hospital visits for intentional self-harm/overdose were significantly reduced during clozapine treatment from 8.3 to 3.1% ($P = 0.004$).

We could not identify any published studies for **zotepine** supporting its long-term use in bipolar disorder. CE "C" evidence in bipolar disorder is, so far, restricted to acute mania (Grunze et al. 2009). When used as maintenance treatment, zotepine might be associated with modest weight gain, hyperlipidaemia and sedation, but to a lesser degree than pharmacologically similar agents such as olanzapine. However, there are surprisingly little data available for the side effect profile of zotepine, especially in direct comparison to other atypical antipsychotics (Riedel et al. 2010; Rummel-Kluge et al. 2010).

Other anticonvulsants used in bipolar disorder

Oxcarbazepine has been infrequently used in bipolar patients as alternative to carbamazepine in patients not tolerating carbamazepine well or in need of co-medication that strongly interferes with carbamazepine. However, also oxcarbazepine has a interaction potential with other medication, and the risk of hyponatraemia might be higher than with carbamazepine (Van Amelsvoort et al. 1994). There is some evidence from acute mania studies supporting oxcarbazepine's use in this indication (Grunze 2010): however, we could identify only one RCT testing the prophylactic efficacy of oxcarbazepine. Vieta et al. (2008a) evaluated the prophylactic efficacy and the long-term tolerability of oxcarbazepine in bipolar I and II disorder as an adjunctive therapy to lithium in a 1-year, double-blind RCT. Bipolar I and II patients currently in remission were randomly assigned to oxcarbazepine ($n = 26$) or placebo ($n = 29$) as adjuncts to on-going treatment with lithium. The primary efficacy variable was the length of the remission period assessed by means of the YMRS and MADRS. The mean time to first recurrence of any type was 19.2 ± 13.9 and 18.6 ± 17.0 weeks for oxcarbazepine and placebo, respectively ($P = 0.32$). Ten (38.5%) patients had a recurrence of any kind in the oxcarbazepine group vs. 17 (58.6%) in the placebo group ($P = 0.14$). There was a trend for depressive episodes being less likely in the oxcarbazepine group compared to the placebo group (11.5 and 31%, respectively, $P = 0.085$). The small number of patients included in this study could be a likely reason for results not reaching significance. Strictly speaking, this trial has failed; however, with the clear numerical superiority of oxcarbazepine addition, we would consider it as a ***CE "C" evidence for PNES any episode and depression and a RG "4".***

Phenytoin has demonstrated relapse preventive effects in small sample of patients (Mishory et al. 2003). Twenty-three stable bipolar patients were studied who had at least one episode per year in the previous 2 years despite on-going prophylaxis. The majority of relapses during the last 2 years were manic/mixed indicating that this population might consist of a larger number of patients with a manic polarity. The period of stability, however, was less well controlled and ranged from 1 to 13 months. Phenytoin or placebo was added to their current therapy in a double-blind cross-over design for 6 months in each phase. The mean dose of phenytoin at month 6 was 380 ± 80 mg. Three patients relapsed on phenytoin and nine on placebo which was a significant difference (Cox's F-test for comparing survival in two groups: $F = 3.44$, $P = 0.02$). Twice as many relapses were into mania compared to depression for both phenytoin and placebo.

Although this is an interesting note for potential prophylactic efficacy of phenytoin, the study does not fulfil the methodological criteria to be counted as evidence sufficient for a CE "B". Thus, similar to oxcarbazepine, phenytoin should be considered as a medication with a ***CE of "C" evidence for PNES any episode, and a RG "4"***.

Gabapentin and topiramate have been tested in RCTs of acute mania, but both failed to separate from placebo (Grunze et al. 2009). As a result, the respective sponsors were not pursuing a bipolar disorder indication, and no conclusive maintenance studies have been conducted. A retrospective chart review of **topiramate** as bipolar maintenance treatment is suggestive of some efficacy, especially in RC patients (Marcotte 1998), and in combination with olanzapine, primarily initiated with the intention to limit weight gain (Vieta et al. 2004). These studies merit a "+" for further evidence (FE) and a CE of "C" for RC patients, in the absence of prospective

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studies in enriched/non-enriched samples (CE "F"). Practicability of its use has no major issues (rating "+"), and the safety/tolerability profile of topiramate appears reasonable in low doses commonly used in bipolar disorder (rating "+"); however, neurological side effects are not entirely dose dependent, including cognitive impairment and rare cases of transient hemiparesis (Jones 1998). There is still some concern about increased suicidality as suggested by the FDA (US Food & Drug Administration 2008); different from lamotrigine, there are no data for topiramate and suicide risk in bipolar patients which may put this into the right perspective. Thus, the rating for PSu would be "–". In summary, and based on the CE "C" for PRC, topiramate would be assigned a **RG "4".**

As with topiramate for weight gain, **gabapentin** is nowadays primarily used in bipolar disorder patients to treat comorbidities as anxiety disorder or substance abuse though there are no controlled data to support this practice (Perugi et al. 2002; Carta et al. 2003). Studies supporting such a use are either retrospective or in small numbers of subjects (FE: "+"). The best evidence, however, for the long-term use of gabapentin in bipolar disorder is a small, but placebo-controlled trial of adjunctive gabapentin for 1 year (Vieta et al. 2006). It included euthymic bipolar I and II patients who were randomly assigned to gabapentin ($N = 13$) or placebo ($N = 12$) added to the current treatment. The primary efficacy parameter was the modified CGI-BP, which was assessed at all visits. After 12 months, mean CGI-BP score change from baseline to endpoint in the gabapentin group was −2.1, and the mean score change in the placebo group was −0.6 ($P = 0.0046$). No emerging manic or depressive symptoms were seen in either group as measured with standard scales, and gabapentin was generally well tolerated.

The study falls short to our pre-set inclusion criteria of at least 25 bipolar I patient (as six patients had a bipolar II diagnosis). However, based on this study, gabapentin can be classified as **CE "C" for any mood episode in PNES.** Gabapentin is mostly well tolerated (ST: "+"), its short half life necessitating three daily dosages, however, limits practicability (PR: "–"). Positive or negative effects on suicidality are unknown by large (PSu: "0").

We could not identify evidence of some impact for the long-term use of the following anticonvulsants in bipolar disorder: eslicarbazepine, pregabalin, levetiracetam, vigabatrine, barbiturates or bromides. However, our search may have missed evidence, especially for the first generation antiepileptics, as it may have been published prior to the inclusion period of our literature search.

Hormones, vitamins, amino acids and fatty acids

Berk et al. (2008a) conducted a placebo-controlled add-on study of *N*-acetylcysteine (NAC, 1 g twice daily) to ongoing treatment in bipolar patients ($n = 75$) with treatment-resistant sub-threshold depression. Study duration was 24 weeks, with a 4-week washout. The two primary outcomes were the MADRS and time to a mood episode. NAC treatment was associated with a significant reduction in symptoms at treatment completion (week 24) on the MADRS primary score (least squares (LS) mean difference (95% CI): −8.05 (−13.16, −2.95), $P = 0.002$). Response, defined as a 50% reduction in total MADRS score, at weeks 20 and 24 compared with baseline was observed in 46 and 51% of participants in the NAC group compared with 21 and 18% in the placebo group, respectively ($P = 0.036$ and $P = 0.001$, respectively. However, there was no effect of NAC on time to a TEE (log-rank test: $P = 0.968$). Similar benefits of NAC were seen in a subgroup analysis of bipolar II patients (Magalhaes et al. 2011). Thus, NAC might be beneficial in treating persistent, sub-threshold depressive symptoms, but does not seem to have protective effects against recurrence of episodes.

The evidence for the use of omega-3 fatty acids, or their active ingredient eicosapentanoic acid, in bipolar disorder is conflicting. For the acute treatment of bipolar depression, diverging results have been described (Frangou et al. 2006; Keck et al. 2006b). In a mixed population of euthymic, depressed and (hypo) manic patients, however, omega-3 fatty acids seemed to ameliorate symptoms and prevent recurrences. Stoll et al. (1999) conducted a 4-month, double-blind, placebo-controlled study, comparing omega-3 fatty acids (9.6 g/day, corresponding to 6.2 g/day eicosapentanoic acid) versus placebo (olive oil), in addition to usual treatment, in 30 patients with bipolar disorder. Patients needed to have had at least one (hypo) manic episode during the year preceding the study. At study entry the majority of subjects still had at least residual symptoms, only six of the 30 were classified as euthymic. The study population was not enriched for previous exposure to omega-3 fatty acids. The primary finding was that the omega-3 fatty acid patient group had a significantly longer period of remission than the placebo group ($P = 0.002$; Mantel–Cox). Omega-3 fatty acids were generally well tolerated, and may have additional benefits in reducing the risk of cardiac mortality in affectively ill patients (Severus et al. 2001).

The random mixture of syndromal and euthymic patients with only a small number of patients entering controlled trial condition in euthymia, however,

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disqualifies this study from CE "A" or "B" evidence, but is considered as sufficient for a CE of "C" for PNES, and by this for an **RG"4".**

Maintenance electroconvulsive therapy (ECT)

Prevention of TEE in enriched samples (PES)

In the literature, the terms "continuation ECT" and "maintenance ECT" are used randomly and interchangeably. Even more than in the case of pharmacotherapy, the distinction between continuation ECT (c-ECT) and maintenance ECT (m-ECT) is purely hypothetical, as m-ECT develops gradually out of c-ECT without fixed boundaries. In addition there is nothing like "prophylactic" ECT which would imply an irrational use of ECT by starting stable and euthymic patients on ECT.

Due to the nature of ECT which makes it unethical to conduct "placebo" studies, e.g., with sham ECT, we have no data available allowing classification as CE "A" and "B". However, there is nowadays a reasonable literature on open and comparator studies (albeit in numbers too small to test for non-inferiority) supporting the use of maintenance ECT (m-ECT) in bipolar depressed patients responding to an acute course of ECT (Loo et al. 2011). A recent review looking into articles published in the English language between 1998 and 2009 identified 32 reports on continuation and/or maintenance ECT. These articles included 24 case reports and retrospective reviews on 284 patients. Two of these reports included comparison groups, and one had a prospective follow-up in a subset of subjects. The authors also identified six prospective naturalistic studies and two randomized controlled trials (Petrides et al. 2011). The overall outcome of all these studies was clearly positive showing a marked reduction of future mood episodes, and supports the use of m-ECT in patients non-responsive or non-tolerant to long-term medication treatment. However, m-ECT protocols (stimulus paradigms, frequency) were not uniform, and direct comparisons between protocols were not made. This leaves some degree of uncertainty for clinicians, and the need to develop individualized treatment protocols based on the patient's history of relapses and recurrences. ***CE in PNES: "C"***

Prevention of TEE in non-enriched samples (PNES)

We could not identify studies where maintenance ECT was conducted without a previous course of acute ECT. Clearly, it would also be paradoxical to use ECT a priori in stable, euthymic patients. ***CE in PNES: "F"***

Prevention of TEE in rapid cyclers (PRC)

In a recent open study, 14 patients with BPD (type I or II), unresponsive to previous medication treatment, and an RC course were treated with monthly m-ECT. Response was assessed as days ill 2 years before and after sessions of m-ECT. The mean treatment duration was 21 months, and all patients improved during treatment. Illness duration decreased 13-fold from 304 to 24 days of illness per year, and illness-free intervals increased from 52 to 334 days per year (all $P < 0.0001$) (Minnai et al. 2011). ***CE in RC: "C"***

Further evidence (FE)

There is also older literature (pre-1998 which was the lower inclusion limit of the review by Petrides et al. 2011), mainly case reports, supporting the use of continuation and maintenance ECT, as reviewed by Rabheru and Persad (1997). ***Rating of FE: "+"***

Safety and tolerability (ST)

Progressive cognitive impairment, especially of memory, is a main worry associated with repetitive ECT sessions. In addition, every session has the inherited risks associated with short-term anaesthesia. The case reports of m-ECT do not explicitly support these concerns; however, in most instances memory impairment was not specifically measured. In addition, evidence based on single cases or series is also more subject to publication bias than controlled studies; unfavourable outcomes are seldom reported. Thus, clinicians should take these concerns serious unless proven otherwise. ***Rating of ST: "–"***

Prevention of suicide (PSu)

There are no data reported on suicide prevention for m-ECT. It is reasonable to assume that successful prevention of new mood episodes in severely ill bipolar patients reflects positively on suicide rates, but, different to, e.g., lithium, we have no data supporting antisuicidal effects independent from treatment success. ***Rating of ST: "0"***

Practicability (PR)

Compared to medication treatment, ECT is clearly associated with more efforts and man power. However, we should keep in mind that m-ECT can usually be administered on a outpatient basis not

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requiring hospitalization, it is mostly a low frequency, biweekly or monthly event with a high adherence (different from medication that has to be taken daily with unclear compliance). ***Rating of PR: "–"***

Recommendation grade (RG)

Given the overall evidence, we would assign m-ECT a **RG "4".** However, in severely ill bipolar patients who have failed on multiple prophylactic medication trials, we would recommend to consider ECT not only for the acute phase (Grunze et al. 2009, 2010) but also as a serious option for long-term treatment.

Other physical treatments

Sleep deprivation, coupled with sleep phase advance, and bright light therapy are regularly applied for the treatment of acute depression, including bipolar depression; however, we did not find published evidence on their long-term use to prevent new episodes in bipolar patients. Some pioneering work has been carried out in the acute treatment of bipolar patients with repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS) and deep brain stimulation (DBS). Whereas the efficacy of rTMS as bipolar maintenance treatment is largely unknown (Agarkar et al. 2011), some open evidence exists for the usefulness of VNS in treatment refractory bipolar depression; however, the reported long-term data do not include separate analysis for bipolar disorder patients (Rush et al. 2005; Nierenberg et al. 2008). The use of DBS to treat bipolar disorder patients has evolved quite recently; in the past, case reports, e.g., from Parkinson patients, were more suggestive of risks to induce mania by DBS (e.g., Raucher-Chene et al. 2008). This might deter research from using DBS in bipolar I disorder patients; the so far largest case series was done in unipolar and bipolar II disorder patients with treatment refractory depression. In an open-label trial with a sham lead-in phase, Holtzheimer et al. (2012) assessed the efficacy and safety of subcallosal cingulate DBS in ten patients with MDD and seven with BP who were enrolled from a total of 323 patients screened. Patients received single-blind sham stimulation for 4 weeks followed by active stimulation for 24 weeks. Patients then entered a single-blind discontinuation phase; this phase was stopped after the first three patients because of ethical concerns. Patients were evaluated for up to 2 years after the onset of active stimulation. A significant decrease in depression and increase in function were associated with chronic stimulation. Remission and response were seen in three patients (18%) and seven (41%) after 24 weeks ($n = 17$), five (36%) and five (36%) after 1 year ($n = 14$), and seven (58%) and 11 (92%) after 2 years ($n = 12$) of active stimulation. No patient achieving remission experienced a spontaneous relapse. Efficacy was similar for patients with unipolar and those with bipolar depression. Chronic DBS was considered as safe and well tolerated, and no hypomanic or manic episodes occurred.

In conclusion, the evidence for physical treatments other than m-ECT is still too weak to give a recommendation for bipolar I disorder patients. For Bipolar II disorder patients, there is some preliminary evidence for DBS to prevent TEE.

The role of psychotherapy and psychoeducation

As we clarified at the beginning, this guideline is not focussing on the evidence of psychotherapies and psychoeducation in the long-term treatment of bipolar disorder. The important role of these techniques for improving compliance and resilience against mood instability are well documented and they are an integrative and established component of treatment, accompanying medication. For an up-to date reviews of their differential efficacy and cost-effectiveness, we refer the reader to recent publications (e.g., Scott et al. 2007, 2009; Beynon et al. 2008).

Conclusion

Using the established approach of the WFSBP guideline series, and making minor modifications to suit the topic of bipolar maintenance, we identified six medications with the two highest recommendation grades, based on their evidence for different aspects of bipolar disorder maintenance treatment in diverse patient population. None of these medications can fully cover all areas and patient groups equally well; so we are pleased to see that the number of alternatives has grown since the first edition of this guideline in 2004 (Grunze et al. 2004). We also notice that despite the development of promising alternatives, lithium is still a top standard for the long-term treatment of bipolar disorder.

By far, the body of evidence originates from RCTs conducted with PAs which have been launched in the last two decades. However, this should not imply that we ignore real world practice and longstanding clinical experience with "old" PAs just because of a lack of RCTs. Even more important, we should be aware of the hazards switching stable bipolar patients

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from their established treatment as it may cause a worsening of disease course, increase of suicidal risk and new side effects. A low recommendation grade (RG) for "old" PA (like carbamazepine or clozapine) could, but does not necessarily mean a lower effectiveness and safety in comparison with other drugs. The reason may also be a historical lack of RCTs fulfilling today's criteria for evidence based medicine.

But not only has the choice of candidate medication increased since the first edition of the WFSBP bipolar maintenance guideline, the field has also advanced otherwise. We had to spend much more thought on trial designs, and how they allow us to extract clinical valuable information. Clinicians want to know the real recurrence preventive properties of a drug, not so much the disastrous effects of drug discontinuation in insufficiently stabilized patients. This is why we spend much thought on trial design when writing the guideline, to help clinicians to develop a more critical reading and appraisal of studies. Given the heterogeneous trial designs, the different strengths and weaknesses of available medication, and finally the subjectivity of experts when making a recommendation – even when based on evidence – we can only encourage the reader to draw his/her own conclusions from the evidence using this guideline as a – hopefully useful – reference.

For the reason of diversity of trials designs, patient populations examined, and pursued outcome, e.g., having strong antimanic or antidepressive prophylaxis in place, we cannot give a general recommendation up to which RG a medication should be used, as we did with the mania and bipolar depression guideline. Clearly, the choice of RG "1" or "2" recommendations is wider in the prophylaxis of mania in patients responsive to acute antimanic treatment than, e.g., specifically in the prevention of rapid cycling, and thus the numerical value of the maximum RG can be lower, e.g., "3" or "4". On the other hand, in clinical manifestations with lack of evidence for treatment, the clinician may consider a top to bottom approach when choosing medication, tailored to the specific need of the patient, down to RG 5 which is based on equivocal evidence. However, additional information on safety, tolerability and suicide prevention should always be considered for the final treatment decision.

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Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders

Gin S Malhi[1,2], Darryl Bassett[3,4], Philip Boyce[5], Richard Bryant[6], Paul B Fitzgerald[7], Kristina Fritz[8], Malcolm Hopwood[9], Bill Lyndon[10,11,12], Roger Mulder[13], Greg Murray[14], Richard Porter[13] and Ajeet B Singh[15]

Abstract

Objectives: To provide guidance for the management of mood disorders, based on scientific evidence supplemented by expert clinical consensus and formulate recommendations to maximise clinical salience and utility.

Methods: Articles and information sourced from search engines including PubMed and EMBASE, MEDLINE, PsycINFO and Google Scholar were supplemented by literature known to the mood disorders committee (MDC) (e.g. books, book chapters and government reports) and from published depression and bipolar disorder guidelines. Information was reviewed and discussed by members of the MDC and findings were then formulated into consensus-based recommendations and clinical guidance. The guidelines were subjected to rigorous successive consultation and external review involving: expert and clinical advisors, the public, key stakeholders, professional bodies and specialist groups with interest in mood disorders.

Results: The Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders (Mood Disorders CPG) provide up-to-date guidance and

[1]Discipline of Psychiatry, Kolling Institute, Sydney Medical School, University of Sydney, Sydney, NSW, Australia
[2]CADE Clinic, Department of Psychiatry, Royal North Shore Hospital, St Leonards, NSW, Australia
[3]School of Psychiatry and Clinical Neurosciences, University of Western Australia, Perth, WA, Australia
[4]School of Medicine, University of Notre Dame, Perth, WA, Australia
[5]Discipline of Psychiatry, Sydney Medical School, Westmead Clinical School, University of Sydney, Sydney, NSW, Australia
[6]School of Psychology, University of New South Wales, Sydney, NSW, Australia
[7]Monash Alfred Psychiatry Research Centre (MAPrc), Monash University Central Clinical School and The Alfred, Melbourne, VIC, Australia
[8]CADE Clinic, Discipline of Psychiatry, Sydney Medical School – Northern, University of Sydney, Sydney, NSW, Australia
[9]Department of Psychiatry, University of Melbourne, Melbourne, VIC, Australia
[10]Sydney Medical School, University of Sydney, Sydney, NSW, Australia
[11]Mood Disorders Unit, Northside Clinic, Greenwich, NSW, Australia
[12]ECT Services Northside Group Hospitals, Greenwich, NSW, Australia
[13]Department of Psychological Medicine, University of Otago–Christchurch, Christchurch, New Zealand
[14]Department of Psychological Sciences, School of Health Sciences, Swinburne University of Technology, Melbourne, VIC, Australia
[15]School of Medicine, Deakin University, Geelong, VIC, Australia
Corresponding author:
Gin S Malhi, CADE Clinic, Department of Psychiatry, Royal North Shore Hospital, St Leonards, NSW 2065, Australia.
Email: gin.malhi@sydney.edu.au

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advice regarding the management of mood disorders that is informed by evidence and clinical experience. The Mood Disorders CPG is intended for clinical use by psychiatrists, psychologists, physicians and others with an interest in mental health care.

Conclusions: The Mood Disorder CPG is the first Clinical Practice Guideline to address both depressive and bipolar disorders. It provides up-to-date recommendations and guidance within an evidence-based framework, supplemented by expert clinical consensus.

Mood Disorders Committee: Professor Gin Malhi (Chair), Professor Darryl Bassett, Professor Philip Boyce, Professor Richard Bryant, Professor Paul Fitzgerald, Dr Kristina Fritz, Professor Malcolm Hopwood, Dr Bill Lyndon, Professor Roger Mulder, Professor Greg Murray, Professor Richard Porter and Associate Professor Ajeet Singh.

International expert advisors: Professor Carlo Altamura, Dr Francesco Colom, Professor Mark George, Professor Guy Goodwin, Professor Roger McIntyre, Dr Roger Ng, Professor John O'Brien, Professor Harold Sackeim, Professor Jan Scott, Dr Nobuhiro Sugiyama, Professor Eduard Vieta, Professor Lakshmi Yatham.

Australian and New Zealand expert advisors: Professor Marie-Paule Austin, Professor Michael Berk, Dr Yulisha Byrow, Professor Helen Christensen, Dr Nick De Felice, A/Professor Seetal Dodd, A/Professor Megan Galbally, Dr Josh Geffen, Professor Philip Hazell, A/Professor David Horgan, A/Professor Felice Jacka, Professor Gordon Johnson, Professor Anthony Jorm, Dr Jon-Paul Khoo, Professor Jayashri Kulkarni, Dr Cameron Lacey, Dr Noeline Latt, Professor Florence Levy, A/Professor Andrew Lewis, Professor Colleen Loo, Dr Thomas Mayze, Dr Linton Meagher, Professor Philip Mitchell, Professor Daniel O'Connor, Dr Nick O'Connor, Dr Tim Outhred, Dr Mark Rowe, Dr Narelle Shadbolt, Dr Martien Snellen, Professor John Tiller, Dr Bill Watkins, Dr Raymond Wu.

Keywords

Guidelines, depression, bipolar disorder, depressive disorder, mania, mood disorders, management, treatment

Introduction

Overview. The mood disorders committee (MDC) has been mindful that effective clinical care involves the art of applying clinical knowledge and skills to the individual needs of those presenting for care. A primary motivation was to ensure that the guideline was engaging and useful to clinicians. For this reason a balance of academically focused and clinically focused experts in the field has been engaged in the writing of the guideline. Genuine involvement of clinicians of other disciplines, people with experience of mental illness, and carers has occurred to better balance the guideline.

Human beings are complex biological systems, with mind as an emergent property. For this reason there are inherent uncertainties regarding diagnostic formulation and optimal care. It is anticipated that this guideline will assist clinicians to better navigate complex and challenging clinical scenarios. Tailoring care to the individual in the context of an effective working relationship is the foundation upon which the proper application of this guideline relies.

Aim. The Mood Disorders Clinical Practice Guideline (Mood Disorders CPG) has been developed by the Royal Australian and New Zealand College of Psychiatrists (RANZCP) to guide the clinical management of real-world depressive and bipolar disorders and to advise specifically on diagnosis and treatment strategies. The guideline focuses primarily on adults and briefly addresses special populations such as children and adolescents, pregnant and post-partum women, the elderly and those with common medical illnesses.

The guideline is primarily directed at psychiatrists, psychologists and physicians with a particular interest in mental health issues. It will also be of benefit to other mental health care professionals, hospital administrators and government policy makers. It amalgamates evidence-based knowledge with clinical wisdom and makes recommendations for real-world practice.

Structure. The Mood Disorders CPG comprises four sections:

Section 1: Classification of mood disorders

Section 2: Clinical management of major depressive disorder (MDD)

Section 3: Clinical management of bipolar disorder (BD)

Section 4: Clinical management of mood disorders with complex presentations and in special populations

Scope. Ever since Kraepelin separated manic-depressive insanity from dementia praecox, the nosological status of mood disorders has been in flux (Kraepelin, 1899). In practice, two diagnostic questions that clinicians commonly face are: (1) How to diagnose depression; and (2) When to diagnose bipolar disorder on the basis of emerging (hypo)manic symptoms. Therefore, this guideline discusses the diagnosis and management of both depressive and bipolar disorders.

The reason for addressing both groups of mood disorders together is that, in recent years, the overlap between these 'categories' has been of particular interest and increasingly they have been conceptualized as part of a spectrum. In clinical practice mood disorders diagnoses often change reflecting movement along this spectrum, e.g. from Major Depressive Disorder (MDD) to Bipolar I Disorder (BD I), sometimes 'via' Bipolar II Disorder (BD II). Research has revealed 'commonalities rather than differences' in the two groups of disorders (depressive disorders and bipolar and related disorders, American Psychiatric Association (APA), 2013; Barlow et al., 2004) and their treatments overlap considerably; with the same medications and similar psychological interventions used in both. Thus a unified approach to the diagnosis and management of mood disorders has been adopted in this guideline (see: Figures 1 and 2 and Table 2).

Methodology. This guideline was developed as part of the RANZCP CPG Project 2013–2015; funded solely by the College. The RANZCP called for expressions of interest from its members and appointed the Chair and the mood disorders committee (MDC) *(see Appendix 5)*. The MDC consists of Australian and New Zealand specialists from Psychiatry and Psychology with clinical and academic expertise in the management of mood disorders.

This guideline has been developed using a number of strategies for searching and synthesizing clinical and research evidence pertaining to the diagnosis and treatment of mood disorders. Members of the MDC both individually and as part of sub-groups were charged with the task of

searching the literature pertinent to particular aspects of managing mood disorders. To ensure content and form were acceptable to end-users, and to pre-empt well-recognised challenges with knowledge translation, two formal rounds of external consultation and review were undertaken with relevant experts, clinicians and consumers *(see Appendix 5)*.

Search strategy: Articles and information sourced from search engines such as PubMed, EMBASE, MEDLINE, PsycINFO and Google Scholar was supplemented by literature known to MDC members (e.g. from books, book chapters and government reports) and from existing depression and bipolar disorder guidelines (Bauer et al., 2002a, 2002b; Cleare et al., 2015; Ellis, 2004; Goodwin, 2009; Grunze et al., 2002, 2003, 2004, 2013; Malhi et al., 2009a, 2009b; NICE, 2006, 2009; RANZCP, 2004; Yatham et al., 2013b). The search was repeated regularly between April 2013 and October 2015.

The MDC convened a teleconference in total 55 times over a 33 month period spanning March 2013–September 2015. Each meeting lasted 1 hour and involved the discussion of key aspects of the guideline and the development of clinical recommendations based on available evidence. This allowed the consideration of new evidence as it emerged and the tempering of advice if deemed necessary.

Recommendation formulation: For intervention studies, levels of evidence were assigned (*see Appendix 1*) and adapted from the Australian National Health and Medical Research Council (NHMRC) levels of evidence for intervention studies (NHMRC, 2009).

This guideline makes two types of recommendations that reflect the reasoning used to formulate advice. First evidence-based recommendations (EBRs) were formulated when the MDC judged there to be sufficient consistent evidence from intervention studies to support a recommendation on a given topic. For each EBR, strength of evidence was rated using the NHMRC levels of evidence for intervention studies and is graded accordingly in the recommendation box (e.g., EBR I, II, III, or IV).

It is important to remember that absence of evidence is not evidence of absence, and so, given our understanding of the nature and optimal management of many aspects of mood disorders is incomplete, a second type of recommendation was also employed. This was also derived through discussion and agreement within the MDC and termed a consensus based recommendation (CBR). CBRs were formulated when: (i) the existing intervention evidence base was absent, ambiguous, or of doubtful clinical impact in the Australian and New Zealand context; and (ii) the MDC (based on collective clinical and research knowledge and experience) reached consensus on the clinical utility of the recommendations. For example, a CBR was developed for the adjunctive psychological treatment of bipolar disorder: the recommendation that treatment *should follow a published evidence-based manual* has not been subject to direct test, but was inferred from the broader psychotherapy literature and the MDC's experience in treatment and training. Similarly, the recommendation that antidepressant therapy should be avoided during mixed mood states is based on clinical experience and is a CBR. If members of the MDC held a view at variance with a CBR it was discarded and no recommendation was made.[1]

The MDC produced a series of draft guidelines that were gradually refined and extensively peer reviewed.

Expert review: Australian, New Zealand and international expert advisers (clinical or academic) were invited by the Chair of the MDC to review a draft copy of the guideline and

provide comment. Expert advisers are listed *(see Appendix 5)*. Expert advisers provided comment and feedback on a voluntary basis with no remuneration and their declarations of interest are documented. The MDC assessed all comments received via expert review and produced a second draft guideline for public consultation.

Public consultation: A revised version of the guideline was released (June–July 2015) for public consultation to encourage community-wide engagement and gain broad representation across Australia and New Zealand. Specifically, the RANZCP invited review and comment from its committees and members, as well as key stakeholders, including professional bodies representing medicine, psychology, nursing, social work and occupational therapy, and special interest groups representing consumers, carers, Aboriginal and Torres Strait Islander peoples and Māori (see Appendix 5). During the consultation period, the draft guideline was publicly available for review and comment on the RANZCP website. Participants were asked to review the guideline and answer four key questions related to each section of the guideline via Survey Monkey. Question criteria were:

- Are there any significant gaps (of topic, literature, other)?
- Are there errors in the content?
- Is the structure logical and easy to use?
- Do you have any other comments?

The MDC considered all responses. For each suggestion, the MDC agreed on whether to revise the guideline. All decisions were recorded and documented. External consultation enabled the MDC to further develop, strengthen and validate recommendations to ensure all relevant issues were identified and considered.

Methodological considerations. Empirical scientific methodologies provide a rational basis to guide patient care. But they are not without their limitations. An understanding of several logistical, ethical, and methodological challenges helps to explain many of the evidence 'blind spots' in medical practice.

Many clinically relevant dilemmas cannot be fully elucidated empirically because of significant ethical issues. An example of this is the evidence for safety of medications in pregnancy. Prospective human comparator trials face an ethical impasse, thus the evidence base is drawn largely from animal studies and association studies in humans. Sufficient power to identify rare adverse associations unfortunately only arises after many years of post-marketing surveillance. Similarly, investigating novel therapies for severe conditions often relies on an augmentation comparator study approach, so that vulnerable patients are not unethically deprived of an established therapy. This can delay the process of demonstrating similar or superior efficacy of novel therapies as standalone treatments in severe illnesses.

Rarer clinical situations are often less well empirically studied because of their inevitably smaller public health footprint drawing less research funding, challenges of finding recruits, and the larger samples needed for rare outcome statistical power. Similar cost and recruitment challenges help to explain the relative paucity of long-term follow-up studies. Importantly, diagnostic and therapeutic areas offering potential for commercialisation are sometimes more intensively studied, with research questions shaped by intellectual property. This may result in publication bias, and relatively less study of approaches that lack commercial

viability. Exclusion of common comorbidities in trials, clinical validity of rating scales and efficacy cut points, and diagnostic instability further impede evidence translation to practice. Finally, inherent clinical heterogeneity limits the utility of predictive and normative evidence-based approaches to guide practice. Hence the focus on personalized medicine has grown and clinicians are faced with having to increasingly manage clinical uncertainty.

Limitations of clinical trials. Many of the studies cited in this guideline were funded by pharmaceutical companies that manufactured the medication under investigation. Understandably, trials are designed to maximise the likelihood of identifying a favourable effect. This factor may contribute to a number of methodological weaknesses in the trial design and reported data. In addition, meta-analyses rely on *all* relevant trials being reported. However, this is not always the case (Ioannidis, 2009) as some studies are not reported because they are small and others because they have a negative outcome (failed trials). Data from such studies is often not made available. Furthermore the degree to which patients in clinical trials are representative of the population being treated is debatable with, for instance, many trials in depression excluding patients who are experiencing suicidal thoughts (a relatively common symptom in severe depressive disorders). Distortions in medication trial construction and interpretation may also occur when funding is being sought from third parties, such as Medicare funding in Australia. Negative outcomes from research reduce opportunities for gaining future financial support and therefore can be overlooked or misrepresented. Trials in bipolar disorder exemplify some of these problems (see Table 1). The scientific literature on psychological therapies is also influenced by publication bias (increased likelihood that positive outcome studies will be published) (Driessen et al., 2015) and researcher allegiance effects (Munder et al., 2013).

Methodological issues in clinical trials may result in 'failed trials' i.e. trials which do not show a difference between the effects of a drug and placebo despite one existing. This is probably a common reason for evidence not being available despite the fact that there is a general clinical impression that certain medications are effective for particular conditions.

Clinical trials of psychotherapies also have potential biases including lack of blinding and expectation effects amongst both therapists and patients. More fundamentally, psychotherapies are complex, multi-component interventions, and contrary to the logic of the randomised controlled trial (RCT), patients' experience of and active participation in psychotherapy systematically influences the content of the intervention they receive. It has therefore been argued that RCTs are not optimal methodologies for validating psychotherapies, and instead process evaluation is required (Moore et al., 2015). Therefore while RCTs carry significant weight in this guideline, it must be remembered that they and their meta-analyses are of variable quality and validity.

Off label prescribing. In this guideline, some therapies identified as effective for the treatment of mood disorders on the basis of available evidence may have yet to receive approval for such use in Australia and/or New Zealand.

The use of such therapeutic agents outside their approved indication(s) is sometimes referred to as '*off label*' use, and in practice this may impact eligibility for third-party payer subsidy. We recommend careful documentation supporting your clinical use of specific therapeutic agents over alternatives which are approved in your country. It is also

recommended that this issue is explained to patients, including informing them that they may have to personally meet added costs due to lack of third-party payer subsidy.

Table 1. Methodological considerations in bipolar disorder trials.

Medication confounds
Recruitment Many patients are recruited into trials on existing medications. The numbers of patients on medication at recruitment is reported in very few trials and no trials specify individual agents. *Withdrawal* Existing medication is withdrawn, usually within 5 half-lives of the medication, probably leading to discontinuation symptoms in a percentage of patients. Withdrawal symptoms are likely to be better treated with, for example, sedative and anticholinergic antipsychotics than by placebo, giving an immediate advantage to these drugs. Rapid withdrawal could also increase the risk of switching and exaggerate the effects of the added agent or, alternatively, mask the difference between the investigational drug and placebo.
Diagnostic inconsistency
Trials contain varying percentages of patients with rapid cycling bipolar disorder who are usually not analysed separately. Some trials exclude patients with mixed features while others include them.
Selection, enrichment and drop-outs
Selection Participant selection can be distorted by the pressure to enrol subjects leading to sub-optimal diagnostic accuracy and the inclusion of patients with illness severity less than the minimum designated. In some medication trials, the participants are offered financial inducements, usually to offset 'out of pocket' costs, but with the potential for distortions in the subjective reports of symptoms and disability. Participants who volunteer for medication trials often have "treatment resistant" illness and are therefore very willing to keep trying new treatments. It is known that some participants will enter multiple successive trials. Patients entering maintenance studies are often highly selected to be those who have tolerated, responded to and stabilised on a medication (enrichment). *Drop-outs* Most trials in mania and depression report high dropout rates, usually within the first ten weeks (e.g. 50% dropout*), and There is usually further drop-out during a variable period of stabilisation that follows acute treatment.

***(Nazer** et al., 2012; Tohen et al., 2003b).

Classification of mood disorders

A pragmatic approach to mood disorder classification. There is growing consensus that psychiatric diagnoses are akin to social constructs (Insel, 2014; Zachar and Kendler, 2007). It is nonetheless appropriate for the structure of this guideline to adopt an accepted mood disorder taxonomy because, (i) there is broad agreement about definitions, and (ii) diagnostic terms have accrued valuable meaning through scientific (e.g. clinical trials) and social processes (e.g. advocacy). (See: Figure 1). Using the terms as pragmatic organising constructs should not translate into their reification - the optimal classification of disorders must await a quantum leap in our understanding of the aetiology and pathophysiology of abnormal behaviour.

The origins and development of mood disorders (however described) is definitively not known, but it is certainly multi-factorial and the clinical expression is likely determined through a combination of genetic predisposition, psychological vulnerabilities and life stressors. Interplay of factors within these domains is thought to eventuate in brain/mind dysfunction. This dysfunction is sometimes observable in neural changes, and is experienced subjectively as distress that can manifest as overt behavioural change. Together these abnormalities result in clinical signs and symptoms, which are grouped into syndromes and termed mood disorders.

A variety of psychological and neurobiological models address the aetiology and pathophysiology of mood disorders (e.g. Berman et al., 2011; Caspi et al., 2003; Charney and Manji, 2004; Hasler et al., 2004; Nolen-Hoeksema, 2000). These 'explanations' offer important insights as to the origin of mood symptoms and provide clinicians a framework for understanding the complex pathology that underpins clinical mood disorders.

Mood disorders diagnostic criteria

Criteria for depressive disorders. Depressive disorders usually feature low mood and/or a loss of pleasure (anhedonia). These are often accompanied by somatic symptoms such as changes to weight, psychomotor disturbance, fatigue and sleep disturbances such as insomnia or hypersomnia, cognitive symptoms, such as diminished concentration and negative cognitions characterised by negative self-evaluation (low self-esteem), excessive guilt, feelings of hopelessness and helplessness, and suicidal ideation or ambivalence about living. Thus functionally, individuals with mood disorders are usually limited in their ability to perform their normal day-to-day duties (APA, 2013). (See: Table 3 Summary of DSM-5 criteria for depressive disorders.)

Depressive disorders comprise several diagnoses distinguished by the precipitants and/or the frequency, intensity and duration of episodes. It is important to note that in practice the term 'major depression' is used to refer both to an episode of illness and the illness as a whole. Technically episodes of depression are discrete single events, which also occur in the context of bipolar disorder. *(See: Criteria for bipolar disorders.)*

Major depressive disorder (MDD) is diagnosed in adults and is the archetypal diagnosis in this group of disorders. *Persistent depressive disorder* (PDD) is a more chronic presentation of depression and combines the DSM-IV diagnoses of dysthymia and chronic MDD. *Disruptive mood dysregulation disorder* (DMDD) is a new category in DSM-5 which is

Table 2. Features of bipolar disorders and depressive disorders (based on DSM-5).

	Episodes	Depression		Mania/Hypomania[a]		Possible Psychosis
		Duration	Severity of symptoms	Duration	Severity of symptoms	
BD I	Mania +/– hypomania +/– depression	2 Weeks	Marked Impairment	Mania 7 days most of the day nearly every day or hospitalisation	Marked impairment (Mania only)	Yes
BD II	Hypomania +Depression	2 Weeks	Marked Impairment	Hypomania[b] 4 consecutive days, present most of the day nearly every day.	No marked impairment	In depression but not in hypomania
Cyclothymia[d]	Subthreshold[c] hypomania + subthreshold[c] depression	2 years with no more than two months symptom-free	Clinically significant impairment	2 years with no more than two months symptom-free	Clinically significant impairment	No
MDD[e]	Depression	2 Weeks	Marked Impairment	N/A	N/A	Yes
PDD[d]	Depression	2 Weeks	Clinically significant impairment	N/A	N/A	No
DMDD[f*]	Chronic irritability and temper outbursts	>12 mths with no more than 3 mths symptom-free	≥3 Temper outbursts per week. Present in ≥2 settings	N/A	N/A	No
PMDD[g*]	Depression	Final week before menses to a few days after.	Causes distress or interference with functioning	N/A	N/A	No

Note: For full criteria for manic, hypomanic and depressive episodes, refer to DSM-5 (APA, 2013). Also see: Figures 1 and 2.

References: [a]The main differences between a manic and hypomanic episode in DSM-5 are: (a) duration of symptoms; and (b) presence or absence of increased *goal-directed* activity. In mania, symptoms occur for most of the day, for more days than not, within one week, and/or hospitalisation is required. (However, note that the utility of hospitalisation as an aspect of diagnosis has been questioned recently (Malhi and Berk, 2014). In hypomania, symptoms occur for 4 consecutive days, for most of the day. Both mania and hypomania are characterised by elevated mood, and persistently increased activity. However mania specifies 'increased goal-directed activity', whereas hypomania simply states 'increased activity'.

[b]Hospitalisation or psychotic symptoms automatically warrant a diagnosis of mania rather than hypomania.

[c]Subthreshold refers to a state in which there are several symptoms of hypomania and/or depression but these are insufficient in number and/or severity to meet criteria for either.

[d]Cyclothymia and dysthymia can be confused with personality or temperament. It is often difficult to determine whether mood fluctuations are within normalcy for an individual or are pathological and warrant a diagnosis.

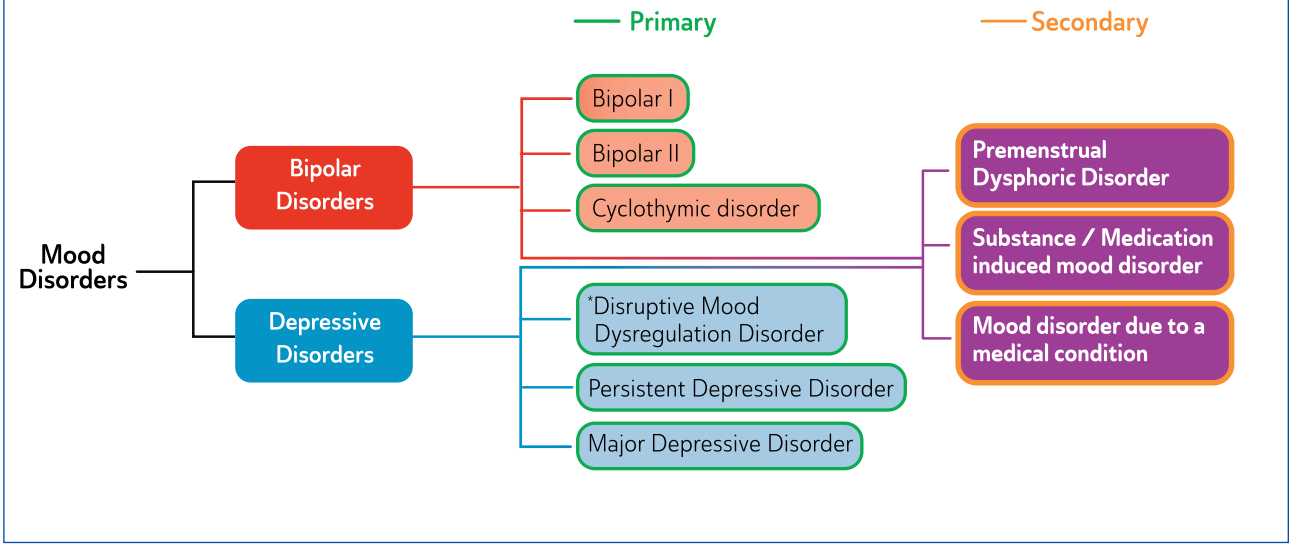
[e]MDD no longer includes bereavement as an exclusion criterion in DSM-5. Bereavement is a severe life stressor and individuals who develop MDD following bereavement benefit from the same treatment strategies. Dysthymia, which is now coded as persistent depressive disorder, reflects a more chronic illness, whereas chronic MDD is a persistent unremitting illness that perhaps reflects treatment non-response (Porter et al., 2013).

[f]Disruptive Mood Dysregulation Disorder (DMDD) is a new category included in DSM-5 to describe children who have persistent irritability. Children with these symptom patterns are often found to go onto develop MDD, which is why this has been included within depressive disorders. Previously, such children may have been diagnosed with paediatric bipolar disorder, which is conceptualised as a more episodic illness and therefore a diagnosis of bipolar disorder is no longer appropriate in these cases. Part of the reason for developing a diagnosis of DMDD is to stem the over-diagnosis of paediatric BD. However, this category remains contentious because of its high comorbidity with other childhood disorders, and the potential risk of further over pathologising healthy children. It is best seen as a category that enables further research on the natural history and best management of such presentations.

[g]Premenstrual Dysphoric Disorder (PMDD) is also a new diagnosis used to describe women of menstruating age who experience severe dysphoria, irritability or mood swings in the week prior to the onset of menses and finishing a few days after the onset of menses. These symptoms need to be prospectively reported for at least two menstrual cycles and be present for at least 12 months.

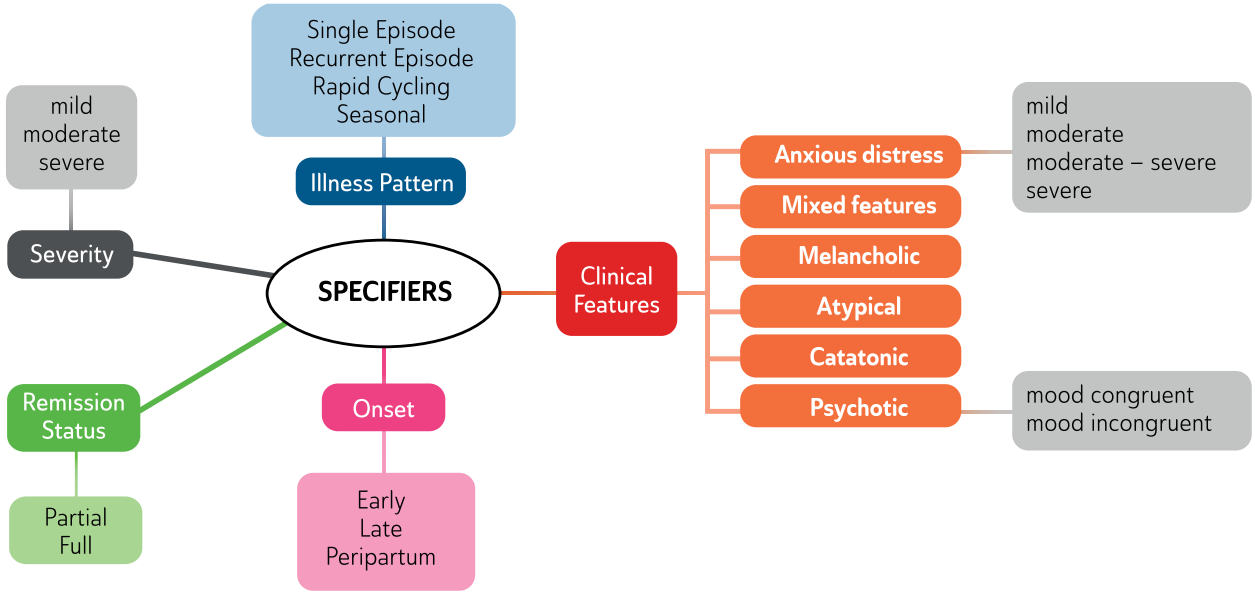
Notes: DSM-5 has introduced 'mixed features' as a specifier that can be applied to both BD and MDD. This is a key change in DSM-5. MDD with short duration hypomania is a tentative condition by DSM-5 so that it can be investigated further. If full criteria for a manic episode are met during a mixed episode then the diagnosis should be manic episode with mixed features.
*not covered in CPG.

Figure 1. Classification of mood disorders.



*Mood disorders can be divided in two ways: either as bipolar and depressive disorders, or as primary and secondary disorders. This creates four types of mood disorder diagnoses; some of which can be further divided into subtypes. For the purposes of classification these are regarded as discrete, non-overlapping entities, but in reality some diagnoses readily transmute into other forms of mood disorders. *Disruptive Mood Dysregulation Disorder is a new diagnosis, which in DSM-5 is grouped with depressive disorders but clinically overlaps considerably with bipolar disorders.*

Figure 2. Mood disorders specifiers.



Specifiers are neither mutually exclusive nor jointly exhaustive. Therefore more than one specifier can be applied. They are used to apply further definition and group individuals who share certain features. They should be used to convey information that is pertinent to management. As such a mood episode may be 'specified' as moderate, recurrent, of late onset, with mixed features and in partial remission.

assigned to children with persistent irritability and frequent outbursts of anger.[2] *Premenstrual dysphoric disorder* (PMDD) is now a formal diagnosis and describes clinically problematic low mood in women that commences following ovulation and lasts until the beginning of the next menstrual cycle. *Substance/medication-induced depressive disorder* and *Depressive disorder due to another medical condition* have been added to DSM-5 (APA, 2013).

This guideline focuses on MDD and PDD because these are the depressive disorders most commonly encountered in clinical practice (see: Table 4). Consequently they also have the greatest abundance of empirical research data to help guide optimal care.

Criteria for bipolar disorders. Presence or history of mania/hypomania is the defining element of bipolar disorders and distinguishes them from depressive disorders. An individual is diagnosed with BD I if he/she has experienced a full manic episode. One manic episode is sufficient to qualify for the diagnosis, but most individuals will also have experienced one or more major depressive episodes, which often precede the onset of mania. BD II is diagnosed if an individual has experienced both an episode of major depression and hypomania in their lifetime, but has never had a manic episode. The phases and stages of bipolar disorder are associated with varying degrees of functional impairment (see: Table 8).

Table 3. Summary of DSM-5 criteria for depressive disorders.

	MDD	PDD (Dysthymia)	DMDD	PMDD
Symptoms				
Mood (Note: can be depressed, irritable or angry and can fluctuate)	Depressed mood	Depressed mood	Severe recurrent temper outbursts Irritable mood	Mood swings Depressed mood Irritable or angry mood
Anhedonia	+	–	–	+
Psychomotor symptoms	Agitation or retardation	–	–	–
Anxiety/tension	–	–	–	+
Suicidal ideation	Recurrent thoughts of death or suicidal ideation, or attempt, or plan	–	–	–
Appetite changes	Significant increase or decrease in weight or appetite	Poor appetite, or overeating	–	Marked change in appetite, over-eating or specific cravings
Insomnia/ hypersomnia	+	+	–	+
Low energy/ fatigue	+	+	–	+
Poor Concentration	+	+	–	+
Low Self-esteem	–	+	–	–
Negative Cognitions	Worthlessness or excessive guilt	Hopelessness	–	Overwhelmed or out of control
Frequency of Symptoms	Nearly every day	Most of the day - for the majority of days (more days than not)	Outburst of anger >3 times per week	Present one week prior to menses and improve within days of onset
Duration of Symptoms	>2 weeks	>2 years >1 year for children and adolescents	>12 months	At least 2 menstrual cycles

Note: Adjustment disorders are now coded under 'trauma and stressor related disorders'. They are characterised by the occurrence of identifiable stressors that trigger mood symptoms.

+ **Symptom** is present and characteristic of an illness as per DSM-5.
– Symptom is not present and not characteristic of an illness as per DSM-5.

Table 4. Depressive disorders (MDD and PDD) facts and figures.

Epidemiological Statistics	1 in 10 patients in primary care present with depressive symptoms.[a] Lifetime risk of depression is 15% and 12 month prevalence is 4.1%. Depression is twice as common in females than males.[b]
Illness Characteristics	Mean age of diagnosis onset is 27 years, but 40% have first episode by the age of 20 years.[c] At least 80% of those affected by depression will experience at least two episodes of illness (recurrence) in their lifetime.
Treatment Responsiveness*	54% of individuals recover within 6 months, 70% within one year. 12–15% fail to recover and develop an unremitting chronic illness.[d]

***These** figures relate primarily to community samples.

References: [a]Backenstrass et al. (2006), [b]Alonso et al. (2004), Australian Bureau of Statistics (2008), Jenkins et al. (1997), Ustün (1999), [c]Eaton et al. (2008), [d]Judd (1997).

Table 5. Bipolar I disorder facts and figures.

Epidemiological Statistics	Lifetime prevalence is 0.6%.[a] Affects both genders equally.[b]
Illness Characteristics	Mean age of diagnosis is late 20s[c]. Mean age of onset is late teens[c]. The ratio of manic episodes to depressive episodes is 1:3[d]. Nearly half of BD I patients experience a recurrence within 2 years.[e] Confers a significant risk of suicide (up to 30–60 times more than in general population)[f] especially during depression or with mixed features and a rapid cycling pattern[g].
Treatment Responsiveness	Age of onset and depressive burden appears to be predictive of future prognosis.[h] Classic BD I patients are likely to respond better to lithium than to other medications.[i] Lithium also protects against suicide.

References: [a]Merikangas et al. (2011), [b]Leibenluft (1996), Goodwin and Jamison (2007), [c]Ghaemi et al. (1999), [d]Judd and Akiskal (2003), [e]Perlis et al. (2006), [f]Gonda et al. (2012), [g]Schaffer et al. (2014, 2015), [h]Etain et al. (2012), [i]Gershon et al. (2009).

Table 6. Bipolar II disorder facts and figures.

Epidemiological Statistics	Lifetime prevalence is 0.4% (Lower than BD I).[a] More common in females than males.[b]
Illness Characteristics	Median age of onset is 29 years (later than BD I).[c] Risk of suicide is as high as BD I with approximately 30% reporting a history of suicide attempts.[d]

References: [a]Merikangas et al. (2011), [b]Goodwin and Jamison (2007), Leibenluft (1996), [c]Beesdo et al. (2009), Tondo et al. (2010a), Vaingankar et al. (2013), [d]Novick et al. (2010), Ruggero et al. (2007).

In DSM-5 the core features in the diagnosis of mania have been extended to include coterminous changes in activity or energy alongside elevated, expansive or irritable mood to facilitate earlier and more accurate diagnosis in clinical settings (APA, 2013).

In individuals with bipolar disorder, the initial presentation is usually that of depression and therefore the correct diagnosis cannot be made until an episode of hypomania/mania occurs. This inevitable delay that can sometimes last up to a decade results in a period of inadvertent suboptimal management. Diagnosis is also hindered by the fact that bipolar disorder has very high rates of comorbidity with anxiety, substance misuse and personality disorders (particularly borderline personality disorder) (Malhi et al., 2012a). Once established bipolar disorder is a recurrent mood disorder that runs a lifelong course and, between episodes of illness, patients often continue to experience subthreshold symptoms, which significantly compromise their quality of life (Judd et al., 2002). Consequently, patients with bipolar disorder have high rates of self-harm and suicide (Leverich et al., 2003; Schaffer et al., 2015). The core 'facts and figures' of bipolar disorders are summarised in Tables 5 and 6.

Table 7. Features that may distinguish bipolar and unipolar depression.

Features	Bipolar	Unipolar^
Family History	Bipolar disorder (more likely) Alcohol and/or substance use (more likely)	Bipolar disorder (less likely) Alcohol and/or substance use (less likely)
Illness onset	Early onset (approx. 20-25 years)	Later onset (approx. 25-30 years)
Onset/Offset	More often abrupt	More often gradual
Comorbidity	ADHD more often	ADHD less often
Duration of episodes	$<$6 months	$>$6 months
Number of Prior Episodes	Multiple prior depressive episodes	Fewer prior episodes
Mood symptoms	Lability of mood/manic symptoms	Depressed mood and low energy
Psychomotor symptoms	Psychomotor retardation	Psychomotor retardation less likely
Sleep disturbances	Hypersomnia and/or increased day time napping	Initial insomnia/reduced sleep
Appetite Changes	Hyperphagia and/or increased weight	Appetite and/or weight loss
Other symptoms	Other 'atypical' depressive symptoms such as hypersomnia, hyperphagia, 'leaden paralysis' Psychotic features and/or pathological guilt	Somatic complaints

Notes: Depressive symptoms common in bipolar disorder are akin to atypical features. A history of hypomania may be easily missed and collateral information from family, health professionals and others is invaluable. If a person presents with this group of depressive features, clinicians should carefully assess for past (hypo)mania. Closely monitor for emergence of such should antidepressant monotherapy be utilised.

^Unipolar depression refers to non-bipolar depression. References: (Angst et al., 2005; Moreno et al., 2012; Perroud et al., 2014).

Distinguishing major depression and bipolar disorder. It is important to note that current classification systems have assigned greater importance to polarity (unipolar/bipolar) than recurrence and that *recurrent mood disorders* feature strongly in both unipolar and bipolar mood disorders. Although not recognised in current classifications, many authorities argue that highly recurrent unipolar depression and bipolar disorder may be related conditions and that the traditional term manic-depressive illness which subsumes both is more apt.

Individuals who only ever experience depression are described as having major depressive disorder (a unipolar illness), whereas those who in addition experience (hypo)mania are diagnosed with bipolar disorder (Malhi et al., 2010). Therefore, in the absence of (hypo) mania, it is difficult to distinguish bipolar and unipolar depression. Clinically this is a common problem because of the natural history of bipolar disorder, which usually begins with depression. Indeed in the majority of cases, individuals with bipolar disorder experience several episodes of depression prior to developing (hypo)mania and for most people with bipolar disorder the predominance of depressive episodes continues throughout the course of the illness. Furthermore, even between episodes of illness, individuals with mood disorders often continue to suffer subthreshold depressive symptoms, which can compromise their quality of life, limit functioning and increase the risk of relapse (Grunze et al., 2009).

There are no definitive clinical criteria that distinguish bipolar and unipolar depression. Some depressive features and symptoms may be more likely in one presentation compared to the other, and together these may provide an 'index of suspicion', particularly when used in conjunction with other risk factors, such as family history (Moreno et al., 2012). It is of note that these are not diagnostic. Actuarial information should also be considered when drawing inferences about a bipolar or unipolar diagnosis from a depressive presentation (Youngstrom et al., 2005) because lifetime prevalence of unipolar depression is 10–15 times higher than bipolar disorder. If bipolar disorder is suspected on the basis of clinical features (see: Table 7) a thorough clinical assessment for (hypo)manic symptoms is essential.

Cognitive impairment in mood disorders. The issue of cognitive impairment in mood disorders has been recognised for many years, particularly in the elderly in whom the phenomenon has been described as pseudodementia. However, while it has been clear for some time now that episodes of mood disturbance are associated with significant cognitive impairment, two issues are becoming increasingly clear.

Firstly, it is clear that in recurrent mood disorders some degree of cognitive impairment remains between episodes. This is the case in both unipolar depression (Bora et al., 2013) and bipolar disorder (Baune and Malhi, 2015; Bourne et al., 2013).

Secondly, this impairment is clinically significant in terms of overall functioning, once again in both unipolar and bipolar disorders (Malhi et al., 2007; Porter et al., 2015; Withall et al., 2009).

Therefore, this is an issue which is receiving increasing attention with research into both pharmacological (Carvalho et al., 2014b) and psychological strategies (Porter et al., 2014) to improve cognition. However, currently there is no clear evidence regarding the effectiveness of specific treatments in remediating cognitive dysfunction in mood disorders but it is an important issue for clinicians to assess.

Table 8. Summary of DSM-5 criteria for bipolar disorders.

	BD I	BD II	Cyclothymia
Main Symptom Criteria (Mania)			
Elevated or irritable mood	+	Often irritable	+
Increased activity or energy	Goal-directed	+	+
Increased self-esteem	+	+	+
Decreased need for sleep	+	+	+
Pressured speech	+	+	+
Distractibility	+	+	+
Increased risk taking behaviour (especially for those with comorbid BPD)	+	+	
Main Symptom Criteria for Depressive episodes (Same as MDD)		+	
Severity and duration of episodes			
(Hypo)Mania	Mania	Hypomania**	Sub-threshold Mania
Number of Symptoms	3–4 symptoms	3–4 symptoms	⩽ 3 symptoms
Duration of Episode	> 7 days	4–7 days	< 4 days
Impact on functioning	Disrupts social and occupational functioning or results in hospitalisation	Not severe enough to disrupt functioning or result in hospitalisation	Symptoms of (hypo) mania/depression cause significant distress or impairment in functioning
Depression	Depression	Depression	Sub-threshold Depression
Number of Symptoms	> 5 symptoms	> 5 symptoms	⩽ 5 symptoms
Duration	2 weeks	2 weeks	< 2 weeks
Frequency of episodes	⩾1 manic episode*	>1 hypomanic + ⩾1 depressive episode	Fluctuating subthreshold hypomanic and depressive symptoms for >2 years (>1 year for children/adolescents)

Note: ** Hypomanic episodes are usually less severe and more likely to feature irritable mood than manic episodes. Presence of a manic episode alone is sufficient to meet criteria for BD I. Patients may also have experienced depressive or hypomanic episodes but this is not essential to qualify for a diagnosis of BD I.

Footnote: *The upper and lower cut-offs for BD II are arbitrary. These durations of illness and number of symptoms used to differentiate BD II and cyclothymia lie on a continuum and therefore mood disorders are also conceptualised as a spectrum within which symptoms are dimensional. Malhi and Berk (2014); Malhi and Porter (2014); Ghaemi et al. (2015).*

Differential diagnoses of mood disorders. Mood disorders can co-occur with all psychiatric disorders. Consequently, there are many possible differential diagnoses and so only those that are common, or particularly important because of impact on treatment pathways, have been considered.

The principal and most probable differential diagnoses for mood disorders are other depressive and bipolar disorders (see: Table 2). Delineating bipolar and unipolar mood disorders has very important implications for optimal management, prognosis, and avoiding iatrogenic worsening of affective instability. As bipolar disorders can appear to be 'unipolar' early in their course it is important to bear in mind a differential diagnosis of bipolar disorders in first episode major depression (see: Table 3). Therefore, as part of a diagnostic assessment of depression, the clinician should actively probe for a history of elated, excited, or irritable mood of any duration along with increased levels of energy, and ask about a family history of mania. Adjustment disorder with depressed mood should also be carefully considered as a differential diagnosis, particularly when the onset of the depressive symptoms is closely related to a major life stressor.[3] Note however, sometimes life stressors can trigger or exacerbate a major depressive episode. Similarly, it is important to consider the overlays of grief with depressive disorders noting that in some instances grief reactions may trigger adjustment disorder reactions and depressive disorders, or exacerbate or perpetuate a depressive episode. Therefore when making a diagnosis of depression the intensity, duration, functional impact, sociocultural and personality congruency of a grief reaction are important considerations.

Anxiety disorders commonly occur contemporaneously with mood disorders and often precede their onset (Malhi et al., 2002). Indeed, marked overlap between these 'distress disorders' is a primary driver of emerging dimensional approaches to nosology (Insel, 2014) and trans-diagnostic approaches to treatment (Buckholtz and Meyer-Lindenberg, 2012). Substance misuse, personality dysfunction and general medical disorders may coexist alongside mood disorders, and appear at any point along the course of illness (McIntyre et al., 2012; Malhi et al., 2012a). Mood disorders may also merge into psychosis, normally at the extremes of severity for both poles.

Several medical illnesses can result in specific mood disorder symptoms or indeed lead to the development of mood disorders, and these need to be borne in mind. Sleep apnoea and hypothyroidism should be considered as differential diagnoses, particularly if other features on history or mental state examination are suggestive of mood disorders. For some patients, an interplay between general medical conditions and mood disorders hampers treatment and worsens prognosis of both conditions. Among older patients presenting with first episode mood disorders, it is necessary to carefully consider organic differential diagnoses, given that major neurocognitive disorders, such as frontotemporal dementia, often present initially with affective symptoms.

Another important differential diagnosis that warrants consideration is that of personality disorders. For further details of comorbid personality disorders and other common comorbidities and how they influence management, please refer to *Management of mood disorders in the context of comorbidities.*

Models and formulation for assessment of mood disorders

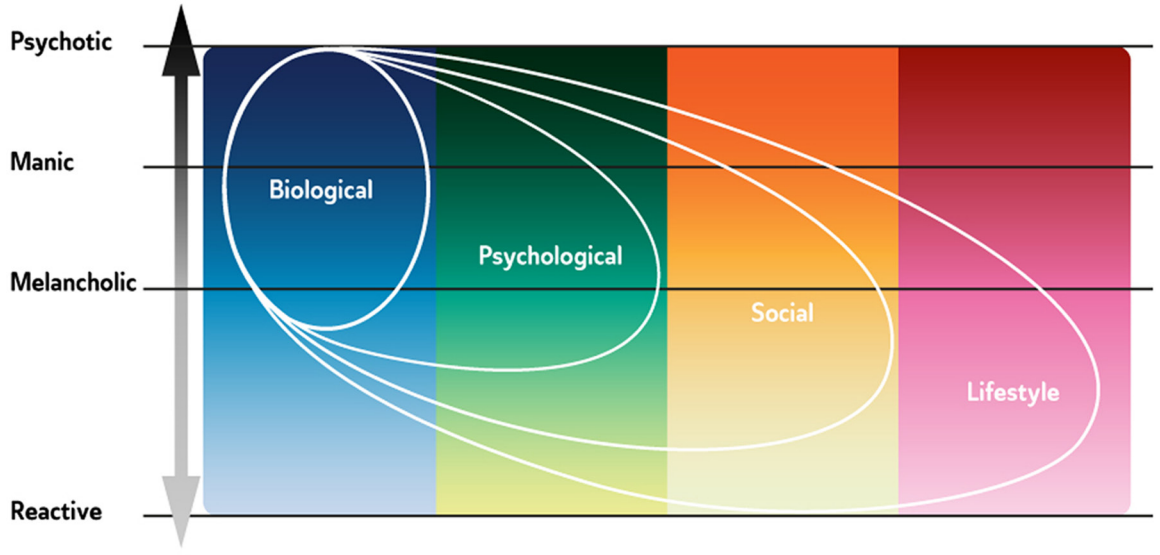
Clinical assessment and diagnosis: setting the stage for management. Prior to formulation, it is useful to construct a template that captures the patients' problems using the biopsychosocial and lifestyle model (BPSL Model) and considers predisposing, precipitating and perpetuating factors. Clinically, it is judicious to initially make a working diagnosis rather than prematurely foreclose on a definite diagnosis. This approach enables the commencement of initial management but at the same time limits the likelihood of assigning an incorrect diagnosis. Making a diagnosis is a sophisticated process. It involves detailed information gathering, a comprehensive clinical assessment, including a detailed mental state examination and the careful piecing together of corroborative information. Even with all of these components at hand, it is sometimes difficult to make a definitive diagnosis of a mood disorder.

As noted above, mood disorder diagnoses are critical clinical tools because of their communication value, and because much of what we know about the treatment for mood disorders is based on trials in patient samples derived using these diagnoses. However, the clinician needs to recognise their limitations and note that diagnoses form one part of an individualised, contextualised characterisation for each patient. The appraisal of context is pivotal because this provides the understanding as to *why* a person has a mood disorder at this particular point in their life, and is best constructed via thorough clinical assessment. To make sense of this information, and to translate it into an effective treatment pathway, it is necessary to have a meaningful framework. This process is called *case formulation* and there is strong consensus that this is the best strategy.

The biopsychosocial and lifestyle model (BPSL). This model (see Figure 3) is useful for understanding potential causes of depression and bipolar disorder and for planning management. Empirically it is useful because the factors that precipitate or maintain depression and lead to its expression usually fall into one of these domains. Hence it has been widely employed in psychiatry, and recently it has been expanded to include lifestyle factors such as substance misuse, diet and smoking; all of which, along with resilience factors, have been shown to impact the development of depression and bipolar disorder.

The components of the model represent seemingly distinct domains, however recent research has shown that there are important iterative links between various components and these cumulatively contribute to the onset and maintenance of mood disorders. For example, genes are typically considered to be biological factors, whereas most stressors are regarded as environmental; but recently it has been discovered that genes impact the environment and that reciprocally the environment can modify genes via epigenetic mechanisms (Niculescu, 2013). Thus, interactions between the two impact aetiology and outcome. Hence, depressive subtypes can be broadly mapped onto the BPSL model and treatments can be categorised according to its components: refer to *Individualised management of mood disorders: case formulation.*

Figure 3. Biopsychosocial & Lifestyle Model (BPSL).

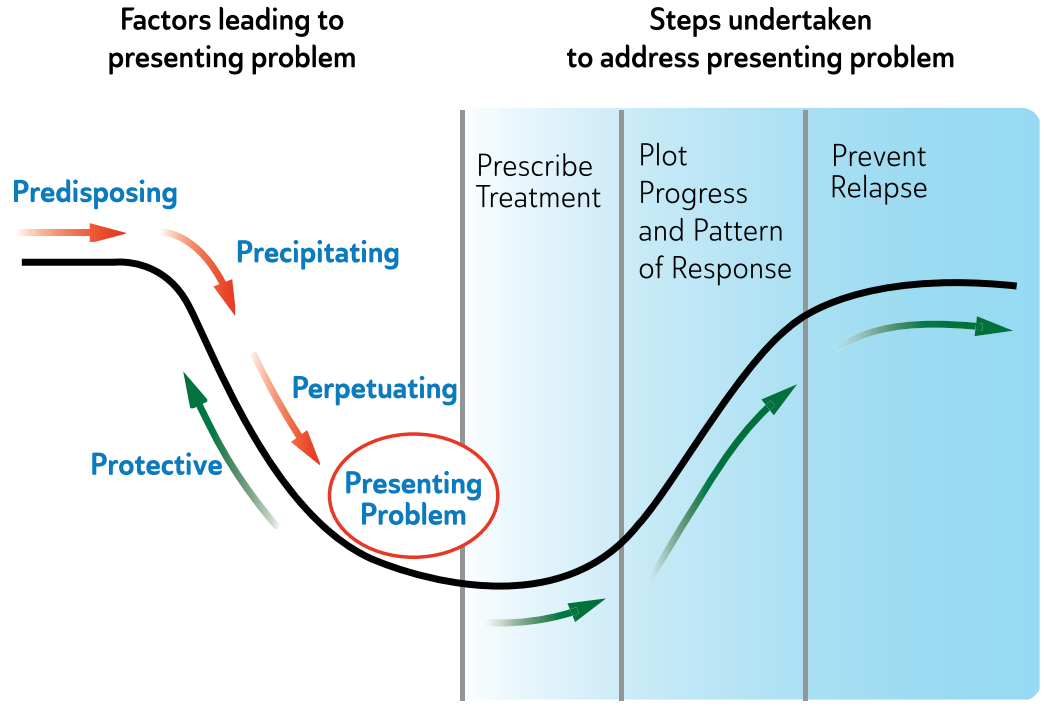


Biological Treatments	Psychological Treatments	Social Treatments	Lifestyle Treatments
· Antidepressants · Antipsychotics · Mood stabilisers · Electroconvulsive therapy · Transcranial magnetic stimulation	· Brief cognitive behavioural therapy · Formal cognitive behavioural therapy · Interpersonal therapy · Mindfulness · Acceptance and commitment therapy · Schema therapy	· Family psychoeducation · Family / friends · Formal support groups · Community groups · Caregivers · Employment · Housing	· Exercise · Diet · Smoking cessation · Alcohol cessation · Ceasing drugs · Managing substance misuse · Sleep

The BPSL Model provides a useful framework for understanding the factors that contribute to the development of mood disorders and for planning clinical management. It encompasses biological, psychological and social perspectives alongside lifestyle factors and is therefore referred to as the BPSL Model. Typically mood disorders arise from factors from more than one domain. Consequently a broad range of treatments are usually needed to satisfactorily treat mood disorders.

Individualised management of mood disorders. The BPSL model provides the necessary framework for the development of a mood disorder formulation in an individual. Formulation builds on diagnosis, which has reliability but lacks the validity of formulation because the latter contextualises the problems of the individual and provides a richer understanding as to why he or she is unwell *now*. Formulation is also necessary because both treatments and diagnoses have been derived from studies of groups whereas management of mood disorders is an individual (personalised) endeavour; therefore it is important to understand the person in the context of their unique circumstances. This is the cornerstone of a successful therapeutic relationship.

Figure 4. 5P+ Model.



The conventional 5P Model approach to formulation has been expanded by adding three phases of management. This extended model (5P plus; 5P+) adds a longitudinal perspective that builds on the initial formulation and informs management.

Case formulation: incorporates an understanding of vulnerabilities and familial predisposition to mood disorders. It draws connections between past experiences and how these relate to the clinical presentation now. It allows mutual enrichment of the context and diagnostic framework. Traditionally the steps involved in formulation involve examining the presenting *problem and predisposing, precipitating and perpetuating* factors alongside *protective* factors. This has been termed the 5P model (see: Figure 4), but these are only a guide and may not be relevant to every person. In most instances there are one or two contributing factors from each component (Rainforth and Laurenson, 2014).

Understanding and piecing together the various factors provides a more comprehensive picture of why the individual has developed the mood disorder in the first place, and what has led to their presentation. It also acts as a forerunner to considering which interventions are most likely to be of benefit. In addition to understanding the individual, their strengths, vulnerabilities and their predicament, it is important to bear in mind that there may be alternative explanations and that different psychiatric diagnoses and general medical causes may ultimately be responsible. In this regard it is important for example in women to enquire about mood change in relation to their menstrual cycle, use of oral contraception and hormone replacement therapy (Craig, 2013; Rasgon et al., 2005; Steiner et al., 2003). Psychiatric assessment should involve a medical examination and investigations as indicated (see: Table 9). These tests need to be conducted on a case-by-case basis and tailored to

individual needs. In most instances the general practitioner may be able to perform these investigations.

Resilience. An important difference between diagnostic and case formulation descriptions is that the latter recognises the resilience and strengths of a patient (Macneil et al., 2012). Resilience refers to the ability to adapt to and recover from stress (Southwick and Charney, 2012) and is not simply the absence of vulnerability: There is evidence that resilience plays an independent (mitigating) role across the three stages of mood disorder (Davydov et al., 2010; Friedman et al., 2014; Oldehinkel et al., 2014; Rutten et al., 2013).

Resilience mechanisms can also be the target of clinical work, particularly in the maintenance phase of mood disorder treatment (Malhi et al., 2013b) (see green Protective arrows in Figure 4). For instance, resilience to mood disorders can be strengthened biologically e.g., using lithium as a neuroprotective agent (Soeiro-de-Souza et al., 2012), psychologically e.g., teaching cognitive reappraisal skills (Troy et al., 2010), socially e.g., improving social support (Pietrzak et al., 2009), and through lifestyle change e.g., building exercise habits (Hare et al., 2014).

Improved resilience is a transdiagnostic treatment goal in recovery-oriented mental health services (AHMAC, Commonwealth of Australia, 2013; Australian Government, 2009; Government, 2011; Services UDoHaH, 2003; World Health Organization VHPF, University of Melbourne, 2004). Driven largely by consumers, the recovery movement highlights the importance of 'hope' and 'empowerment' in mental health service delivery, and a clinical focus on resilience supports these subjective outcomes.

General principles for managing mood disorders

Aims of treatment. The general aims of treatment of any mood disorder are to relieve symptoms, reduce the morbidity associated with the mood disorder and limit the disability and self-harm risk or potential risk of fatality. The end goal is achieving recovery to premorbid level of functioning with improved health awareness and quality of life.[4] It is important to remember the management of mood disorders is mediated entirely through the person experiencing the symptoms and as such improved subjective quality of life, personal recovery, empowerment, good therapeutic relationship – based on respect, support, warmth and empathy – are all critical to optimal outcomes.

There are broadly three ***stages*** of illness that coincide with three ***phases*** of treatment (see: Figure 5).

- Response to treatment is the initial aim and this usually occurs within the *acute phase* of treatment. A clinical *response* is defined as a significant reduction in signs/symptoms and is normally quantified as a 50% reduction in the total score on a standardised rating scale, such as the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960).

Table 9. Physical examination and investigation of patients presenting with mood disorders.

EXAMINATION*	
	Rationale
	Bradycardia may occur in hypothyroid states Sinus tachycardia may reflect anxiety.
Body mass index and waist circumference	To assess current general health status and gauge subsequent psychotropic associated weight gain.
Signs of possible self-harm	Old scars (including tracheostomy scars)
Endocrine disorders	Goiter, hyper/hypo-thyroid features, Cushingoid features
Respiratory disorders	Observed sleep apnoea/snoring, restless leg syndrome, COPD features, wheeze/asthma, lung malignancy.
Neurological disorders	Parkinsonism, motor/sensory deficits, cerebrovascular disease features, motor tics.
Organ insufficiency	Jaundice, AV fistula for dialysis, dyspnoea, peripheral oedema
INVESTIGATION*	
	Rationale
Full Blood Examination (FBE)	Some psychotropics are associated with neutropenia and agranulocytosis.[a] Neutropenia has been particularly associated with clozapine and carbamazepine, and reported with olanzapine.[b] Macrocytosis is seen in heavy drinkers. (20–30% in the community and in 50–70% hospital patients.)
Urea and Electrolytes (U&Es) and Liver function tests (LFTs)	Psychotropics may alter LFTs and U&Es Psychotropic pharmacokinetics may be influenced by otherwise clinically silent renal or hepatic impairments. Possibility of hyponatremia especially in elderly patients on multiple medications. Isolated escalation of gamma-glutamyltransferase (GGT) suggests alcohol misuse.[c] GGT is elevated in 30–50% heavy drinkers in the community and in 50–80% hospital patients.
Electrocardiogram (ECG)	Some psychotropics are associated with a prolonged QTc interval.[d] QTc prolongation has been particularly associated with TCAs, citalopram at high doses, ziprasidone, paliperidone, and lurasidone.[e,f,g,h]
Thyroid function tests (TFTs) and thyroid auto-antibodies	Thyroid dysfunction can cause changes in mood. Thyroid dysfunction can be induced by treatments such as lithium.[i]
Inflammatory markers and microbial serology	Needs assessment on a case by case basis
Vitamin levels	There is an association between vitamin deficiencies and mood disorders. Vitamin B12, folate and Vitamin D, studies are relevant in some cases.[j,k]
Sexually Transmitted Disease (STD) testing	If history suggests impulsive unprotected behaviour with sexual activity
Pregnancy testing (beta HCG)	If history suggests impulsive unprotected sexual activity. Necessary prior to starting psychotropics in any woman that is potentially pregnant.
Urine and Blood Drug Screening	Screen for benzodiazepines, opioids, psychostimulants, cannabis, hallucinogens.

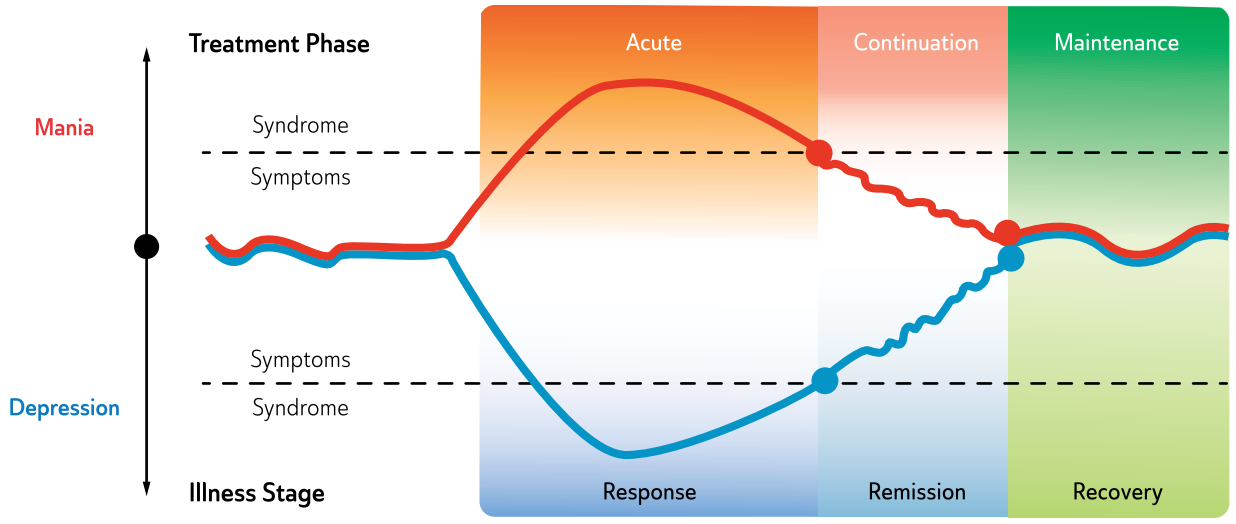
***Dodd** et al. (2011).

Notes: Clinically appropriate examination and investigation needs to be conducted on an individual basis and ideally baseline investigations should be performed prior to commencing psychotropic agents. Often the person's general practitioner will be best placed to conduct an examination and consider investigations at the point of referral for specialist care. In unusual or particularly refractory

mood disorders, more detailed investigation, including brain imaging, may be appropriate. Features on history should guide optimal investigation – for example history of severe insomnia and snoring may require specialist referral and sleep studies and neurological signs and symptoms may require a neurology opinion and specialized investigations such as an EEG and lumbar puncture. On occasion more extensive investigation may be required such as MRI scans of the brain. An emerging area is that of genotyping: It has been suggested that HLA-B*1502 testing should be considered in Asian patients prior to commencing carbamazepine treatment because of a potential risk of Stevens Johnson Syndrome[l], and pharmacogenetic testing may prove useful in the future in patients with a history of medication intolerance or resistance.[m]

References: [a]Nazer et al. (2012), [b]Flanagan and Dunk (2008), [c]Franzini et al. (2013), [d]Beach et al. (2013), [e]Ellingrod (2012), [f]Citrome (2011), [g]Camm et al. (2012), [h]Suzuki et al. (2012), [i]Hage and Azar (2011), [j]Anglin et al. (2013), [k]Matharoo et al. (2000), [l]Barbarino et al. (2015), US Food and Drug Administration (2012), [m]Hicks et al. (2013, 2015), Singh (2015).

Figure 5. Mood disorders stages of illness and phases of treatment.



Derived originally from Kupfer (1991) and adapted from Malhi et al. (2009b). The red line represents a tendency towards mania and the blue line represents a tendency towards depression. In the management of both mania and depression, the three **stages of illness** *each correspond with one of the* **three phases of treatment**. *Obtaining a* **response** *is the initial objective, which occurs within the acute phase of treatment. With continuing improvement (continuation phase of treatment), the person reaches* **remission**, *a state in which there are minimal or no signs/symptoms. Those who respond but do not remit to treatment are very likely to relapse. Once the individual is fully functional and has returned to premorbid functioning* **(recovery)**, *ongoing treatment is often necessary (maintenance phase of treatment) to maintain recovery. It is on this basis that continuation treatment prevents* **relapse** *and maintenance treatment prevents* **recurrence**. *Note, in practice, depression and mania often do not manifest as discrete episodes and the stages of illness within an episode can be difficult to define. Therefore, clinically, relapse and recurrence are often used interchangeably.*

- In the *continuation phase* of treatment, amelioration of symptoms continues, and the goal of treatment shifts to *remission* – formally defined by a cut-off score of less than 5 on the HAM-D (Hamilton, 1960), or equivalent on the Montgomery-Asberg Depression Rating Scale (MADRS) (Berk et al., 2008b; Montgomery and Asberg, 1979). In *remission* there are only minimal residual signs/symptoms but the individual is not yet fully functional, and without ongoing treatment remains vulnerable to *relapse* (Nierenberg and Wright, 1998).

- Following remission, treatment continues (continuation phase) until the patient regains complete functioning and returns to their premorbid state (*recovery*). At this stage, ongoing treatment may still be necessary (*maintenance phase*) to prevent *recurrence* and enhance resilience but the current episode has been treated.

Context of treatment

The person with the disorder. There is growing recognition that mood disorders are in many cases chronic illnesses with a waxing and waning course. They are therefore best managed using a chronic illness model, which elevates the person's active engagement in the management of their condition. Unlike acute illnesses, where the clinician's expert tools are the primary lever for change, chronic illness management centres on the person with the disorder. Consequently, while current classification systems and the treatment science that depends on them emphasise objective features of the case, clinicians must be equally attentive to the patient's subjective experience of the disorder and the management they are receiving (Berk et al., 2004). The patient's perception of the quality of the therapeutic alliance is a strong predictor of adherence, leading some authorities to argue for collaborative treatment plans involving shared decision making (Berk et al., 2010).

Indeed, some guidelines argue that evidence-based practice in mood disorders should integrate patient preferences with clinical expertise and empirical information (APA, 2005). This patient-centric perspective is at the core of the recovery paradigm which dominates mental health service delivery in the Anglosphere. It also underpins efforts to provide patients with thorough psychoeducation, and aligns with calls to elevate subjective quality of life as a clinical outcome.

From multiple perspectives, therefore, a critical treatment context in the treatment of mood disorders is the person with the disorder. A key clinical challenge is to optimally integrate the clinician's 'technical' expertise with the patient's 'lived experience' expertise of the disorder.

Integrated care team. The optimal management of people with moderate to severe mood disorders requires not only the involvement of several health care professionals including a general practitioner (GP), mental health nurse, psychiatrist and psychological counsellors but the active partnership of family, carers and support groups as part of an integrated care team. The severity, diagnostic complexity, and treatment resistance of the presentation will influence which practitioners and how many will need to be involved for optimal care. Usually the point of entry for care is a GP or psychologist. Often patients will have an existing GP and may be more comfortable raising emotional issues with them when faced with a problem and not being able to cope. One of the key roles of the GP is to determine the severity and complexity of emotional symptoms and to make an accurate diagnosis and decide if referral to a psychiatrist or psychologist is required. For mild depressive symptoms and in the absence of suicidality or diagnostic uncertainty, management by the GP is usually sufficient with or without added psychiatric input. However, where there is diagnostic complexity, a high risk of self-harm, non-response or severe debility, referral for psychiatric assessment is indicated. For chronic severe mood disorders, a mental health case manager (usually a nurse experienced in providing mental health care) may be necessary and can be assigned by a local community mental health team or mental health team in the private sector. Health care professionals span both inpatient and outpatient services and, in conjunction with family and friends, provide crucial support throughout the course of the illness. Specialised care is of greater benefit (Kessing et al., 2013) than standard community

care and assessment in specialised units is useful when managing complex and severe mood disorders (Vieta, 2013).

All providers involved in the clinical care of an individual need to be informed of the diagnosis and on-going plan for management. Therefore relevant clinical information (such as changes to treatment and hospital admission) needs to be shared regularly. Where there is lack of consensus on management, input from a psychiatrist is needed, and a second psychiatric opinion may on occasion be necessary. Clinical responsibility ultimately lies with the psychiatrist, but clinical outcomes are optimal when the various professionals involved work as a collaborative team. A successful outcome requires regular communication concerning diagnosis, formulation, treatment planning and details of current treatment, including both psychological therapy and pharmacotherapy.

Therefore, it is advisable that one of the health providers (usually the GP) acts as the *primary clinical coordinator* who then maintains open and regular communication between all parties to ensure that everyone is able to work together as a cohesive team. This will prevent the miscommunication of advice and provide a consistent message regarding important aspects of management such as treatment adherence. Indeed, patients often report that those involved in their care sometimes express differing views and opinions with respect to diagnosis and management. In the minds of patients and their families this can create an impression that the health care professionals are uncertain about the best course of action and this may add to their ongoing stress.

Particularly important is the relationship between providers of medication and psychological management. Patients rarely have a model of their condition that comfortably reconciles psychological and biological paradigms, and it is critical that the preferred biopsychosocial formulation is reinforced by all professionals.

Integrating online resources. There is great interest in the use of the internet as a tool to aid delivery of psychological interventions, especially CBT. Internet-based interventions have the potential to overcome many barriers to accessing evidence-based psychological interventions for mood disorders, including cost, time, and trust in professionals (Leitan et al., 2015). Internet-based interventions for depressive symptoms have demonstrated efficacy, and could be considered as an initial intervention for mild depression in the stepped management of mood disorders in primary care (RACGP, 2015). Many models of online delivery have been explored (Batterham et al., 2015), ranging from simple information, through self-help strategies, to supported time-limited structured therapies. Research is ongoing into online modalities as part of stepped care, and in hybrid formats (with psychoeducation content covered online, and more individualised therapy conducted face-to-face). Most research to date has excluded complex and/or severe presentations, and those at elevated risk of suicide or self-harm. There is clinical consensus that, in such patients, risks currently outweigh benefits for stand-alone online interventions.

For mild/moderate unipolar depression, seven RCTs provide strong effectiveness evidence for MoodGYM (moodgym@anu.edu.au) as a CBT intervention to prevent and treat depression (and associated anxiety) in adolescents and adults. As with all self-guided interventions, attrition is an issue in MoodGYM: Clinicians should encourage engagement and not assume completion of the program. A number of online interventions for bipolar disorder are in development (Lauder et al., 2013; Murray et al., 2015), but not yet in routine clinical use.

Peer-reviewed information about the range of validated and emerging online interventions relevant to management of mood disorders can be found at https://beacon.anu.edu.au

Table 10. Recommended indications for psychiatric admission.

Category of Indication	Specific Indication
Clinical Presentation	Severe depression with significant disability 1a. Suicidal ideation with seemingly imminent risk 1b. Medical risk (i.e., inadequate fluid intake)^ Mania 2a. Likelihood of escalating manic symptoms/early warning signs of imminent manic episode 2b. Significant impulsivity or reckless disinhibition in context of mania Insight is severely limited to the extent that outpatient treatment is not possible Significant psychotic symptoms
Comorbidities	Medical illness that influences course and treatment of mood disorder Alcohol and other substance misuse (particularly psychostimulants, cannabis, hallucinogens, benzodiazepines)
Psychosocial Variables	Lack of significant social supports (especially recent loss of supports) Stressful home environment
Treatment Variables	Inability to engage in community based care Failure to respond to community based care Initiation of complex treatments (e.g. Electroconvulsive therapy [ECT])

^In such instances, admission to a medical setting may be more appropriate.

Note: Decisions about admission involve weighing a number of the above clinical and psychosocial factors, together with the perspectives of carers and others involved in the community treatment setting.

Hospitalisation and indications for treatment away from home. In most cases, mood disorders can be managed on an outpatient basis, but it is not uncommon for patients to require inpatient treatment under the care of a psychiatrist. Notably, approximately one-half of all psychiatric hospital admissions are due to a primary mood disorder (Banta et al., 2010; Brown, 2001; Hudson, 2004) and involve inpatient management in either the private or public sector.[5]

Hospitalisation, particularly when involuntary, is often stressful and sometimes traumatic. The benefits of constraint, intensive monitoring and opportunity to trial new treatment regimens in the inpatient setting are often unambiguous. Nonetheless, the personal meaning of hospitalisation should be carefully addressed by the treatment team prior to and subsequent to the event to ensure that patient autonomy is maximised. In many jurisdictions, advance care directives are an important tool in this context.

Whether a patient with a mood disorder is hospitalised or not is a matter of clinical judgment (see: Table 10), and is most often considered when patients have suicidal intent or develop mania. A structured risk assessment may be helpful in identifying suicide risks, such as suicidal ideation and plans (means and opportunity to enact suicide), past history of

self-harm, psychotic symptoms, impulsivity, irritability/agitation (Goossens et al., 2010; Perich et al., 2012), substance misuse and the extent of social supports.

Physical risk from malnourishment and dehydration, and comorbidities, such as severe medical ill health or substance misuse, may also warrant inpatient treatment. However, in cases of severe alcohol or other substance use disorders or dependence, a definitive psychiatric diagnosis should be withheld until symptoms of intoxication, detoxification, or of withdrawal, have completely abated.

Beyond risk containment, inpatient care allows detailed observation and assessment to clarify diagnosis or alter management. Hospitalisation for the treatment of acute mania is essential and particularly useful early in the episode to provide a low stimulus setting and limit risk-taking behaviours. In this context, early warning signs that indicate a manic episode is imminent can be used to facilitate an early admission to hospital so as to modify management and curtail the development of a full-blown manic episode (Perry et al., 1999), though this is not always effective (Lobban et al., 2010).

Inpatient treatment is also necessary in instances where it has not been possible to achieve effective engagement or adherence with therapy in outpatient settings, or treatments have simply failed and ongoing symptoms continue to confer significant disability. In general, hospitalisation should not be utilised when a less restrictive option is available, but for some treatments, such as ECT, hospitalisation is often necessary.

Clinical management of major depressive disorder

The successful treatment of mood disorders depends on valid diagnosis. It is important to be confident of both the mood disorder diagnosis and the stage of the illness (*see: Mood disorders diagnostic criteria; see also Models and formulation for assessment of mood disorders).* The evidence base for treating mood disorders is strongly tied to the currently accepted diagnoses, so identifying the diagnosis that best matches a client's presentation is a prerequisite for evidence-informed practice.

Treatment varies according to the type of mood disorder and the stage of the illness.There are broadly three *stages* of illness that coincide with three phases of treatment (see: Figure 5), *and three kinds of therapy* (psychological interventions, pharmacotherapy and physical treatments) that are effective in treating depression.

Treatment options for mild or moderate major depressive disorder

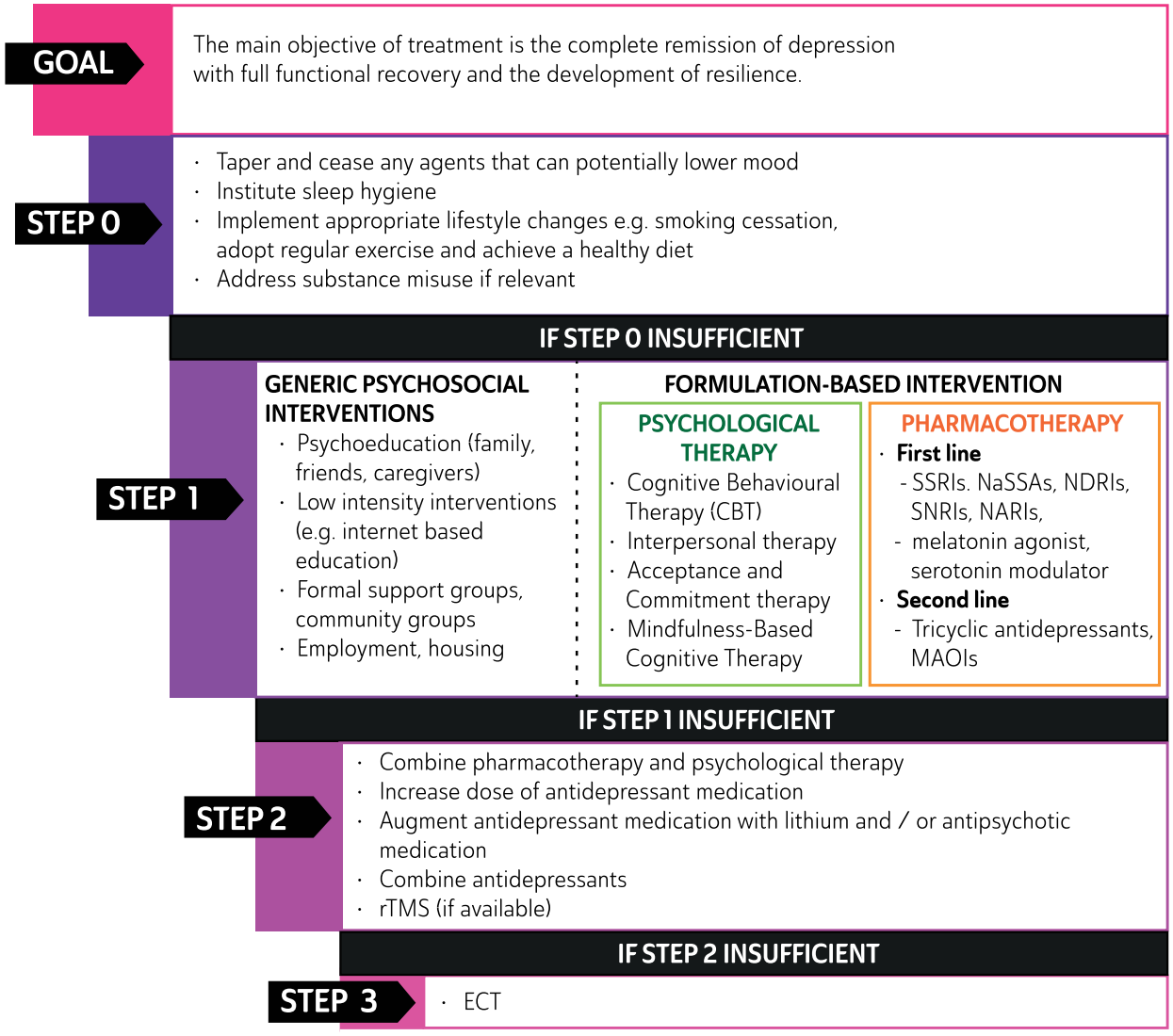
In mild to moderate episodes of MDD, psychological management alone may be adequate, especially early in the course of illness. However, episodes of greater severity, and those that run a chronic course, are likely to require the addition of antidepressant medication, or some other combination of psychological and pharmacological treatment. (*See*: Figure 6)

Treatment options for severe major depressive disorder

In severe episodes of MDD pharmacotherapy is typically needed and, where there is a high risk of suicide or when the patient's welfare is threatened by a lack of nutrition or fluid intake,

urgent intervention is sometimes necessary and may include electroconvulsive therapy (ECT). (*See*: Figure 6).

Figure 6. Management of major depressive disorder.



Schematic illustration of step-wise management of major depressive disorder: In Step 1 a whole host of interventions and therapies need to be considered and choice of treatment should be based on individual formulation. Note the various steps are not necessarily sequential and in some instances treatment may commence with options from Step 2 and Step 3.

Treatment options available

Psychological therapy for major depressive disorder. A number of psychotherapies have been demonstrated to be efficacious for the acute treatment of depression (see: Tables 11 and 12). Effects are similar across many acute sub-populations of depressed patients (older,

postpartum, inpatients, primary care, etc.), and treatment modalities (with some benefits for individual versus group delivery, and benefits for supported versus unsupported online treatments). Psychotherapies should only be delivered by competent practitioners with training in the specific approach, guided by an evidence-based treatment manual and attention to the therapeutic alliance (NICE, 2009).

Table 11. Psychotherapy for depression acute phase and maintenance/relapse.

Psychotherapy	Depression acute phase	Depression maintenance/relapse
Cognitive (behavioural) therapy (CBT)	+	+
Interpersonal psychotherapy (IPT)	+	+
Non-directive supportive therapy	+	O
Problem-solving therapy	+	O
Behavioural activation therapy	+	O
Self-control therapy	+	O
Short-term psychodynamic therapy	+	O
Mindfulness-based cognitive therapy (MBCT)	O	+

Note: See Appendix 2 for meta-analytic data on comparative efficacy. 'O' indicates no information available.

Effect sizes identified in the original meta-analyses are of moderate magnitude (Cuijpers et al., 2011a), but effect sizes have also been shown to be elevated in studies judged to be methodologically weaker (number needed to treat [NNT] = 2) versus stronger (NNT = 8) (Cuijpers et al., 2010a). The real effect of psychotherapies for depression is therefore likely to be modest, but not without value: Eleven high quality studies reviewed by Cuijpers et al. used active control conditions, so significant findings can be understood as specific treatment effects relative to the substantial non-specific treatment effects of control conditions (Cuijpers et al., 2014a).

Recently, two Cochrane reviews investigated the effectiveness of 'third wave' psychotherapies (Acceptance and Commitment Therapy (ACT), compassionate mind training, functional analytic psychotherapy, extended behavioural activation and metacognitive therapy) in the treatment of acute depression. The conclusions of both reviews were restricted by the very limited evidence base. The first found third wave psychotherapies superior to treatment as usual (risk ratio = 0.51 (Churchill et al., 2013)) and the second found no differences between third wave psychotherapies and 'traditional' cognitive behavioural therapy (CBT) (Hunot et al., 2013).

Relative effectiveness of psychological therapies. A series of meta-analyses and a network meta-analysis suggest that psychological treatments are equally efficacious in the acute treatment of depression (Barth et al., 2013; Cuijpers et al., 2011a). Although some other analyses have shown superiority for CBT (Tolin, 2010). There is some evidence that

therapies differ in the robustness of effects: Barth et al., (2013) and Cuijpers et al., (2011a) found that, when analyses were conducted only on studies with moderate (⩾ 25) or large (⩾ 50) sample sizes, CBT, IPT and problem-solving therapy showed moderate effects versus waitlist, while effects were less robust for psychodynamic therapy, behavioural activation and supportive counselling. Underlining the similarities of effects across therapies, recent studies have found no significant differences between CBT and BA (behavioural activation, a component of CBT, but easier to deliver) (Cuijpers et al., 2007) and between CBT and brief psychodynamic psychotherapy (Driessen et al., 2013).

Similarly, although the evidence base is much wider for CBT, there is no clear evidence of superiority of one type of psychotherapy over any other for prevention of depressive relapse or recurrence: a systematic review found similar effect sizes for CBT, MBCT, and IPT (Biesheuvel-Leliefeld et al., 2015). Though there is little evidence for differential effectiveness across the various psychotherapies, this does not imply that unstructured or eclectic approaches are supported in the psychological treatment of depression. There is strong clinical consensus that treatment is best guided by an evidence-based treatment manual, tailored to the individual patient, and with proper attention to the therapeutic relationship.

Effect sizes for psychotherapies relative to antidepressant medication. There is consensus that *CBT is as effective as antidepressant medication for depression of mild-moderate severity* (Lampe et al., 2013). This conclusion is underlined by a recent meta-analysis of 10 relevant studies, which found the effect size of psychotherapy compared with pill placebo to be $d = 0.25$ (NNT = 7.14), which is comparable to the effects of antidepressant versus pill placebo (Cuijpers et al., 2014b).

Findings are more complex in relation to severe depression. Early research based on the large Treatment of Depression Collaborative Research Program found that while antidepressant medication was superior to placebo for more severely depressed patients, CBT was not (Elkin et al., 1989). However, a more recent meta-analysis found the positive effects of psychotherapy were not moderated by severity of baseline depression (Driessen et al., 2010). In fact, that analysis found some evidence for enhanced effectiveness of psychotherapy for outpatients with severe relative to more moderate forms of depression. In direct comparison with antidepressant medication, one review concluded that psychotherapies are as effective for severe depression, but only if therapists are experienced and well trained (DeRubeis et al., 2005). There is some evidence that the presence of comorbid personality disorders may predict a better response to antidepressant medication relative to psychotherapy (Fournier et al., 2008).

Table 12. Common psychotherapies for treatment of major depressive disorder.

CBT Cognitive-behavioural therapy (CBT) aims to modify dysfunctional cognitions and related behaviours that are presumed to maintain depression. Amongst evidence-based psychological therapies, CBT is the most widely researched treatment for depression, and it is recommended by all international guidelines (NICE, 2009; Parikh et al., 2009).
IPT Interpersonal psychotherapy (IPT) is a brief structured approach that addresses interpersonal issues and role transitions. It has Level I evidence for the treatment of major depression. IPT has Level 1 evidence for both acute depression and depression maintenance/ relapse.
MBCT and ***ACT*** Recently developed structured therapies, such as mindfulness-based cognitive therapy (MBCT) and acceptance and commitment therapy (ACT) have not been evaluated as thoroughly as CBT and IPT, but appear to be effective in reducing depressive symptoms and in preventing relapse of depression (specificity for subtype and/or severity of depression remains unclear) (Fjorback et al., 2011). MBCT may be better for patients prone to worry and ACT may be best for patients needing to accept and adjust to persisting problems.

Suitability for psychological treatment. There are many factors that can influence whether psychological treatment is more appropriate than pharmacotherapy, including adherence to medications, timing of treatment, formulation, patient preference, psychological insight and extent of life stressors involved in onset. There is often an optimal time within an episode for an individual to engage with psychological treatments, and if a patient is psychologically minded (the capacity or preference for self-examination and introspection), *psychological therapy should be initiated early in the course of the illness and this can be stand alone (monotherapy)*. However, if there is minimal response within a reasonable period of time, then pharmacotherapy should be considered. Depending on the severity and symptom profile of the depressed patient, psychological treatment may be best administered after initiating pharmacotherapy, and in this context clinical features such as melancholic features that may predict better response to SSRIs than CBT should be taken into consideration (Simon and Perlis, 2010). It is recommended that *some form of psychological intervention (at a minimum, psychoeducation) accompany pharmacotherapy whenever possible* because sometimes where medications produce response but do not achieve remission, the addition of psychological interventions may enable remission.

Overall, evidence from existing studies suggests that psychological therapies (particularly CBT and related approaches, and IPT) are as effective in reducing mild to moderate depression as pharmacological treatments, provided the therapists administering therapy are experienced and well trained (see: Recommendation Box 1).

Pharmacotherapy for major depressive disorder

Antidepressants (Level I). The efficacy of antidepressants in the treatment of major depression has been extensively studied and substantiated relative to placebo in randomised, double-blinded, clinical trials. However, the decision to treat an individual patient with an antidepressant remains very much a matter of clinical judgment. This is because there are no reliable predictors of response to medication. Psychosocial factors such as abuse or personality traits can be informative, but the decision to pursue pharmacotherapy and the choice of antidepressant is usually based on illness severity,

degree of associated impairment, patient preference and additional factors. These include previous response, the presence of atypical features, melancholic features, psychomotor retardation or psychotic features, and/or a family history of response to treatment. Significant dysfunctional premorbid personality factors (including child abuse history) (Nanni et al., 2012) and psychosocial precipitating factors suggest that antidepressants may be less likely to achieve remission as monotherapy. This step of initiating treatment and selecting a suitable antidepressant is critical and therefore any potential predictors of treatment response are invaluable. In this context, the search for pharmacogenetic predictors and other treatment biomarkers that may inform antidepressant choice continues.

With the exception of some early agents, such as the tricyclic antidepressants which are classified according to chemical structure, most antidepressants are grouped according to their primary mode of action. Table 13 lists antidepressant classes according to their principal mechanism of action and the key features they target.

While it is important to consider the mode of action of antidepressants, this does not predict response. Neurotransmitter systems in the brain do not act independently of each other and a medication which affects one system will also have an effect on other systems. It is still not known precisely how antidepressants exert their therapeutic effect but it is clear that increasing the concentration of synaptic neurotransmitters is only one component of a complex array of intracellular and neuroplastic mechanisms. Therefore rather than primarily relying on neurotransmitter profile the choice of antidepressant should be based on a range of factors, such as side effect profile and tolerability, cost, suicide risk and clinician's experience.

Recommendation Box 1.

PSYCHOLOGICAL THERAPY FOR MDD	Grade
1.1. Psychological interventions should only be delivered by clinicians trained in the relevant evidence-based approach.	CBR
1.2. Treatment should be guided by a published manual, tailored to the individual, and should pay particular attention to establishing and maintaining the therapeutic alliance.	CBR
1.3. Patients with *mild-moderate depression* should be offered one of the evidence-based psychotherapies as first line treatment.	EBR I
1.4. Patients with *moderate-severe depression* should be offered combined pharmacotherapy and psychotherapy as first line treatment.	EBR I
1.5. Patients with *chronic depressive disorders* should be offered combined psychotherapy and pharmacotherapy as first line treatment.	EBR I

Principles of antidepressant treatment. Once a potentially suitable antidepressant has been selected (Malhi et al., 2009b, 2013a), the first step is to ensure that it is administered appropriately. For antidepressants to be effective they must be administered at an adequate dose for a reasonable period of time. Therefore, at the outset, tolerability is key and adherence to medication can be enhanced through education, prompt management of side effects and frequent monitoring of progress (Berk et al., 2010). The support of a family member, friend or carer can be helpful in avoiding premature discontinuation. Many patients

are also likely to obtain information themselves from the internet and this should be discussed with them to make best application of it.

An adequate trial of an antidepressant should be a minimum of three weeks at the recommended therapeutic dose. Note, some antidepressants require titration to the maximum recommended dose, whereas others, in particular SSRIs, generally have a flat dose-response curve and high doses do not necessarily improve efficacy (Adli et al., 2005). At the same time, it is important not to increase the dose of an antidepressant too rapidly because this increases the likelihood of side-effects and treatment discontinuation. In instances of excessive sensitivity to side effects, it is worthwhile considering metaboliser status and nocebo effects.[6]

Response. An antidepressant response is usually discernible in the first two weeks of treatment (Posternak and Zimmerman, 2005; Stassen et al., 1998), and therefore, early follow-ups are important. This also ensures assessment of treatment emergent suicidality often seen in those below age 25 years (Stone et al., 2009). In some instances an antidepressant response takes longer to emerge, but if no improvement is apparent within the first three weeks of adequate treatment, a dose increase or augmentation should be considered, especially if the depressive symptoms are severe and/or disabling. If an adequate dose has been found effective, remission usually requires six weeks of treatment. Switching is an important strategy but should only be considered once an adequate trial at an adequate dose has been achieved.

Response has two important aspects that need to be considered: extent and timing. The extent of response ranges from complete (full) to no (nil) response, with partial response in between. The timing of a response can be prompt (within 7–10 days), delayed (more than 4 weeks) or never occur. Combining the two parameters provides a variety of possible outcomes, the most common of which are depicted in Figure 7.

Efficacy. The efficacy[7] of antidepressants is usually determined in comparison to placebo, and though it is important to know whether an antidepressant is efficacious per se, it is particularly useful to know its differential efficacy as compared to alternative antidepressants. By using clinical trial methodology it is difficult to establish superiority of one antidepressant over another because of the large sample sizes required to detect small differences in efficacy. Therefore, the *evidence for differential efficacy across the patient population, or for specific clinical profiles, is relatively modest*. Meta-analyses have been used to combine the evidence from a large number of studies of individual antidepressants compared to placebo, but this can only be applied to antidepressants where a sufficient number of studies have been conducted, noting that negative studies often remain unpublished. Using this approach there is some evidence for superiority of venlafaxine over SSRIs (Bauer et al., 2009; Nemeroff et al., 2008; Weinmann et al., 2008), escitalopram over citalopram, venlafaxine, and duloxetine (Kennedy et al., 2008) and sertraline over fluoxetine and other SSRIs as a class (Cipriani et al., 2008). However, other systematic reviews have failed to identify differential efficacy between the newer generations of antidepressants (NICE, 2009; Sartorius et al., 2007). A study that used multiple treatment analysis of 12 new generation antidepressants (Cipriani et al., 2009) examined both efficacy and a measure of tolerability to rate antidepressants and found that mirtazapine, escitalopram, venlafaxine and sertraline were more efficacious than duloxetine, fluoxetine, paroxetine, fluvoxamine and reboxetine.

Table 13. Summary of antidepressant clinical use – acute.

Typical recommendation[a]	Antidepressant Class	Generic Name of Medication	Principal Mechanism of Action	Features of depression for which antidepressant is most likely to be useful
1st line	SSRI	Citalopram, Escitalopram, Fluvoxamine, Fluoxetine, Paroxetine, Sertraline	Selective 5-HT reuptake blockade	Anxiety
	NARI	Reboxetine[b]	Reuptake inhibitor for noradrenaline and adrenaline	Activation (e.g., motivation & withdrawal)
	NaSSA	Mirtazapine Mianserin	Blocks the reuptake of serotonin via 5-HT_{2A} & 5-HT_{2C} receptors. Also blocks $5HT_3$ & Alpha-2 receptors.	Insomnia, circadian disruption, weight loss, reduced appetite
	Melatonergic agonist	Agomelatine	Melatonin agonist (M1 and 2 receptors) and 5-HT_{2C} antagonist	Sleep problems, sexual dysfunction, poor hedonic drive
	NDRI	Bupropion[c]	Blocks the action of the noradrenaline transporter and dopamine transporter	Fatigue
2nd line	SNRI[d]	Desvenlafaxine, Venlafaxine,[e] Duloxetine, Milnacipran	Block both serotonergic and noradrenergic reuptake. Latter leads to an increase in prefrontal dopamine.	Melancholia; severe depression. *Velafaxine*: treatment resistant depression. *Duloxetine*: pain
	TCA	Amitriptyline, Clomipramine, Dothiepin, Imipramine, Nortryptiline Trimipramine Doxepin	Block NA reuptake. Some also block 5-HT reuptake. All TCAs inhibit H_1, α1, & M_1, receptors. Some also block 5-HT_{2C} & 5-HT receptors. Broad spectrum of actions, including blockade of voltage-sensitive sodium channels.	Pain Melancholia
	Serotonin Modulator*	Vortioxetine	5HT1a agonist, 5HT1b partial agonist, 5HT3a and 7 antagonist 5HT transporter inhibitor	Melancholia Severe *depression* Enhances *cognition*
3rd line	MAOI	Phenelzine, Tranylcypromine	Irreversibly inhibit the mitochondrial enzymes MAO-A (metabolises 5-HT, NA & DA) and MAO-B (preferentially metabolises DA)	Melancholia Atypical symptoms[f] Treatment resistant depression
	Reversible MAOI	Moclobemide	Reversible inhibitor of MAO-A (RIMA)	Mild to moderate depression with anxiety
Adjunctive	SARI	Trazodone	Serotonin 2A/2C antagonist and reuptake inhibitor (at high dosage). At low doses blocks 5-HT2A, α1, & H_1 receptors (hypnotic action)	Used when patients do not respond well to 1st line

Notes: (1) SSRI, selective serotonin reuptake inhibitor; NARI, noradrenaline reuptake inhibitor; NaSSA, noradrenaline and specific serotonergic antidepressant; NDRI, noradrenaline-dopamine reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor; TCA, tricyclic antidepressant; SM, serotonin modulator, MAOI, monoamine oxidase inhibitor; SARI, serotonin antagonist and reuptake inhibitor. (2) In New Zealand, certain antidepressants are not funded unless suitable alternatives have been trialled first.

***References:** (Boulenger et al., 2012; Citrome, 2015; Katona and Katona, 2014; McIntyre et al., 2014; Mahableshwarkar et al., 2015; Sanchez et al., 2015; Schatzberg et al., 2014).

[a]**There** is some flexibility in terms of 1st, 2nd, and 3rd treatment, based on patient's symptoms (e.g., MAOIs would be prescribed 1st line for atypical depression); [b]Atomoxetine is prescribed for ADHD and is therefore not recommended 1st line for depression; [c]Only indicated in Australia for smoking cessation; [d]SNRIs have been positioned as 2nd line only because of greater toxicity in overdose; [e]Low dose; [f]Evidence is equivocal Trimipramine: refractory insomnia.

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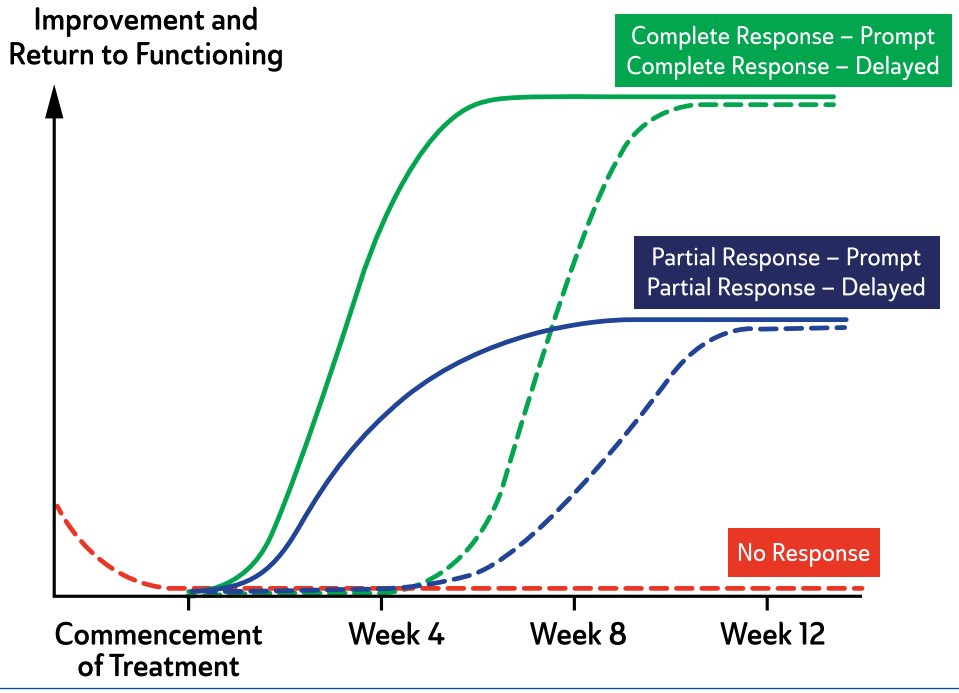
The latter was found to be the least efficacious, although concerns regarding potential inadvertent bias have been raised because of the possibility of unpublished data not being included. The clinical utility of these differences is unclear.

The question of whether newer generations of antidepressants are as effective as tricyclic antidepressants is also unclear. A meta-analysis of the effectiveness and tolerability of TCAs versus SSRIs (Anderson, 2000), for example, failed to demonstrate a significant difference in efficacy but the SSRIs were much better tolerated. However, other studies comparing TCAs and SSRIs in patients with depression have shown that TCAs, such as amitriptyline, have superior efficacy (Barbui and Hotopf, 2001; Faravelli et al., 2003).

Vortioxetine is a new generation antidepressant, which appears to have comparable antidepressant efficacy to SRRIs, SNRIs and agomelatine, but a comparison of efficacy with TCAs and MAOIs is not yet available (Citrome, 2015; Katona and Katona, 2014; Sanchez et al., 2015; Schatzberg et al., 2014).

Overall, the differential efficacy of antidepressants in the treatment of major depressive disorders is not striking. This is partly because of the heterogeneity of the populations treated and the paucity of studies that have conducted a direct comparison. Clinically, traditional antidepressants (TCAs and MAOIs) appear to have greater efficacy, especially in the treatment of melancholic depression, but tolerability and safety concerns in overdose usually relegate these agents to second line administration.

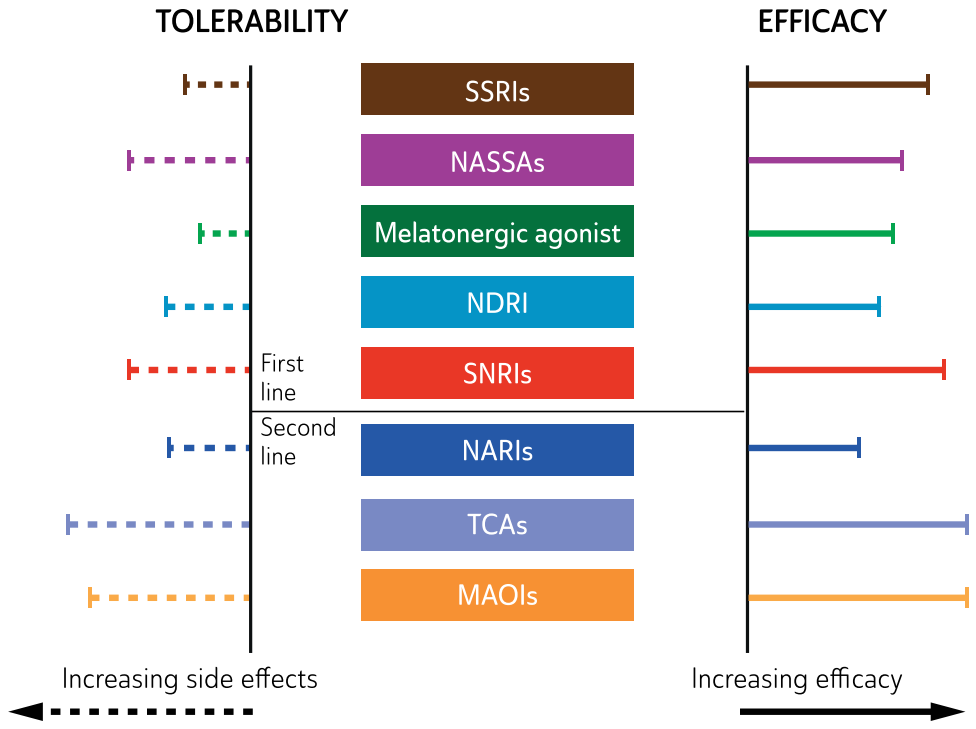
Figure 7. Typical Patterns of Treatment Response.



An ideal response is timely and complete. The individual shows a prompt response to treatment and achieves remission (within six weeks) (green solid line). The response can be delayed with improvement being slow or taking time to appear (delayed response) (dashed lines). The final response can also be incomplete (partial response), and fail to achieve complete remission of symptoms (blue lines). In some cases there is no discernible response whatsoever (no response) (red line). NB. Solid lines indicate prompt/immediate response; dotted lines indicate delayed response.

Figure 7 shows the initial patterns of response that are common following the commencement of treatment. Remission following treatment of the first antidepressant trial, as illustrated by the green curve, only occurs in a quarter to a third of patients with major depression (Rush, 2007). In some patients there may be considerable delay before symptoms improve significantly, but there is a discernible change with treatment (see: Figure 7). Therefore, it is important to administer an adequate dose for at least three weeks and try to foster compliance.

Figure 8. Clinical utility of antidepressants.



Based on average ratings from expert panel. Antidepressant agents rated according to efficacy and tolerability. N.B. Some agents have not been included as there was insufficient experience to make clinically meaningful ratings.

Safety. When prescribing an antidepressant, safety issues are of considerable importance, particularly in adolescence, old age, pregnancy and breastfeeding and in the context of depression with comorbid medical illness. The effects of an antidepressant in the event it is taken in overdose is also an important consideration when selecting an appropriate medication for depressed patients who are likely to be at risk of self-harm or suicide. In this regard, the new generation antidepressants, while not without risk (particularly venlafaxine), are significantly safer than the TCAs or irreversible MAOIs.

TCAs can be lethal in overdose because of their cardiovascular side effects (tachycardia, postural hypotension, slowed cardiac conduction). They also increase cardiac morbidity and mortality in patients with ischaemic heart disease (Roose and Miyazaki, 2005). In addition, there is an increased risk of seizures with tricyclics, especially in overdose, particularly dothiepin and clomipramine, and care should be taken in prescribing these to patients with

a history of epilepsy, as the seizure threshold can be reduced more so than with other While less toxic than TCAs, venlafaxine has been shown to be more hazardous in overdose than the SSRIs with an increased mortality from cardiac complications (Deshauer, 2007) and an increased risk of seizures (Montgomery, 2005).

In general, new generation antidepressants are safer options for first line treatment (Peretti, 2000). There are, however, safety issues with SSRIs that require caution (Moret et al., 2009; Roose and Miyazaki, 2005). These include hyponatraemia and osteoporosis, especially in the elderly, and a small risk of prolonged bleeding. Treatment with SSRIs during pregnancy has been associated with a small increased risk of foetal cardiac abnormalities (paroxetine) and potentially fatal pulmonary hypertension in the newborn and a neonatal withdrawal syndrome that can result in seizures has been identified (Moret et al., 2009). This needs to be balanced against the possible harmful effects of depression itself on pregnancy outcomes and its potential impact on the developing foetus (Chaudron, 2013).

Though the risk with therapeutic doses appears to be low, clinicians should be cautious about prescribing doses of SSRIs in excess of the recommended maximum, especially in patients with known cardiovascular disease,[8] due to possible QTc prolongation. Where high doses are needed, an ECG should be considered.

Table 14. Side effects associated with common antidepressant classes.

	Weight gain	Sexual dysfunction	CNS effect (e.g., sedation, fatigue or agitation)	Anticholinergic effect (e.g., dry mouth, tremor)	GI distress
SSRI	+	+++	++	++	++
SM	+	++	+	+	+++
NARI	++	+	+	+	++
NaSSA	++	++	+++	++	+
Melatonergic agonist	+	+	+	+	+
NDRI	++	+	++	++	+
SNRI	+	+++	++	++	++
TCA	++	+	+++	+++	+
MAOI[1]	+	+	+	+	+
SARI	+	+	+++	+	++

KEY: + <10%, ++ 10-30%, +++ >30%. SM, serotonin modulator. (For other abbreviations see legend of Table 13.)
1. Some combinations of MAOIs with other drugs can be fatal. Dietary restrictions are necessary to prevent hypertensive crisis.
References: (Citrome, 2015; Katona and Katona, 2014; Sanchez et al., 2015; Schatzberg et al., 2014).

Concerns have been raised about the potential for antidepressants, particularly SSRIs, to cause suicidal thoughts and behaviour especially in adolescents and young adults. These concerns have prompted regulatory authorities in many countries to issue warnings to

clinicians. A consensus statement by the World Psychiatric Association (WPA) (Möller et al., 2008) concluded that in the absence of randomised controlled trial evidence, the risk is difficult to assess but that the available data indicated that there was a small risk of SSRIs inducing suicidal thoughts in patients up to the age of 25. The WPA advised that this risk needed to be balanced against the known benefits of treating depression and in preventing suicide. Clinicians should therefore advise young patients and their families of the small chance of suicidal thoughts emerging during the early phase of treatment with SSRIs and monitor all patients for the emergence or worsening of suicidal thoughts during the first 2–4 weeks of treatment. The activation/agitation observed with the initial stages of taking an SSRI can be managed with a low dose of a benzodiazepine prescribed for a limited period of time.

Side-effect profile. *General considerations*: Tolerability to side effects is an important determinant of adherence to medication and should be weighed against the efficacy profile of the antidepressant (see: Figure 8)

New generation antidepressants are in general better tolerated than tricyclics or MAOIs and cause fewer problems with anticholinergic side effects such as sedation, dry mouth and constipation (see: Tables 14 and 15).

Table 15. Clinical considerations of antidepressant classes.

Antidepressant class*	Clinical considerations
SSRI	SSRIs are suitable first-line and are generally better tolerated than other classes of antidepressants but can cause emotional blunting. Sexual dysfunction and gastrointestinal symptoms are common. Many SSRIs (especially fluoxetine and paroxetine) cause significant CYP450 inhibition and care is needed when co-prescribed with other medications. Paroxetine can cause withdrawal agitation.
NARI (reboxetine)	Reboxetine is suitable first-line. Common side effects include insomnia, fatigue, nausea, dry mouth and constipation.
NaSSA (mirtazapine and mianserin)	Mirtazapine is a suitable first-line option, but is associated with increased appetite, weight gain, somnolence, dry mouth and constipation. The last 3 side effects are also common with mianserin.
Melatonergic agonist (agomelatine)	Common side effects include sedation and dizziness. Risk of hepatotoxicity.
NDRI (bupropion)	Common side effects include dry mouth, nausea and insomnia.
SNRI (venlafaxine, desvenlafaxine, duloxetine)	SNRIs appear to be more effective than SSRIs in treating severe depressive symptoms (HAM-D$\geqslant$25) and melancholia. In some cases, adverse effects may limit SNRIs to second-line treatment. However, if depression is severe (i.e. HAM-D$>$25), then SNRIs are a suitable first-line option. Headache, sexual dysfunction, sweating and gastrointestinal symptoms are common with venlafaxine. Can also cause withdrawal agitation.
SM (vortioxetine)	Vortioxetine appears to have a particularly significant beneficial effect upon cognitive function in the treatment of depression. However the evidence requires further replication. Nausea, vomiting and diarrhoea are the major adverse effects.
TCA	In comparison to SSRIs, TCAs have a greater side effect burden (anticholinergic and CNS) and toxicity in overdose and therefore, are considered second-line. However, TCAs (especially those that have both noradrenergic and serotonergic activity such as amitriptyline and clomipramine) may be more effective compared to other antidepressants in treating severe depressive symptoms (HAM-D$\geqslant$25), in particular patients with melancholia and those hospitalised due to severe depression.
MAOI	Efficacious antidepressants but not recommended first-line due to risk of hypertensive crisis if necessary dietary and drug interaction restrictions are not adhered to.

*Antidepressants are grouped according to principal mechanisms of action (e.g., SSRI) or molecular structure (e.g. TCA). References: SSRI (Gillman, 2007; Katzman et al., 2007); NARI (Andreoli et al., 2002; Papakostas et al., 2008; Versiani et al., 2000; Wiles et al., 2012): NaSSA (Amini et al., 2005; Anttila and Leinonen, 2001; Benkert et al., 2000; Leinonen et al., 1999; Watanabe et al., 2010); Melatonergic (Rouillon, 2006); NDRI (Stahl et al., 2004); SNRI (Levitt and Boyle, 2002; Machado and Einarson, 2010; Papakostas et al., 2007b; Tzanakaki et al., 2000); SM (Citrome, 2015; Katona and Katona, 2014; Mahableshwarkar et al., 2015; Sanchez et al., 2015; Schatzberg et al., 2014); TCA (Anderson, 2000; Cohn et al., 1996; Danish University Antidepressant Group, 1986; Danish University Antidepressant Group, 1990; Danish University Antidepressant Group, 1993; Doogan and Langdon, 1994; Fabre et al., 1996; Feighner and Boyer, 1989; Furukawa et al., 2009; Gillman, 2007; Guaiana et al., 2007; Kocsis, 2013; Lydiard et al., 1989; Perry, 1996; Reimherr et al., 1990; Rickels et al., 1994; Stark and Hardison, 1985); MAOI (Shulman et al., 2013).

However, the newer antidepressants have a range of side effects which can be unacceptable to some patients necessitating a change of medication. It is important to note that there is considerable variability among antidepressants in the nature and severity of side-effects, and these also vary from one individual to another (Gartlehner et al., 2008, 2011).

Common side effects of SSRIs and SNRIs include nausea, headache, dry mouth, agitation, insomnia, sweating, bruxism, sexual dysfunction and weight gain. Most of these side-effects diminish to tolerable levels during the first one to two weeks of treatment but they can be troublesome and occasionally persist. Short-term use of adjunctive medications, such as benzodiazepines, anxiolytics and hypnotics, may be helpful in managing some of these initial side-effects.

Additional specific considerations: escitalopram and sertraline may have marginally better tolerability than other antidepressants (Cipriani et al., 2009). A small group of patients may experience an immediate and distressing level of agitation with serotonergic drugs, and for these patients, SSRIs may need to be avoided. In the medium to long-term, SSRI induced sexual dysfunction, though sometimes clinically indicative of adequate CNS bioavailability, may necessitate a change to another antidepressant class.

Monitoring response. Following the initial response to an antidepressant, the long-term response is equally variable. Once a patient shows short-term improvement, the symptoms either continue to improve and reach remission, or the response plateaus. When the latter scenario occurs, a change of treatment strategy may be necessary. The STAR*D study. (Rush et al., 2006) showed that after four successive trials of antidepressants a cumulative remission rate of 67% was reached, though it may require 2–3 antidepressant trials before complete remission is reached. Even with switching to an alternative medication or adding an augmenting agent, only 30% of depressed patients achieve a partial response or remain non-responsive (refractory). These patients require a more extensive re-evaluation of both the diagnosis and perpetuating factors, or are candidates for physical therapies such as ECT.

Combined psychological therapy and antidepressants (Level I). For most patients with depression, a combined treatment approach is more effective than either psychological or antidepressant treatment alone. This applies particularly to depression of moderate or greater severity (HAM-D $\geqslant$18) and chronic depression (Level I) (Cuijpers et al., 2009; De Maat et al., 2006; Manber et al., 2008; Pampallona et al., 2004; Schramm et al., 2007, 2008; Simon et al., 2006). In most cases of depression there are significant psychological issues, either aetiological or maintaining/perpetuating the illness. Comorbid anxiety and/or personality vulnerabilities also play a significant role. Depressive illness is inevitably a traumatic experience which impacts psychosocial, occupational, and relationship functioning, and therefore, psychological support at some point in the course of the illness is often necessary for early episodes. With regard to the structured psychotherapies, a systematic review of combined treatment with antidepressants (Oestergaard and Møldrup, 2011) concluded that pharmacotherapy combined with psychotherapy is associated with a higher probability of remission and a lower risk of relapse. Combination therapy should be considered when response to a single modality has been suboptimal or unsuccessful (Driessen and Hollon, 2010).

Recommendation Box 2.

ANTIDEPRESSANT THERAPY FOR MDD	Grade
2.1. An *adequate trial of antidepressant therapy for MDD* should be a minimum of three weeks at the recommended therapeutic dose using a suitable medication.	EBR III
2.2. When *commencing antidepressant therapy* clinical response and side effects should be closely monitored from the outset.	CBR

Footnote: Tolerability (side effect profile) is as important as efficacy when choosing an antidepressant.
Tricyclics, MAOIs and dual action agents may be more efficacious than newer agents in the treatment of moderate-severe depression.

Recommendation Box 3.

COMBINATION THERAPY FOR MDD	Grade
3.1. A combination of psychological and pharmacological therapy should be considered when response to either modality alone has been suboptimal or unsuccessful.	CBR

Table 16. First- and second-line indications for ECT.

Indications for ECT	
First-line treatment	Severe melancholic depression, especially when the patient is refusing to eat/drink High risk of suicide High levels of distress Psychotic depression or catatonia Previous response, patient choice
Second-line treatment	Patients who have not responded to several trials of medication, including for example TCAs, MAOIs.

Brain stimulation methods

Electroconvulsive therapy (Level I). Electroconvulsive therapy (ECT) is a safe and effective treatment for the more severe forms of depression (Carney, 2003), where its antidepressant effect is found to be superior to medication strategies (Lisanby, 2007).

Therefore, in practice it is usually reserved for patients who have not responded to several trials of medication. ECT is recommended as first-line treatment in extremely severe melancholic depression, particularly when the patient refuses to eat or drink and/or is a very high suicide risk, or when the patient has very high levels of distress, has psychotic depression, catatonia or has previously responded to ECT *(see: Table 16)*.

ECT is highly effective in the treatment of psychotic depression for which it is a first-line option (Lisanby, 2007). A large multicentre study of the efficacy of bitemporal ECT showed a remission rate of 95% for completers with psychotic depression (Petrides et al., 2001).

Electrode placement. The choice of electrode placement and dose of ECT needs to be determined for the individual patient, balancing efficacy against side effects. These

parameters influence effectiveness, particularly for unilateral ECT (Loo et al., 2006). Doses as high as six times threshold can maximise the efficacy of unilateral ECT, while for bilateral placements (bitemporal or bifrontal) doses at 50–100% above threshold are usually sufficient.

The electrode placements currently in use are *right unilateral, bitemporal* and *bifrontal*. The relative efficacy of each is dependent on dose above seizure threshold and the data from comparative studies is difficult to interpret because of inconsistent methodologies. Generally, *bitemporal* ECT is more effective than *unilateral*, and *high dose* is more effective than *low dose* for both placements, but cognitive side-effects are greater with bitemporal placement and at higher doses (Carney, 2003). At six times threshold the efficacy of unilateral ECT approaches that of bitemporal ECT, but at the cost of greater cognitive impairment compared to lower doses (Loo et al., 2006).

Bifrontal ECT, while less studied, appears to be as effective as high dose unilateral ECT and bitemporal placement. Data from early studies (Bailine et al., 2000; Dunne and McLoughlin, 2012; Ranjkesh et al., 2005) and pooled analyses of data from studies comparing bifrontal with unilateral and bitemporal ECT show fewer cognitive side effects for bifrontal ECT compared with bitemporal ECT (Plakiotis and O'Connor, 2009). However, a much larger multicentre study failed to show a cognitive advantage for bifrontal ECT (Kellner et al., 2010) though the large amount of missing cognitive data in this study makes the findings difficult to interpret.

Overall, the evidence is insufficient to conclude a cognitive benefit for bifrontal over bitemporal ECT. Clinical experience however suggests that bifrontal ECT can be associated with fewer cognitive side effects than bitemporal ECT and may be a useful option for some patients. There is evidence that bifrontal ECT is associated with a lower rate of ECT-induced cardiac arrhythmias (Stewart et al., 2011) so it may also have safety advantages over unilateral and bitemporal ECT, particularly in patients with cardiac problems.

The introduction of *ultra-brief pulse width (0.3msec) unilateral ECT* has made possible effective treatment with markedly fewer cognitive side-effects (Loo et al., 2008; Sackeim et al., 2008; Spaans et al., 2013; Verwijk et al., 2012). The efficacy of unilateral ultra-brief ECT appears to be equivalent to standard brief pulse unilateral ECT but more treatments may need to be given to achieve remission (Loo et al., 2007). Ultra-brief pulse width bifrontal ECT has been shown to be effective with cognitive sparing (Sienaert et al., 2009) but bitemporal ultra-brief ECT has been shown to be ineffective (Sackeim et al., 2008) and is *not* recommended.

As a general recommendation and balancing efficacy against cognitive side-effects, electroconvulsive therapy for most patients should begin with unilateral ultrabrief pulse width ECT at six times threshold, or brief pulse width ECT at 3-6 times threshold. When administering ECT, both options should be available and choice should be determined by balancing the need for speed of response against concern regarding potential cognitive side effects. Consideration should be given to using bifrontal or bitemporal ECT if speed and reliability of response is paramount, for instance if patients are dehydrated or extremely suicidal. If treatment is commenced unilaterally, switching to bifrontal or bitemporal ECT should be considered after approximately six treatments if there is no response.

Following a course of ECT, relapse rates within six months have been shown to be over 50% despite maintenance pharmacotherapy (Kellner et al., 2006). Therefore in some cases maintenance ECT may be necessary.

Side effects. The efficacy of ECT needs to be balanced against potential cognitive side-effects, which increase with increasing doses of ECT. Memory impairment is the side-effect of most concern to patients. Both anterograde and retrograde memory are variably affected. Anterograde memory changes generally return to normal or may be improved compared to pre-ECT levels within 2–4 weeks (Semkovska and McLoughlin, 2010) but retrograde impairment, which is more likely with bitemporal placement, can persist for prolonged periods (Sackeim et al., 2007). It is important that patients and their immediate family/partner are made aware of the potential effects on memory before undergoing ECT.

Repetitive transcranial magnetic stimulation (rTMS). Repetitive transcranial magnetic stimulation is a technique that, having been the subject of intensive research since the mid-1990s, is now being increasingly used in clinical practice in many countries. rTMS is a treatment method that utilises a pulsed magnetic field to stimulate and potentially alter brain activity. Repeated cortical stimulation with TMS pulses can either increase or decrease local brain activity depending on the frequency of stimulation. A typical rTMS treatment course involves daily treatment provided Monday to Friday over 4 to 6 weeks. Stimulation is applied daily for between 30 and 45 minutes. Patients receiving rTMS do not require a general anaesthetic and are typically able to return to work or drive immediately after the end of outpatient treatment. rTMS can be applied as an outpatient or to hospital inpatients. Unlike ECT there are no cognitive side effects, and unlike medications, there are no drug-drug interactions or systemic side effects.

When used to treat depression rTMS is most commonly administered as repeated short bursts of high frequency stimulation (~10 Hz) to the left dorsolateral prefrontal cortex (DLPFC). A large body of clinical sham controlled trials have demonstrated the antidepressant efficacy of this form of rTMS; supported by several meta-analyses (Level I) (Schutter, 2009; Slotema et al., 2010). There is also significant evidence (summarised in a meta-analysis) to support the antidepressant efficacy of *low frequency rTMS* (an alternate form of rTMS) applied to the right DLPFC (Level I) (Schutter, 2009). Bilateral rTMS does not appear to produce better results than unilateral rTMS, and therefore unilateral approaches that can be generally delivered more quickly are preferable (Chen et al., 2014).

The majority of clinical trials conducted evaluating the use of rTMS in depression have been conducted in patients who have failed to respond to one or more antidepressant medication strategies. rTMS treatment appears to be effective whether it is applied as a monotherapy or in conjunction with antidepressant medication (Slotema et al., 2010). Further research is required to evaluate whether rTMS can be successfully utilised as a maintenance treatment strategy and early studies suggest that this may be possible (Fitzgerald et al., 2013a). The findings from studies supporting the use of rTMS treatment have led to its approval and use in many countries, and it is increasingly being used in clinical practice in Australia.

Recommendation Box 4.

ECT and rTMS FOR MDD	Grade
4.1. ECT is a safe and effective treatment for more severe presentations of depression* and should be considered first-line for psychotic depression or when an immediate response is necessary.	EBR I
4.2. Patients with non-psychotic depression may be treated with rTMS once they have failed one or more trials of standard antidepressant medications and psychological therapies.	EBR I

Footnote: *Includes major depressive episodes occurring in context of Bipolar Disorder.

Side effects. rTMS is generally well tolerated. The major treatment related side effects are headache and scalp discomfort at the site of stimulation (Rossi et al., 2009). Treatment discontinuation rates in clinical trials and in clinical practice are typically quite low. There is a potential risk of seizure induction with rTMS treatment although with suitably selected patients this risk appears extremely low (Rossi et al., 2009). In a manner similar to other antidepressant treatments, there is a risk of manic switch with rTMS treatment in patients with bipolar disorder, although the risk of this is considered low (Rossi et al., 2009), and patients with metal implants from neurosurgery or pacemakers may be unsuitable for rTMS due to risks of interference from the high power magnetic field.

Transcranial direct current stimulation (tDCS). tDCS involves the application of a weak electrical current through an anode and cathode to subtly modify brain activity. Initial research suggests that tDCS can modify mood in depressed patients, although it is unclear at this stage whether these effects are clinically relevant. Antidepressant effects of tDCS have been supported in recent larger studies (Brunoni et al., 2013; Loo et al., 2012) and a meta-analysis (Shiozawa et al., 2014), but another recent meta-analysis found no difference between active and sham tDCS on clinically relevant endpoints, such as response and remission rates (Berlim et al., 2013). Definitive recommendations await the outcomes of large multi-site trials of tDCS that are currently underway.

Magnetic seizure therapy (MST). MST is a new form of convulsive therapy that is being evaluated as an antidepressant strategy. MST involves the induction of a seizure in a procedure similar to that undertaken with ECT (Fitzgerald et al., 2013a; Lisanby et al., 2001). However, instead of inducing a seizure with an electrical current, the MST seizure is produced using a high intensity transcranial magnetic stimulation device, which instigates the seizure via high frequency rTMS pulses. Initial data suggest that MST might have efficacy similar to ECT without equivalent cognitive side-effects (Kayser et al., 2011), but only limited evaluation of this technique has occurred to date.

Deep brain stimulation (DBS). DBS is a procedure which involves the implantation of a small series of stimulating electrodes into the brain connected to a pacemaker type pulse generator which is placed below the clavicle in the chest. DBS is used extensively for patients with advanced Parkinson's disease and a number of other neurological conditions. In recent years a number of groups have explored the use of DBS applied to several brain regions in the treatment of patients with highly refractory depression. Small studies have suggested that DBS in several brain regions including the subgenual cingulate cortex and

Table 17. Complementary therapies* for depression.

Therapy/Agent	Controlled Trial Evidence	Interactions/Hazards	Notes
Omega-3 fatty acids (eicosapentaenoic acid)	May help alleviate depressive symptoms in milder cases of major depression and bipolar depression when used as an adjunct to prescription medication[a]	Nil at recommended doses. Caution with patients on warfarin.	Dietary enhancement initially (e.g. increasing the intake of Omega 3 rich fish) then consider dietary supplementation with Omega 3 preparations.
St John's Wort	Similar efficacy to SSRIs in mild to moderate major depression[b].	Risk of serotonin syndrome if combined with other antidepressants.	Consider cost to patient versus prescription agents. Variance in active ingredient(s) between manufacturers may limit efficacy.
S-adenosyl-methionine (SAMe)	May help alleviate depressive symptoms when uses as adjunct to prescription medication.[c]	Nil at recommended doses. Caution with patients on warfarin.	Consider cost to patient versus prescription agents. Variance in active ingredient(s) between manufacturers may limit efficacy.
Zinc	May assist depressive symptoms as adjunct to prescription medication[d]	Nil at recommended doses. Caution with patients on warfarin.	Consider dietary enhancement first. Variance in active ingredient(s) between manufacturers may limit efficacy.
N-acetyl cysteine	Appears to have symptom reduction efficacy in bipolar depression at a dose of 1g bd[e] and possibly in major depression[f]	Nil at recommended doses. Caution with patients on warfarin.	Consider dietary enhancement first. Consider cost to patient versus prescription agents. Variance in active ingredient(s) between manufacturers may limit efficacy.
Multivitamins	No benefits evident.[g]	Nil at recommended doses. Caution with patients on warfarin.	Encourage dietary enhancement instead.
Folate, (including L-Methylfolate)	May assist depressive symptoms as adjunct to prescription medication.[h]	Nil at recommended doses. Caution with patients on warfarin.	Consider dietary enhancement first. Variance in active ingredient(s) between manufacturers may limit efficacy. Clinical utility of MTHFR* genotying is unclear[i]

Note: *Complementary therapies are not necessarily tested to the same standard as conventional medicines.
MTHFR = Methylenetetrahydrofolate.
References: [a]Martins (2009), Sarris et al. (2012), [b]Linde et al. (2008), [c]Papakostas et al. (2010), [d]Lai et al. (2012), [e]Berk et al. (2008a), [f]Berk et al. (2014), [g]Pipingas et al. (2013), [h]Taylor et al. (2004), [i]Nielsen et al. (2015)

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the nucleus accumbens may have antidepressant effects (Bewernick et al., 2010; Holtzheimer et al., 2012; Lozano et al., 2012; Merkl et al., 2013). However, two recent industry sponsored trials have been terminated early due to the lack of positive interim results (Dougherty et al., 2014; Morishita et al., 2014). DBS is potentially associated with a number of serious but uncommon surgical complications including haemorrhage or infection and a wider range of reversible stimulation effects such as insomnia.

Vagus nerve stimulation (VNS). Vagus nerve stimulation involves the surgical implantation of a pulse generator, similar to a pacemaker, in the chest wall that is connected to stimulating electrodes attached to the vagus nerve in the neck. The main existing indication for VNS is in the treatment of refractory epilepsy. A small series of studies has evaluated whether VNS has antidepressant effects (Nemeroff et al., 2006), and it appears to produce some antidepressant response but this emerges slowly and only in a minority of patients. Clinical treatment of depression using VNS is not available in most countries but a transcutaneous form of VNS that does not require surgery targeting the auricular branch has been developed and is being evaluated for clinical use.

Complementary therapies. The marked growth in complementary therapies health spending reflects the public demand for non-prescription medicines and health supplements (MacLennan et al., 2002; Xue et al., 2007). While this in part may reflect limitations of existing pharmacological therapies, it appears many people use complementary therapies not as an alternative to prescription medicine (Ennis, 2014), but to enhance a general sense of health and wellbeing (Astin, 1998; Moerman and Jonas, 2002). Clinicians should be aware of the safety and efficacy profiles of these therapies in order to help guide patients that elect to take them (Braun et al., 2010). Awareness of some potential interactions with prescription medications is also important (Gouws et al., 2012). An open discussion with patients about their use of complementary therapies can assist overall engagement with care and help build rapport. The discussion should also include advice on the importance of a healthy diet and regular exercise for optimal recovery and wellbeing (Berk et al., 2013). Complementary therapies have mainly been studied in the setting of mild to moderate depression, and as adjuncts to prescription medication in more severe depression and in bipolar disorders.

Several of the more commonly used complementary therapies to assist mood are summarised in Table 17. Given the morbidity and mortality risks of severe depression and bipolar disorders, complementary therapies should not be used instead of established prescription agents. A problematic issue with complementary therapies is the marked variability in active ingredient between brands, reflective of lower regulatory requirements (Breach et al., 2003; Petroczi et al., 2011). This makes it harder to translate the limited evidence base to many of the commercially available products. Given the sometimes substantial costs of complementary therapies, it is reasonable to discuss the merits of their ongoing use in a vulnerable patient group with often scarce resources. By the same token, if complementary therapies provide subjective benefit to patients, are affordable, are free of serious adverse effects, and do not prevent use of more proven conventional treatments, then the use of such therapies by patients should be respected. For some patients the sense of active coping and empowerment from using complementary therapies may enhance their sense of wellbeing and control, producing psychologically meaningful effects for them (Moerman and Jonas, 2002).

Healthy Lifestyles

Diet and mental health. Since the end of 2009, there has been an exponential rise in the number of published studies documenting associations between higher diet quality and a reduced likelihood or risk for depression, as well as an increased likelihood or risk for depression with higher intakes of unhealthy food products; such studies have been published from countries across the globe in children, adolescents and adults (Jacka et al., 2010, 2011, 2013; Sanchez-Villegas et al., 2009). A recent meta-analysis has confirmed that adherence to a 'healthy' diet pattern is associated with a reduced likelihood of depression in adults. Although studies were too few for confirmation, there was a strong trend also observed for a positive relationship between 'western' style (unhealthy) dietary pattern and depression (Lai et al., 2014). Similarly, another recent meta-analysis reported that high adherence to a Mediterranean diet, also a very healthful dietary pattern, is associated with a 30% reduced risk for depression (Psaltopoulou et al., 2013). More recently still, a systematic review confirmed relationships between unhealthy dietary patterns and poorer mental health in children and adolescents (O'Neil et al., 2014).

Although the evidence base for the relationship between dietary intake and mental disorders is very new, and thus largely limited to animal studies and observational studies in humans to date, a recent large-scale dietary intervention provides important support for the findings of the meta-analyses. In the PREDIMED study, individuals at increased risk for cardiovascular events were randomised to a Mediterranean diet supplemented with either extra-virgin olive oil (EVOO) or mixed nuts, with a low-fat control diet. Although not statistically powered to assess prevention of depression, the results demonstrated a strong trend to a reduced risk for incident depression for those randomised to a Mediterranean diet with nuts, and this protective effect was particularly evident in those with type 2 diabetes (Sanchez-Villegas et al., 2013). Similarly, a recent prevention trial in older adults in the US showed that dietary counselling was as effective as psychological therapy in reducing rates of transition to case-level depression (O'Neil et al., 2013; Stahl et al., 2014). The first RCT to test causal relationships between dietary improvement and improvements in mental health is underway (O'Neil et al., 2013), and existing observational and prevention data support a causal relationship between diet quality and depression (Jacka et al., 2012) and are supported by extensive pre-clinical data.

Physical activity/exercise. The existing observational data have shown that regular exercise is protective against the development of depression, while physical inactivity is a risk factor for the development of depressive symptoms. For example, results from the Nurse's Health Study, involving nearly 50,000 American women, showed that women who were more physically active had a reduced risk for clinical depression over a ten year follow up period (Lucas et al., 2011). In the 1958 and the 1970 British birth cohort studies, comprising nearly 30,000 people, increased leisure-time physical activity in adolescence was consistently related to increased well-being in adulthood (Sacker and Cable, 2006). Physical activity is also associated with a reduced risk of developing de-novo depression in elderly people (Pasco et al., 2011). A recent meta-analysis supports the link that physical activity prevents depression (Mammen and Faulkner, 2013). Physical activity is thus important in reducing relapse or the transition to case level disorder in those with subsyndromal symptoms as well as in preventing de novo depression.

Exercise is also established as an effective treatment strategy for depression. A meta-analysis, including results from 11 randomised controlled clinical trials, concluded that exercise is highly

effective as a treatment intervention in depression with a large pooled effect size (Stathopoulou et al., 2006). Another meta-analysis including 90 articles and over 10,000 patients confirmed that exercise reduces depressive symptoms in patients with chronic illness, suggesting that patients with comorbid physical conditions also benefit from recommendations to exercise (Herring et al., 2012).

Exercise is important for general wellbeing and seems to have efficacy as an augmentation strategy in major depression (Rimer et al., 2012). A possible mechanism appears to involve brain-derived neurotrophic factor (BDNF) (Szuhany et al., 2015). However, motivating more severely depressed patients to engage is a challenge (Schuch et al., 2015). Positive studies in the field may in part be mediated by selection bias with less severely depressed cases and those improving more likely to engage in studies. Also, blinding in comparator trials is a problem. Nonetheless, it stands to common reason that for both mood and general medical wellbeing sedentary patients should be actively encouraged to engage in regular exercise.

Smoking. Evidence from observational studies supports smoking as an independent risk factor for mood and anxiety disorders (Moylan et al., 2012). Importantly, a recent systematic review and meta-analysis showed that smoking cessation is associated with reduced depression, anxiety, and stress and improved positive mood and quality of life compared with continuing to smoke. The effect sizes were as large for those with psychiatric disorders as those without and were equal or larger than those of antidepressant treatment for mood and anxiety disorders (Taylor et al., 2014). Thus, smoking cessation should receive more prominence as a clinical target in those with mood disorders.

The WHO has stated "there is no health without mental health" and therefore, recommendations and encouragement to follow national guidelines for dietary and exercise practices should be a prominent component of care for all people with depression and depressive symptoms.

Omega-3 PUFAs for mood disorders. Mood disorders are associated with pronounced reductions in Omega-3 PUFA (polyunsaturated fatty acids) status (Lin et al., 2010). Meta-analyses that have applied methodological rigour to the investigation of the role of Omega-3 PUFAs as treatments for clinical depression, rather than including studies based on self-report depression, show omega-3 PUFA, particularly EPA, to be efficacious (Lin et al., 2012).

The biological mechanisms underlying the antidepressant effects of Omega-3 PUFAs include, but are not limited to, regulation of neurotransmitters serotonin and dopamine; mood stabilization via arachidonic acid cascade; anti-inflammatory and anti-oxidant effects; and positive actions on neuroplasticity and neurogenesis. As such, the biological actions of Omega-3 PUFAs are similar to those of standard medications (e.g. antidepressants) and should be considered for use in patients for whom other treatment options are not acceptable. They should also be considered as adjunctive treatment. For this reason, clinical recommendations for the use of omega-3 PUFA, particularly those with a higher ratio of EPA to DHA, can be strengthened.

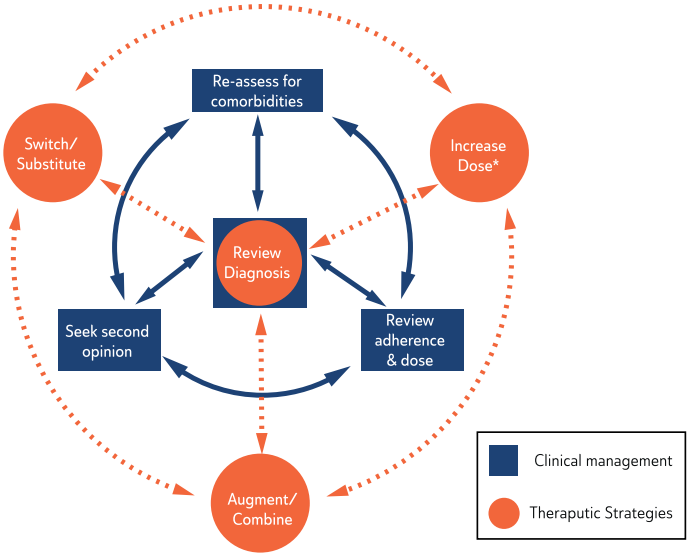
Sleep. With the exception of light treatment for seasonal affective disorder, and agomelatine (melatonergic agonist) for depression, there is not strong evidence for chronobiological treatment of acute depression (Kuiper et al., 2013).

Nonetheless, there is robust evidence for causal (often bidirectional) links between sleep and negative mood, including major depression (Harvey, 2011; Malhi and Kuiper, 2013). Consequently, a comprehensive approach to lifestyle in the maintenance phase of major depression should include assessment and where appropriate behavioural intervention for improving sleep (Asarnow et al., 2014). As with diet and exercise prescription, clinicians may not require specialised skills in behavioural sleep interventions. Rather, providing encouragement and psychoeducation to follow recognised sleep hygiene guidelines for achieving adequate sleep are likely sufficient.

Managing suboptimal response

Assessing treatment of poor response. Given the difficulties in defining treatment resistance or non-response (Malhi et al., 2005b), a practical approach is to consider partial or non-response to treatment as the persistence of depressive symptoms and a lack of

Figure 9. Strategies to address medication non-response.



Managing partial or no treatment response requires integration of clinical management and therapeutic strategies. Clinical management involves re-evaluating the diagnosis and formulation and then reviewing the dosage of medication prescribed and its relevance. It is also important to reassess for comorbidities especially anxiety, substance misuse or personality factors and at the same time consult colleagues for a second opinion. It is particularly important to seek the advice of others with experience/expertise when prescribing novel treatments.

*Therapeutic strategies also involve reviewing the diagnosis and formulation prior to optimising existing treatments. The latter may include checking medication plasma levels where relevant and increasing the dose administered. (*Note an increase in dose is only useful for those medications that have a steep dose-response curve.) Existing treatment can then be augmented with psychological and pharmacological strategies and combinations of treatments can be trialled. Finally, it may be necessary to change strategy and substitute treatment altogether by switching to alternative medications and/or psychological interventions.*

functional recovery (Malhi et al., 2009b). In practice, despite a clinician's best effort to subtype and tailor a patient's treatment, some patients do not respond to treatment as anticipated. Therefore, this section outlines how to assess non-response and implement appropriate strategies when a patient is non-responsive to treatment. The literature on non-response to pharmacological treatment is modest, and research on non-response to psychological therapy is limited.

Poor response to psychological therapy. Time to respond to treatment is shown to be longer with psychological treatment than pharmacological treatment (Hollon et al., 2005b). But, significant early improvement has been shown even after a few weeks of psychological therapy (Keller and Hautzinger, 2007) and an early response to psychological treatment is a strong predictor of achieving a stable response after longer term treatment (Tadić et al., 2010). However, not all patients will engage with or respond to psychological treatment, and it is these patients that require further assessment.

If a patient fails to respond after multiple sessions of CBT/psychological treatment, the first step should be to re-evaluate the diagnosis, taking note that the patient may have developed new symptoms, the depression may be more complex than originally thought, personality features may be contributing, or an alternative diagnosis, for example substance abuse, better fits the patient's symptoms. Sometimes a poor response may be the result of the therapist, such as a 'poor fit' between patient and therapist or the therapist not adhering to the treatment protocol, and chronic patients may indeed do worse with CBT (Scott et al., 2006). At this point it may be helpful to seek advice from colleagues. If it has been established that the original diagnosis was valid, then refer the patient to a psychiatrist for pharmacological treatment.

Poor response to pharmacological treatment. Antidepressant efficacy trials generally report response rates of 60–70% but the rate of remission is much lower at 30–40% (Nierenberg et al., 2007). Interestingly as the use of antidepressants has broadened, response rates have dropped by 3 points on the HAMD every decade antidepressants have been in use. In the STAR*D study (Trivedi et al., 2006), the remission rate following 10 weeks of citalopram therapy was 28% (HAM-D $\leqslant$7) whereas the response rate was 47% (QIDS-SR $\leqslant$5). As a rule of thumb, only 1/3 of patients will remit with initial antidepressant treatment. Treatment non-response is therefore a significant issue in managing depression. The first step in assessment of non-response is to review the diagnosis and treatment adherence.

After ensuring that the patient has been taking their medication as prescribed (many patients fail to collect a second script and/or or take it when they 'feel' depressed), several different strategies can be utilised (see: Figure 9), including increasing the dose of the current medication, augmentation, or switching to a different antidepressant (all strategies are discussed later). If at any point in the treatment process the patient is not responding to the treatment, an important step is to re-evaluate the diagnosis. Note that the patient may have developed new symptoms, the depression may be more complex than originally thought, or an alternative diagnosis better explains the patient's symptoms. Treatment may therefore need to pursue a new treatment algorithm. During this assessment, other unique and individual factors should be taken into consideration, such as the patient's personality and lifestyle, social factors or substance abuse, all of which can be contributing to depression. In some cases it may be necessary to seek advice from colleagues to provide a fresh perspective and

framework for management. If it has been established that the original diagnosis was valid, then it may be necessary to switch the patient to a new antidepressant.

When choosing a new antidepressant, consider one with different mechanisms of action to the original antidepressant. Before switching the patient's medication, consider which switching strategy will be utilised *(see: Switching strategies)* and inform the patient about the strategy and the new medication. If there is a reduction in the severity of symptoms, continue with the treatment and assess again in a month with the goal of achieving remission. If the symptoms plateau (only a partial response has been achieved), maximise the dose of the partially effective agent and then consider adding an augmenting agent or combining antidepressants (see the section on *Augmentation (Level I)* and the section on *Combining treatment*). If, after further evaluation of the patient, it is determined that the patient is still not responsive to antidepressant medication, the patient is considered to have treatment resistant depression (TRD), defined as a lack of improvement following adequate trials of two or more antidepressants. Note, when communicating this to the patient the term 'difficult to treat' is preferable because treatment resistant or refractory implies no hope of a response and may also be viewed as assigning blame. In TRD, research supports persisting with pharmacological strategies, but consideration of ECT, rTMS and/or psychotherapeutic approaches is also important (Parikh et al., 2009). These strategies are addressed below.

Re-evaluate diagnosis. Diagnostic review should include re-assessment of the subtype of depression (e.g. psychotic, melancholic, atypical), personality issues that could be underpinning depressive symptoms, any history of bipolarity and investigation of any underlying neurological medical conditions, particularly in the elderly. Unrecognised comorbid medical or psychiatric conditions, such as anxiety and undisclosed substance misuse often contribute to non-response (Papakostas et al., 2012). Re-evaluation of medical comorbidity may require appropriate investigations or referral. Review of psychosocial and personality issues may reveal significant perpetuating factors that have not been adequately addressed (such as issues pertaining to compensation following injury at work). Psychological treatment may therefore have been inadequate and should be reviewed. A review of pharmacological treatment should concentrate on assessing adherence, tolerability and adequacy of dosage. Assessing the ongoing morbidity and associated disability assists in monitoring suicide risk, which may worsen with failure to respond, and will also guide decisions about continuing outpatient management or admitting the patient to hospital. Referral for a second opinion can be a valuable step in reassessing management.

Comorbidity and undiagnosed bipolar disorder. It is unlikely that core features of major depression, such as depressed mood, anhedonia and feelings of hopelessness, occur in isolation from symptoms of anxiety, substance misuse, personality, adjustment or eating disorders; in fact, a large proportion (estimated 50–70%) of patients with depression report anxiety symptoms (Fava et al., 2004, 2008; Kessler et al., 1996), which is associated with reduced efficacy of antidepressant treatment (Papakostas et al., 2012).

These commonly co-occurring symptoms and comorbidities complicate diagnosis and treatment, and generally contribute to a poorer prognosis (Coryell et al., 1995; Fiedorowicz et al., 2011; Newton-Howes et al., 2006; Rief et al., 2000). Therefore, re-evaluating the diagnosis following partial or non-response to antidepressant treatment is crucial, and it is

important to consider the possibility of complex mood disorders in which depression may not be the primary or sole diagnosis.

Bipolar depression is another possibility that warrants consideration when diagnosing and treating depression, given that at least 10% of patients initially diagnosed with unipolar depression will subsequently experience hypomania/mania in the course of their illness, resulting in a revision of diagnosis to bipolar disorder and the modification of therapy – usually involving the addition of a mood stabiliser (Coryell et al., 1995; Fiedorowicz et al., 2011). There is also growing evidence to suggest that mixed symptoms commonly occur in a subset of patients with depression and these contribute to poor treatment response (Angst et al., 2010; Malhi, 2013; Malhi et al., 2014).

Paradigm shift. If the patient remains inadequately responsive despite having explored several reasonable treatment options, it is important to consider further individual patient factors, and unique illness characteristics that may be contributing to treatment resistance. In addition, it may be necessary to give consideration to alternative treatment options, outside of the standard treatment algorithm and seek a second opinion. Furthermore, it is important to bear in mind that the patient may have developed new symptoms, the depression may simply be more complex than originally thought or there may be social/lifestyle factors that are significant contributing factors. For example, since the commencement of the initial antidepressant, the patient may have experienced a change in their employment or lost their role altogether resulting in additional adjustment stress and complicating their care further. This would most likely have a negative impact on their relationships and social circumstances. In this instance, a comprehensive reassessment is needed. It is possible that the original diagnosis is incorrect or the formulation has been inadequate in capturing relevant factors. Returning to the 5P+ model and reassessing the patient's problems is in the best interests of the patient and may open up new possibilities for treatment (see: Figure 4).

If it has been established that the original diagnosis and formulation appears to be correct and the patient's symptoms are non-responsive to the previously suggested treatment options, novel treatment options may be warranted.

Continuing treatment. This may be an option if reassessment suggests that the duration of treatment has been inadequate, and frequent changes in medication have not allowed adequate time for effective treatment. For the most part, however, waiting before changing management unnecessarily risks delaying potential recovery. Most patients who are eventually going to respond to antidepressant treatment will show improvement within three weeks at a sufficient dose of medication (Posternak and Zimmerman, 2005; Tadić et al., 2010). If there is no improvement after three weeks, then an alternative strategy should be considered, particularly when the symptoms and impairment are severe. The involvement of a specialist (where available) is recommended and a second opinion should be sought.

Increasing the dose. Increasing the dose of antidepressant beyond the recommended maximum dose may increase efficacy for some but not all antidepressants. This option should be considered if the patient has had a partial response. This strategy is unlikely to be of benefit if there has been no response whatsoever. The evidence for the benefit of

high dose treatment is sparse with few randomised studies, though STAR*D did show some differential efficacy with an increase in the dose of SSRIs. However, a systematic review (Adli et al., 2005) was supportive of high dose treatment with tricyclics and tranylcypromine, but not SSRIs, suggesting they have a relatively flat dose-response curve in the treatment of depression.There was insufficient evidence for high dose treatment with SNRIs to draw any clear conclusions, but serum levels of antidepressants, if available, may help guide dosage, and this is particularly relevant for tricyclics. In this context, pharmacogenetic approaches to guide dosing may be available in the near future (Singh et al., 2014).

Before altering any treatment it is important to allow a trial of appropriate duration, usually three weeks, at adequate dosage (Licht and Qvitzau, 2002; Ruhé et al., 2006a). It is noteworthy that in practice high dose medication can often serve as a proxy marker of non-response. Many antidepressants have a relatively narrow therapeutic range in which the agent is considered effective and safe, and research shows that increasing the dose of these medications does not always increase effectiveness but may assist some individuals (Ruhé et al., 2006a). However, antidepressants, such as venlafaxine and TCAs (other than nortriptyline), have very broad dose ranges with up to a ten-fold increase in oral dosage, e.g., venlafaxine can be safely administered at effective doses from 37.5 mg to 375 mg (Debonnel et al., 2007). Clinical monitoring at high doses is especially important as side effects and therapy discontinuations usually increase with dosage, and it is prudent to seek a second opinion and institute QTc monitoring if an increase in dose above the recommended dose range is planned.

It is difficult to be prescriptive regarding duration of medication during any particular phase of treatment because both clinical improvement and lack of response are susceptible to many factors that can alter outcome. Therefore, duration recommendations are only a rough guide. If an adequate[9] dose has been administered for three weeks and with no response then switch medications, but if a partial response occurs, continue the current medication for a further week (at the same dose; but a future dose increase can be considered if remission is not achieved). If after four weeks of treatment there is no significant improvement, alternative strategies should be implemented.

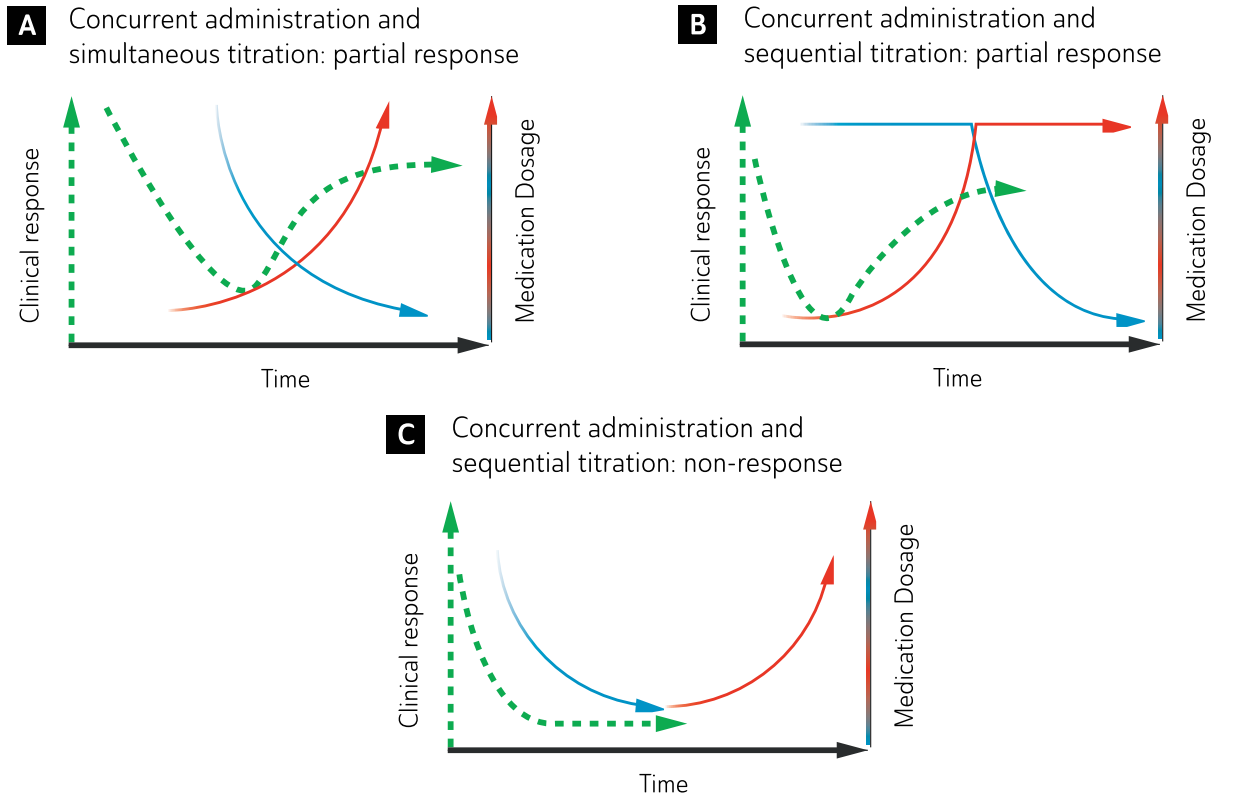
Switching antidepressants. Changing antidepressant medication and using an antidepressant from a different class is a common strategy in managing partial or non-response. This raises two considerations: 1) whether the decision to change medication is an effective strategy, and 2) when changing antidepressants, does it matter which antidepressant is prescribed?

With respect to the first question, a systematic review of three randomised controlled studies that examined switching antidepressant compared to continuation of the same antidepressant failed to show any overall advantage for switching (Bschor and Baethge, 2010). The three switching strategies studied were from fluoxetine to mianserin, from nortriptyline to fluoxetine and from venlafaxine to fluoxetine. However, clinical experience would suggest that switching is a helpful strategy in many cases and indeed there are few alternatives once an antidepressant trial has failed other than employing a case by case personalised approach.

The evidence to guide the choice of a second antidepressant agent is also inconclusive (Nierenberg et al., 2007). The STAR*D study, an open naturalistic study, showed equivalent

remission rates regardless of whether the patient switched from citalopram to bupropion, sertraline or venlafaxine (Rush et al., 2006). There is randomised controlled evidence for improved outcomes with switching from an SSRI to venlafaxine and mirtazapine, and from

Figure 10. Strategies for switching antidepressant medication.



The preferred switching strategy chosen should depend on the degree of response achieved from the initial antidepressant trial: Green dotted line depicts treatment response. Red line shows dose of initial (ongoing) antidepressant medication. Blue line shows dose of second (added) antidepressant medication. (A) changes in dose of both medications are implemented simultaneously, thus, beneficial for partial response; (B) dose changes are only implemented in one medication at a time, while maintaining the initial medication dose constant until the second medication has reached optimal dose; thus, this strategy is suitable for partial response; (C) this option is the safest strategy (least likely to cause any interactions) for switching from one medication to another, and is preferable for those who did not respond to the initial medication. (Adapted from Malhi et al., 2013a).

a tricyclic to an irreversible MAOI, but the evidence for switching from an SSRI to a TCA is inadequate even though clinical experience and expert opinion supports this strategy particularly in more severe depression (Nierenberg et al., 2007).

Once a decision to switch antidepressant treatment has been made, there are two main considerations: First, which *antidepressant* to trial next, and second, which *strategy* to employ when switching. RCTs have found that switching to a different antidepressant improves response and remission rates when switching for reasons of either non-response (Nakajima et al., 2011) or intolerability. Switching within a class (e.g., from one SSRI to another) is no less effective when compared to switching out of class (e.g., from an SSRI to a non-SSRI) (Ruhé et al., 2006b; Rush, 2007; Souery et al., 2011). If treatment has been

curtailed (e.g., medication has only been taken for a few days) because of side effects, then switching within a class to another agent may be a worthwhile option.

In primary care, the majority of patients are prescribed an SSRI antidepressant first-line. Patients who are intolerant to the initial SSRI often benefit from a second SSRI. It is recommended that patients use a lower dose of the second SSRI initially, and in some instances, it may be necessary to taper the first SSRI for a longer period (e.g., switching from citalopram to escitalopram can be immediate, but switching from fluoxetine to another antidepressant requires a wash-out period of at least a week before commencing the second agent at a lower dose). However, if the patient was non-responsive to the initial SSRI, switching out of class to a SNRI (i.e., venlafaxine), NDRI or TCA, is recommended (Ruhé et al., 2006b; Rush et al., 2006). Switching to a TCA carries the benefit of potentially higher response rates but is disadvantaged by the greater likelihood of side effects. If a patient begins antidepressant treatment with a TCA, for example as an inpatient, switching to another TCA has the advantage that a switch can occur without a wash-out period.

In most instances SSRIs are the starting point for antidepressant treatment, and therefore the majority of research has examined switching from SSRIs to another antidepressant. Thus, there is a lack of evidence for other switching combinations but most sequences have been trialled and there is ample empirical evidence for the majority. Of note, if side effects have contributed to poor response then switching to agents that are better tolerated is a useful option.

Switching strategies. There are three main strategies that should be considered when deciding the best way to switch medications: (i) overlap, (ii) taper or stop/start; and (iii) washout. The most common clinical strategy utilised is to introduce and withdraw medication seamlessly in order to minimise any un-medicated interim period and limit the possibility of serotonin syndrome. In practice, the choice of switching strategy depends on the degree of response achieved from the initial antidepressant trial (see: Figure 10).

The three strategies for switching antidepressant medication are:

(A) *Concurrent administration and simultaneous titration*: Changes in dose of both medications are implemented simultaneously, thus, overlapping medications. Although this option offers the advantage that the individual is always medicated and switching is achieved quickly, there is an increased likelihood of interactions and side effects because the medications are administered jointly.

(B) *Concurrent administration and sequential titration*: Dose changes are only implemented in one medication at a time. The initial medication is continued at full dose while gradually commencing the new medication. Begin tapering the medication that is being substituted once optimal dose has been met on the new medication.

This strategy is preferred for partial response because the cross-over is important to help retain any benefit achieved from the initial medication thus far. Similar to concurrent switch, there is an increased risk of interactions and side effects because the medications overlap. However, the cause of iatrogenic side effects is more easily identified because only one medication is modified at a time.

(C) *Separate administration and sequential titration*: Taper the initial medication and once this has been fully withdrawn, gradually introduce and titrate the new medication to optimal dosage. This option is the cleanest way of substituting one medication for another but takes much longer, especially if it also includes a washout period. This option also increases the chance of worsening because there is a considerable period when medication is at a sub-therapeutic dose. Therefore, this strategy is preferable for those who did not respond to the initial medication, because this switch can be done quickly without a washout period and has the advantage of not overlapping medications which increases the likelihood of side effects. However, switching to, or from, an MAOI requires a clear washout period of at least a week (and up to 5 weeks in the case of fluoxetine) to limit the risk of interactions.

Precision medicine. Familial patterns of response to psychotropics have long been observed (Propping and Kopun, 1973) and posited to be mediated by inter-individual genetic variability (O'Reilly et al., 1994). Genetic and dietary variability between ethnic groups can also result in wide pharmacokinetic variance (Silva, 2013). Yet most psychotropic agents have only been extensively studied in Caucasian populations (Ninnemann, 2012). Some have described this latter area as Ethno-psychopharmacology – ethnic variations influencing the effectiveness of psychotropics (Wong and Pi, 2012). This term has now been subsumed under the broader concept of pharmacogenetics – the study of how genetic factors influence efficacy, tolerability and safety of medications. It is hoped that genetics may enable more tailored psychotropic prescribing termed personalized medicine, and this concept is gaining momentum as the cost of genotyping has reduced (Insel, 2014). 'Precision Medicine' is the dominant umbrella term used to describe genetically guided prescribing (Collins and Varmus, 2015).

Genetic variations (polymorphisms) of metabolizing enzymes, drug transporters (such as those at the blood-brain-barrier), and target receptors coupled with nutrition factors (potentially inducing/inhibiting metabolism) are relevant in understanding both inter-ethnic (ethno-psychopharmacology) and inter-individual (precision/personalized medicine) variability of medication response (Ninnemann, 2012; Singh et al., 2014). Despite the rapidly diminishing cost of genetic testing, randomized controlled trials to firmly elucidate the clinical utility of routine genetically guided prescribing are needed (Singh et al., 2014). Nonetheless, this emerging genetic technology may be particularly relevant in prescribing optimally to ethnic groups other than Caucasians – such as Māori and Aboriginal and Torres Strait Islander populations. It may also reduce trial and error prescribing – an issue particularly relevant in mood disorders due to the relatively long time period between commencing a medication and discerning clinical efficacy.

HLA genotyping in patients of Asian background who may be treated with the mood stabilizer and anticonvulsant carbamazepine offer a good example of precision medicine in practice. Carbamazepine has an up to 75-fold risk of causing the potentially fatal skin reaction Stevens-Johnson syndrome and its related disease toxic epidermal necrolysis in patients of Asian ethnicity compared to Caucasians (Kulkantrakorn et al., 2012). It is now recommended such testing be carried out *prior* to prescribing carbamazepine (Chen et al., 2011). In years to come similar guidelines for lamotrigine are likely to emerge (Li et al., 2015). The relevance of this to Māori and Aboriginal and Torres Strait Islander populations is unclear as there is a lack of empirical data and pharmacogenetic studies are needed in these groups.

Some ethnic groups have higher rates of rapid metabolizer status at the hepatic cytochrome P450 enzyme system – potentially translating to higher doses of medication being needed (Cai et al., 2006; De Leon et al., 2006). Conversely, some ethnic groups may have higher rates of poor metabolizers and require lower doses to avoid toxicity (De Leon et al., 2006). Hepatic cytochrome P450 2D6 and 2C19 metabolizer status seem the most relevant for antidepressants, with dose adjustment guidelines stemming from earlier association studies (PharmGKB, 2015), But genetically guided versus unguided randomized controlled trials are needed to robustly elucidate the clinical utility of *a priori* genetic testing (Singh et al., 2014). Two such trials have been conducted (Singh, 2015; Winner, 2013) and should positive findings be replicated and have a clinically meaningful effect size, precision medicine in psychiatry will likely gain wider traction. At this stage – other than HLA testing of carbamazepine among patient of Asian ethnicity – precision medicine in psychiatry remains at the 'early adopter' stage (Thompson et al., 2015).

Augmentation (Level I). Augmentation refers to the addition of another agent that exerts a synergistic antidepressant effect. There is evidence from randomised controlled trials for the effectiveness of lithium and some second generation antipsychotics as augmenting agents.

Lithium, a widely supported and used augmentation agent, is found to be more effective than placebo in augmentation of TCAs, SSRIs and other antidepressants (Bauer et al., 2000; Crossley and Bauer, 2007). It is recommended that lithium be administered once daily at an oral dose that achieves trough plasma levels (blood sample taken 12 hours after last dose of lithium) within the therapeutic range (0.5 mmol/L to 0.8 mmol/l) (Berghofer et al., 2006; Malhi et al., 2011). If there is no response to lithium within 7–10 days, alternative strategies should be considered. Care should be taken when discontinuing the use of lithium as research shows that abrupt withdrawal of lithium following antidepressant augmentation with lithium results in significantly higher relapse rates (Bschor et al., 1999). Predictors of likely response to lithium augmentation include recurrent major depression with more than 3 recurrences and a family history in first degree relatives of bipolar or unipolar depression (Sugawara et al., 2010).

Second generation antipsychotics are widely used as add-on agents for TRD in clinical practice. In addition to empirical evidence, research studies support this strategy (Papakostas et al., 2007a; Philip et al., 2008). Placebo-controlled studies have found that aripiprazole, olanzapine, quetiapine and risperidone can be effective as augmentation agents. These are generally administered at much lower doses than those recommended for schizophrenia and bipolar disorder (Berman et al., 2007; Marcus et al., 2008; Philip et al., 2008) but this practice is off-label and these agents are not formally indicated for augmentation. Furthermore, adverse effects of these agents must be closely monitored, as weight gain, potential metabolic syndrome and extrapyramidal side effects are of great concern, especially in the context of long-term therapy. Once a stable response with augmentation has been achieved the gradual withdrawal of the augmenting second generation antipsychotic (SGA) agent should be considered. In some instances this may precipitate relapse and therefore ongoing use may be necessary.

Thyroid hormone has also been used to augment the effects of antidepressants in the treatment of major depression, however, the results from clinical studies are inconsistent. Most studies have been of T3 (liothyronine) augmentation, while T4 (thyroxine) has been evaluated to a lesser extent. It is reasonable to extrapolate the findings of T3 studies to T4

augmentation because T4 is a precursor of T3, which is similar in action but more potent. Earlier studies that examined T3 augmentation of tricyclic antidepressants had mixed results (Lam et al., 2009), and systematic review of T3 augmentation of SSRIs (Cooper-Kazaz and Lerer, 2008) provides equivocal evidence for its efficacy. T3 is beneficial for depressed patients with subclinical hypothyroidism, but T3 is also used as an augmentation agent for depressed patients without hypothyroidism. Patients augmented with T3 should be monitored in the same way as patients with hypothyroidism, with TSH, free T4 and T3 levels measured regularly (Rosenthal et al., 2011). In practice, despite conflicting evidence, thyroid augmentation is well tolerated (Cooper-Kazaz and Lerer, 2008) and may be a low-risk augmentation option for some patients.

A number of novel augmentation strategies have been trialled with variable success. Placebo controlled studies of augmentation with *buspirone* or *pindolol* have been unconvincing and hence these are not recommended (Lam et al., 2009; Martiny et al., 2012; Portella et al., 2011). Two randomised placebo controlled trials of augmentation with the stimulant *methylphenidate* have also failed to demonstrate efficacy (Patkar et al., 2006; Ravindran et al., 2008). A Cochrane systematic review of a range of stimulants that have been used for augmentation (Candy et al., 2008) found that the quality of randomised trials was overall poor and that although there was evidence that stimulants (including modafinil) reduced symptoms of depression, this was usually short-lived, clinical benefit was unclear, and effects non-specific. At present there is insufficient evidence to recommend the routine use of psychostimulants as an augmentation strategy. Similarly, the evidence base for the routine use of the dopamine agonist pramipexol is currently too limited to advise routine use (Cusin et al., 2013). As the literature is still evolving (Corp et al., 2014) clinicians are advised to exhaustively trial more evidence established therapies first and look for replicated RCT studies before considering such augmenting agents.

Combining treatment. Combining antidepressants has been a commonly used augmentation strategy among clinicians (Horgan et al., 2007).

A systematic review of clinical trials which assessed the efficacy of antidepressant combinations for the management of major depressive disorders concluded that there was evidence of greater efficiency than a single antidepressant in obtaining improvement using several combinations (mirtazapine plus SSRI and tricyclic plus SSRI), however the small number of clinical trials (5 trials) and methodological restrictions, made firm conclusions difficult (Rocha et al., 2012). A study that randomised 665 depressed patients to treatment with escitalopram plus placebo, or the combinations of bupropion with escitalopram or venlafaxine with mirtazapine (Friedman et al., 2012) showed no benefit for either combination treatment over escitalopram monotherapy.

There is some research, however, to suggest that combinations of antidepressants can be more effective than monotherapy without compromising tolerance (Bech and Csillag, 2012; Blier et al., 2010). A double-blind randomised trial where patients were treated with combinations of mirtazapine with fluoxetine, venlafaxine or buproprion showed that these were more effective for depression than fluoxetine monotherapy and that they were well tolerated (Blier et al., 2010). A recent meta-analysis found that mirtazapine and tricyclic antidepressants in combination with SSRIs are better than SSRI monotherapy in achieving remission (Rocha et al., 2012). Additionally, of the studies that reported dropout rates and

side effects, there was no difference between the combined and monotherapy groups. Similarly, a double-blind study that compared mirtazapine monotherapy and paroxetine monotherapy against a combination of both antidepressants reported that remission rates after 6 weeks were highest for the latter (Blier et al., 2009). However, not all research has supported the use of combinations and not all combinations are pharmacologically sound (Licht and Qvitzau, 2002). Long-term placebo-controlled comparator studies are needed to substantiate a recommendation of polypharmacy (Rush, 2010). When determining which antidepressants to combine, a rationale based on pharmacokinetic advantage or synergistic action, should inform the decision, in addition to past experience and knowledge. For example, venlafaxine and mirtazapine are pharmacologically synergistic or complementary because of their distinct receptor profiles (Malhi et al., 2008).

Controversy remains regarding this practice but many psychiatrists use antidepressant combinations in some of their depressed patients with positive reports (Dodd et al., 2005; Keks et al., 2007; Malhi et al., 2013a; Ng et al., 2006; Rush et al., 2011; Thase, 2013). Given this uncertainty and the potential for adverse interactions with medication combinations, patients should be well advised and their consent obtained before antidepressant combinations are employed.

Recommendation Box 5.

THE MANAGEMENT OF TREATMENT RESISTANT MDD*	Grade
5.1. The first step when faced with non-response should be to re-evaluate the formulation in particular the diagnosis.	CBR
5.2. The clinical assessment of a patient with treatment resistant depression should include a review of their treatment history, in particular their engagement with psychotherapy, and adherence to medication at the dosages prescribed. A re-evaluation of potential personality, psychiatric and medical comorbidities, and ongoing psychosocial stressors is also necessary. If the diagnosis is uncertain, or the reason for treatment non-response is not evident, then (where possible) a second opinion should be promptly sought.	CBR
5.3. In instances where a partial response has been achieved, if feasible an increase in antidepressant dose should be considered.	CBR
5.4. If after a partial response has been achieved further improvement does not occur, then, where possible, first consider augmentation and/or combination therapy prior to considering alternative strategies such as switching/substitution.	CBR
5.5. Optimal treatment for both acute severe depression and chronic depression is a combination of pharmacotherapy and psychotherapy. The combination can consequently be considered first line for treatment resistant depression.	CBR

Footnote: If inexperienced in using medication doses above the recommended maximum, then consider seeking a second opinion. If symptoms have not significantly improved after a few weeks of treatment, re-evaluate the diagnosis.

*** Also** refer to Recommendation Box 6.

Brain stimulation strategies to address poor response in acute major depressive disorder

Electroconvulsive therapy. Although ECT has been seen as a last resort in treatment resistant depression it can be regarded as a reasonably efficacious option to consider before esoteric medication combinations. The response rate to unilateral ECT in patients with non-psychotic depression who have failed one or more medication trials has been shown to be as high as 48% (Prudic et al., 1996). A more recent meta-analysis (Heijnen et al., 2010) found remission rates with ECT of 48% for medication refractory patients compared to 64.9% for patients who had not received pharmacological treatment prior to ECT. Heijnen et al. (2010) made the point that most studies examined response rates to unilateral ECT at a time when doses for unilateral were low (2–2.5 x seizure threshold) relative to current practice (5–6 x threshold) and response rates may therefore be under-estimated. These remission rates can be compared with those demonstrated by the STAR*D study which showed that the remission rates for the first, second, third and fourth treatment steps were 36.8%, 30.6%, 13.7% and 13% respectively (Rush et al., 2006). For antidepressant monotherapy strategies, switching to a third antidepressant after two consecutive failures produced a low remission rate of less than 20% (Fava et al., 2006).

These data suggest that ECT may be a more effective treatment than further pharmacological strategies in many patients who have failed to respond to one or more medication trials. It should therefore be considered as an option for treatment non-response early in the treatment algorithm and not left until there have been multiple treatment failures. The decision to recommend ECT after the first or subsequent medication failures needs to be made after considering the issues of ECT side-effects, safety and patient acceptance or preference. These need to be balanced against the potential adverse consequences of delaying recovery by persisting with less effective pharmacological strategies.

Repetitive transcranial magnetic stimulation. All substantive evaluations of the efficacy of rTMS have been conducted in patients with some degree of treatment resistance with many of the trials including patients who have failed to respond to 2 or more antidepressant medication trials where the likelihood of further medication response is quite low. In this context, rTMS has established efficacy, as confirmed by multiple meta-analyses (for example Schutter, 2009; Slotema et al., 2010). Therefore, it is a sensible treatment option in patients who have failed to respond to initial antidepressant therapy, or who have significant problems with tolerating medication treatment.

Treatment options in major depressive disorder maintenance phase

The clinical aim during maintenance phase is to prevent relapse/recurrence, and to decrease future risk of relapse/recurrence by increasing resilience at biological, psychological, social and lifestyle levels. A number of psychosocial variables and lifestyle factors (e.g., accommodation, social support, employment) are likely to influence the risk of relapse or illness recurrence. These include substance use, the experience of significant life events or ongoing psychosocial stressors, the presence of comorbid medical or psychiatric illnesses and the characteristics of the depressive illness itself (McGrath et al., 2006; Rucci et al., 2011). For example, more severe depression and a history of more frequent or longer

duration episodes are associated with higher relapse rates. Particular attention should be paid to minimising or ameliorating residual symptoms, which are strongly linked to increased relapse rates (Kessing and Andersen, 2005; Ramana et al., 1995).

Monitoring and adherence. The therapeutic relationship established during initial treatment and further developed during the continuation phase is critical to optimal maintenance phase treatment. During this time, patients should be monitored for early signs of relapse. Sessions

Recommendation Box 6.

* ECT and rTMS IN THE MANAGEMENT OF TREATMENT RESISTANT DEPRESSION	Grade
6.1. ECT is an effective therapy for medication resistant depression that should be considered after one or more unsuccessful medication trials.	EBR I
6.2. rTMS is an effective therapy that may be considered when patients have failed one or more trials of medication	EBR I
6.3. ECT is an effective therapy for medication resistant depression that may still be considered after failure of rTMS.	CBR
6.4. ECT should not be regarded a treatment of last resort and its administration should be considered on the basis of individual patient and illness factors.	EBR IV

Footnote: The option of using ECT before or after rTMS is a matter for clinical judgement; the evidence supporting the effectiveness of ECT is stronger but the side effect profile is better for TMS.

***Also** refer to Recommendation Box 5.

should include discussion of any side effects, and problem solving of stressful life events. Maintenance of a strong therapeutic relationship remains critical for continued engagement.

Many patients are likely to be reluctant to continue medication treatment after the initial resolution of a depressive episode. The clinician should encourage open discussion about the benefits and burdens of maintenance pharmacotherapy versus the probability and risks of relapse.

Monitoring for early signs of recurrence is critical and a plan to do this should be formulated early in the maintenance phase. The patient should be helped to identify symptoms that have emerged early in prior depressive episodes and thought given to whether these are likely to be identified by the patient or whether other individuals, such as family members, could be engaged in a process of monitoring for these. A clear plan should be outlined as to how the patient should respond if they notice the emergence of these early signs of relapse.

There is evidence that an active depression relapse prevention plan can improve antidepressant medication adherence, and reduce depressive symptoms but not necessarily reduce overall recurrence rates (Katon et al., 2001) (Level II). Relapse rates are greatest immediately following remission and diminish with time (Belsher and Costello, 1988). The risk of relapse during the continuation phase of treatment is relatively high and is increased by a variety of factors (see: Table 18).

Psychological treatments. Depression is predominantly a recurrent condition, and existing literature has paid insufficient attention to maintenance and relapse prevention relative to acute symptom relief (Mulder, 2015). Evidence-based psychotherapies share a

skill-development focus, and it is important to develop an understanding of how psychotherapies might interact with lifetime vulnerability to depressive episodes.

A 2015 meta-analysis and meta-regression (Biesheuvel-Leliefeld et al., 2015) found preventative psychological interventions across 25 identified studies were superior to treatment as usual (NNT = 5), and to a lesser extent antidepressant medication (NNT = 13).

Two psychotherapies have Level I evidence for effectiveness in preventing depressive relapse and/or recurrence. Cognitive behavioural therapy (CBT) has been found to reduce relapse and recurrence rates relative to treatment as usual in a meta-analysis limited to (*n* = 9) well controlled trials (Lynch, et al. 2010). In this meta-analysis, the pooled odds ratio for studies in which patients were on antidepressant treatment was 0.52, and for patients not on ADM was 0.45. A highly cited study compared relapse rates amongst three groups – responders to acute cognitive therapy who had therapy withdrawn, responders to acute medication with continuation medication, and responders to acute medication with placebo withdrawal (Hollon, et al., 2005). Those who had received cognitive therapy were less likely to relapse during continuation than those who had received medications (30.8% vs 76.2%), and were no more likely to relapse than patients who were maintained on continuation medication (30.8% vs 47.2%). There is some evidence that CBT's maintenance effects are more pronounced amongst people who have had several episodes of depression (e.g., Bockting et al., 2005).

Mindfulness-based cognitive therapy (MBCT), designed to reduce relapse or recurrence of depression, has been found effective over control in a meta-analysis (six included studies) with a mean risk ratio of 0.66 (Piet & Hougaard, 2011). The relapse rate for MBCT participants (*n* = 200) was 38%, compared to 58% for controls (*n* = 208). A second meta-analysis (four included studies, patients with three or more prior depressive episodes), also demonstrated the effectiveness of MBCT, with an aggregate odds ratio of 0.36 versus treatment as usual (Chiesa & Serretti, 2011). As noted above in the context of CBT, there is some evidence that MBCT is more effective amongst those with a greater number of prior episodes: planned subgroup analyses by Piet and Hougaard found relative risk reduction was 43% for participants with three or more previous episodes, and not significant for those with only two.

There is limited research into interpersonal therapy (IPT) as prophylactic against depressive recurrences, but initial studies have been positive (Beshai, et al., 2011). Some, but not all studies have found IPT to match the prophylactic effect of antidepressant medication (Lampe et al., 2013).

Table 18. Factors increasing the risk of acute relapse in depression.

Concurrent factors	Gender (female) Life events/social stress Comorbid medical illness Poor compliance Persistent insomnia Personality Substance use Stress Poor supports Unemployment
Depressive features	Severity of depression Duration of episode Presence of psychosis Residual symptoms Treatment resistance

Note: Concurrent factors should be taken into consideration when choosing treatment options.

References: (Backs-Dermott et al., 2010; Dombrovski et al., 2007; Dotoli et al., 2006; Iosifescu et al., 2004; Kanai et al., 2003; Kessing, 2003; Kessing and Andersen, 2005; McGrath et al., 2006; Ramana et al., 1995; Reynolds et al., 2006; Rush et al., 2006; Thase, 2011).
Pharmacological treatments

Pharmacological treatments

Antidepressant medication in maintenance phase. Ongoing antidepressant treatment following an initial treatment response has been shown to be of significant value in the prevention of relapse and/or recurrence of depression, with better medication adherence associated with lower recurrence rates (Akerblad et al., 2006) (Level I). A significant reduction in relapse or recurrence rates has been demonstrated for several classes of antidepressant medications including TCAs and SSRIs (Hirschfeld, 2001). Nearly all studies were limited to 12 months duration or less. There is some evidence of efficacy for up to three years in patients with recurrent depression (Kupfer et al., 1992) but the numbers studied are very small. The relapse rate between antidepressants and placebo lessen significantly after six months post randomisation so the evidence for continuing them beyond 12 months remains weak. Even with ongoing maintenance treatment recurrences can occur (Byrne and Rothschild, 1998).

Lithium in maintenance phase. In the majority of circumstances, patients should continue receiving the antidepressant medication that they responded to during the acute phase. If this was administered as an adjunct to lithium, then this too should be continued throughout the continuation and maintenance phases. However, in major depression, lithium monotherapy is an effective alternative maintenance treatment option (Cipriani et al., 2006) and may be considered if antidepressants cannot be tolerated (e.g., due to sexual dysfunction). Multiple trials over time have established the effectiveness of lithium monotherapy in the prevention of depressive relapse as confirmed by meta-analyses (Souza and Goodwin, 1991), with recommended levels typically at the lower end of the therapeutic range (Malhi et al., 2011; Schou, 1989). However, long-term administration of

lithium can be associated with serious side effects, such as renal and thyroid dysfunction (Van Gerven and Boer, 2006) which may complicate long-term treatment (Malhi et al., 2012d). Therefore, lithium levels must be monitored regularly.

Combined psychological and pharmacological treatments. Combining psychological and pharmacological treatments has been shown to improve clinical outcome and significantly decrease relapse and recurrence rates (Beshai et al., 2011), which may be partially due to the effect of psychological treatments on adherence (Pampallona et al., 2004). More specifically, research trials have found that maintenance CBT in combination with antidepressant medication was superior in preventing relapse to maintenance antidepressant medication alone (Beshai et al., 2011; Paykel et al., 1999), and the observed advantage persisted several years later (Paykel et al., 2005). IPT in combination with pharmacotherapy is more effective than either treatment alone (Cuijpers et al., 2011b), but more research is needed on IPT in combination, as well as other psychological interventions.

Electroconvulsive therapy treatment in maintenance phase. Continuation and maintenance phase ECT is sometimes utilised in patients who have achieved acute clinical response to this treatment. However, the evidence base for this approach is relatively limited and comprises predominately uncontrolled case series. A RCT of maintenance ECT compared with continuation pharmacotherapy (lithium plus nortriptyline) showed no difference between the groups, both having approximately 46% of patients with continued remission after 6 months. This is a relatively high relapse rate for either therapy given that approximately 40% of the patients who remitted with ECT were then excluded within one week and before randomisation, 20% because of relapse (Kellner et al., 2006). Further, in a retrospective chart review based case-control analysis, relapse rates with maintenance ECT over a number of years were shown to be substantially lower than that with antidepressant medication alone in a similar group of patients who had responded to acute phase ECT (Gagne et al., 2000) (Level III). One small randomised trial in elderly patients with psychotic depression compared maintenance treatment with nortriptyline to nortriptyline plus ECT. They found that relapse occurred sooner in the medication alone treatment group compared with those who were treated with combination pharmacotherapy and ECT (Navarro et al., 2008) (Level II).

Recommendation Box 7.

MAINTENANCE TREATMENT OF MDD	Grade
7.1. Patients with depression should be monitored regularly beyond the acute phase of treatment to ensure complete remission of symptoms and full functional recovery.	CBR
7.2. MBCT or CBT should be offered as a relapse prevention intervention, particularly amongst patients with recurrent depressive episodes.	EBR I
7.3. Once a satisfactory therapeutic response has been achieved, antidepressant dosage should remain the same during continuation and maintenance phases of treatment.	EBR I
7.4. Maintenance antidepressant treatment should be continued for at least six months and up to one year[a].	CBR

Notes: Once remission has been achieved, antidepressant medication confers preventive benefit.
The choice of antidepressant dose is also determined by additional factors such as prior illness severity and response to treatment, comorbid disorders and medication tolerance.
Footnote: a. This is particularly important if a recurrent pattern of illness has been established.

Duration and discontinuation of maintenance treatment. Limited research has explored optimal duration of medication treatment in the maintenance phase. One clinical trial has shown that following maintenance therapy the relapse rate when transferring from active treatment to placebo is lower if maintenance therapy has continued for a longer period of time (Reimherr et al., 1998). Recurrence rates when patients remain on medication past one year are likely to be lower over subsequent years (Kornstein, 2008). A second trial demonstrated that antidepressant medications continue to have relapse prevention benefits for up to 5 years following commencement of treatment (Kupfer et al., 1992) (Level II). Once remission has been achieved, expert consensus recommends continuation of antidepressant treatment at the therapeutic dose that was effective during acute treatment for at least 1 year following an initial episode and at least 3 years for recurrent episodes (Bauer, 2007) and episodes which included psychotic features (Viguera et al., 1998) (CBR). Maintaining the therapeutic dose that was effective during acute treatment is important because this dosage is generally more efficacious in preventing relapse or recurrence than lower 'maintenance doses' (Dawson et al., 1998; Reynolds et al., 1999; Thase, 2006).

When patients have received maintenance antidepressant medication, cessation of medication should occur slowly with a taper over an extended period of time because withdrawal symptoms may be experienced. Discontinuation symptoms may emerge following the cessation of all classes of antidepressants. The risk of discontinuation symptoms is greatest with higher doses of antidepressants and longer duration of treatment, however symptoms are usually transient and mild, and resolve with antidepressant reinstatement (Perahia et al., 2005). Amongst the antidepressants, discontinuation symptoms are more likely with venlafaxine (Haddad and Anderson, 2007; Tint et al., 2008) and short-acting SSRIs (especially paroxetine), but less likely with fluoxetine (Michelson et al., 2000; Schatzberg et al., 2006). Abrupt cessation of TCAs may cause cholinergic-rebound phenomena (flu-like illness, myalgia and abdominal cramps). Therefore, a slow taper of medication over a longer period of time is preferred in order to reduce the likelihood of discontinuation symptoms but may not impact the likelihood of early relapse (Viguera et al., 1998) (Level II).

Further, when patients are withdrawn from medication a clear plan for monitoring for potential symptom re-emergence should be put in place. During medication withdrawal, more frequent visits should be scheduled to ensure adequate monitoring and detection of early signs of depression recurrence. Patients should be informed as to the potential symptoms that might emerge. Family members or carers may also need to be engaged in this process and, it would generally be prudent to avoid tapering off medications when patients are concurrently negotiating life events.

Clinical management of bipolar disorder

Compared with major depressive disorder, bipolar disorder is more complex and difficult to treat and polypharmacy is more common. There is no evidence for psychological monotherapy and adjunctive psychological therapies are primarily used during the maintenance phase of treatment.

Management of mania

Manic symptoms can occur within depression as mixed features, and with increasing severity from hypomania and mania through to mania with psychosis.

Severe mania. Patients suffering from acute mania often have moderated insight – especially when experiencing psychotic symptoms. In these instances involuntary treatment may be required and this should be given with as much empathy and information as possible, while recognising that this may not be fully accepted or assimilated at the time. The purpose of treatment is to protect the patient and others from the adverse effects of the illness while actively relieving distress and treating the core symptoms of the disorder, which comprise acute symptoms of mania, behavioural disturbance and cognitive disturbance (See Tables 2 and 8 and Figure 11).

Acute mania is a medical emergency, and often necessitates use of mental health legislation. Care should be provided in a low stimulus environment with support from health professionals. Treatment usually requires short-term use of a combination of benzodiazepines and antipsychotics, but delirious mania and mania with catatonic features (not attributable to an organic cause) also respond particularly well (and promptly) to ECT. Therefore ECT should not be unduly delayed, but at the same time adequate consideration needs to be given to the restraint needed for anaesthesia (England, et al. 2011; Grenier et al. 2011; Jacobowski et al. 2013; Malhi et al. 2012c).

Hypomania. At the other end of the spectrum manic symptoms and signs often present in less severe form and for shorter periods of time. Hypomania can be difficult to distinguish from normal experiences and behaviour and patients are often unaware that their thoughts, feelings and behaviour are in any way unusual. Consequently they may be reluctant to accept that anything is wrong or that they need treatment. Indeed, the hypomanic state is one of the primary reasons for patient ambivalence about the diagnosis of bipolar disorder and prophylactic treatment (Lobban et al., 2012). By definition hypomania is self-limiting and often resolves with only modest use of medications and psychosocial interventions, but usually some adjustments to treatment are necessary and these should follow the general principles of managing mania. (APA, 2013; Walsh et al. 2015; Woo et al., 2015).

Mania. It is crucial to taper and cease any agents with mood-elevating properties (e.g. antidepressants, stimulants) and institute general measures such as reducing stimulation, lowering activity level, delaying the individual from making important decisions and maintaining a structured routine. To achieve this safely, it may be sufficient to develop a therapeutic alliance and offer a diagnosis, but often admission to a suitable containment facility is required (Berk et al., 2004). Individuals suffering a manic episode can be persuasive,

push limits and rationalise their impulsive or reckless behaviour to make a case for not being admitted. Medications are essential to address the biological symptoms of mania, and counter heightened arousal (Geddes and Miklowitz, 2013; Malhi et al., 2009d, 2012a; Nivoli et al., 2012; Vieta et al., 2008b; Yildiz et al., 2011). But equally, inclusion and informative counselling of family members/carers is an important consideration from the outset and their involvement will be particularly important during the patient's subsequent care (Berk et al., 2011).

Pharmacotherapy. The pharmacotherapy of mania involves treatment with anti-manic agents. The fundamental goals of such medications are to reduce arousal, agitation and aggression, and begin the process of treating core manic symptoms including behavioural disturbances and psychosis, if it is present. Therefore, a combination of medications is often necessary. *See*: Figure 11, *Tables 19*, and *20* for a step-by-step approach to medication choices for the treatment of acute mania. The choice of medications and their route of administration is determined by the availability of medications, the required speed of onset of action, the degree of cooperation by the patient with prescribed treatment, and the proposed future choice of medications (Cipriani et al., 2011) (*see: Table 19*).

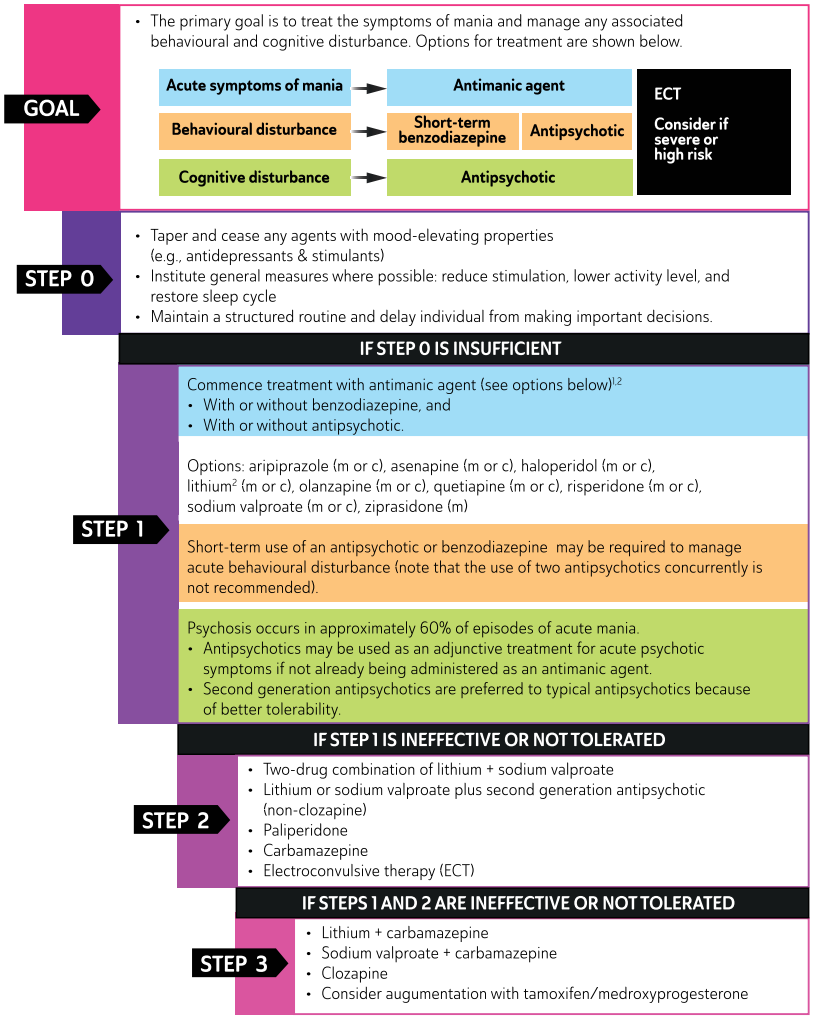
Brain stimulation methods. There is a limited but consistent evidence base supporting the use of ECT for the treatment of acute mania. A recent systematic review (Versiani et al., 2011) identified 28 studies investigating ECT as a treatment for acute mania. Although identifying methodological shortcomings in the studies reviewed, the systematic review concluded that ECT was an effective treatment for mania, especially in more severe or refractory cases. A recent literature review (Loo et al., 2011) concluded that in acute mania, ECT has clinically meaningful efficacy, including in patients who have failed to respond to medication. However, there is insufficient evidence to support one electrode placement over another in treating mania and methodological problems such as inadequate dosing for unilateral ECT hamper meaningful comparisons between unilateral and bilateral placements.

Although preliminary studies have explored the use of rTMS in mania, especially the use of high frequency stimulation applied to the right prefrontal cortex, there is insufficient evidence to support its clinical use at this stage.

Psychological interventions. The cognitive, emotional and behavioural dysregulation of acute mania is a barrier to the skill-development targets of the structured psychological interventions (Geddes and Miklowitz, 2013). A handful of preliminary studies have investigated the efficacy of psychological interventions for inpatient treatment of acute mania, providing some suggestion that chronobiological strategies (especially those that can be imposed, like dark therapy) warrant further investigation (Crowe and Porter, 2014).

There is strong clinical consensus about the benefits of engaging with people even in acute mania, making all reasonable efforts to work in a genuinely collaborative and normalising way (Cooke et al., 2010). Unstructured supportive psychotherapy (which may include psychoeducation about bipolar disorder) is likely to be useful for the patient and their family during acute mania. Acute settings also provide an opportunity to engage individuals for future psychological therapy, especially after the most severe elements of mania begin to

Figure 11. Management of Mania.



The management of mania is illustrated as a series of steps. The primary targets of treatment are 'ABC': Acute symptoms of mania, Behaviour disturbance and Cognitive disturbance.

m = monotherapy, c = combination.

[1]Oral risperidone, olanzapine, quetiapine or asenapine statim OR intramuscular haloperidol, olanzapine statim; choice determined by the patient's capacity to cooperate with oral medication.

With olanzapine, benzodiazepines need to be administered with caution because of potential for oversedation (see footnote in Table 19: Medications used in the management of mania).

Whereas, in conjunction with haloperidol, a benzodiazepine is useful because of the risk of acute dystonia.

Plan to change to oral medications as soon as possible and supplement oral medications with haloperidol if required by the patient's mental state.

If oral medications cannot be used after 2–3 injections of short acting intramuscular antipsychotics, zuclopenthixol acetate 50–100 mg may be used intramuscularly to provide parenteral medication without the need for frequent injections.

[2]Add lithium slow-release 450 mg (or immediate release 500 mg) at night OR add valproate 500 mg twice daily, if concerned about use of lithium (or patient refuses). Use non teratogenic agents (SGAs) if patient is pregnant.

Check the blood level of lithium or valproate after five days.

For lithium, check full blood count, renal function, thyroid function, and calcium level prior to starting lithium or as soon as possible following introduction and screen for pregnancy using beta hCG.

Table 19. Medications used in the management of mania.

Generic name	Routes of administration	Dose range	Effectiveness	Extra notes	Level of evidence	Emergency management*
MOOD STABILISER						
Lithium	Oral	Start 500–750 mg at night (depending on body mass). Serum trough level 0.8 to 1.2 mmol/L. Reduce to 0.6 to 0.8 mmol/L. once euthymia is achieved.	High but takes 7 days or more	Most effective mood stabiliser. May reduce suicide risk. Note side effects with long-term use and teratogenic risk.	I	
ANTICONVULSANTS						
Carbamazepine	Oral	Starting dose of 400 mg daily. Serum levels and clinical efficacy not closely correlated.	Moderately high but takes 7 days or more	Induces CYP enzymes 1A2, 2C9, 2C19, 3A3 & 4^. Complicated dosing of other agents if they are needed. Note teratogenic effects.	I	
Oxcarbazepine*	Oral	600 to 1,200 mg daily.	Moderately high but takes 7 days or more	Induces CYP enzymes 2C19 and 3A3 & 4. Less frequent blood dyscrasias than carbamazepine. Note teratogenic effects.	III	
Valproate	Oral	Starting dose 1000 mg daily Serum levels and clinical efficacy not closely correlated.	High but can take up to 7 days	Note teratogenic effects.	I	
ANTIPSYCHOTICS						
Amisulpride	Oral (tablet)	Initially 400 mg daily Up to 800 mg daily (or more).	High	Hyperprolactinaemia, akathisia	III[a]	
Aripiprazole	Oral (tablet) Intramuscular (not readily available)	Oral: 10 mg up to 30 mg daily Intramuscular: 9.75 to 15 mg. Elderly: Oral: 5 mg Intramuscular: 4.88 to 9.75 mg	High	Akathisia can be severe	I	Same as acute treatment
Asenapine	Oral (Sub-lingual wafer)	Initially 5 mg at night Up to 20 mg (or more) daily (starting with divided doses)	High	Moderate sedation. Lower likelihood of metabolic syndrome Requires cooperation with sub-lingual use Akathisia can be significant	II	

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Table 19. (Continued)

Generic name	Routes of administration	Dose range	Effectiveness	Extra notes	Level of evidence	Emergency management*
Clozapine (not approved for use in Australia and New Zealand for conditions other than schizophrenia)	Oral (tablet)	12.5 to 400 mg daily	High	Significant restrictions upon prescription and specified monitoring of physiological state Highly sedating Increased appetite Metabolic syndrome Cardiac risk	IV (in acute mania)	Not appropriate for emergency use as postural hypotension means gradual dose escalation is needed when initiating
Chlorpromazine	Oral (tablets and liquid)	Oral 100 to 1,000 mg	High	Risk of extrapyramidal side effects and acute dystonia (including laryngeal). Intramuscular injection is painful and carries risk of sterile abscess and therefore should not be used	II	
Haloperidol	Oral (tablets, liquid) Intramuscular Intravenous (monitor vital signs)	2 to 10 mg; Higher doses may be required, with careful monitoring of vital signs. EPS and dystonic reactions with drug naïve.	Very high and rapid	Extrapyramidal side effects are common, especially with advancing age. Risk of acute dystonia high in young, medication naive patients. Low doses (e.g. 0.5 mg) may be effective in other circumstances, such as puerperal psychosis. Use low doses in the elderly (0.5–1.0 mg).	I	Up to 20 mg May need to be repeated after 30–60 minutes. Combine with intramuscular injection of benzodiazepine
Olanzapine	Oral (tablet and wafer) Intramuscular (prepared from powder and solute)	Oral: 5 to 10 mg (can titrate up to 20 mg daily) Intramuscular: up to 30 mg daily	High	Very sedating Increased appetite Metabolic syndrome Lower dose in elderly	I	Same as acute treatment
Paliperidone	Oral (slow release capsule)	6-12 mg daily	Moderately high	Advantage of predominantly renal excretion. May have advantage over risperidone in CYP2D6 poor metabolisers	II	

(Continued)

Table 19. (Continued)

Generic name	Routes of administration	Dose range	Effectiveness	Extra notes	Level of evidence	Emergency management*
Clozapine (not approved for use in Australia and New Zealand for conditions other than schizophrenia)	Oral (tablet)	12.5 to 400 mg daily	High	Significant restrictions upon prescription and specified monitoring of physiological state Highly sedating Increased appetite Metabolic syndrome Cardiac risk	IV (in acute mania)	Not appropriate for emergency use as postural hypotension means gradual dose escalation is needed when initiating
Chlorpromazine	Oral (tablets and liquid)	Oral 100 to 1,000 mg	High	Risk of extrapyramidal side effects and acute dystonia (including laryngeal). Intramuscular injection is painful and carries risk of sterile abscess and therefore should not be used	II	
Haloperidol	Oral (tablets, liquid) Intramuscular Intravenous (monitor vital signs)	2 to 10 mg; Higher doses may be required, with careful monitoring of vital signs. EPS and dystonic reactions with drug naïve.	Very high and rapid	Extrapyramidal side effects are common, especially with advancing age. Risk of acute dystonia high in young, medication naive patients. Low doses (e.g. 0.5 mg) may be effective in other circumstances, such as puerperal psychosis. Use low doses in the elderly (0.5–1.0 mg).	I	Up to 20 mg May need to be repeated after 30–60 minutes. Combine with intramuscular injection of benzodiazepine
Olanzapine	Oral (tablet and wafer) Intramuscular (prepared from powder and solute)	Oral: 5 to 10 mg (can titrate up to 20 mg daily) Intramuscular: up to 30 mg daily	High	Very sedating Increased appetite Metabolic syndrome Lower dose in elderly	I	Same as acute treatment
Paliperidone	Oral (slow release capsule)	6-12 mg daily	Moderately high	Advantage of predominantly renal excretion. May have advantage over risperidone in CYP2D6 poor metabolisers	II	

Table 19. (Continued)

Generic name	Routes of administration	Dose range	Effectiveness	Extra notes	Level of evidence	Emergency management*
Quetiapine	Tablets (immediate or slow release)	Initially 50 mg daily up to 800 mg daily	High	High level of sedation	I	
Risperidone	Oral (tablet and rapidly dissolving "Quicklet")	1 to 4 mg up to 4 mg daily	High	May be less effective in CYP2D6 poor metabolisers[b]	I	
Ziprasidone	Oral (tablet) Intramuscular (not readily available)	Oral: 160 mg daily Intramuscular: 10 mg up to 30 mg daily.	High	Akathisia can be severe Best avoided in the elderly because of QT prolongation	I	Same as acute treatment

Notes: ^FDA recommends HLA-B1502 genotyping in patients of Asian ancestry to help gauge risk of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Intramuscular administration for emergency medication unless indicated otherwise.
References: [a]Cartwright et al. (2013), [b]De Leon et al. (2010).
Note: Not all agents listed above are approved in Australia and New Zealand for use in mania. In Australia and New Zealand, clozapine is not indicated for conditions other than schizophrenia.
An authority to prescribe is not given for other conditions, including mood disorders and the clozapine monitoring service will not allow clozapine to be used other than for schizophrenia.

Table 20. Adjunctive treatments.

Generic name	Routes of administration	Dose range	Effectiveness	Extra notes	Level of evidence	Emergency management
ANTIPSYCHOTICS						
Zuclopenthixol	Oral Intramuscular brief duration depot (acetate)	Oral: 10 to 50 mg daily. Less in elderly. Intramuscular: 25 – 50 mg Up to 150 mg daily Avoid intramuscular use in elderly.	Very high	Useful because of duration of action but also carries serious risks with extrapyramidal dystonia Avoid use in neuroleptic naive patients Short term depot usually given at intervals of 2 to 3 days	III	May be given twice in 24 hours to establish optimal dose, but should only be considered where repeated IM medication is needed.
BENZODIAZEPINES[#, **]						
Clonazepam	Oral (tablet) Intramuscular	Oral: 0.5 to 2 mg Maximum of 20 mg daily oral Intramuscular: 0.25 to 2 mg Maximum of 2 mg daily.	High	Absorption is slow and duration of action long Duration of several hours to 24 hours, longer in the elderly Risks of excessive dosing are significant Respiratory suppression may occur Intramuscular administration is painful Ataxia and dysarthria Tachyphylaxis and risk of dependence Paradoxical reactions with aggression and/or delirium may occur, particularly in the elderly	III	Repeat dose may be required after 12 hours
Diazepam	Oral (tablet) Intramuscular	Oral: 5 to 20 mg Maximum daily dose of 80 mg Intramuscular: 5 to 10 mg	Moderately high	Rapidly absorbed orally Sedative action when administered intramuscularly is unpredictable and the injection is painful Respiratory suppression may occur especially in the elderly Paradoxical reactions with aggression and/or delirium may occur, particularly in the elderly Tachyphylaxis and risk of dependence	CBR	

(Continued)

Table 20. (Continued)

Generic name	Routes of administration	Dose range	Effectiveness	Extra notes	Level of evidence	Emergency management
Lorazepam	Oral (tablet) Intramuscular	Oral: 1 to 5 mg Intramuscular: 1 to 4 mg. Maximum daily dose = 20 mg	High	Rapidly absorbed Respiratory suppression may occur, particularly with intramuscular administration Paradoxical reactions with aggression and/or delirium may occur, particularly in the elderly and patients with brain impairment Tachyphylaxis and risk of dependence	II	Same as acute treatment
Midazolam	Intramuscular	0.1 mg per kg body weight	High	Rapidly acting sedation, with a relatively high risk of respiratory suppression. Management of overdose: 1) Support of respiration. 2) Flumazenil 0.2 intravenously (up to 0.6 mg); can be lifesaving but may precipitate benzodiazepine withdrawal symptoms. Rapidly absorbed by injection and minimally painful.	III	Duration of action is very brief (<15 minutes) and may need to be repeated
NOVEL AGENTS						
Tamoxifen	Oral (tablet)	20–140 mg daily		Has been trialled as augmentation agent (with lithium) and adjunctive agent with medroxyprogesterone	III	

Note: Antipsychotic medications, Level I, Maximum doses suggested may be usefully exceeded according to need and blood levels, but the risks of adverse reactions increase significantly;
Benzodiazepines, Level III, Paradoxical reactions may occur with benzodiazepines in which hyperarousal, aggression and even delirium may occur.
#No benzodiazepines should be administered concurrently for the first hour of treatment.
****High** dose of benzodiazepines can cause respiratory compromise; therefore, resuscitation facilities should be available.

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subside and the patient is starting to reflect on the consequences of the episode. Supportive psychotherapy may be particularly indicated if involuntary treatment has been required.

Patients with mania test boundaries and cause interpersonal conflicts within a treating team. Clear communication and limits on behaviour are essential psychological strategies underpinning all management (Janowsky et al., 1970). While a lack of insight and involuntary treatment early in the illness makes establishing a therapeutic relationship difficult, the capacity of the therapist to engage the patient (and their family) in a therapeutic alliance and introduce psychoeducation about the disorder and its management is of fundamental importance to long-term success. Mania is often provoked and exacerbated by emotional stressors. Relief from these stressors and the adoption of more effective coping strategies, will assist in recovery.

Supportive psychotherapy provides authentic concern for the patient's welfare, basic information about the illness and its treatment, and conveys hope for a productive recovery: Importantly, this mode of counselling is less likely to overstimulate the patient.

Simple verbal interventions to reduce conflict and enhance meaningful relationships with significant others (such as family members) can be productive.

Treatment non-response

Assessing treatment non-response

Review the diagnosis. Often, the features of mania are clearly persistent, but may also change in form and/or relative intensity. The most obvious features may resolve, but a manic process may continue with less obvious features, such as 'racing thoughts', increased energy without obvious increased activity (including speech), expansive or negative thought content or rage that is not expressed, increased libido without sexual behaviour, and reduced need for sleep, which is not obvious to an observer. Psychotic symptoms may be easily missed, particularly if the patient has sufficient insight to know that their thoughts are considered an indication of illness. Therefore it is important to assess the patient's symptoms through self-report, observation and corroboration from family in order to understand the patient's entire manic process. Observation by health professionals will be an essential source of information, and an overall pattern of subtle core manic signs and symptoms may only be apparent when assessed continuously over hours or days, and even weeks. Further, the nature of non-response might extend beyond the persistence of core manic symptoms to comorbidity, such as substance abuse and lack of compliance with treatment. Clarification of the source of such further difficulties in management requires careful clinical assessment (Fountoulakis et al., 2012a; Grunze et al., 2013; Sienaert et al., 2013) (Level III).

It is also important to consider 'rapid cycling' bipolar disorder (*see: Rapid cycling bipolar disorder*) or 'mixed' features, with implications of potentially less satisfactory response to treatment (Cirillo et al., 2012; Czepielewski et al., 2013; Farren et al., 2012; Iacovides and Andreoulakis, 2011; Karaahmet et al., 2013; Krishnan, 2005; McElroy et al., 2006; Skirrow et al., 2012) (Level IV).

Review investigations. Routine investigations should be repeated such as full blood count, electrolyte levels, renal, liver, and thyroid function tests, along with (if indicated) neuro-imaging of the brain and urine screens for substances to determine whether there are rare organic reasons for non-response.

Strategies to address non-response

Address adherence to treatment. Firstly, it is important to identify if the patient is non-responsive as a result of poor adherence to treatment. Review both the patient's medication administration and blood levels, when available. Psychoeducation regarding the nature of the illness, rationale for treatment and its benefits is essential, within the limits of the patient's capacity for comprehension (Velligan et al., 2009) and insight (Berk et al., 2010; Rouget and Aubry, 2007) (Level I). Clearly in acute mania engagement is difficult and unlikely. If the patient has poor adherence, careful supervision of medication administration, use of dosette devices and improved routines for medication use (for example linking consumption to another regular life event) can be very helpful, as are the use of olanzapine wafers, risperidone quicklets, haloperidol and chlorpromazine syrups and asenapine wafers, as they offer a more reliable means of oral administration. Asenapine wafers are more difficult to use than the other options, because they need to be applied sublingually and the patient has to refrain from imbibing any foods or fluids. Further, depot antipsychotic medications, such as risperidone injection, olanzapine pamoate monohydrate, haloperidol decanoate, zuclopenthixol decanoate, flupenthixol decanoate, fluphenazine decanoate and paliperidone palmitate, may offer greatly improved adherence to treatment, so it may be worth adding these to the patient's treatment regime (CBR). However, it is important to recognise that some agents, such as olanzapine, can cause acute sedation and others, such as risperidone, may take weeks to achieve a therapeutic level. Risperidone Consta is slow to achieve adequate bioavailability, and therefore, is not useful for acute mania. Paliperidone palmitate is slow to become efficacious and therefore is more difficult to use in acute mania. If it has been verified that the patient has adhered to their treatment plan, review medication dosages and increase to maximal tolerated levels, using blood levels as a guide (CBR). Ultimately, managing side effects and ongoing dialogue with patients about preferred side effect profile of different medication options will assist compliance.

Change medication. Changing medication to a different anti-manic or second-generation anti-psychotic medication can be effective. However, prior to switching maximise doses of existing agents in case of 'pharmacokinetic' treatment resistance.

Combination therapy. Combining an atypical antipsychotic with lithium or valproate is a common strategy employed by clinicians. It is an option that is supported by recent research, for example aripiprazole is superior compared to placebo as an adjunct to lithium or valproate. However, although efficacy is greater with combination therapy, discontinuation rates are also higher because of adverse effects (De Bartolomeis and Perugi, 2012; Geoffroy et al., 2012; Yatham et al., 2013a).

Conventional treatments such as lithium have also been combined with hormonal therapies such as tamoxifen, hormone replacement therapies and oral contraceptives in the treatment of mania. Tamoxifen is a selective oestrogen receptor modulator with both agonist and antagonist actions peripherally and within the brain. Specifically, it is a protein kinase C

(PKC) inhibitor, which has shown some promise as an effective treatment of mania when augmenting lithium and could be useful in the management of treatment resistance. It has been shown to be superior as an adjunct to lithium compared with lithium monotherapy (Amrollahi et al., 2011; Zarate et al., 2007) (Level III), but may be less effective than alternative combinations such as medroxyprogesterone augmentation (Kulkarni et al., 2014; Nguyen and Low, 2012).

ECT. *ECT* is highly effective in the treatment of refractory mania (Level II) and can be particularly useful in the management of treatment resistant mania (Sienaert and Peuskens, 2006).

Management of bipolar depression

Bipolar depression is the predominant and most disabling component of both BD I and BD II (Judd et al., 2003a) and patients with bipolar disorder spend a considerable proportion of their lives with syndromal or subsyndromal depressive symptoms (Judd et al., 2003a, 2003b). This is also important because much of the increased risk of suicide in bipolar disorder is a consequence of depression. The treatment of bipolar depression is difficult and outcomes are often poor, partly because no medications have been specifically developed to treat this phase of bipolar disorder but also because management requires careful consideration of complex issues, such as treatment emergent affective switching (TEAS) into mania or hypomania, possible cycle acceleration, and the precipitation of mixed symptoms.

Treatment options for bipolar depression. Patients with bipolar depression either present *de novo* – on no medication – or have a breakthrough episode whilst on maintenance treatment.

- *De novo bipolar depression:* patients on no medication are either medication naive or are yet to commence treatment for the first time, or have simply stopped taking treatment that has been previously prescribed.
- *Breakthrough bipolar depression:* patients have either recently commenced treatment, which is still being titrated and they are yet to respond, or more commonly they have become unwell whilst taking treatment.

In terms of prescribing medications there are two options:

- monotherapy or combinations.
- Both options can be administered in either context:
  - de novo or
  - breakthrough bipolar depression.

This section, therefore, considers monotherapy and the combination of agents including the option of adding medication to ongoing treatment. Where possible, monotherapy is preferable but in most instances combinations of medications are more effective making this the preferred option even though it may be less well tolerated (see Figures 12 and 13).

The evidence for treating bipolar II depression is still emerging and the extent to which the evidence from BD I can be extrapolated to BD II is not clear. The key points of difference are noted below.

The treatment options for the management of bipolar depression include psychological, pharmacological, and physical interventions. These can be administered separately or in conjunction with one another. Psychological interventions are potentially useful early in the course of the illness and should be considered soon after diagnosis but only as adjunctive to pharmacotherapy. Pharmacological treatment is the mainstay of long term bipolar disorder management, though ECT may be necessary in providing relief when patients are acutely depressed or less commonly manic, especially in urgent situations such as when patients are experiencing substantive suicidal ideation.

Pharmacological strategies for bipolar depression

Monotherapy. As can be seen from Figures 12 and 13 monotherapy has demonstrated efficacy in the treatment of bipolar depression and comprises two groups of medications: second generation antipsychotics (SGAs) and mood stabilising agents (MSAs). Notably the use of adjunctive antidepressants remains contentious and the efficacy of this strategy longterm is unclear. In contrast, there is growing consensus that, if possible, antidepressant monotherapy should be avoided.

The second generation antipsychotics include quetiapine, lurasidone and olanzapine (rank order–noting that the latter is least favoured because it has the greatest likelihood of causing metabolic syndrome). The MSAs; lithium, lamotrigine and valproate can also be prescribed as individual agents. Therefore the SGAs and MSAs constitute a total of six possible monotherapy options. Note, the specific combination of olanzapine and fluoxetine (OFC) which is available in some countries as a single formulation is not classified as monotherapy because it consists of two established pharmacological agents.

In practice, a trial of monotherapy is often necessary to identify those patients who can be managed with a single agent. But while monotherapy is ideal, frequently patients require combinations of medications.

Combination. Whereas monotherapy is the preferred strategy for treating major depression, the effective treatment of bipolar depression often requires combinations of medications. The second generation antipsychotics and mood stabilising agents with efficacy as monotherapy agents can be combined or used in conjunction with antidepressants.

Second Generation (Atypical) Antipsychotics: Effective monotherapy options can be added to either mood stabilising agents or antidepressants.

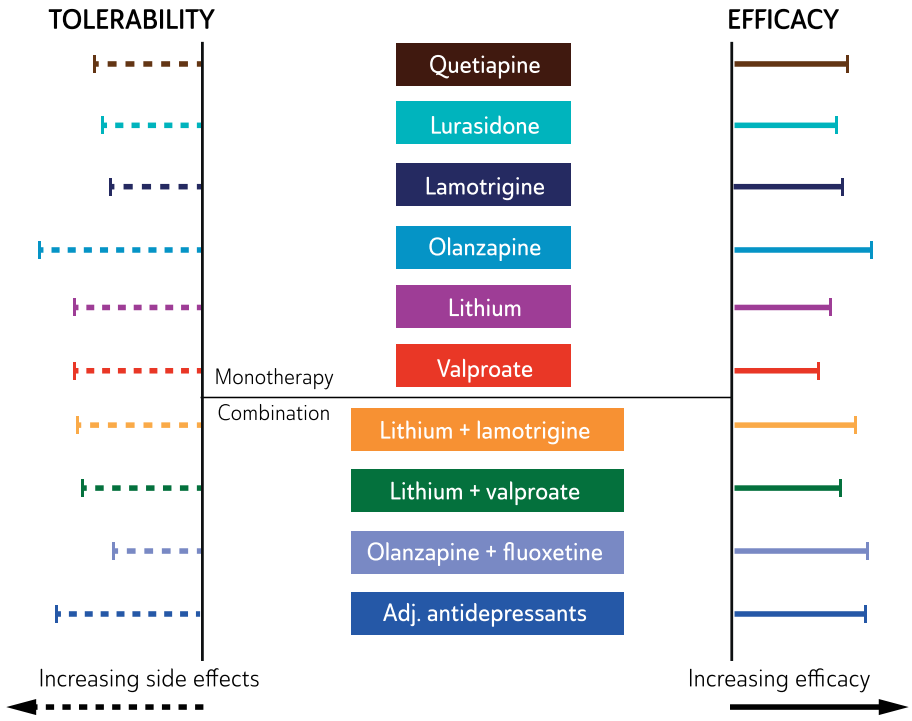
Mood Stabilising Agents: Lithium can be combined with all other monotherapy options; valproate can similarly be combined with all monotherapy options but should be used with caution in women of childbearing age and when combined with lamotrigine.[10]

Antidepressants: antidepressants can be added to all effective monotherapy options with the exception of lamotrigine, however the benefits of this strategy remain unclear. There is specific clinical trial evidence that fluoxetine is more effective than placebo when added to olanzapine.

In practice there may also be instances in which a SGA is added to a MSA and an antidepressant (triple therapy). However, evidence for efficacy and tolerability of such combinations is lacking.

Regarding the prescription of antidepressants in the treatment of bipolar I depression, these should be avoided if there have been one to two manic symptoms as part of the depressive episode, or psychomotor agitation, or rapid cycling is a feature of the illness (Pacchiarotti et al., 2013a) or if there is a history of antidepressant-induced mood elevation, or ongoing active substance use (see Recommendation Box 8).

Figure 12. Effectiveness of medications used to treat bipolar depression.

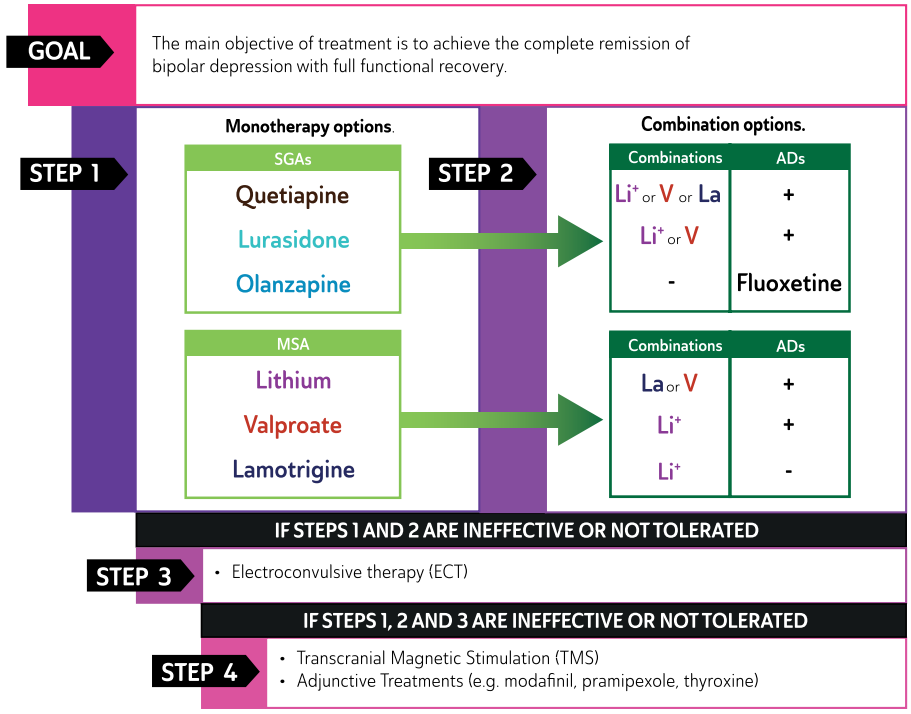


The figure shows monotherapy and combination therapy options for the treatment of bipolar depression. Horizontal bars indicate efficacy (solid line) and tolerability (dashed line). Their length is based on expert panel average ratings.

Adj = adjunctive; note that other potentially effective options, such as Quetiapine + Lithium, and Lurasidone + Lithium or Valproate are not shown in the figure.

Pharmacological strategies for treatment of depressive episodes in bipolar II depression. The evidence for bipolar II depression is still emerging. In practice evidence from the treatment of bipolar I depression is extrapolated to the treatment of bipolar II depression. However key differences regarding the evidence as compared with bipolar I depression are that antidepressants *may* be used as monotherapy noting that the evidence is modest at best, and that benefits are most likely early in the course of illness. Amongst the two groups of monotherapy agents (SGAs and MSAs), quetiapine and lamotrigine are the most favoured respectively in clinical practice.

Figure 13. Management of Bipolar Depression.



The biological management of bipolar depression (using mainly pharmacotherapy) is illustrated as a series of steps. The diagram illustrates the potential binary combinations between second-generation antipsychotics (SGAs), mood stabilizing agents (MSAs) and antidepressants (ADs) when considered appropriate. Lithium (Li^+) and ADs can be added to all agents but each has one exception: olanzapine and lamotrigine (La) respectively. The combination of SGAs with each other has no confirmed benefits in efficacy but MSAs may usefully be combined, provided one is lithium. The combination of lithium and lamotrigine carries the complication of increased blood levels of both medications, making close monitoring critically important. '+' means that agent can be added, '-' means that it should not be added.

Monotherapy evidence

Antidepressants. The issue of the use of conventional antidepressant agents in bipolar depression remains controversial. As the recent ISBD task force report noted, "There is a striking incongruity between the wide use of and the weak evidence base for the efficacy and safety of antidepressant drugs in bipolar disorder" (Pacchiarotti et al., 2013a). In practice, antidepressants are often prescribed for bipolar depression as monotherapy or in combination with other medications. The most recent meta-analyses provide conflicting evidence regarding the efficacy of antidepressants in bipolar depression compared with placebo (Sidor and MacQueen, 2011; Vázquez et al., 2011). Inconsistent research findings do not allow for a final evaluation and recommendation of antidepressants in the treatment of bipolar depression, therefore the ISBD task force concludes that "clinical trials do not provide adequate support for the efficacy of antidepressant monotherapy in treating bipolar depression".

Bipolar depression refractory to mood stabilisers is a common clinical problem (Sachs, 1996). It appears that some mood stabilisers may have greater efficacy during the depressive phase, therefore consideration of adding or switching to such agents is advisable (Chiesa et al., 2012; De Fruyt et al., 2012; Van Lieshout and MacQueen, 2010). While some patients appear to benefit from carefully monitored use of antidepressants, others suffer iatrogenic mood destabilization due to induced elevated states (Amsterdam and Shults, 2010b; Sidor and MacQueen, 2011; Tondo et al., 2010b; Vázquez et al., 2011).

Two recent studies provide contrary findings (Malhi, 2015a), with one suggesting that long-term continuation of antidepressants in patients with rapid-cycling bipolar disorder leads to a threefold increase in mood episodes during the first year of follow up (El-Mallakh et al., 2015) whereas continuation of antidepressant monotherapy in BD II provides prophylaxis with only minimal risk of switching (Amsterdam et al., 2015). Given these complex issues, use of antidepressants in bipolar patients should be generally overseen by a psychiatrist where possible. Prior to considering an antidepressant, mixed states, substance induced states, akathisia and adjustment disorders should be excluded. Patients and carers must be clearly informed of the risk of elevated states being induced with antidepressant therapy (Miklowitz et al., 2003).

Therefore, clinically, when treating bipolar depression the patient's mental state needs to be closely monitored for the emergence of elevated states. Where possible it is best to use an antidepressant that has been previously effective and tolerable for the particular patient.

SNRIs and TCAs may have greater propensity to induce elevated states, making other classes of antidepressants initially preferable (Gijsman et al., 2004; Giorlando et al., 2013; Post et al., 2006). Furthermore, antidepressant agents that can assist sleep cycle restoration may also have a clinical advantage over more activating agents except in patients with significant hypersomnia and anergia where activation may be desired. However, a recent study that investigated adjunctive therapy for bipolar depression found that agomelatine was not superior to placebo (Yatham et al., 2015).

In the treatment of bipolar depression, adjunctive antidepressants should be prescribed at usual dose ranges as there is no biological basis for employing doses not able to lead to adequate CNS bioavailability. The clinical risk benefit ratio of antidepressants in bipolar depression needs to be determined on a case-by-case basis given considerable clinical

heterogeneity in response patterns. In addition, treatment choice should take into account the likelihood that an agent may be used to provide prophylaxis against future episodes of depression *(see: Treatment options in major depressive disorder maintenance phase).*

For these reasons antidepressants should be used with caution in bipolar depression (limiting duration as far as possible), always co-prescribed with a mood stabilising agent, and with very close mental state review given the risk of mood destabilisation in some patients. However, this potential hazard needs to be balanced against the reality that in clinical practice many bipolar patients appear to benefit from antidepressants, and the risks associated with refractory depression. Mood stabiliser monotherapy is therefore preferable because, if it provides adequate control of the depressive phase, the short and long term risks of iatrogenic elevated states are averted. Such deliberations are best made by an experienced clinician.

Recommendation Box 8.

ADMINISTRATION OF ANTIDEPRESSANTS IN BIPOLAR DISORDER	Grade
GENERAL CONSIDERATIONS	
8.1. The use of antidepressants in the treatment of bipolar disorder should be overseen by a psychiatrist where possible.	CBR
8.2. The clinical risks versus benefits of antidepressants in treating bipolar depression should be determined on an individual basis.	CBR
TREATMENT	
8.3. Antidepressant monotherapy should be avoided in the treatment of bipolar depression with two or more coterminous manic symptoms.	EBR III
8.4. Antidepressant monotherapy should be avoided for the treatment of an acute bipolar depressive episode that features psychomotor agitation or in the context of rapid cycling.	EBR III
8.5. Antidepressant monotherapy should be avoided in Bipolar I disorder.	EBR III
TREATMENT EMERGENT AFFECTIVE SWITCH (TEAS)	
8.6. Upon commencing antidepressants, patients with bipolar disorder should be closely monitored for symptoms of mania, and if these emerge antidepressant therapy should be discontinued.	CBR
8.7. Antidepressant therapy should be avoided in bipolar disorder patients with a history of rapid cycling and/or a high level of mood instability.	CBR
8.8. Antidepressant therapy should be avoided during 'mixed states' (mania with depressive features or depression with manic features).	CBR
8.9. The prescription of antidepressants should take into account any past history of a treatment emergent affective switch (TEAS).	CBR

Second generation antipsychotics. Randomised controlled trials report that olanzapine (Tohen et al., 2003c, 2012), quetiapine (Calabrese et al., 2005b; McElroy et al., 2010; Thase, 2006; Young et al., 2010) and lurasidone (Loebel et al., 2014a, 2014b) are effective treatments for bipolar depression, but these studies have significant methodological issues that moderate the strength of the evidence. In considering treatment choice, the high

drop-out rate and long term likelihood that olanzapine and quetiapine will lead to metabolic disturbance need to be taken into consideration. In this regard, based on available evidence, lurasidone is preferable (Loebel et al., 2014b; Selle et al., 2014) also because the combination study demonstrating its efficacy has fewer methodological issues.

Mood stabilising agents (MSA). *Lithium* monotherapy has not been demonstrated to be convincingly superior to placebo as monotherapy in the treatment of bipolar depression (Young et al., 2010). However, empirical evidence, along with its proven value in mania prophylaxis and efficacy in unipolar depression as an augmentation strategy, make it a suitable first choice, particularly in classic bipolar I disorder depression (Malhi et al., 2015b). In addition, lithium has the added value of reducing the risk of suicide in mood disorders (Cipriani et al., 2013) *(see: Lithium in maintenance phase)*.

Evidence regarding the beneficial effects of *valproate* monotherapy in the acute treatment of bipolar depression is limited to three very small (n = 18, n = 25, n = 54) trials, a long-term trial and a small meta-analysis, all of which showed significant benefit compared with placebo (Bond et al., 2010; Bowden, 2003; Davis et al., 2005; Ghaemi et al., 2007; Muzina et al., 2011; Smith et al., 2010).

Lamotrigine monotherapy has modest efficacy in the treatment of bipolar I depression. Its suitability as a bipolar antidepressant agent in patients with BD I who are drug naïve or who have ceased medication should be considered, in the context of the overall history of the illness and in particular, the severity and frequency of manic episodes. A trial of a recognised mania prophylactic should also be considered. Clinically, lamotrigine seems to have better utility in bipolar II depression. See Figure 13 for treatment recommendations in the management of bipolar depression.

Antidepressant-induced mania, switching and cycle acceleration. Given the spontaneous occurrence of switching in bipolar disorder, it has been difficult to determine the extent to which switching can be attributed to antidepressants (Malhi et al., 2015). The natural history of BD I and BD II differs with respect to switching, which is more a feature of BD I as compared to BD II (Judd et al., 2003a, 2003b). Furthermore, the rate of switching appears to vary depending on the class of antidepressant. For example, TCAs (7–11%) and venlafaxine (13–15%) are associated with a higher risk of inducing mania compared with SSRIs and bupropion (Gijsman et al., 2004; Leverich et al., 2006; Nemeroff et al., 2001; Peet, 1994; Post et al., 2006; Sachs et al., 1994; Vieta et al., 2002). Indeed, a recent analysis reported that SSRIs or bupropion had a switch rate only 1.16% higher than placebo (Vázquez et al., 2013). Amongst the SSRIs fluoxetine seems to be less likely to cause switching (Amsterdam and Shults, 2010a) but a paucity of studies warrants cautious use.

Despite longstanding concerns and suggestions that antidepressants may induce cycle acceleration (Altshuler et al., 1995), which is not only more disruptive clinically but also more difficult to treat, there is little evidence regarding whether antidepressants do, in fact, cause this. No increased rate of switching compared with placebo has been found in other trials of monotherapy with lamotrigine (Calabrese et al., 2008; Geddes et al., 2009), second generation antipsychotics (quetiapine, olanzapine, aripiprazole, ziprasidone) (De Fruyt et al., 2012), or lithium (Young et al., 2010).

However, a recent consensus statement from experts in the field recommends that, (a) patients should not use antidepressants if they have a history of past mania, hypomania or mixed episodes emerging during antidepressant treatment, and (b) antidepressants should be avoided in patients with high mood instability or with a history of rapid cycling (Pacchiarotti et al., 2013a, 2013b).

Psychological interventions for bipolar depression. (See Table 21.) The majority of research into psychological interventions for bipolar depression has focused on the maintenance phase, and there is some suggestion that psychological interventions are best commenced outside acute episodes (see below). However, the large STEP-BD trial provides Level II evidence for the efficacy of adjunctive psychological intervention when commenced during acute bipolar depression. Up to 30 sessions of Cognitive-Behavioural Therapy (CBT), Interpersonal and Social Rhythm Therapy (IPSRT) or Family-Focused Therapy (FFT – see Table 21) were compared against a minimal psychological intervention of 3 sessions of 'collaborative care' for patients recruited in an acute depressive episode and continuing on pharmacotherapy (Miklowitz et al., 2007). The structured, intensive psychotherapies were associated with more frequent (and rapid) recovery from depression and better psychosocial functioning than collaborative care: year end recovery rates were 64.4% compared to 51.5%, and in any given month of the 12-month follow-up, patients in the intensive interventions were 1.6 times more likely to be clinically well. No differences were found between the three specific psychological therapies, so the evidence supports psychological intervention generally without specifying which type (see below).

Indirect evidence for the efficacy of adjunctive psychological interventions in acute bipolar depression includes: (a) Level I evidence for the efficacy of psychological interventions for the residual depressive symptoms of bipolar disorder (see Table 21), and (b) Level I evidence for psychological interventions in preventing depressive relapse in bipolar disorder. One meta-analysis (8 included studies) found CBT to be as efficacious for symptoms of bipolar depression as unipolar depression (Zaretsky et al., 2007), and another (10 studies) found significant benefits for bipolar depression symptoms at 6 and 12 months follow-up (Szentagotai and David, 2010).

Consequently, recent NICE guidelines recommend psychological interventions (particularly CBT and FFT) for acute bipolar depression (National Collaborating Centre for Mental Health (NCCMH), 2014). These guidelines also recommend that evidence-based psychological interventions for unipolar depression are potentially useful for the depressions of bipolar disorder.

In sum, although research is limited, there is strong clinical consensus that the highly prevalent and highly impairing depressive phase of BD should be managed in a comprehensive biopsychosocial manner (Berk et al., 2013; Malhi et al., 2012b), and adjunctive structured psychological interventions should be offered to help stabilise depressive episodes (Goodwin, 2009; Kendall et al., 2014; Yatham et al., 2013b).

Electroconvulsive therapy and other brain stimulation methods. Compared to ECT in unipolar depression, much less attention has been paid to the investigation of ECT in treating bipolar depression, and most studies are of treatment resistant cases. A systematic review (Versiani et al., 2011) identified only 9 studies, none of which were prospective randomised

controlled trials. However, this review identified 10 controlled studies that compared the efficacy of ECT in treating bipolar versus non-bipolar depression, with half of these being prospective. All but one of these studies demonstrated that ECT was equally effective for both bipolar and non-bipolar depression with some evidence that the response was more rapid in bipolar depression.

Another review of ECT in bipolar disorder (Loo et al., 2011) identified four studies that suggested a more rapid response in bipolar depression. Studies comparing ECT and medication in the treatment of bipolar depression have been inconclusive and no difference has been found though this may be a consequence of methodological shortcomings (Loo et al., 2011; Versiani et al., 2011). A large multicentre study (n = 220), comparing unilateral, bitemporal and bifrontal ECT in the treatment of depression (Kellner et al., 2010) included 50 bipolar subjects. The study compared the response rate in the bipolar subgroup with the non-bipolar group (Bailine et al., 2010) and found no difference.

ECT-induced mania. While ECT-induced switching into mania is recognised as a potential adverse effect, few studies have examined the rate of switching (Loo et al., 2011) and estimates of the rate vary. Reports of switching in controlled studies of ECT in bipolar depression are relatively uncommon. For example, of the 50 bipolar depressed patients treated with ECT in the multicentre study quoted above, none switched into mania (Bailine et al., 2010).

There are insufficient data to guide the treatment of ECT-induced mania and its management may depend on the availability of services to treat a sudden switch. Many clinicians advocate continuing with ECT, as it is an effective treatment for mania as well as depression. There may be some risk that this approach further escalates mania and, if appropriate facilities for managing mania are not immediately available, then ceasing ECT and treating pharmacologically is a suitable alternative.

Table 21. Psychotherapy for depressive phase and for maintenance phase of Bipolar Disorder.

Evidence-based psychological treatments	Depression symptoms*	Relapse prevention
Psychological treatments as a set (individual, group, family)	Level I	Level I
Cognitive Behavioural Therapy (CBT)	Level I	Level I
Psychoeducation	Level I	Level I
Family-Focused Therapy (FFT)	Level II	Level II
Interpersonal and Social Rhythm Therapy (IPSRT)	Level III	Level III

***Insufficient** studies directly address the treatment of acute bipolar depression, so this column refers to studies reporting outcomes for depression syndromes and symptoms.

Treatment non-response

Assessing treatment non-response. Ongoing subsyndromal depressive symptoms are common in bipolar disorder, as is a high rate of treatment non-response. Treatment resistant bipolar I depression can be defined as failure to reach remission with adequately dosed lithium (blood level 0.6–0.8 mMol/L) or to other adequate ongoing mood-stabilizing treatment, plus lamotrigine (50–200 mg/day) or with full dose quetiapine (⩾ 600 mg/day) as monotherapy. Similarly, treatment resistant bipolar II depression can be defined as failure to reach remission with adequately dosed lithium (blood level 0.6–0.8 mMol/L) or to other adequate ongoing mood-stabilizing treatment, plus lamotrigine (50–200 mg/day) or with full dose quetiapine (300–600 mg/day) as monotherapy. If treatment resistance is diagnosed, then a total reassessment of the nature of the bipolar depression is indicated. This is similar to the re-assessment recommended for the treatment of unipolar major depression (*see: Managing suboptimal response*), but there are a number of additional factors in bipolar depression that need to be considered. These include: thyroid dysfunction (Cole et al., 2002), non-adherence with pharmacological treatment (Perlis et al., 2010), rapid cycling (Coryell et al., 2003) (in which the episode is likely to resolve spontaneously and more quickly), and mixed features (Goldberg and McElroy, 2007).

Pharmacological strategies to address non-response. Research and clinical practice have provided options for the management of treatment resistant bipolar depression using medications, although the results vary widely and clinicians must use their knowledge of each patient to guide their choices. The following are suggested (Pacchiarotti et al., 2009) steps for such management and should involve supervision by a specialist:

Bipolar I depression. Quetiapine (or other atypical antipsychotic or mood stabilizer if preferred) alone → Quetiapine or Lithium + Lamotrigine (latter with care) or Olanzapine + Fluoxetine → Lithium or Quetiapine + SSRI or Bupropion → Pramipexole or Modafanil → Electroconvulsive therapy.

Bipolar II depression. Similar to management of bipolar I depression but include irreversible monoamine inhibitors as options when combining Lithium or Quetiapine (or other atypical antipsychotic or mood stabilizer if preferred) with an antidepressant (with care if combining lithium with MAOI).

Brain stimulation approaches. Very few studies have evaluated the use of rTMS treatment in homogeneous groups of patients with bipolar depression. However, many depressed patients with bipolar disorder have been included in trials of rTMS with no evidence that bipolar patients are less likely to respond to rTMS than patients with unipolar depression (Fitzgerald et al., 2013b), and overall, the rate of manic switch with rTMS treatment appears to be low.

Physical treatments such as ECT, appropriately timed bright light therapy (particularly if a seasonal component is involved) (Poon et al., 2012), vagus nerve stimulation (Rizvi et al., 2011) and repeated transcranial magnetic stimulation (George, 2010) should all be reserved for specialist centres and patients need to be monitored medically and for the emergence of manic switches.

Adjunctive strategies

Pharmacotherapy. Several medications may be added to existing treatment regimens including thyroid hormones (Bauer et al., 2005), glutamate antagonists (memantine/riluzole) (Owen, 2012), intravenous ketamine (Zarate et al., 2012), and modafinil/armodafinil (latter is the R-enantiomer of modafinil) (Calabrese et al., 2010). All these medications require further study and are best regarded as experimental.

Amongst these agents, ketamine has emerged as a potential antidepressant. Studies investigating its therapeutic effects have found a reduction in depressive symptoms in those suffering from treatment resistant depression along with mitigation of suicidality (Murrough et al., 2013; Price et al., 2009). Improvement is also seen in bipolar depression, however, the effects are short-term and often transient.

Specifically, following an initial improvement, mood can rapidly decline after a single treatment of ketamine, thus potentially enhancing the risk of suicide. Nevertheless, ketamine does appear to be more effective than placebo at reducing the symptoms of depression, albeit for a week or so (McCloud et al., 2015). The evidence favouring bipolar depression is even more tentative (McCloud et al., 2015). Based on available evidence, it is not possible to recommend ketamine as an option for treatment non-response in either unipolar or bipolar depression.

Complementary therapies. Omega-3-fatty acids (Sarris et al., 2012), N-acetyl cysteine (NAC) (Berk et al., 2008a) and other nutraceuticals (Sarris et al., 2011) may also be considered. Meta-analytic evidence supports the adjuvant use of Omega-3 for bipolar depression, although not for mania (Sarris et al., 2012). According to a recent review (Sylvia et al., 2013), preliminary data yields conflicting but mainly positive evidence for the use of chromium in the treatment of bipolar depression. Moreover, preliminary randomized, controlled trials suggest that adjunctive choline, magnesium, folate and tryptophan may be beneficial for reducing symptoms of mania (Sylvia et al., 2013).

Another recent systematic review (Sarris et al., 2011) found positive evidence with large effect sizes for NAC (d = 1.04) and a chelated mineral and vitamin formula (d = 1.70) in the adjunctive treatment of bipolar depression. Regarding the treatment of bipolar mania, several adjunctive nutraceuticals reduced the symptoms of mania with strong clinical effects: a chelated mineral formula (d = 0.83), L-tryptophan (d = 1.47), magnesium (d = 1.44), folic acid (d = 0.40), and branched-chain amino acids (d = 1.60) (Sarris et al., 2011).

Long-term management of bipolar disorder

Bipolar disorder is a recurrent illness with episodes occurring on average every 17 to 30 months (Angst and Sellaro, 2000). Once an acute episode has resolved, the clinical focus of management shifts to continuation and then to maintenance treatment. The primary aims of long-term treatment are to prevent relapse or recurrence of manic and depressive symptoms and to optimise functional recovery.

Successful long-term management of bipolar disorder requires a collaborative therapeutic relationship in which there is a clear understanding of these goals and management is tailored to the individual. Treatment needs to take into consideration comorbid medical and psychiatric illnesses, personality variables (Lozano and Johnson, 2001) and lifestyle factors

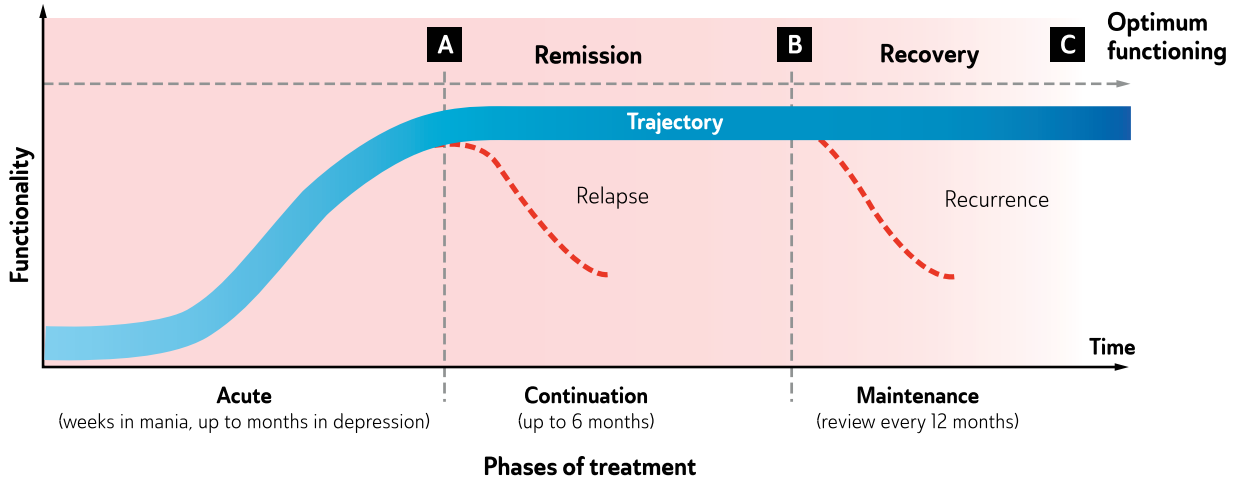
(e.g., accommodation, social support, employment), all of which can contribute to life events or psychosocial stressors, impeding functional recovery. The long-term treatment of bipolar disorder requires both psychotherapeutic and pharmacological approaches.

Phases of long-term treatment. The transition from acute symptoms to remission and subsequent achievement of recovery divides long-term treatment into *continuation* and *maintenance* phases *(see*: Figures 5 and 14) and separates any recrudescence of symptoms into *relapse* and *recurrence*, respectively.

The majority of patients with bipolar disorder will suffer from multiple episodes of depression and mania during their lifetime and, therefore, in almost all cases long-term treatment is necessary. The course of illness and trajectory are difficult to predict and even with adequate treatment, almost half of all bipolar patients will have another episode within two years, and the majority will experience further illness within five years.

In long-term treatment, the first decision point occurs at the transition from acute treatment to continuation treatment (Point A in Figure 14). At this point it is important to begin withdrawal of adjunctive agents such as benzodiazepines that have been used to manage acute behavioural and cognitive disturbance associated with a mood episode. However, it is important to maintain euthymia and only if this can be ensured should a gradual reduction of medication dosage be considered along with withdrawing medication to achieve monotherapy. Maintaining compliance and ensuring adequate adherence to treatment instructions is extremely important and therefore active engagement is necessary and should include regular review for therapeutic monitoring and reappraisal of the benefits and risks of ongoing therapy.

Figure 14. Trajectory of functional recovery.



Long-term pharmacological management comprises decision points along a trajectory through successive phases of treatments. Key functional improvements mark traumatic points from one phase of treatment to the next. E.g. achievement of remission (A) makes transition from acute to continuous phase of treatment. Similarly, achievement of recovery (B) marks transition from continuation treatment to maintenance therapy–ultimately leading to applied functioning.

The second decision point occurs at the transition from continuation treatment to maintenance treatment (Point B in Figure 14). At this point it is important to reassess the efficacy of treatment thus far, the mood stability that has been achieved with acute and continuation treatment, and the number, polarity and severity of relapses/recurrences, which have occurred over the individual's lifetime. It is also important to assess the extent to which the onset of episodes is predictable; for example, whether they are insidious, abrupt, related to life stresses or contain a seasonal component. Often, symptoms gradually increase in number and severity. These are described as '*early warning signs*' and individuals can learn to detect these and anticipate the onset of episodes of illness. Adjunctive psychological interventions aimed at relapse prevention are typically introduced in the inter-episode period. Inter-episode periods should also be appraised to determine whether they feature subsyndromal symptoms and assess the maximum functional capacity that an individual has achieved. Specifically, it is important to gauge their quality of life whilst on maintenance treatment. This requires evaluating the tolerability of past treatments and the severity of illness overall, in particular its impact on the individual's capabilities. This is an important exercise and is critical in informing maintenance treatment. In most cases of BD maintenance therapy is necessary, but it is particularly mandated if the individual has had many past episodes (which increase the risk of relapse and impede response to treatment) and is therefore at considerable risk of recurrence.

Continuation treatment. The *continuation phase* of treatment begins immediately after the remission of acute symptoms. The primary aim of treatment in this phase is to continue to achieve mood stability and prevent relapse. Ongoing treatment during the continuation phase is determined by the treatment which has been effective in the acute phase of illness and the predominant mood polarity, the current polarity, the illness stage and the history of the patient's previous response to intervention. Time to achieve mood stability varies, but once three months of continuous mood stability has been achieved, treatment considerations shift to prophylaxis and maintenance therapy.

Key tasks during continuation treatment include maintaining clinical improvement and monitoring for side effects, which can prove troublesome and decrease adherence to treatment. During this stage of treatment, medications used to treat acute symptoms are usually tapered gradually and eventually stopped altogether as the illness stabilises. This ensures that only necessary medications are continued long-term and side effects are avoided, or kept within tolerable levels. Medication withdrawal necessarily risks relapse, and therefore, treatments should be withdrawn gradually with regular clinical monitoring.

Continuation therapy (Marked 'A' in Figure 15) aims to achieve optimal mood stability and prevent the occurrence of a relapse into the most recent mood episode. Monotherapy is desirable but combination strategies are often necessary. Suitable combination strategies include lithium or valproate in combination with olanzapine, quetiapine, lamotrigine or aripiprazole. These combinations are useful for treating bipolar disorder in which depression predominates or both depression and mania occur equally. With respect to monotherapy, lithium and olanzapine are more useful where mania has been a significant feature of the illness, whereas lamotrigine is better suited to a pattern in which depression predominates. Quetiapine monotherapy is useful where both phases of illness feature strongly.

Continuation therapy may last for up to six months during which time a period of at least 6 months mood stability should be achieved, after which it transitions to *maintenance*

therapy. During this time, if any of the initial strategies for relapse prevention are unsuccessful in achieving optimal mood stability, then ongoing treatment can be substituted or augmented adjunctively. Other previously well tolerated treatments utilised successfully in acute treatment can also be prescribed. In some cases, a combination of lithium and valproate may be necessary, and in exceptional cases clozapine may be considered in conjunction with an anticonvulsant or lithium.

Longitudinal mental state review and continuity of care enable identification of illness profile and treatment efficacy on a case-by-case basis. This facilitates optimal clinical outcome and may from time to time involve soliciting a second opinion from a psychiatric colleague or specialist clinic.

Maintenance treatment. The main goal of maintenance treatment is to prevent future episodes of illness (recurrence) and enhance resilience. In practice, even with optimal treatment, complete prophylaxis is seldom achieved; therefore, subsidiary goals warrant consideration. These include reducing the number, intensity and length of episodes and achieving functional mood stability with fewer inter-episode subsyndromal symptoms.

Maintenance treatment should be considered after the first episode of mania and subsequently it is useful to gauge the predominant polarity of the illness (Kessing et al., 2014). Because the occurrence of mania confers the diagnosis of bipolar disorder, it raises clinical issues that can take considerable time to resolve (Malhi and Porter, 2014). For example, acceptance of both the diagnosis and the need for long-term treatment are difficult issues to come to terms with, especially when patients dealing with these concerns are usually adolescents or young adults. Failure to support patients through this acceptance process can hinder long term engagement with care and moderate outcomes (Berk et al., 2010).

In terms of treatment, monotherapy is the gold standard of maintenance medication, but in reality it is often an elusive goal. Most individuals with bipolar disorder require more than one medication long-term in order to maintain mood stability. Generally, the initiation of medications is easier than their cessation and each additional medication adds potential side effects and increases risk of poor compliance. Therefore, the benefits and risks of each medication need to be carefully balanced, and long-term medication necessitates regular monitoring for clinical symptoms and the emergence of side effects to ensure ongoing efficacy and maximise compliance and adherence.

When planning maintenance treatment, the first step is to review the treatments that have been used during the continuation phase of management. These will have been determined by the nature of the acute episode and it is useful to gauge the predominant polarity of the illness. Medications necessary for treating acute symptoms may have been tapered or completely withdrawn during continuation treatment and long-term maintenance may require the initiation of new medications. The choice of medication in maintenance is governed by different factors to those relevant to continuation treatment and the cost/benefit ratio of side effects to efficacy may require further consideration.

The principal aims of maintenance treatment are:

- Maintaining mood stability;[11]
- Achieving complete functional recovery;

- Providing long-term prophylaxis; or
- Reducing attraction to the euphoria and enhanced abilities of past hypomanic states
- Building resilience and improving QoL

A clinical review of previous inter-episode treatment is essential, so as to determine which therapies and combinations of medications have been effective in the past and to consider potential problems with treatment adherence. This information is critical in formulating maintenance treatment.

Mood stability is the core objective of maintenance treatment and therefore a 'mood stabilizing' medication(s) is an essential ingredient and should be the first to be considered. At this stage it is useful to gauge the predominant polarity of the illness (Carvalho et al., 2014a). A past history of predominance of one pole or other provides an indication of future recurrences, and this informs prophylaxis as medications differ with respect to efficacy in preventing relapse of depression or mania (Yatham et al., 2013a) (see: Figure 17). However, bipolar disorder is capricious by nature and in many cases a clear pattern of polarity may be difficult to determine.

Medications prescribed during continuation treatment can be continued in maintenance treatment if side effects are tolerable and safe and the patient has managed to demonstrate compliance. If, however, on reviewing past history, recurrence is less likely, then medications can be tapered especially if they are likely to be difficult to tolerate at the present dosages, or cause serious side effects when prescribed long-term. On occasion, switching may be necessary, especially if the individual is experiencing breakthrough symptoms and current medications lack efficacy. Ongoing maintenance treatment requires regular re-evaluation to assess the effectiveness of treatment (efficacy and tolerability) and overall functioning and quality of life. (See Figure 16)

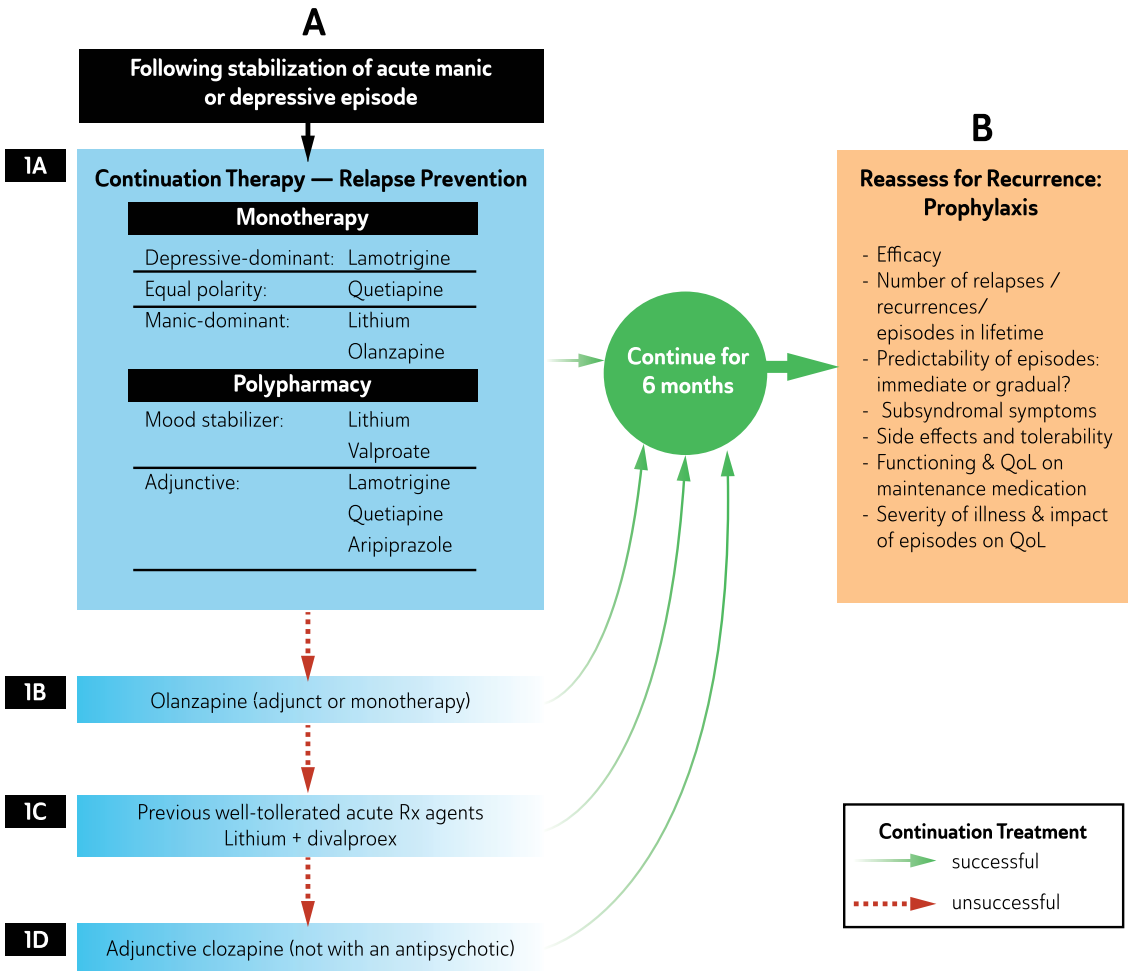
Duration of prophylaxis. In instances of long-term mood stability, individuals often question the need for ongoing prophylaxis and want to stop maintenance treatment. This is more likely:

- Early in the course of illness
- If the individual:
  - suffers intolerable/unsafe side effects
  - has only experienced a few episodes in their lifetime
  - is yearning for the perceived pleasure of the elevated subjective state

Stopping treatment or interrupting it for a brief period to gain respite or test its feasibility ('a medication holiday') requires a careful discussion and evaluation of the impact of the medication on quality of life and whether its benefit outweighs any associated risks. Patients often need to be reminded that recurrence carries significant risks to their health and may provoke considerable losses (e.g. occupation, relationships, financial status). Furthermore, there is no guarantee that medications that have maintained mood stability in the past will once again be successful if reinitiated after stopping. However, there is a small possibility that some individuals

remain well in the absence of long-term ongoing maintenance treatment, but it should be emphasised that this is rare (Angst et al., 2003; Simhandl et al., 2014).

Figure 15. Continuation Therapy of Bipolar Disorder.



Decision making diagram for continuation therapy of Bipolar Disorder. Rx = treatment. QoL = Quality of life.

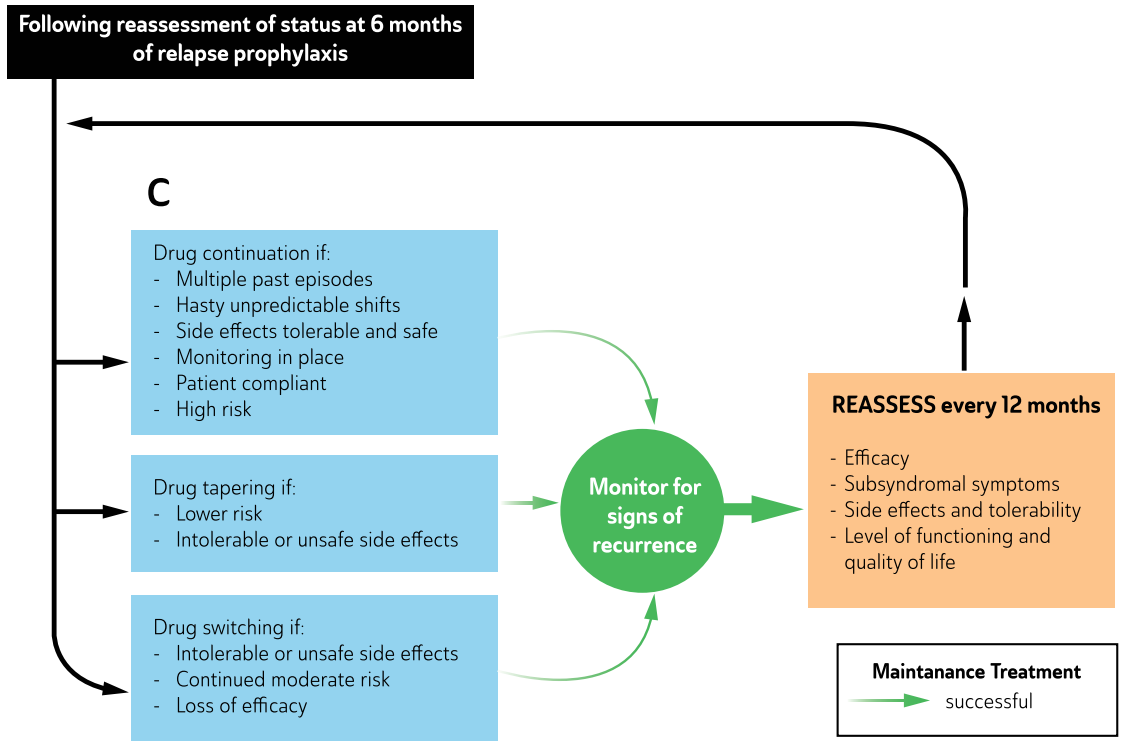
Recommended treatments

Pharmacological treatments. Medications used in bipolar disorder prophylaxis have differing levels of efficacy, and some agents show selectivity in their ability to prevent mania or depression (Miura et al., 2014; Yatham et al., 2013a). Much of the evidence for prophylaxis pertains to bipolar I disorder, with relatively little data to inform the management of bipolar II disorder.

Selection of maintenance medication. Maintenance medication should be selected on the basis of both efficacy and tolerability profiles (see: Figure 17). The latter is critical for long-term treatment and these factors need to be balanced alongside individual patient

considerations (including preference), past response and safety considerations (risk of suicide). The efficacy of conventional antidepressants (e.g., TCAs, SSRIs and SNRIs) in the maintenance phase of bipolar disorder is not established (Ghaemi et al., 2008), and in some instances treatment may worsen mania with no improvement of depression however, maintenance treatment with adjunctive antidepressants may be considered if a patient relapses into a depressive episode after stopping antidepressant therapy (Pacchiarotti et al., 2013a). Antidepressant treatment in combination with a mood stabilising agent is less likely to precipitate a manic mood switch, but antidepressants should be avoided if there is a past history of (hypo)mania, mixed states or rapid cycling during antidepressant treatment. In some instances, attempts to cease antidepressants during maintenance treatment can precipitate the recurrence of depression, and therefore, adjunctive antidepressant maintenance therapy alongside a mood stabilising medication may be necessary.

Figure 16. Maintenance Therapy of Bipolar Disorder.



Decision making diagram for maintenance therapy of Bipolar Disorder.

Lithium. *Lithium* is the oldest and only agent developed specifically for the treatment of bipolar disorder (Malhi, et al., 2009c). Therefore, it has the largest body of evidence in relation to its efficacy, though much of this is anecdotal and borne out of clinical experience. A meta-analysis of clinical trials up to a decade ago demonstrated that lithium may greatly reduce the overall

risk of relapse of a manic episode by 40% to 61%, with modestly lower efficacy in the prevention of depressive relapse (Geddes et al., 2004). Amongst the many studies that have demonstrated its superiority, the BALANCE study (Geddes et al., 2010) is noteworthy because it demonstrated that lithium alone and in combination with valproate is effective in prophylaxis. Lithium is more effective alone than valproate alone, and carries the extra significant benefit of reducing suicidal behaviour and death by suicide. Clinically, lithium has a specific therapeutic serum range that necessitates regular monitoring (Malhi et al., 2011) and long-term administration runs the risk of potential, serious adverse effects, including renal insufficiency and thyroid dysfunction (*see: Table 20 Adjuctive treatments*) (McKnight et al., 2012; Malhi et al., 2012d; Malhi, 2015b; Shine et al, 2015; Van Gerven and Boer, 2006).

Anticonvulsant agents. *Valproate* is not formally approved for use as a maintenance agent and remarkably there are no RCTs that have demonstrated its efficacy in long-term prophylaxis. In comparison to lithium, it is less effective (Geddes et al., 2010) but does have modest efficacy in acute mania (Calabrese et al., 2005a; Macritchie et al., 2001; Tohen et al., 2003a). It is therefore often advocated in those patients that have a predominance of manic episodes.

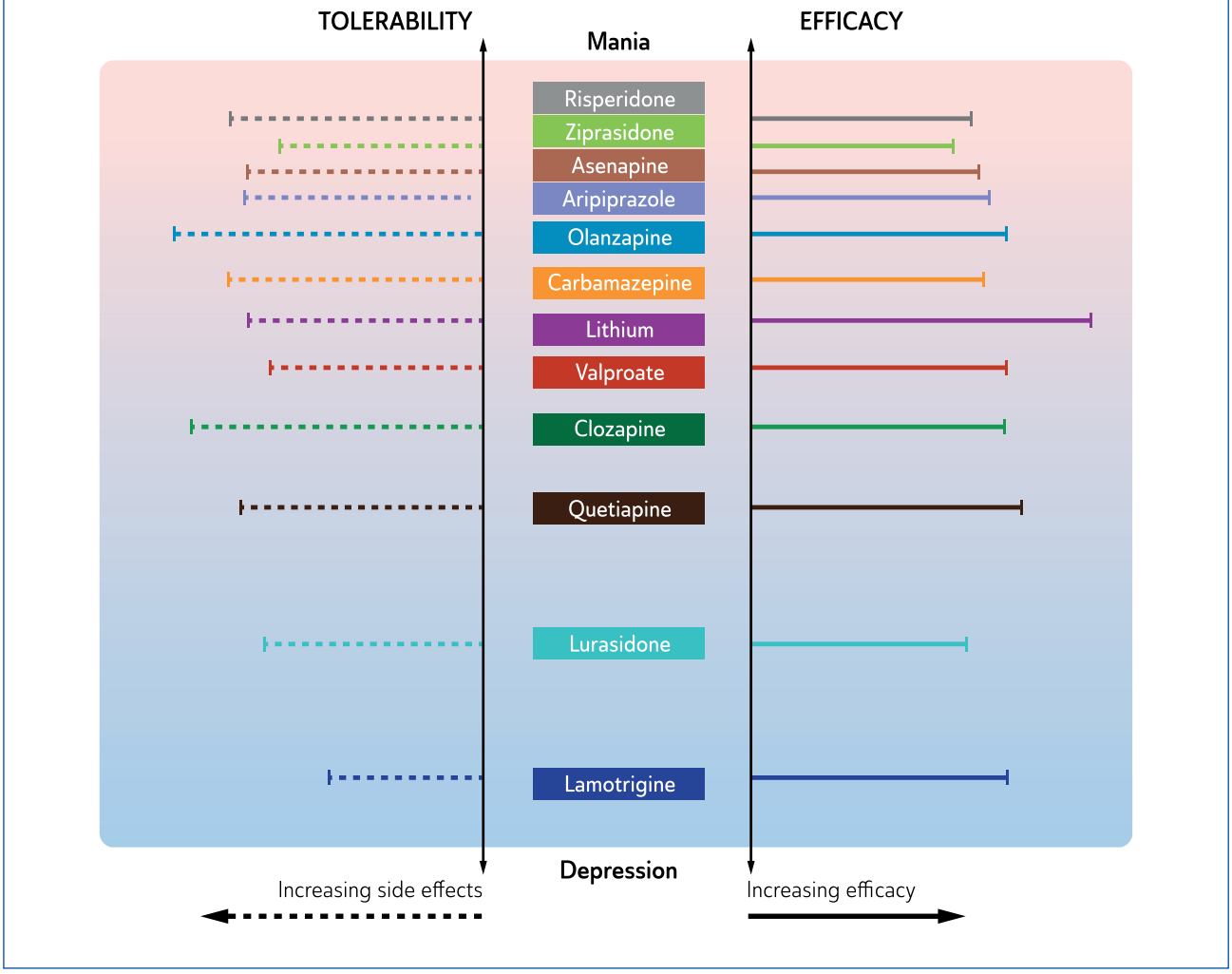
Lamotrigine has greater efficacy in the prevention of depressive relapse but relatively modest impact on risk of manic relapse (Level I) (Bowden et al., 2003; Calabrese et al., 2003; Goodwin et al., 2004; Licht et al., 2010; Van der Loos et al., 2011). Its use is further complicated by the need for slow titration of its dose to limit the risk of severe skin reactions, such as Stevens-Johnson syndrome. Its advantages include its better overall tolerability and relatively low risk of weight gain or sedative side effects (Miura et al., 2014).

Carbamazepine is less effective than lithium in preventing mood episodes in bipolar disorder. It is probably better suited to patients with mixed features (Weisler et al., 2004) and may be useful in combination with lithium, especially where there is marked mood instability. In practice, carbamazepine should be regarded as third/fourth line treatment. Serum levels should be monitored with long-term use, mostly for monitoring adherence or to avoid toxicity and side effects such as skin reactions. A derivative of carbamazepine, oxcarbazepine, has been trialled in a controlled maintenance study as an adjunctive treatment with lithium, and was found to reduce relapse into depression and decrease impulsivity. The evidence for efficacy of oxcarbazepine remains weaker than for carbamazepine (Pratoomsri et al., 2006; Vieta et al., 2008a).

It is noteworthy that there is no evidence for the use of other anticonvulsants such as gabapentin and topiramate in the long-term maintenance treatment of bipolar disorder.

Second generation antipsychotic agents. Research on the efficacy of second generation antipsychotics for bipolar maintenance is rapidly evolving, with current evidence supporting quetiapine and olanzapine in the prevention of manic and depressive relapse as monotherapy or adjunctive therapy (both Level I), but care should be taken especially with olanzapine because of its propensity for metabolic syndrome and because its effect on depressive relapse may not be substantive (Miura et al., 2014). Long-acting injectable risperidone and ziprasidone have some support in the prevention of both manic and depressive episodes (Level II) (Yatham et al., 2009), and paliperidone has been trialled in the prevention of mania

Figure 17. Clinical utility of medications used for maintenance therapy in bipolar disorder.



Medications used for maintenance therapy in bipolar disorder rated according to efficacy of preventing mania and/or depression and their tolerability. Horizontal bars indicate efficacy (solid lines) and tolerability (dashed lines). Their length is based on expert panel average ratings. Medications have also been positioned along an axis that represents mania–depression prophylaxis. For example, lamotrigine is predominately useful for prophylaxis of depression whereas risperidone is largely useful for preventing mania.

(Berwaerts et al., 2012) and aripiprazole monotherapy has evidence for the prevention of manic relapse (Level II).

Despite a lack of RCT evidence, clozapine is widely regarded as an option for treating severe refractory bipolar disorder. However, its significant side effects and ongoing need for monitoring limit its use long term.

Evidence on the use of other atypical antipsychotic agents is emerging, but most studies are of insufficient duration to properly study the maintenance stage of bipolar disorder (McIntyre et al., 2010a). Many patients do not achieve remission with medication monotherapy. The combination of medications increases the risks of adverse interactions and the balance of risks and benefits must be considered. However bipolar disorders are highly disruptive to

patients' lives and cause considerable distress to patients and others, even when substantially recovered but not in remission.

Research on antipsychotic long-term use for all second generation antipsychotics recommends doses within the established recommended dose range for other indications, but it is desirable to keep the maintenance dose to the minimum effective level so as to prevent side effects. In practice, this requires clinical consideration of the risk of relapse and an estimate of the minimum effective dose needed once it is established that antipsychotic maintenance therapy is required. Usually, this is achieved by a gradual taper to the estimated minimum dose.

Prospective advances in long-term pharmacological treatment. A number of medications that have existing psychiatric indications are being trialled for use in the long-term treatment of bipolar disorder. These include *lurasidone*, a second generation antipsychotic that has been used in the treatment of schizophrenia. In a recent study it has shown efficacy in the treatment of acute bipolar depression, both as monotherapy and as an adjunct to lithium or valproate with better tolerability (Loebel et al., 2014a).

Paliperidone in extended release form is also being investigated for maintenance treatment of bipolar disorder. Early indications are that it is effective in delaying recurrence as compared to placebo, especially with respect to manic symptoms, with possibly little effect on depressive symptoms.

In addition to the prevention of relapse/recurrence, the reduction of residual symptoms is also an important outcome/endpoint. In this context, novel agents, *agomelatine* and *ramelteon*, that have an effect of stabilising circadian rhythms, could theoretically be used. Ramelteon has been used with some positive findings as an adjunctive agent to treat insomnia (McElroy et al., 2011; Norris et al., 2013) and agomelatine has had mixed findings for the treatment of bipolar depression (Calabrese et al., 2007; Fornaro et al., 2013; Yatham, 2015).

Psychological treatment in long-term management of bipolar disorder. Compared with the evidence base for psychological interventions for major depressive disorder, evidence for efficacy of psychological interventions for bipolar disorder is of low quality (small number of studies, inconsistency of methods and outcome measures, weak control conditions, elevated risk of bias, limited blinding, etc.). All studies to date have investigated psychological interventions as adjunctive to pharmacotherapy. To understand the literature, it is important to appreciate that (a) there has been almost no research comparing the evidence-based 'brands', and (b) all have significant shared content, aims and therapeutic process; consequently, existing guidelines refer interchangeably to 'psychotherapies' and specific psychotherapies (CBT, etc.).

There is Level I evidence for the effectiveness of structured psychological interventions as a set (group, individual and family-based) in preventing relapse of any kind, with one meta-analysis suggesting a 40% reduction in relapse compared to standard treatment alone (Scott et al., 2007). There is some evidence that relapse prevention is most effective for the depressive pole (Lauder et al., 2010).

Other reviews question the magnitude of effects across different outcome measures (Lynch et al., 2010; Szentagotai and David, 2010) but on balance the literature supports structured

psychological interventions for improvement of depressive symptoms, delaying or minimising recurrences and hospitalisations, and enhancing psychosocial functioning (Goodwin, 2009; Kendall et al., 2014; Yatham et al., 2013b). The literature also indicates that psychological interventions are attractive to many people with bipolar disorder, do not generate negative effects, and have important secondary benefits for quality of life, and personal and functional recovery. For example, CBT has been found in a meta-analysis (10 studies) to improve medication adherence, decrease depressive symptoms and enhance quality of life and social adjustment (Szentagotai and David, 2010). Psychoeducation and CBT have shown strong effects in reducing the subjective burden of disease (Vieta and Colom, 2004; Zaretsky et al., 2007).

Existing adjunctive psychological interventions for maintenance treatment of bipolar disorder are based on a biopsychosocial diathesis-stress model and focus on empowerment, knowledge and skills (Mansell et al., 2005). They arise out of growing evidence that initial onset and course of bipolar disorder are moderated by social and psychological factors, particularly stressful events, family conflict, social and circadian rhythm disruption and medication non-adherence (Gilman et al., 2014; Miklowitz and Johnson, 2009). Research into moderators and mediators of outcome is limited, but there is some evidence that psychological interventions may be more effective when provided earlier in the course of the disorder (Geddes and Miklowitz, 2013) and outside acute episodes (Scott et al., 2007).

Across various outcomes, the best quality evidence is for the efficacy of structured psychological interventions in general, while evidence for specific psychological therapies is weaker. Importantly, the specific psychological therapies investigated to date have substantial content overlap (*see: Table 22)*, and there is little evidence to support efficacy ranking of the 'brands'. Consequently, guidelines often recommend offering any of the evidence-based treatments (e.g., NCCMH, 2014). As with guidelines for unipolar depression, absence of evidence differentiating the psychosocial treatments should not be taken as support for unstructured eclecticism. There is strong clinical consensus that psychosocial treatment is best guided by an evidence-based treatment manual, tailored to the individual client, and with proper attention to the critical therapeutic relationship.

In sum, evidence suggests that a structured psychological intervention should be part of long-term management of bipolar disorder, but does not determine which particular therapy to offer. To ensure that all key content elements are covered (Table 22), therapy should be informed by a published treatment manual for one of the four evidence-based therapies (Table 23). Choice of approach will then be influenced by the local availability of therapeutic expertise (training in, e.g., CBT, family systems, social rhythms, etc.).

Translation and models of care. In the absence of evidence distinguishing the effectiveness of existing psychological interventions, ease of dissemination is a critical consideration. Psychoeducation is a relatively simple, cost-effective psychological intervention (Parikh et al., 2012). Brief psychoeducation (3–6 sessions, preferably in a group format) has been proposed as the first offering to all patients in a stepped care approach to management of bipolar disorder, with more intensive interventions reserved for more complex cases (Parikh, 2014). This suggestion aligns with preliminary evidence for the effectiveness of web-delivered, group-based, and other self-management interventions (Castle et al., 2010; Lauder et al., 2013; Murray et al., 2011b, 2015; Todd et al., 2014), and with cautions that the more complex formulation-based interventions should only be delivered by psychologically trained clinicians with expertise in bipolar disorder (Goodwin, 2009).

People with bipolar disorder can 'fall between the gaps' in mental health services, because of their fluctuating levels of functioning and the dearth of specialist psychological expertise around bipolar disorder. Two large RCTs have used managed-care cooperatives in the US to investigate collaborative care programmes, integrating pharmacotherapy, group psychoeducation and intensive patient monitoring by a nurse care manager (Bauer et al., 2006). Neither found significant reductions in relapse rates, but collaborative care was associated with fewer weeks in manic episodes, improved social functioning and quality of life.

Kessing et al. showed that, compared with standard decentralised care, patients receiving evidence-based psychoeducation and pharmacotherapy had improved readmission rates (Kessing et al., 2013). Specialised care was also associated with increased consumer satisfaction and greater mean costs per patient in the specialist clinic were more than offset by reduced readmission costs.

Some of the content elements shared across evidence-based therapies have been subjected to systematic review, with Level I evidence for both relapse prevention training and psychoeducation (particularly group-delivered) as effective in preventing any kind of relapse (Bond and Anderson, 2015; Morriss et al., 2007).

Electroconvulsive therapy. Electroconvulsive therapy can be invaluable as maintenance treatment for a small number of patients with otherwise treatment resistant bipolar disorder, including recurrent mania. Before such treatment is indicated, patients have usually had inadequate response from multiple appropriate pharmacological and psychosocial interventions. Maintenance ECT is usually administered weekly and the frequency of treatment is usually progressively reduced to treatments every four weeks. Maintenance ECT is usually well tolerated and cognitive impairment does not appear to be progressive during maintenance ECT (Level III).

Duration and discontinuation of maintenance treatment. Patients with bipolar disorder are best advised to use mood stabilising and prophylactic medication indefinitely to prevent future episodes of illness. The discontinuation of long-term treatment risks relapse/recurrence, but equally the long-term use of medications can lead to significant adverse effects. Therefore, a balanced discussion of both the benefits and negative consequences in conjunction with the individual and their carers is necessary at the outset of treatment and whenever a significant change is being considered.

Requests to discontinue medication from patients need to be dealt with promptly. One special circumstance is when a woman is considering becoming pregnant, in which case a detailed risk/benefit analysis should be conducted (see section *Pregnant and breastfeeding women*). Such requests usually reflect one or more of three concerns.

- First, the current regimen is ineffective and the person has ongoing symptoms. This should prompt re-evaluation of medication, and its optimisation so as to alleviate ongoing symptoms.
- Second, the side effects of medication are intolerable. In this instance medication dosage should be reviewed and tapered where possible, otherwise substitutions may be necessary.

- Third, the individual feels they have recovered but because of continuing to take medication are reminded of their illness or fail to appreciate its preventative benefit. This requires detailed discussion and perhaps further psychoeducation.

Patient choice is paramount unless the patient is deemed not to have the capacity to make an informed decision regarding their illness and treatment. Therefore, ongoing psychoeducation about the risks and benefits of treatment discontinuation is essential. Note rapid discontinuation, which is more likely to occur when patients are disengaged and decide to 'manage themselves', incurs significant risks, especially of relapse/recurrence and possible suicide. This underscores the need for a highly effective therapeutic alliance.

In situations where a pattern of relapse and recurrence has not been shown, a carefully monitored gradual withdrawal of medication may be appropriate. This may be indicated for example, if planning a pregnancy. The empirical evidence to guide best practice in this instance is lacking and clinical experience is varied. In cases where a single catastrophic mood episode necessitated treatment, there may be reason for ongoing medication, even in the absence of an established pattern of relapse/recurrence. In instances where substance abuse or possible antidepressant-induced elevation obfuscated diagnosis,[12] a lower threshold may apply when considering medication withdrawal after a sustained period of euthymia.

Table 22. Shared content elements of evidence-based psychological interventions.

Improve ability to recognise changes in mood and signs of prodromal periods, and to respond quickly and effectively (via pre-planning) to these prodromal symptoms
Increase knowledge about and acceptance of BD, including acceptance of, and adherence to medication regimens
Encourage daily monitoring of mood and sleep
Improve interpersonal communication, particularly in the family
Improve significant others' understanding of BD, including ability to identify and productively respond to prodromal symptoms
Re-engage with social, familial and occupational roles
Improve stress response and emotion regulation skills, especially around goals and reward activation
Proactively stabilise sleep/wake and other social rhythms
Identify and critique maladaptive thoughts and beliefs, particularly in relation to the self and the disorder
Reduce drug or alcohol misuse

Table 23. Specific psychological interventions for bipolar disorder.

Four specific psychological interventions can be considered evidence-based (i.e., have at least one positive RCT), and have associated published manuals to guide treatment.

Psychological Intervention	Description
Cognitive-Behavioural Therapy (CBT) (Lam et al., 2010).	Focuses on the reciprocal relationships between thinking, behaviour and emotions to decrease symptoms and relapse risk.
Psychoeducation (Colom and Vieta, 2006)	Aims to assist people to become experts on managing their bipolar disorder, emphasising adherence to medication and stabilising moods. Psychoeducation is a descriptive term referring to providing information about the condition, but has been developed into manualised high intensity treatments by two groups of researchers (Bauer et al., 1998; Colom et al., 2003) and these formal interventions are the focus of the majority of the evidence base.
Family-Focused Therapy (FFT) (Miklowitz, 2008)	Based on evidence that family stress and interactions moderate relapse, FFT aims to improve communication and problem-solving skills in the family. Although only one family member may have a diagnosis of bipolar disorder, the entire family is considered 'the client'.
Interpersonal and Social Rhythm Therapy (IPSRT) (Frank, 2005)	An amalgamation of interpersonal therapy addressing losses, role conflicts and other interpersonal problems with behaviours aimed at stabilising circadian rhythms via stabilising social rhythms (e.g., fixing wake time across 7 days of the week).

Recommendation Box 9.

PSYCHOSOCIAL INTERVENTIONS AUGMENTING PHARMACOTHERAPY FOR BIPOLAR DISORDER	Grade
9.1. Adults with bipolar disorder should be offered adjunctive psychosocial intervention to ameliorate residual symptoms, reduce risk of relapse and improve quality of life.	EBR I
9.2. Intervention should be delivered by an appropriately trained professional with experience in managing bipolar disorder, and should be guided by one of the evidence-based treatment manuals.	CBR

Principles of monitoring. Regular contact with health professionals is essential for appropriate management, but the frequency of visits can vary considerably, and rapid access for additional consultations when early warning signs are emerging, or significant life changes are about to happen, should be allowed for. The frequency of contact is usually no less than biannual visits once long-term stability is achieved and/or only specialist management is required regarding the management of mood stability. Follow-up is more frequent depending upon the history of the illness and time since the last mood episode.

Monitoring sessions are important because they strengthen rapport and ensure the maintenance of an ongoing alliance, which provides an opportunity for additional psychoeducation, psychological interventions, life-style management, monitoring of blood levels and side effects, and continuing tailoring of treatment. In addition, patients will usually have more frequent follow-up appointments with other health professionals in their treating team, such as their general practitioner, psychologist, or case worker. Regular visits may gradually become less frequent if the illness remains in remission, but access to help in a crisis situation must be available to both the patient and significant others, and the plan of action should be known to the patient and all members of the treating team.

Patient self-monitoring is also essential and should be combined with psychoeducation and identification of early warning signs with an action plan to deal with them, particularly a plan to get rapid access to a psychiatrist (or other health professional). The use of mood charts to monitor mood is recommended, which can be a focus of discussion at monitoring visits. Recently wearable devices and 'apps' in mobile phones have become popular means of monitoring activity levels. These may have clinical applications in the near future for monitoring mood stability.

Many medications utilised in the long-term management of bipolar disorder are associated with significant metabolic effects that potentially contribute to the excess medical morbidity and mortality associated with bipolar disorders. In any patient with bipolar disorder, and particularly those on medications with known metabolic risks there is thus a requirement for regular monitoring of weight, abdominal girth, blood pressure and serum lipids and glucose. These measures should be performed at least annually and more frequently dependent on need. A range of guidelines exist for metabolic monitoring *(see: Table 24)* and these can readily be utilised to provide a planned process that is easily instituted. For some patients it may be possible for their GP to undertake monitoring and conduct the necessary tests but the treating psychiatrist should ensure these are conducted and take overarching responsibility.

Carers and the care of individuals with bipolar disorder. In the care of an individual with bipolar disorder, it is central to acknowledge the impact of the illness upon the affected individual, their family, and other carers. Equally, the carers form an integral part of the management team with their capacity to provide often-crucial additional information, and to assist in the implementation of interventions. It is further essential to acknowledge the impact of serious mental illness like bipolar disorder on carers, the level of stress that carers may experience and their heightened risk for the development of their own mental health problems such as anxiety or depression.

Involving carers from assessment and throughout management should now be considered standard care. At times this may lead to concerns in relation to the privacy of the patient, including occasional active discouragement of carer involvement by the patient. In practice, this is considerably less common than a failure by treating clinicians to consider involvement of carers and their needs and roles. Pragmatically most patients will welcome carer involvement and involvement of their carers will only enhance their recovery. It is thus appropriate to raise carer involvement early in therapeutic engagement. This discussion also needs to involve a consideration of any specific aspects that may be highly sensitive,

such as issues related to substance abuse or other disinhibited behaviour during manic episodes.

The issues surrounding carer involvement and confidentiality are often particularly sensitive where capacity to consent to treatment is impaired and involuntary treatment is required. It is important to be aware that several jurisdictions have recently reviewed their mental health legislations to specifically deal with such situations. It is a requirement for practitioners to be familiar with the relevant legislation in their region.

Clinical management of mood disorders with complex presentations and in special populations

Thus far, these guidelines have addressed the management of relatively straightforward mood disorder presentations in adults. In practice, the identification of mood disorders is far more complex with subtypes of mood disorders manifesting throughout the life cycle, often with varied patterns, and usually accompanied by comorbidities, all of which warrant more sophisticated management.

Managing particular types of mood disorders

This section considers some of the recognised subtypes of mood disorders and the intricacies of management.

Mood disorder subtypes. It is important to note at the outset that there are no definitive kinds of mood disorders; even major depression can eventually manifest as bipolar disorder over time. However, some features of mood disorders do appear to co-occur and form characteristic syndromes – and these are termed subtypes.

Table 24. Tests to be conducted and parameters to be monitored during long-term treatment of bipolar disorder.

		Suggested assessments timetable during therapy			
Medication	Investigations and examinations	Initiation	6 months	12 months	24 months
Lithium#	Renal (urea, creatinine, electrolytes)	✓	✓	✓	✓
	Endocrine (TSH, Serum Ca^{2+}, PTH)	✓	✓	✓	✓
	Serum lithium estimations (trough)	✓	✓	✓	✓
Valproate	Full blood count	✓	✓	✓	✓
	Physical (waist circumference, BMI)	✓	✓	✓	✓
	LFTs*	✓	✓	✓	✓
Carbamazepine	Full blood count	✓	✓	✓	✓
	LFTs	✓	✓	✓	✓
	Carbamazepine level^	✓	✓	✓	✓

Notes: Abnormal findings should prompt investigation and more frequent monitoring. BMI = body mass index; TSH = thyroid stimulating hormone; LFTs = liver function tests. PTH = parathyroid hormone.

Lithium is also associated with a narrow therapeutic index and specific issues of toxicity form an important part of monitoring. There is some variance in current guidelines as to the type of testing required (NICE, 2006), but as a minimum, thyroid and renal function (eGFR and Serum creatinine) tests should be done biannually or more frequently if necessary. Frequency should be higher in the elderly; in those patients with established renal impairment; those patients on medications known to influence lithium excretion (thiazide diuretics, Non Steroidal Anti-inflammatory agents and ACE inhibitors) (Wilting et al., 2005; Yatham et al., 2009) or where the patient is likely to suffer dehydration and inadvertent lithium toxicity, such as due to recurrent diarrhoea or living in extremely warm climates. Should the patient have any change in these circumstances or symptoms suggestive of lithium toxicity, urgent serum lithium estimation should be obtained. Where renal impairment is present, consultation with a renal physician in relation to ongoing therapy is appropriate. The occurrence of hypothyroidism may be treatable with thyroid hormone replacement therapy, which should initially be done in consultation with an appropriate specialist.

***The** risk of severe liver damage is greatest in first 6 months of therapy.

^ Carbamazepine induces its own metabolism, therefore steady state takes 2–4 weeks to be established. Also, therapeutic and toxic levels are close.

Melancholia

Features. There is reasonable consensus that there is one subtype of depression that has a neurobiological basis that requires pharmacological treatment. However, the clinical features of this subtype of depression remain elusive; a consequence of the commonality of clinical features associated with all forms of depression. This has resulted in considerable debate about whether melancholia (endogenous or autonomous depression) is a distinct subtype of depression or whether it is a marker of severity (Parker and Hadzi-Pavlovic, 1996; Taylor and Fink, 2006).

While the clinical descriptors of this subtype of depression are elusive, there are some clinical features, treatment outcomes and biomarkers associated with it. Clinical features include: psychomotor change, anhedonia, affective non-reactivity, vegetative symptoms and cognitive changes. Treatment outcomes are superior with biological treatments (dual action

antidepressants, ECT and a low placebo response). Biomarkers include: abnormal Dexamethasone Suppression Test or Corticotrophin Releasing Hormone test, high night time cortisol levels, reduced Rapid Eye Movement latency or another sleep related biomarker (such as reduced duration of Slow Wave Sleep).

Melancholia is a historically and conceptually important subtype of depression, with a putatively stronger biological basis than other unipolar depressive presentations (Hadzi-Pavlovic and Boyce, 2012; Parker and Hadzi-Pavlovic, 1996). It is characterised by psychomotor change, anhedonia, affective non-reactivity, vegetative symptoms and cognitive changes. In DSM-5, with melancholic features is one of the specifiers for depressive episode, characterised by anhedonia, non reactivity and 3 or more of: distinct quality of depressed mood; depression worse in the morning; early morning awakening; marked psychomotor change; significant anorexia or weight loss and excessive or inappropriate guilt. Major depressive disorder with melancholic features has been associated with elevated suicide risk in some studies (Grunebaum et al., 2004; Jeon et al., 2013), and because of these features, melancholic depression is an important subtype clinically.

Treatment. Despite much investigation, consistent empirical associations between melancholic features and superior response to antidepressant medication have not been established (Dodd and Berk, 2004; Georgotas et al., 1986; Mallinckrodt et al., 2005; Nierenberg, 2003; Peselow et al., 1992; Souery et al., 2007; Trivedi et al., 2006; Uher et al., 2011; Uher et al., 2012). However, most studies have not consistently stratified differential efficacy by depression severity, possibly limiting interpretation of these findings (Cameron et al., 2014; Fournier et al., 2010). Clinical opinion would suggest that serotonin noradrenalin reuptake inhibitors (SNRIs) and TCAs may have an advantage over SSRIs for this patient population (Clerc et al., 1994; Malhi et al., 2005; Perry, 1996; Singh et al., 2013), but SSRIs have also been shown to have efficacy (Yang et al., 2012). Psychotherapy may be less effective than medications in this group (Parker et al., 2013; Thase and Friedman, 1999), but combined medication and subsequently added CBT may provide optimal care (Gilfillan et al., 2014).

ECT appears to have preferential efficacy in severe refractory cases with melancholic features (Hickie et al., 1996; Pagnin et al., 2004; Parker et al., 1999), preliminary studies suggest that rTMS may also have benefit in this subtype of depression (Baeken et al., 2010, 2014).

From a clinical perspective, should melancholic features be pronounced it is reasonable to tend towards biological approaches, but remain mindful that integrated biopsychosocial care is needed for optimal functional recovery. Equally when the severity of depression is significant and melancholic features are pronounced, aggressive biological therapies are indicated and the recommended cornerstone of care.

Atypical depression

Features. Along with common symptoms of depression, atypical depression is characterised by reactive mood, marked fatigue and weakness, hypersomnia, hyperphagia with weight gain, and feeling extremely sensitive to rejection (Davidson et al., 1982). Atypical depression may be more common in bipolar depression (Akiskal and Benazzi, 2005; Baldessarini et al., 2010; Blanco et al., 2012; Mitchell et al., 2008).

Treatment. Cognitive therapy, antidepressants and ECT have been shown to be effective in treating atypical depression. A double-blind, randomised control trial studying the differential efficacy of the MAOI phenelzine versus cognitive therapy found both were superior to placebo, and each mode of treatment had a similar response rate of 58% (Jarrett et al., 1999). A lack of difference between medications and counselling was also noted in a retrospective study of 715 subjects (Parker and Crawford, 2009).

It has been proposed that atypical depression responds best to MAOIs. Four randomized controlled trials demonstrated superior efficacy for phenelzine compared to imipramine (Liebowitz et al., 1988; McGrath et al., 1993; Quitkin et al., 1990, 1991). A meta-analysis of 11 studies concluded that MAOIs may be more effective for atypical major depressive disorder than tricyclic antidepressants but there were insufficient data to demonstrate a differential response between MAOIs and SSRIs (Henkel et al., 2006). Conversely, patients with atypical depression appear less likely to remit with the SSRI citalopram than those without atypical features (Stewart et al., 2010; Trivedi et al., 2006). A recent study of 811 subjects with MDD treated with SSRI or tricyclic antidepressant (TCA) found atypical depression did not predict differential antidepressant response (Uher et al., 2011), indicating that TCAs and SSRIs appear to have similar efficacy.

ECT has been shown to be an effective treatment. A prospective study of 489 severely depressed patients treated with ECT demonstrated a superior response rate among patients with atypical features (80%) compared to typical depression (67%) (Husain et al., 2008).

Psychotic depression

Features. Psychotic depression typically refers to an episode of severe depression (melancholia) characterised by the presence of psychotic symptoms, most commonly delusions and/or hallucinations. It can also produce catatonia in which the individual loses motor skill and holds rigid poses for prolonged periods of time or becomes hyperactive and excitable (Fink, 2013).

Treatment. Psychotic depression has potentially dangerous consequences, frequently warranting intensive care (Vega et al., 2000). Combined use of an antidepressant and antipsychotic medication or ECT are the preferred treatments (Davidson, 2010; Lam et al., 2009; Nutt et al., 2010; Wijkstra et al., 2009). This is because antidepressant monotherapy in psychotic depression has lower efficacy than ECT or combined antidepressant and antipsychotic medication (Farahani and Correll, 2012), but the literature is mixed with regard to the optimal pharmacotherapy (Birkenhager et al., 2008; Künzel et al., 2009; Meyers et al., 2009; Parker et al., 1992; Rothschild et al., 2004; Simpson et al., 2003; Spiker et al., 1985; Wijkstra et al., 2010).

Most of the studies demonstrating the efficacy of the combination of antidepressants and antipsychotics have utilised tricyclic antidepressants and typical antipsychotics. Psychotic major depression appears to have a preferential response to ECT, making ECT a treatment of choice (Andrade et al., 1988; Parker et al., 1992). Similarly, ECT is an effective treatment in the context of psychotic bipolar depression. Catatonia necessitates careful organic screening, and is typically responsive to ECT, but there has been little study of major depression with catatonic symptoms probably because of the rarity of this subtype (Parker and Hadzi-Pavlovic, 1996). Following recovery, adequate maintenance treatment should be

continued for 6–12 months or longer if the illness is recurrent. This will require ongoing combined antidepressant/antipsychotic medication or maintenance ECT depending on individual circumstances.

The role of TMS in psychotic depression has not been systematically examined, and a single case report noted a negative finding (Krisanaprakornkit et al., 2010; Ren et al., 2014). A recent meta-analysis has suggested superiority of ECT over TMS in psychotic depression specifically, with much less differentiation between the treatments in non psychotic depression.

CBT and other forms of psychotherapy should not be utilised as monotherapy in this group, but be employed in the recovery phase once gross mental state disturbances have been corrected with biological therapies such as medication and ECT.

Persistent depressive disorder (dysthymia)

Features. Persistent depressive disorder (dysthymia) is a consolidation of chronic major depressive disorder and dysthymic disorder. It describes a state in which the person experiences more days than not in a depressed mood for at least 2 years (mood can be irritable and duration can be 1 year in children and adolescents). During this time there has never been a symptom free period of 2 months or more. Typical symptoms include, 2 or more of, poor appetite or overeating, insomnia or hypersomnia, low energy or fatigue, low self-esteem, poor concentration or difficulty making decisions, and/or feelings of hopelessness. It is important to note that personality disorders and traits are common comorbidities with prolonged depression.

Treatment. Compared to major depression there is far less empirical data on optimal management of dysthymia. Nonetheless, these conditions do present clinically and may impair quality of life. A recent meta-analysis suggests that antidepressants are superior to placebo for the treatment of PDD, with SSRIs having better tolerability than TCAs (Levkovitz et al., 2011; Von Wolff et al., 2013). But the utility of antidepressants for subthreshold depressive symptoms is not established (Cameron et al., 2014), despite earlier data indicating antidepressants appear to have efficacy (De Lima et al., 1999). CBT appears less effective than SSRIs, but the combination of therapies appears more effective than either alone (Cuijpers et al., 2010b). Internet based CBT may be effective for minor depressive symptoms among older adults (Spek et al., 2008). Given the lack of clear efficacy of antidepressants in this group, psychosocial interventions should be encouraged prior to considering medications.

Cyclothymia

Features. Cyclothymic disorders (cyclothymia) describes prolonged states (1 year in children and adolescents, 2 years in adults) during which periods of subsyndromal hypomania and depressive symptoms have been present for the majority of the time ($>$50%) and there has been no period of more than 2 months when the individual has been symptom free.

Treatment. Despite the higher prevalence of bipolar spectrum disorders (Merikangas et al., 2007, 2011), cyclothymic disorder has the least empirical base to guide optimal management, because of greater focus on the more debilitating bipolar I and II disorders. As with bipolar

II disorder, much of the clinical management of cyclothymic disorder is extrapolated from the management guidelines for bipolar I disorder. The validity of this is unclear, and the key clinical issue is the risk-benefit analysis between hazards of the untreated condition versus hazards from treatment. Where distress and dysfunction arising from cyclothymic disorder are mild, conservative non-pharmacological approaches alone should be trialled initially. Indeed, even with more severe symptoms it is unclear if pharmacotherapy is useful (Findling et al., 2007).

Research on psychosocial treatments for cyclothymia is limited. One randomised controlled trial found augmented CBT was effective for depressive and hypomanic symptoms, compared with clinical management (Fava et al., 2011). Over half those in the intervention group no longer met criteria for the disorder post-treatment, and gains were maintained at 1- and 2-year follow-up (Fava et al., 2011).

However, cyclothymia may be a precursor to bipolar I or II disorder and, therefore, longitudinal mental state review and psychoeducation of patients as to when to seek further review is advisable (Alloy et al., 2012). Family involvement may be particularly beneficial in the care of such patients (Pfennig et al., 2014). Borderline personality disorder needs to be considered as a potential differential diagnosis in some cases (Bayes et al., 2014).

Bipolar II Disorder (BD II)

Features. BD II differs from BD I along a dimension in which the severity of manic features become progressively more severe with respect to elevation of mood (euphoric or irritable), intensity of energy, disruption of function (both in mental state and daily activities) and the recognition by others that a mental state problem is present. The boundaries of hypomania are ill defined (Malhi et al., 2010) but the absence of psychosis, and the absence of severe life disruption because of manic symptoms (Malhi and Berk, 2014), are useful parameters. BD II is also characterised by the predominance of depressive features, both as discrete depressed episodes and as mixed affective states. The impact of BD II upon quality of life is at least as substantial as with BD I, if not greater because of the tenacity of chronic depressive features (Judd et al., 2003b). The risk of suicide is also high and comparable with BD I (Holma et al., 2014; Novick et al., 2010). No neurobiological differences with BD I have been established, further blurring the distinction between these two forms of bipolar disorder.

Treatment. Optimal management of BD II has been much less studied than BD I disorder, with many BD II treatment recommendations 'extrapolated' from the BD I literature (Tamayo et al., 2013). For this reason, the management of BD II disorder clinically (currently) mirrors that of BD I except that the focus is more upon depressive episodes and residual depressive and mixed symptoms, than mania. Lithium and sodium valproate are less suited to relieving mood instability in BD II disorder as compared to their role in BD I disorder. In selecting therapies, attention should be paid to the balance of hazards of the untreated condition versus hazards from treatment. For this reason, biological therapies with lower toxicity profiles are generally preferred in managing BD II disorder, but by the same token risk of suicide in the depressive phase should not be underestimated. Mood stabilisation is critical for prophylaxis and alongside pharmacotherapy, psychotherapies appear to be of value (Berk et al., 2010; Lauder et al., 2010; Schöttle et al., 2011).

Indeed, because of the predominance of depressive symptoms (for which psychosocial treatments are effective in MDD), we might expect psychological treatments to have particular application in BD II. Research on this issue is limited.

Post-hoc analyses of two large RCTs suggest that adjunctive psychosocial interventions effective in BD I are equally effective in BD II. Decreased relapses and symptom load have been found amongst BD II patients receiving adjunctive group psychoeducation (Colom et al., 2009). In the large STEP-BD trial, cognitive behaviour therapy (CBT), interpersonal and social rhythm therapy (IPSRT) and family-focused therapy (FFT) were (equally) superior to collaborative care in accelerating recovery from a depressive episode and maximizing the probability of remaining well across 12 months: No main effect of diagnosis (BD I vs. BD II) was found (Miklowitz et al., 2007). One small randomised trial of acute Bipolar II depression found IPSRT monotherapy to be equivalent to quetiapine monotherapy (Miklowitz et al., 2007). In sum, as with pharmacological intervention, clinicians are asked to cautiously generalise evidence-based psychological treatments from BD I to BD II.

Lamotrigine has received considerable support from many clinicians and some controlled trials (Bowden and Singh, 2012; Reinares et al., 2013; Selle et al., 2014; Sienaert et al., 2013; Trankner et al., 2013), in the management of bipolar depression. Whilst lamotrigine has been found to be effective for some patients with BD II, for other patients it may not provide any benefit. Atypical antipsychotic medications such as quetiapine, olanzapine and lurasidone, have shown significant benefits in bipolar depression (Level II) (Azorin et al., 2013; Bawa and Scarff, 2015; Janicak and Rado, 2011; Loebel et al., 2014a; Sanford and Dhillon, 2015; Sanford and Keating, 2012; Tohen et al., 2013; Vieta and Valenti, 2013). Asenapine may also be helpful (Azorin et al., 2013). The use of antidepressant medications is a controversial issue and perhaps more so in BD II because depressive features are so much more prominent. However, expert opinion recommends caution in their use (Mauer et al., 2014; Pacchiarotti et al., 2013a). The risks of rapid cycling, mixed states and switching into mania, are potential consequences, and efficacy is sometimes disappointing. Agomelatine, pramipexole and modafinil have found some supportive evidence but remain of uncertain value beyond intervention for treatment resistant patients (Fornaro et al., 2013), and there is some preliminary evidence that adjunctive NAC may be of benefit in the treatment of BD II (Magalhaes et al., 2011).

Mood disorders patterns. The description of mood disorders is largelycross-sectional but the course of illness is equally important. Some patterns such as mixed states/features defy classification and therefore require separate consideration (see Figure 18).

Mixed features

Features. In DSM-5, a ‘mixed features’ ‘specifier’ is used to indicate the occurrence of three or more symptoms from the opposite pole. Therefore depression, mania and hypomania can each be further specified with ‘mixed features’. This change is recent and therefore little is known about the diagnosis and treatment of mixed features presentations as defined by DSM-5 (Malhi, 2013, 2014). Earlier studies that examined DSM-IV mixed episodes rarely studied these separately. Usually, mixed episodes have been grouped alongside acute mania. Therefore, treatment guidelines for mixed features draw heavily on clinical experience and consensus recommendations.

Treatment. For depressed patients with mixed features, taper and cease substances with a mood-elevating effect or those that may induce inter-episode switching (e.g., antidepressants, stimulants). Consider treating the patient with olanzapine (Level II) (Tohen et al., 2014), quetiapine, or valproate as monotherapy or in combination with an antidepressant, or valproate in combination with olanzapine (Level II) (Benazzi et al., 2009). Lamotrigine adjunctive to an antimanic agent may be a useful option for mixed states to treat depressive symptoms (Krüger et al., 2005; Swann et al., 1997), though the therapeutic effect is likely to be delayed as this requires slow titration, especially when administered in

Figure 18. Rapid cycling and mixed states in bipolar disorder.

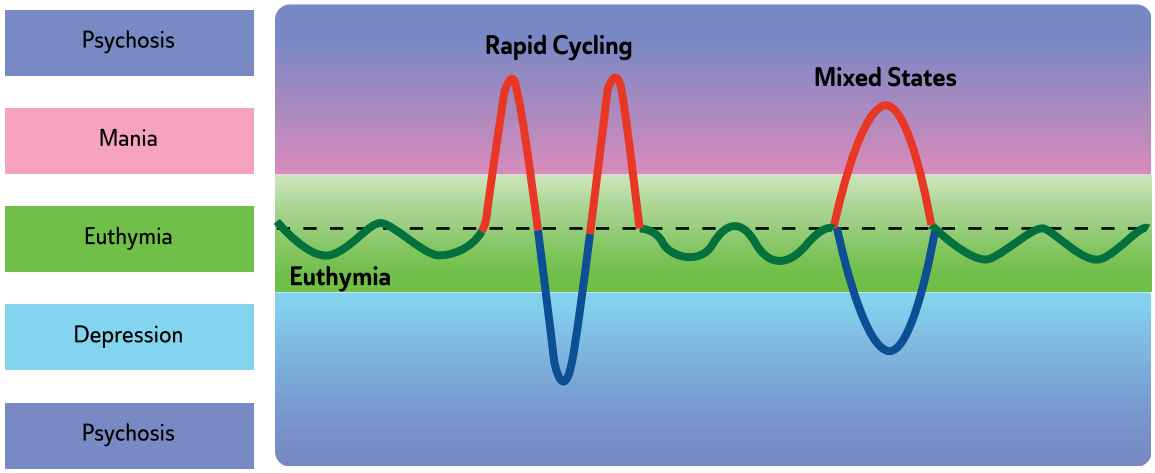


Illustration of rapid cycling and mixed states in bipolar disorder. Rapid cycling is defined as experiencing 4 or more discrete mood episodes per year. Mixed states is defined in DSM-5 by a specifier based on the presence of 3 or more depressed features during a manic episode, or 3 or more manic features during a depressive episode. * (DSM-5 considers only non-overlapping symptoms).*

conjunction with valproate. If symptoms and/or behavioural disturbance are severe or protracted, then consider ECT (Level III) (Valenti et al., 2008).

The mixed features specifier in DSM-5 for mania or hypomania emphasises dysphoria or depressed mood, loss of interest or pleasure, psychomotor retardation, fatigue, feeling of worthlessness or guilt and recurrent thoughts of death being present during an episode. There are limited trials of specific medications to use for acute dysphoric manic states with most of the data coming from retrospective analyses of trials of mania that have included those with mixed states.

For manic patients with depressive features (dysphoric mania), antidepressants should be prescribed with care, as these may aggravate the mixed state or promote rapid cycling (Fountoulakis et al., 2012b; Pacchiarotti et al., 2013b; Swann et al., 2013; Valentí et al., 2011).

Second generation antipsychotic medications, in conjunction with a mood stabiliser (Muralidharan et al., 2013) are more effective than mood stabilisers alone and are

recommended for use in dysphoric mania, with Level II evidence for asenapine (McIntyre et al., 2013; Muralidharan et al., 2013; Ouanes et al., 2014), olanzapine (Fountoulakis et al., 2012b; Muralidharan et al., 2013; Ouanes et al., 2014), aripiprazole, ziprasidone and risperidone (Muralidharan et al., 2013). There is an absence of evidence regarding the use of quetiapine for the acute treatment of mixed states.

With regard to maintenance therapy, valproate appears to be more effective than lithium (Krüger et al., 2005), but the evidence regarding carbamazepine is equivocal.

Rapid cycling bipolar disorder

Features. Rapid cycling bipolar disorder refers to the presence of at least four mood episodes of mania, hypomania or depression in the previous 12 months. Described in the early 1970s as a course specifier for bipolar illnesses (Dunner and Fieve, 1974) a rapid cycling pattern is relatively common – and affects almost one third of bipolar disorder patients. In a proportion of these patients rapid cycling is associated with female gender, hypothyroidism, depression, greater illness severity and longer illness duration (Carvalho A et al., 2014; Fountoulakis et al., 2013). Clinically, rapid cycling is a transitional stage of bipolar disorder that can be easily confused with mixed states. The presence of rapid cycling complicates management and increases the risk of suicide attempts and greater depressive morbidity (Coryell et al., 2003) partly because of poorer treatment adherence (Perlis et al., 2010; Schneck, 2006; Tondo et al., 2003; Vieta et al., 2004). It is important to screen for rapid cycling, and where possible, address factors that may precipitate or exacerbate cycling, such as antidepressants, substance misuse, and medical illness, such as hypothyroidism (Schneck, 2006).

Treatment. Rapid cycling has significant implications for the treatment of depressive symptoms, with the focus being more on the long term stabilisation of mood than the treatment of the particular episode.

The evidence-base for rapid-cycling is limited and overall treatments are less effective in countering depressive symptoms than manic symptoms (Calabrese et al., 2003; Schneck, 2006). Choice of treatment is governed by the current mood state and the need to prevent cycling (Carvalho et al., 2014; Fountoulakis et al., 2013). Pharmacological monotherapy options include valproate (Level II), lithium (Level II), olanzapine (Level II) (Sanger et al., 2003), lamotrigine (Level II) (Calabrese and Delucchi, 1990; Calabrese et al., 1993, 2000, 2005a; McElroy et al., 1998; Tondo et al., 2003; Vieta et al., 2004), quetiapine (Level III) (Goldberg et al., 2008), aripiprazole (Muzina et al., 2008). There is limited evidence for medication combinations but where necessary combinations, such as lithium and valproate (Calabrese et al., 2005c) (Level III), lithium and carbamazepine (Level III) (Denicoff et al., 1997), or adjunctive lamotrigine (CBR) (Calabrese et al., 2005a) can be trialled. Adjunctive psychological interventions (CBR), as discussed may also be of benefit. Similarly, ECT has been found to be effective in some cases and can be trialled when necessary (Level III) (Calabrese et al., 2001; Papadimitriou et al., 2007).

Seasonal patterns. Seasonal effects on mood have been discussed since antiquity, and there is some scientific evidence for seasonal variation in mood: a prospective study in the general population found some 2% of variance in positive affect to be explained by

decreases in winter and increases in spring/summer (Murray et al., 2001). It has also been hypothesised that objective seasonal factors (particularly decreased daylight in winter) are causal in episodes of mood disorder. A strong version of this hypothesis is that some forms of mood disorder are predominantly explained by objective seasonal factors: Seasonal Affective Disorder (SAD), first defined in the 1970s, is such a hypothesis.

Winter pattern SAD (winter depression) is characterised by episode onset in autumn/winter and remission in spring/summer (Rosenthal et al., 1984). Symptoms are generally mild to moderate in severity, and include hypersomnia with difficulty waking and daytime fatigue, appetite increase, carbohydrate craving and weight gain. Bright light is the first line treatment for winter pattern SAD, with effect sizes comparable to antidepressant medication in nonseasonal depression (Golden et al., 2005) and parallel benefits for quality of life (Michalak et al., 2007). There is some evidence that light treatment can be effective at lower intensity if the source emits blue-enriched light (Meesters et al., 2011). Guidelines for bright light treatment of winter SAD with an MDD diagnosis have been published, and there is growing research interest in bright light for depressions in BD (Benedetti, 2012).

Evidence that SAD also responds to antidepressants (Lam et al., 2006) and CBT (Rohan et al., 2009), while nonseasonal depressions also respond to bright light (Golden et al., 2005) raises doubts about SAD as a distinct clinical entity. Indeed, DSM has never accepted SAD as a diagnosis, recognising instead that some people with recurrent mood disorders have seasonal patterns to their recurrence. Although autumn/winter pattern depressions are most typical of the seasonal pattern course specifier, DSM recognises any seasonal pattern not explained by psychosocial factors. In DSM-5, the seasonal pattern specifier can be applied independently to any of depressive, manic or hypomanic episodes.

Seasonal pattern of mood episodes has a complex relationship to mood disorder diagnosis (Roecklein et al., 2010). It is slightly more common amongst people with BD (15–22%) than MDD (10–20%); amongst people with BD, seasonality may be associated with BD II and depressive polarity; amongst people with winter SAD, 80–90% warrant a diagnosis of MDD, while 10–20% warrant a BD diagnosis. Seasonal patterns of symptoms vary between people and within people across time: In BD populations, rigorous prospective studies have failed to find coordinated seasonal patterns in depression or mania (Murray et al., 2011a).

Management of mood disorders in the context of comorbidities

It is important to remember that unusual or atypical presentations may reflect concomitant psychopathology because of comorbid psychiatric or medical illness. Furthermore, new symptoms in patients already engaged in treatment may be a consequence of medication or psychological interventions.

Anxiety

Depression with comorbid anxiety. Depression with comorbid anxiety is a common clinical presentation (Malhi et al., 2002). While antidepressant medications have evidence of efficacy in this group, outcomes are often poorer than for subjects without comorbid anxiety (Papakostas et al., 2012; Souery et al., 2007; Tollefson et al., 1994). This is also true for psychotherapeutic approaches (Deckersbach et al., 2014). Nonetheless, second generation antidepressants appear to have some efficacy in this patient group (Fawcett and Barkin, 1998; Rudolph et al., 1998; Tourian et al., 2010) with a recent study suggesting agomelatine

may have superior efficacy (Stein et al., 2013). Research also supports the use of psychological therapies (Cape et al., 2010), but head-to-head and combined psychological and pharmacological treatment studies are lacking. In less severe and/or less refractory cases, non-pharmacological approaches are preferred due to better risk/benefit profiles. Long-term use of clonazepam in otherwise refractory cases of depression with marked anxiety (especially panic) have been reported, but constitute the exception rather than the rule due to risks of tachyphylaxis and impaired alertness (Nardi et al., 2012; Tesar et al., 1987; Winkler et al., 2003). Nonetheless, clinically it seems there is a small proportion of patients with otherwise disabling depression and panic symptoms who do well with long-term clonazepam without tachyphylaxis or side effect burden (Nardi et al., 2012). Before such an approach is considered, psychiatric opinion is advisable.

Bipolar disorder with comorbid anxiety. Anxiety symptoms and disorders are commonly present in bipolar disorder either as comorbid conditions or a component of bipolar disorder itself (McIntyre et al., 2006; Schaffer et al., 2012) and are linked to a poorer outcome (Freeman et al., 2002; Kim et al., 2014). When an anxiety disorder is present along with bipolar disorder, the first aim of management is to achieve mood stabilisation (Freeman et al., 2002). There is limited evidence for specificity of treatments for treatment of comorbid anxiety disorders in bipolar disorder, especially for psychological treatments and serotonergic antidepressants. Psychological interventions for anxiety comorbidity in bipolar disorder have great potential, given the challenges of adding anxiolytics to mood stabilising pharmacotherapy regimens. Studies to date have investigated psychological interventions targeting both anxiety and bipolar disorders (N = 7), specific anxiety disorders in bipolar disorder populations (N = 7) and bipolar disorder only but reporting on anxiety outcomes (N = 8). Research has overwhelmingly focused on the inter-episode period, and has found significant if modest benefits with no evidence of harm (Stratford et al., 2015). The set of studies are extremely heterogeneous, but CBT for bipolar disorder augmented with anxiety strategies may have the strongest evidence.

Pregabalin has been shown to have modest efficacy in the treatment of comorbid anxiety and depression (Stein et al., 2008), and there is evidence for the efficacy of the second generation antipsychotic medications such as quetiapine (Sheehan et al., 2013) and olanzapine (Level II) (Suppes et al., 2014) but not risperidone (Sheehan et al., 2009) and the anticonvulsant mood stabilisers (sodium valproate and lamotrigine (Level II)) for the treatment of comorbid anxiety disorders (Stein et al., 2008). Part of risk/ benefit analysis in using atypicals to manage anxiety comorbidities is to consider risk of metabolic syndrome and balance this against risk of other treatment options to control anxiety.

Based on clinical experience, short-term use of benzodiazepines (less than 4 weeks) may be of benefit for severe anxiety symptoms prior to mood stabilisation being achieved, but supportive research evidence is lacking (Bobo et al., 2014).

Substance use. Comorbid substance use and mood disorder is often seen in clinical practice. Substance use may cause, mimic, underlie or complicate mental health disorders. It is important to ensure that the symptoms of a mood disorder are not attributable to either the physiological or pharmacological effects of a substance or to signs and symptoms of substance withdrawal.

Comorbid substance use may be a consequence of:

1. The underlying primary mood disorder, reflecting attempts to 'self-medicate' mood symptoms. However, eventually depressive symptoms may emerge because of the depressogenic effects of the substance or because the mood disorder has taken hold. In essence, there is a complex and interactive relationship between substance misuse (especially alcohol) and depressive symptoms.
2. The mood disorder being a psychiatric complication of substance use (e.g. euphoria during the initial phase of psychostimulant use followed by depression during the 'crash' phase). It is noteworthy that co-morbid alcohol and substance use disorders are associated with a worse course of bipolar disorder including more mood symptoms, recurrent mood episodes and decreased likelihood of recovery, more suicides, more hospitalisations and higher levels of aggressiveness (Suppes and Cosgrove, 2014).

If appropriate assessment, diagnosis and management of substance use are not undertaken, comorbid substance use may result in incorrect diagnosis and ineffective treatment of mental health disorders such as depression or bipolar disorder (Gao et al., 2010; Worthington et al., 1996). The risk of suicide increases, as does the probability of hospitalization and of aggressive behaviour. Importantly, many patients with comorbid bipolar disorder and substance abuse need to recover from elements of their mood disorder before their substance abuse can be usefully addressed.

For this reason, a full assessment and diagnosis of substance use and its management including detoxification is necessary, ideally prior to diagnosing and treating underlying mood disorders both to enable accurate diagnosis and effective therapy (Magidson et al., 2013). However, it is important to note that in many instances mood disorder patients with comorbid substance dependency will not be able to shift their usage until aspects of their mood disorders are contained. Often in outpatient practice settings, treatment of the mood disorder and substance use disorder needs to occur concurrently.

Treatment of depression with comorbid substance use disorder. A meta-analysis of comorbid substance use disorder with major depression found depressive symptoms did not significantly improve with SSRI treatment, but other classes of antidepressants (notably TCAs) may have some efficacy (Torrens et al., 2005). No antidepressant effect was found in comorbid cocaine dependence or opioid dependence (Torrens et al., 2005). Interestingly, venlafaxine has been shown to be ineffective in treating depressive symptoms comorbid with cannabis use, and may in fact be associated with greater cannabis use (Levin et al., 2013).

Patients with nicotine dependence and depression may potentially benefit from bupropion or nortriptyline, possibly because these agents are associated with greater smoking cessation rates (Hughes et al., 2007). Special caution is needed when prescribing antidepressants to patients who misuse stimulant drugs, as there may be heightened risk of serotonin syndrome (Silins et al., 2007). Among patients with hepatic impairments (e.g. alcoholic cirrhosis, hepatitis C from IV drug use) desvenlafaxine may offer some benefit over antidepressants which are metabolised by the liver (Baird-Bellaire et al., 2013).

Treatment of bipolar disorder with comorbid substance use disorder. Substance use disorders are commonly comorbid with bipolar disorders and rates as high as 67% have been described. Bipolar disorder with comorbid substance use is associated with greater illness morbidity (Mazza et al., 2009) and mortality (Level IV evidence: (Yoon et al., 2011)).

Empirical evidence to guide optimal management of bipolar disorder and comorbid substance abuse is scarce, partly because such patients are difficult to engage in trials (Malhi et al., 2012a). One study suggests that integrating CBT with group drug counselling has better outcomes than group drug counselling alone (Weiss et al., 2009). Alcohol has been studied more than other comorbid substances, but again the evidence base to guide clinicians remains poor (Azorin et al., 2010).

Use of valproate may help reduce alcohol consumption in some patients (Salloum et al., 2005; Sattar, 2007) with possible additional benefit if naltrexone is added (Salloum et al., 2006). Adjunctive quetiapine may help reduce alcohol use comorbid with bipolar disorder (Martinotti et al., 2008), but the limited literature is mixed (Brown et al., 2008), preventing empirical guidance. Importantly, patients with bipolar disorder have a five-fold greater chance of smoking compared to the general public (Diaz et al., 2009). Identifying nicotine dependence among bipolar patients and attempts to tackle it should form a routine element of patient care especially as treatments targeting smoking cessation are now emerging (Chengappa et al., 2014; Evins et al., 2014).

Appropriate assessment, diagnosis and management of alcohol or substance use disorder prior to mood therapy are advisable to best inform underlying diagnosis and best enhance odds of mood therapy efficacy. This may require a period of inpatient care in some instances, and engagement with formal drug and alcohol relapse prevention programs to encourage sustained abstinence. Ongoing comorbid substance misuse has a poor prognosis with mood disorder. A variety of strategies may be employed including supportive programmes (telephone, group), nicotine supplements and varenicline (Chengappa et al., 2014; Evins et al., 2014).

Personality disorder. Personality disorders are common in patients with major depression, with studies reporting prevalence rates ranging from 43–58% (Mulder, 2004). Cluster C personality disorders (avoidant, dependant and obsessive compulsive) are most commonly associated with major depressive disorders (Friborg et al., 2014). Depressed patients with a comorbid personality disorder have twice the chance of poor outcome with an OR 2.16 (CI 1.83 to 2.56) (Level I) (Newton-Howes et al., 2014). There is some evidence SSRIs may be superior to TCAs in depressed patients with comorbid Cluster B personality disorders (Level II) (Mulder et al., 2003), and preliminary evidence suggests CBT may be more effective than IPT in patients with comorbid major depression (Level II) (Joyce et al., 2007).There is consistent evidence that active treatment of major depression is associated with improvement in personality disorder symptoms (Fava et al., 2002; Mulder et al., 2010) Overall, however, there is insufficient evidence to formulate evidence-based recommendations in the management of co-occurring mood disorders in patients with personality disorders.

Borderline personality disorder and mood disorders

Clinical features. It is common for people with Borderline Personality Disorder to also suffer from a Major Depressive Disorder, and Bipolar Disorders (more commonly BD II) are present

in about 9–16% of people with a Borderline Personality Disorder (Paris et al., 2007). This comorbidity amplifies the symptoms of each disorder and increases the time before remission (Gunderson et al., 2014). The presence of Borderline Personality Disorder with Major Depressive Disorder increases interpersonal difficulties (Yoshimatsu and Palmer, 2014), while the co-occurrence of Borderline Personality Disorder and Bipolar Disorder is associated with more impulsive behaviour and transient dissociative symptoms (Zimmerman et al., 2013, 2014). It is important to note that the concurrent treatment of both Borderline Personality Disorder and mood disorders offers a better probability of improvement in both sets of illness symptoms and in function (Beatson and Rao, 2013; Gunderson et al., 2014; Paris and Black, 2015; Yoshimatsu and Palmer, 2014).

The relationship between Borderline Personality Disorder and Bipolar Disorder remains subject to controversy, but the consensus is that they are distinct disorders (Antoniadis et al., 2012; Bassett, 2012; Belli et al., 2012; Coulston et al., 2012; Yoshimatsu and Palmer, 2014). Possible over-diagnosis of BD II can arise as a result of the overlap of symptoms between Borderline Personality Disorder and BD II. Table 25 summarizes the similarities and differences between Mood Disorders and Borderline Personality Disorder. Accurate diagnosis is based upon a detailed longitudinal history, with emphasis upon the accurate assessment of hypomanic episodes, and interpersonal and family history (Bayes et al., 2014; Ghaemi and Dalley, 2014; Paris and Black, 2015). The management of co-morbid occurrence must therefore address the specific needs of each patient, with attention to the contributions of each of these disorders, while accepting a degree of commonality.

Psychotherapy. Psychotherapy is fundamental to the management of Borderline Personality Disorder and of considerable importance in the management of mood disorders. The approach in psychotherapy is different with Borderline Personality Disorder from mood disorders, requiring close attention to the disrupted sense of self and the development of a capacity to establish and maintain close, meaningful relationships. However, the management of patients suffering both disorders at the same time has not been the subject of study. While no specific form of psychotherapy has been shown to be optimal in efficacy in Borderline Personality Disorder, Dialectical Behaviour Therapy (DBT) is particularly useful (Bateman et al., 2015), and Psychodynamic Psychotherapy can be helpful. Cognitive and Behavioural Therapies (CBT) are of particular value in Major Depressive Disorder and Bipolar Disorders. The cognitively orientated therapies (such as DBT and CBT), tend to provide benefit within months, while the transference orientated therapies (such as Psychodynamic Psychotherapy) tend to require periods of years to provide significant benefits. Patients in both groups of disorders respond to supportive psychotherapies and both can benefit from DBT and CBT (Bassett, 2012; Bayes et al., 2014; Belli et al., 2012; Friborg et al., 2014; Ghaemi et al., 2014; Martín-Blanco et al., 2014; Zimmerman and Morgan, 2013). There is evidence that comorbid Borderline Personality Disorder and Bipolar Disorder increases the risk of suicide attempts (Zimmerman et al., 2014). Therefore, it is important to diagnose both conditions when they are present, because they identify the comorbid patients who are at particularly high risk for suicide attempts.

Table 25. Summary of the relationships of mood disorders and borderline personality disorder.

Clinical data	Major Depressive Disorder (MDD)	Bipolar Disorders (BD)	Borderline Personality Disorder (BPD)	Grade
Affective dysregulation	Mood is depressed with varying severity.	Mood varies between depression, euphoria, or irritability (suggests mixed states).	Mood often contains intense rage, with intermittent anxiety and depression.	EBR I
Age of presentation (typically)	Any age, but particularly early adulthood.	Late adolescence and young adulthood.	Early adolescence.	EBR I
Illness trajectory	Recurrence is common.	Onset: usually prominent affective signs and symptoms. Course: Depressive and mixed episodes become *more common* with advancing age.	Onset: usually behavioural and interpersonal difficulties. Course: intensity of core features *improves* approaching the fourth decade. May then exhibit *improved* capacity to maintain close relationships, and improved affective regulation.	EBR II
Depressive features	Large range of affective features.	Features of melancholia, agitation, mixed affective episodes, all occur commonly. Intense guilt when depressed.	Shame, 'a noxious sense of self' (intense self-loathing and self-denigration). Prominent cognitive, self-defeating core beliefs and projection. MDD may arise comorbidly.	EBR I
Manic features	Nil.	Hypomania is an essential clinical component. Irritable mood/affect is *common* but not always present.	Affective instability is key feature rather than prolonged shifts in mood and affect. Irritability is *ubiquitous*.	EBR I
Impulsivity	Low.	High, but *fluctuates markedly* with periods of mania.	High and *persistent*. Often a trait as well as state phenomenon.	EBR II
Social cognition	Good appreciation of the emotional states of others and meaning for them, when euthymic.	Good appreciation of the emotional states of others and meaning for them when euthymic.	Poor appreciation of the emotional states of others and meaning for them. Often respond to these distorted perceptions negatively (sometimes positively) and may use this to cope with internal emotional pain.	EBR I
Psychosis	May be present.	Present only in BD I.	Psychotic episodes may arise and periods are of brief duration (hours or days), paranoid in content, may include delusions and hallucinations. Occur at times of intense emotional stress. Dissociative phenomena may be misdiagnosed as psychosis.	EBR I
Self/identity	Mostly positive sense of self, except when severely depressed.	Mostly positive sense of self, except when severely depressed. Elevated sense of self importance and potency when hypomanic.	'Noxious sense of self' with self-loathing, sometimes alternating with fragile self-grandiosity.	EBR I
Relationship quality	Relationships often suffer adversely from the disorder.	Relationships often suffer adversely from the disorder.	Relationship difficulties are a primary deficit in this disorder. Interpersonal chaos is common. Intense ambivalence and fear of abandonment are core problems. Improve with age.	EBR I
Family history	Family history of mood disorder is common.	Family history of mood disorder is common.	Family history of mood disorder and/or personality disorder is common.	EBR I
Childhood trauma	Common (physical, neglect and abandonment, sexual).	Common (physical, neglect and abandonment, sexual).	Very common (physical, neglect and abandonment, sexual).	EBR II
Self-harm	Recurrent, deliberate self-harm occur intermittently.	Recurrent, deliberate self-harm occur intermittently.	Recurrent, deliberate self-harm occur frequently.	EBR I

References: (Antoniadis et al., 2012; Bassett, 2012; Coulston et al., 2012; Fletcher et al., 2014; Ghaemi et al., 2014; Malhi et al., 2013c; Renaud et al., 2012; Roepke et al., 2012; Witt et al., 2014; Zimmerman et al., 2013).

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Recommendation Box 10.

MANAGEMENT OF BIPOLAR DISORDER WITH COMORBID SUBSTANCE USE	Grade
10.1. Prior to making a definitive diagnosis of a mood disorder and commencing antidepressant/mood stabiliser therapy, a proper assessment and diagnosis of substance use issues should be conducted and if possible effective treatment of a substance use disorder should be implemented.	CBR
10.2. In cases of comorbidity with *substance dependence* or *severe substance use disorders*, detoxification followed by relapse prevention measures should be implemented first.	CBR
10.3. When considering the use of TCAs in patients with major depression continuing to misuse substances, the potential benefits should be balanced against the risk of suicide.	CBR
10.4. For patients with severe alcohol or other substance use disorders (DSM-5), detoxification should occur followed by relapse prevention measures integrated with CBT (Integrative Group Therapy – IGT) to maintain abstinence.	EBR III
10.5. Early intervention should be considered in patients with mild substance use disorders	EBR III

Pharmacotherapy: Borderline Personality Disorder. Medications have limited benefits in the management of Borderline Personality Disorder, with atypical antipsychotic agents having the best established efficacy (Ripoll, 2013; Stoffers et al., 2010). Atypical antipsychotics and mood stabilzers (including lithium, sodium valproate and lamotrigine) can be valuable to assist with concurrent Bipolar Disorders, affective instability, impulsivity and aggression. Antidepressants and atypical antipsychotics have value when Borderline Personality Disorder is comorbid with Major Depressive Disorder.

Schizophrenia. Co-occurring depression is common in patients with schizophrenia. In the Australian Survey of High Impact Psychosis, 55% of patients with a psychotic disorder, such as schizophrenia, had depressed mood in the year prior to the survey (Morgan et al., 2012). When a patient with schizophrenia presents with significant depressive symptoms, a number of differential diagnoses need to be considered (Siris, 2000): first, rule out the presence of medical factors contributing to depressed mood (e.g., cardiovascular disorders or cancer); second, the role of prescribed drugs, such as beta-blockers or the use of illicit substances, including alcohol; and third, the role of dopaminergic blockers in the development of dysphoric symptoms, given that antipsychotics block dopamine receptors with high potency potentially disrupting activity in reward related brain pathways, resulting in anhedonia or dysphoric symptoms.

Another important diagnostic consideration is the overlap between depression and the negative symptoms of schizophrenia (Fitzgerald et al., 2002). The presence of cognitive features of depression, such as guilt, hopelessness and suicidal thoughts, along with distinct sadness rather than blunting of affect are more suggestive of depression.

Post-psychotic depression has been used to describe the onset of depressive symptoms following the resolution of an acute psychotic episode (Birchwood et al., 2005). Given the

particularly traumatic nature of psychosis and the disruption this has on patients' lives, developing a stress-related reaction including symptoms of post-traumatic stress disorder or depression is likely to be a relatively common occurrence in patients, especially those experiencing traumatic events around the time of hospitalisation. At any point in time, the impact of life stressors, the impact of chronic illness and stigma and discrimination associated with the diagnosis of schizophrenia should be considered as possibly related to emerging depressive symptoms.

Finally, in patients who are relatively clinically stable, it is possible that the onset of depressive symptoms is a prodrome of psychotic relapse (Siris, 2000). This might be accompanied by other non-specific symptoms, such as anxiety. Evaluation requires a careful exploration of the possible presence of subtle subthreshold psychotic symptoms which would confirm that the mood change is related to a relapse of psychosis.

The management of emerging depression in a patient with schizophrenia will take all of these factors into account whilst ensuring any emerging risks are appropriately managed. Once organic factors are excluded, any suggestion of emerging psychosis should be treated appropriately with antipsychotic medication (Siris, 2000). The patient should be provided appropriate support and monitoring including supportive psychotherapy to address illness and lifestyle related stressors. The dose and type of ongoing antipsychotic medication should be reviewed with possible dose reduction or switch to a less potent dopamine blocker considered if this is thought to be an aetiological factor.

The role of antidepressant medication in the treatment of depression and schizophrenia has been evaluated by a series of clinical trials, although most of the clinical trials have been conducted with tricyclic antidepressants being co-prescribed with older first generation antipsychotic medications. A meta-analysis of this data was equivocal reflecting the lack of substantial studies (Whitehead et al., 2002). Studies, however, have suggested that antidepressant medications may reduce suicide in patients with schizophrenia (Tiihonen et al., 2012; Zisook et al., 2010). Lithium has also been suggested as a potentially useful agent in the treatment of depression and schizophrenia although this is not supported by substantial clinical trials (Siris, 2000).

Attention-deficit/hyperactivity disorder. Attention-Deficit/Hyperactivity Disorder (ADHD) is a disease characterised by attention-deficit, impulsivity and hyperactivity (*see also: Children and adolescents*). It is known that 3% to 7% of school-age children have ADHD globally (Kessler et al., 2006). The relationship between ADHD and Major Depression has been well examined with clear evidence that the presence of childhood and adult ADHD is associated with an increased incidence of depression throughout the lifespan. For example, a major North American national survey of healthy children aged 6–17 years reported depression in 14% of ADHD children versus 1% of those without ADHD (Larson et al., 2011). The incidence of depressive disorders in adolescents with ADHD ranges from 12% to 50% (Angold et al., 1999), and the likelihood of developing depression is five times greater in adults with ADHD compared to adults without ADHD. The pathway from ADHD to Major Depression often progresses through behaviour disorders (more often in males) and anxiety (more often in females) (Burke et al., 2005; Roy et al., 2014). Adults with ADHD also experience an earlier onset of depression, increased morbidity, more severe symptoms and a higher suicide rate compared with adults without ADHD (Nierenberg et al., 2005).

A prospective population study found higher rates of emergent bipolar disorder amongst individuals with a childhood diagnosis of ADHD than those without ADHD (Chen et al., 2013). Data suggest that 9 to 21% of adults with bipolar disorder also have comorbid ADHD (Kessler et al., 2006; Marin et al., 2013; Nierenberg et al., 2005). Diagnostic differentiation between the symptoms of ADHD and bipolar disorder can be difficult. What is thought to be ADHD could be an early expression of the emergent bipolar disorder. This tension was emphasised in a study of inpatients with recent bipolar disorder relapse, of whom 82% scored positively on a standardised diagnostic instrument for a diagnosis of lifetime ADHD (Marin et al., 2013). When a childhood history was taken carefully, this figure reduced to 26%, still a significant proportion. In the absence of a clear diagnostic marker, careful exploration of history of symptomatology, inter-episode functioning and the presence or absence of contemporaneous evidence of ADHD in childhood remain the most useful clinical tools.

Data on the effective treatment of mood disorders in the presence of comorbid ADHD is generally lacking. The treatment of depression in the setting of comorbid ADHD is generally more difficult and treatment resistance is more common (Biederman et al., 2008; Nierenberg et al., 2005). This underlines the importance of identifying comorbid ADHD as early as possible. The Texas Algorithm Project provides a guide to the treatment of ADHD comorbid with depression. In the first instance treatment is directed at the more severe of the two conditions, but the algorithm allows for combination therapy when needed (Pliszka et al., 2006). Sometimes treatment for ADHD must be withdrawn if it is aggravating the depression. Some mood disorder guidelines suggest that combinations of antidepressants with stimulant medication are relatively safe and that antidepressants with dopaminergic activity may be helpful for symptoms of both ADHD and depression. Perhaps more significantly, they have also warned of the possibility of stimulant medication utilised for comorbid ADHD destabilising the treatment of bipolar disorder, particularly in those with rapid cycling or mixed affective states (Malhi et al., 2009d; Pacchiarotti et al., 2013a).

Medical conditions, including 'vascular depression'. Mood disorders and physical health have a strong and complex bidirectional relationship that is important to recognise and manage. Depression can impede engagement in therapies for comorbid medical conditions thus worsening prognosis. Medical comorbidities – particularly chronic pain – appear to reduce antidepressant efficacy (Bair et al., 2003; Howland et al., 2008; Pohle et al., 2009), but antidepressants still appear to have efficacy over placebo (Gill and Hatcher, 2000). SSRIs are effective in ischemic heart disease and comorbid major depression (Pizzi et al., 2011), and appear more effective than psychological counselling alone (Dickens et al., 2013; Lespérance et al., 2007). Psychological therapies, including on-line formats, are effective, especially where chronic pain exists (Buhrman et al., 2013; Hoffman et al., 2007). Vascular depression is not part of the current DSM nosology, but has been proposed to be a subtype of depression (Alexopoulos et al., 1997), possibly related to microvascular events in fronto-limbic tracts and with poorer antidepressant efficacy and tolerability noted (Baldwin et al., 2004). Citalopram has been associated with prolonged QTc interval at high doses but clinical relevance is unclear (Vieweg et al., 2012). SSRIs have been associated with greater perioperative bleeding but it is unclear if they are causative or mediated by covariates (Auerbach et al., 2013).

Recent population-based studies confirm that bipolar disorder is commonly comorbid with a range of medical disorders, with consequent increased morbidity and mortality. Measured

prevalence rates of comorbid medical conditions range from 41% to 58% (Carney and Jones, 2006; Kemp et al., 2014; Magalhaes et al., 2012). Conditions most commonly reported are obesity, migraine, hypertension, hyperlipidaemia, asthma, diabetes, endocrine and metabolic syndromes. Less commonly reported conditions include thyroid and parathyroid disorders, liver disease, hepatitis C, HIV, peptic ulcer disease, pancreatitis, autoimmune disorders and renal impairment. Medical comorbidity is so common that it has been suggested that it should be regarded as a core feature of bipolar disorder (Magalhaes et al., 2012), or that bipolar disorder should be regarded as a multi-system disorder (Leboyer et al., 2012).

The clinical characteristics associated with medical comorbidity were explored in a study of over 3000 bipolar patients from the STEP-BD study (Magalhaes et al., 2012). Comorbid medical conditions were more likely to occur in those patients who had an early onset and highly recurrent disorder, with comorbid anxiety and substance abuse and a history of smoking. Bipolar disorder is linked to an increased risk of developing dementia, and with a greater number of episodes of increased illness (Kessing and Andersen, 2004).

It is useful to consider medical illness in bipolar disorder patients as being: truly comorbid; conditions related to treatment; and conditions related to behaviours associated with bipolar disorder (Carney and Jones, 2006).

Comorbid disorders that may be related to lifestyle or treatment include migraine (Oedegaard et al., 2011), diabetes, hypertension and metabolic syndrome. An association has been found between bipolar disorder and thyroid dysfunction, particularly in women, independent of the effect of lithium. Dysfunction identified includes hyperthyroidism in hospitalised patients (Thomsen and Kessing, 2005); increased levels of TSH especially in women (Ozerdem and Rasgon, 2014); and increased levels of T3 (Krishna et al., 2013). High rates of subclinical hypothyroidism and thyroid antibodies have been found mainly in female bipolar patients and are associated with poorer response to mood stabilisers (Bauer et al., 2014). This study also showed that female patients have less ability to compensate for the effects of lithium on thyroid function and respond better than males to thyroid supplements.

Cardiovascular disease is a leading cause of mortality in bipolar disorder, even above the mortality from suicide (Leboyer et al., 2012). It can be comorbid, secondary to lifestyle behaviours or may relate to treatment. Obesity, metabolic syndrome, hypertension and diabetes can be complications of treatment with lithium, second generation antipsychotics and anticonvulsants. Hyperphagia during depressive episodes, a sedentary lifestyle, poor diet and smoking contribute to cardiovascular disease. However, a recent review (Leboyer et al., 2012) found that when the effects of lifestyle and medication were controlled for, the association between bipolar disorder and cardiovascular disease remains significant. Likewise the metabolic syndrome has been shown to be associated with bipolar disorder independent of medication effects and is associated with a more complex illness presentation, less favourable response to treatment and adverse outcomes including increased disease burden and suicide (McIntyre et al., 2010b).

Other treatments which can induce medical conditions include lithium (obesity, hypothyroidism, hyperparathyroidism, renal impairment and lithium toxicity); valproate (obesity, ataxia, menstrual disturbance, polycystic ovarian syndrome, foetal abnormalities, abnormal liver function, pancreatitis, leucopaenia); carbamazepine (weight gain, neurological symptoms,

abnormal liver function, leucopaenia, foetal abnormalities, Stevens-Johnson syndrome); and lamotrigine (Stevens-Johnson Syndrome).

Illness-related behaviours such as substance misuse, smoking, promiscuity and impulsive recklessness can lead to infections with hepatitis B and C and HIV; alcohol-related liver disease and pancreatitis; sexually transmitted disease; asthma and obstructive pulmonary disease; and injury through accidents.

Recommendation Box 11.

MANAGEMENT OF MOOD DISORDERS WITH COMORBID MEDICAL ILLNESSES	Grade
11.1. Newly diagnosed mood disorders patients should undergo medical evaluation to determine baseline comorbidities – such as: hypertension, obesity, diabetes, sleep apnoea, and thyroid, renal and liver dysfunction.	EBR III
11.2. Illness-related behaviours and lifestyle risk factors should be identified and monitored during the management of mood disorders alongside appropriate counselling aimed at behaviour modification and prevention of medical comorbidity.	EBR II
11.3. Tailored monitoring of medication related effects on medical health should be conducted routinely and include, monitoring of weight; lipids and blood sugars; blood pressure; thyroid, renal and liver function; white cell count; and menstrual function in women.	CBR
Recommendations related to particular agents:	EBR III
11.4. When treating mood disorders patients with cardiac problems second generation antidepressants should be given preference because of better overall tolerability and safer cardiac and anticholinergic side effect profiles.	EBR III
11.5. Desvenlafaxine should be given preference over venlafaxine when hepatic interactions are clinically relevant.	EBR III
11.6. In the treatment of comorbid pain and depression tricyclic antidepressants should be given particular consideration*.	EBR II

Footnote: *(Nicholas et al., 2009).

Management of mood disorders in the context of special populations

Pregnant and breastfeeding women. The prevalence of major depression and bipolar disorder peaks during the childbearing years, and so there are high rates of depression across the perinatal period (the time from conception to the end of the first postnatal year). The postpartum period is also a time of high risk for bipolar relapse and for the development of postpartum or puerperal psychosis, which is currently thought to be a variant of bipolar disorder (Bergink et al., 2015; Munk-Olsen et al., 2012; Pfuhlmann et al., 2002). A key consideration in the management of perinatal mood disorders is the neurodevelopmental impact of the disorder, and its treatment, on the foetus, the nursing infant and quality of the mother-infant relationship and attachment (Lewis et al., 2014; Stein et al., 2014).

Whenever psychotropic medication is prescribed to pregnant and breastfeeding women, informed consent should be obtained. In order to obtain informed consent for the provision of pharmacological treatment during pregnancy and breastfeeding, a risk/benefit analysis needs to be performed giving consideration to the risks for the mother as well as the risks to the foetus, and the risks to either of non-treatment. All risks need to be identified and disclosed, both proven and speculative, giving particular consideration to what is of significance to any particular patient. Details of any risk/benefit discussion and the woman's decision should be carefully documented (Snellen et al., 2014).

The organisation of services for women with mood disorders over the perinatal period and the use of screening instruments have been described in specialised guidelines from the United Kingdom's National Institute for Clinical Excellence (NICE, 2007), Australia's Beyond Blue (BeyondBlue, 2011), and the Scottish Intercollegiate Guidelines Network (SIGN, 2012).

DSM-5 includes a peripartum onset specifier that can apply to the current episode or, if the full criteria are not currently met for a mood episode, most recent episode of mania, hypomania or depression in BD I or BD II, if onset of mood symptoms occurs during pregnancy or in the 4 weeks following delivery. This specifier does not take into account onsets of depression prior to conception or episodes of depression that arise any time in the first year postpartum that are commonly considered as perinatal depression or perinatal mood disorder. The specifier starts off differently for major depressive disorder. This specifier can be applied to the current or, if full criteria are not currently met for a major depressive episode, most recent episode of major depression if onset of mood symptoms occurs during pregnancy or in the 4 weeks following delivery.

The prevalence of perinatal depression lies between 6.5% to 12.9% (Gavin et al., 2005). While it used to be considered most episodes of depression arose postpartum, it is now recognised that major depression commonly occurs during pregnancy, emanating either from a pre-existing depressive episode or a new onset episode. A clinical assessment of depression in pregnancy needs to take into account the fact that some 'depressive' symptoms can arise from physical symptoms associated with pregnancy, such as insomnia and weight change (Matthey and Ross-Hamid, 2011; Yonkers et al., 2009), the same caveat applies postpartum when 'depressive-like symptoms' may be the consequence of being a nursing mother. The clinical picture of perinatal depression (whether arising in pregnancy or postnatally) is, in essence, no different from major depression arising at other times in life. Treating perinatal depression is important because the illness can adversely affect pregnancy, the developing foetus and the mother-infant relationship.

Treatment of depression in pregnant and breastfeeding women. Maternal depression (depression during pregnancy) has been associated with increased risk of premature delivery, low birth weight, gestational hypertension (Grigoriadis et al., 2013c; Grote et al., 2010) and perinatal death (Howard et al., 2007). Depression in pregnancy may have an adverse impact on infant emotional and cognitive development (Chaudron, 2013; Deave et al., 2008), and postnatal depression may have an adverse effect on the mother-infant relationship, that in turn leads to poor infant development and outcomes (Goodman et al., 2011; Tronick and Reck, 2009).

The potential adverse effects on the foetus and on infant development make it an imperative to treat depression during pregnancy.

The treatment of perinatal depression follows the same approaches used for the treatment of depression at other times; women with mild-to-moderate depression should be offered formulation based psychological treatments such as interpersonal therapy or cognitive behaviour therapy (Dennis et al., 2010; Spinelli, 1997). Women with more severe depression should be offered antidepressant medication even though there is an absence of evidence regarding the efficacy of antidepressants in the perinatal period.

The use of antidepressant medication for women in the perinatal period, especially during pregnancy, requires a careful risk/benefit analysis, as the developing foetus and the breastfeeding infant will invariably be exposed to antidepressant medication. The essence of this is shown in *Table 26:* Risks vs benefits of medication in pregnancy.

Risks associated with antidepressant use in pregnancy are small, but meta-analyses have identified statistically significantly increased risk of congenital abnormalities with first trimester exposure to antidepressant medications (Grigoriadis et al., 2013b; Myles et al., 2013). They have also identified a small, but significant, risk of the foetus developing persistent pulmonary hypertension of the newborn (Byatt et al., 2013; De Vera and Bérard, 2012). There is also a significantly increased risk of the infants developing a poor neonatal adaptation syndrome (PNAS) in the first week postpartum (Galbally et al., 2009; Grigoriadis et al., 2013a) with up to 30% of infants having symptoms. Tapering down the dose of an SSRI or SNRI in the late third trimester has been proposed as a strategy to reduce the severity of the PNAS (Byatt et al., 2013; Grigoriadis et al., 2013a). However, there is insufficient evidence to demonstrate that it does reduce PNAS, and therefore, this strategy needs to be balanced against the risk of the woman having a depressive relapse (Koren and Boucher, 2009; Koren et al., 2005; Warburton et al., 2010).

There is also an increased risk of women developing gestational hypertension and potentially pre-eclampsia following exposures to SSRIs (Toh et al., 2009) and suggestions of an increased risk of postpartum hemorrhage (Palmsten et al., 2013).

ECT has been safely used for the treatment of severe depression during pregnancy, and it may be the treatment of choice for patients with severe depression or bipolar episodes carrying a significant risk to the mother and/or the foetus (BeyondBlue, 2011). Anaesthesia in pregnancy carries increased risk of rapid desaturation and reflux with aspiration (Lakshmana et al., 2014). For these reasons ECT should be undertaken in a unit where there is ready access to foetal and maternal monitoring and access to appropriate post-anaesthetic recovery services, especially in the third trimester and late second trimester.

TMS may become an alternative to medications in this group in the future, but to date there is limited data available in pregnancy (Garcia et al., 2010; Nahas et al., 1999; Tan et al., 2008).

Bright light therapy has been evaluated for the treatment of depression during pregnancy (Wirz-Justice et al., 2011) in two trials for postnatal depression (Crowley and Youngstedt, 2012). While these small trials provide some evidence for its use, there is insufficient evidence to recommend its use as a first line treatment.

Postpartum depression. The treatment of postpartum depression depends on the type and severity of the depression. Episodes of depression arising within the first 4 weeks postpartum tend to be melancholic in nature and require assertive management with antidepressants.

ECT should be used for women with psychotic (delusional) depression to ensure quick recovery from the depressive episode to minimise disruption to the mother-infant relationship.

In addition to providing treatment to the depressed mother, attention also needs to be paid to the mother-infant dyad. First, the safety of the infant and the woman's capacity to provide a safe and nurturing environment needs to be assessed. This will also require an assessment of the woman's intimate relationship as this may impact on safety issues, especially when domestic violence is present (and may be contributing to the woman's depression). In such cases, liaison with child protection services is recommended. Second, an assessment of the quality of the mother-infant relationship and if problems are identified, specific interventions to address this may need to be implemented.

Psychosocial treatments, such as CBT, non-directive counselling and IPT (Dennis and Hodnett, 2007) are the first line of treatment for mild-moderate depression arising postpartum. Women with mild to moderate postnatal depression require additional support to assist them in compensating for fatigue induced by sleep deprivation as a result of nursing the baby. The provision of both practical and emotional support is of critical importance in helping women with postnatal depression.

For more severe depression antidepressant medication is indicated, though here consideration needs to be taken whether the mother is breastfeeding. If this is the case then the risk of the nursing infant being exposed to the medication needs to be balanced against the importance of the mother continuing breastfeeding and the necessity for medication. In the main, only small amounts of SSRIs and TCAs pass through to the breast milk and are generally considered safe (Eberhard-Gran et al., 2006) except for fluoxetine, which has a long half-life increasing the risk of reaching higher levels than other SSRIs and SNRIs (Weissman et al., 2004). Information about individual antidepressants and their passage through breast milk can be found on websites such as LactMed (NLM NLoM, 2014). Consideration needs to be paid to the side-effects of the medication and the impact upon the nursing mother, such as sedation that might interfere with night time feeds and breastfeeding.

Postpartum with pre-existing bipolar disorder. Women with pre-existing bipolar disorder are at high risk of having a relapse postpartum, with estimates suggesting that up to 50% of women will relapse in the first 3 weeks postpartum. Postpartum psychosis affects 1–2 women per 1000 deliveries and has a rapid onset of illness within the first three weeks following childbirth. Indeed, bipolar disorder is the most likely cause of admission for psychotic illness in the first three weeks postpartum (Munk-Olsen et al., 2012). Follow-up studies of puerperal psychosis would suggest that it is a variant of bipolar disorder (Munk-Olsen et al., 2012).

The management of bipolar disorder over the perinatal period is intrinsically complicated because it is a time of high risk for relapse, and mood stabilisers can have a deleterious effect on the developing foetus.

Table 26. Risks vs benefits of medication in pregnancy.

	No medication	Taking medication
Woman	Persistent depression Distress Adverse effect on pregnancy outcome	Maternal wellbeing
Developing foetus	No risk of harm from medication Possible adverse impact on foetal development from exposure to maternal mental illness	Possible reduced risk of effects of severe depression on foetal development Risk of harm from exposing foetus to medication

Pregnancy planning for women with bipolar disorder. For women with pre-existing bipolar disorder who wish to conceive, a careful risk-benefit analysis for remaining on mood stabilising medication needs to be done. It is essential that the women should be provided with good antenatal care and referral to a high risk clinic is recommended. There is good evidence that the anticonvulsant mood stabiliser sodium valproate can cause significant harm to the foetus, which has a foetal congenital abnormality rate ranging from 5 to 17% (Galbally et al., 2010a). Sodium valproate has also been shown to contribute to intellectual impairment in children who have been exposed to it in utero (Meador et al., 2009, 2012), whereas the risks of congenital abnormalities are lower for carbamazepine (3%) and lamotrigine (2%) (Hernandez-Diaz et al., 2012). Lithium has also been associated with a small increased risk of foetal cardiac defects (Cohen et al., 1994) but a recent meta-analysis (McKnight et al., 2012) did not find an increased risk for Epstein's anomaly and concluded that the evidence that exposure to lithium is teratogenic is quite weak, and findings accord with the notion that the risk has been overestimated. A recent study found a significantly increased risk (OR 4.75) of cardiovascular anomalies compared to a non-exposed group (Diav-Citrin et al., 2014). For women with severe bipolar disorder lithium appears to be the safest option amongst available mood stabilisers. Its use has to be balanced against the potential risks for the developing foetus and the risk of relapse during pregnancy if lithium is discontinued. Women should have folate supplementation and an ultrasound to determine whether an abnormality is present (along with a plan as to what to do should an abnormality be found).

If mood stabilisers are to be withdrawn, it is recommended that the dose be tapered down slowly as this reduces the risk of relapse (Baldessarini et al., 1999).

Lithium is effective in preventing relapse (Bergink et al., 2012), and lithium prophylaxis should be offered to women with bipolar disorder with the proviso that breastfeeding is contraindicated with lithium. Lithium can be safely reintroduced in the latter stages of the pregnancy in order to provide prophylaxis against relapse. Lithium management in the latter stages of pregnancy is more complex and requires careful monitoring and dose reduction prior to delivery to avoid exposing the foetus to toxic levels of lithium (Galbally et al., 2010b). The use of the anticonvulsant mood stabilisers to prevent relapse is controversial, as evidence to support their use in preventing postpartum relapse is minimal.

SGA medications can be used as an alternative to mood stabilisers; there is insufficient evidence to suggest harm to the foetus and they are generally regarded as relatively safe. They can be used to treat psychotic symptoms during pregnancy, and as an alternative to mood stabilisers, but caution needs to be taken because of the possible risk of excess weight gain and/or gestational diabetes.

Postpartum relapse of bipolar disorder. There is a high risk (~50%) of a bipolar relapse in the first month following delivery. Women need to be monitored carefully over this period for any emergent symptoms and appropriate treatment applied when they emerge. There is evidence to suggest that sleep preservation reduces the risk of manic relapse and consideration should be given to the use of hypnotics, and the short term use of benzodiazepines can be of benefit in reducing anxiety symptoms or emergent psychotic symptoms (Bergink et al., 2012) (Plante and Winkelman, 2008). If a mother and baby unit is available, it is advisable to have a planned admission to monitor progress of the first month postpartum.

Mood stabilisers can be reintroduced following delivery. The reintroduction of lithium should be at the pre-pregnancy therapeutic dose (with serum lithium assessed shortly after the re-introduction). Anticonvulsant mood stabilisers should be at the previous therapeutic dose. Breastfeeding is contraindicated with lithium but recent data suggest that anticonvulsant mood stabilisers and second-generation antipsychotics can be taken if the woman is breastfeeding. Benzodiazepines, or a sedating antipsychotic can be used in the short term to assist in restoring a stable sleep–wake cycle if the woman is having trouble with her sleep. This needs to be done cautiously, as this could impact on her capacity to care for the newborn overnight, and to safely manage feeds. It is particularly important that women who receive sedating medications be advised to never co-sleep with their babies due to the inherent risks.

It is important to ensure adequate contraception and contraceptive advice is provided to the woman, especially if the woman has had a manic relapse with its attendant impulsivity.

There is no evidence to guide us about when to reintroduce mood stabilisers. General considerations would include, the risk of the medication passing through breast milk (if the woman is breastfeeding), side effects that could interfere with the woman's capacity to care for her infant (sedation) and the severity of her illness (frequency of episodes). Ideally the woman should return to the effective mood stabilizer she had previously taken. Notwithstanding this, contraception should be discussed as soon as possible following delivery.

If prophylaxis is not used it is recommended that women are reviewed regularly over the first few months postpartum to ensure that mood stability has been achieved. A postpartum relapse could be to either pole of illness. Should a relapse occur, the safety of the woman and her infant becomes paramount. It is recommended that the woman be treated in a specialised mother and baby unit to allow for high quality psychiatric treatment while ensuring the safety of her infant and allowing for the mother-infant relationship to develop.

The treatment for the relapse is no different to the acute treatment of either (hypo)mania or major depression at any other time, using either antipsychotics, mood stabilizers or antidepressants or ECT as indicated.

While breastfeeding is recognised as desirable, in some instances, it may be necessary to cease breastfeeding if the woman is too unwell to breastfeed, requires sedation to ensure

sleep, and disruption to this (to feed the infant) would have an adverse effect on her mental state or if lithium is indicated.

Children and adolescents

Major depression. In Australia, approximately 1.1% of children (4–11 years) and 5.0% of adolescents (12–17 years) meet diagnostic criteria for major depressive disorder based on parent/carer report. Based on self-report, the prevalence in adolescents increases to 7.7%. As measured on the K10, some 20% of adolescents report high or very high levels of psychological distress (Lawrence et al., 2015). However, closer to 10% are estimated to have subsyndromal symptoms. Depression is the major risk factor for suicide: in the management of depression in young people, therefore, there is a tension between the goal of conservative intervention for the developing brain/person and the need for prompt symptom relief.

Symptoms of mood disorders in children and adolescents often appear similar to those in adult patients, but with some differences that are attributed to their ongoing emotional, cognitive and social development (Fergusson et al., 2005; Kaufman et al., 2001; Klein et al., 2005). Children may display mood lability, temper tantrums, somatic complaints, and/or social withdrawal rather than verbally expressing their feelings of depression. Indeed, recognition and treatment of depressive and bipolar disorders in children and adolescence is often complex and has been hampered by a limited existing evidence base (Goldstein et al., 2012; Hazell, 2011; Hetrick et al., 2012). Partly, this relates to how to include appropriate allowances for the developmental variability and immaturity of children and adolescents (Carlson, 2000). To address this complexity, DSM-5 introduced Disruptive Mood Dysregulation Disorder (DMDD), a new diagnosis intended to decrease the use of the bipolar disorder diagnosis in young people. DMDD has poor test-retest reliability (kappa = 0.25), and is highly contentious because of its elevated comorbidity with other childhood disorders, and the potential risk of pathologising healthy children (Fristad and Algorta, 2013).

Psychological interventions, particularly CBT and IPT, are indicated as first-line treatments for child and adolescent MDD, especially when it is of mild to moderate severity. A recent network meta-analysis (a relatively new technique that integrates direct and indirect evidence from randomised controlled trials) compared the efficacy and acceptability of psychotherapies for depression in young people. Comparing 52 studies (N = 3805), post-treatment effects over control were significant for interpersonal therapy and cognitive behavioural therapy (standardised mean differences range from -0.47 to -0.96) (Zhou et al., 2015).

Evidence and treatment guidelines support parent/family involvement, particularly with children (David-Ferdon and Kaslow, 2008). Two recent Cochrane reviews address the treatment of major depression in children and adolescents, both highlighting significant methodological limitations of the available literature. The first focused on antidepressant medication, and found Level I evidence for a small beneficial effect of SSRIs amongst young adults (6–18 years): remission rates increased from 380 per 1000 to 448 per 1000 with antidepressant relative to placebo. The same review also highlighted the increased risk (58%) of suicide-related outcome amongst those receiving antidepressants relative to placebo (Hetrick et al., 2012). Of the SSRIs, fluoxetine has the most consistent evidence of efficacy over placebo, and it is recommended as the first line antidepressant for young people in treatment guidelines (NICE, 2005). A highly cited systematic review concluded that the efficacy of antidepressants correlates with depression severity, and that the benefits over

placebo are substantial for severe symptoms, but minimal or nonexistant with mild-moderate depression (Fournier et al., 2010).

Recommendation Box 12.

MANAGING MOOD DISORDERS IN PREGNANCY AND POST PARTUM	Grade
12.1. All women of reproductive age diagnosed with a mood disorder should be offered a referral for contraceptive advice[a].	CBR
12.2. Psychoeducation on the possible harmful effects of antidepressants, mood stabilizers and antipsychotics on a developing foetus, and the risk of postpartum relapse should be provided to all women of child bearing age at the time of diagnosis.	CBR
12.3. Psychological interventions, particularly IPT and CBT[b], should be the preferred treatment modality for MDD during pregnancy and postpartum.	EBR III
12.4. The administration of antidepressants, mood stabilizers and antipsychotics during pregnancy should involve close liaison between a treating psychiatrist, obstetrician and neonatologist.	CBR
12.5. A careful risk-benefit analysis should be undertaken in planning pharmacological management of a pregnant woman with a mood disorder: specifically, the risks of harm to the developing foetus from pharmacotherapy should be balanced against potential harm to the mother because of not being treated pharmacologically for her depressive illness.	CBR
12.6. For severe cases of MDD during pregnancy, antidepressant medication may be trialled with preference for SSRIs, but paroxetine, fluoxetine, and venlafaxine should be avoided where/if possible.	EBR II
12.7. Sodium valproate should be avoided in women of childbearing age[c].	EBR II
12.8. ECT should be considered for severe refractory cases of mood disorders during pregnancy.	EBR IV
12.9. Infants exposed to antidepressants, mood stabilizers and antipsychotics in pregnancy should be observed for the first three days postpartum for any known adverse effects.	CBR

Footnote: [a]Snellen and Malhi (2014), [b]For mild to moderate cases of MDD psychological interventions, particularly CBT and IPT, should be the preferred treatment modality. [c]In instances of treatment resistance it may be necessary to trial sodium valproate.

A second Cochrane review compared the efficacy of psychotherapy, antidepressants and the combination of psychotherapy and medication. The authors found limited evidence for an advantage of antidepressants in young people (Cox et al., 2014). Specifically, two studies (a total of 220 participants) found a significant advantage for antidepressants (67.8% remission rates) over psychotherapy (53.7%), but only on clinician-rated measures immediately post-intervention. Hetrick et al. (2012) noted that there was evidence of increased suicidal ideation with medication: one study (N = 188) found suicidal ideation to be 3–4 times more common amongst participants receiving medication relative to psychological therapy, a ratio that was maintained at 6 to 9 months. The review also found evidence that adding psychotherapy to medication was beneficial for remission rates immediately post intervention, but no evidence that adding medication to psychotherapy was beneficial.

In sum, much remains unknown about the optimal treatment of depression in children and adolescents. As with adult major depression, there is Level I evidence for psychological treatments (CBT and IPT), and Level I evidence for the efficacy of antidepressant medication (fluoxetine) for young people. Little is known about the moderation of psychotherapy's effectiveness by depression severity, but antidepressant medication appears to be more effective for severe relative to mild/moderate depression. Given the absence of evidence for superiority of medication monotherapy over psychotherapy monotherapy, the risks associated with antidepressant medication have influenced treatment guidelines in this area. The evidence-supported psychotherapies (individual CBT and IPT) are considered first line for management of MDD in young people of all levels of severity, with potential addition of fluoxetine being considered when depression is moderate–severe, or when psychotherapy has been trialled and found ineffective. Clinicians with child/adolescent expertise can consider non-fluoxetine medications (sertraline, citalopram, and if necessary antipsychotic augmentation) for recurrent, unresponsive or psychotic depression. Young people prescribed antidepressants of all kinds must be closely monitored for emergent suicidality, hostility, agitation, mania, and unusual changes in behaviour (NICE, 2005).

Bipolar disorder. Prevalence estimates are unclear as epidemiological surveys have seldom addressed BD in children and adolescents and there are significant international differences in the rate of diagnosing early onset BD (Stringaris and Youngstrom, 2014). Estimates for BD I range between 0.4–1.6%, with up to an additional 1% meeting criteria for BD II disorder (McClellan et al., 2007).

Most controversially there has been a suggested broadening of the definition of childhood bipolar disorder, whereby irritability has been adopted as a defining symptom, together with permitting a persistent or chronic pattern of symptoms to define the course rather than a relapsing or remitting pattern. As noted by Goodwin et al. (2008) this recent broadening of the diagnosis has tended to confound the bipolar diagnosis with alternative childhood psychopathology resulting, for example, in extremely high co-morbidity rates with ADHD, with figures between 70% and 98% being reported.

Such broadening of diagnostic criteria has also been associated with a lack of predictive validity and stability in juvenile bipolar disorder (Hazell et al., 2003), compared to the high diagnostic stability of the narrowly defined phenotype. The resulting risk has been the extrapolating of adult bipolar treatment options to significant numbers of young children, including preschoolers, identified with this broadly defined phenotype, before adequate efficacy and safety studies have been performed (Goodwin et al., 2008; McClellan et al., 2007). In contrast, there has also been concern over under-recognition of the onset of narrowly defined bipolar disorder (Goodwin et al., 2008). DSM has adopted an intermediate position on the phenotype: children and adolescents whose mood is predominantly irritable, if episodic, are considered part of the bipolar spectrum (Fristad and MacPherson, 2014).

The DSM-5 has explicitly reserved BD I for episodic presentation of bipolar symptoms (with mania taken to include states defined by severe irritability). Non-episodic presentations of severe irritability are thought to be common, and are now captured by the contentious DMDD diagnosis (see above) (APA, 2013). Importantly, outcome studies have generally not supported children and adolescents with ADHD (see also: *Attention-deficit/hyperactivity*

disorder) or dysregulated mood symptomology being at increased risk of developing BD in adulthood (McClellan et al., 2007).

A diagnosis of BD in a young person is prognostically significant. The development of BD in early adolescence has been linked to a range of adverse outcomes as compared with a later onset, including cormorbidity with other psychiatric disorders, primarily ADHD (Moreno et al., 2007; Soutullo et al., 2009) and substance abuse (Soutullo et al., 2009), severe manic irritability (Soutullo et al., 2009), and treatment resistance (Jolin et al., 2005). Risk of suicide is also increased amongst people whose BD appears in childhood/adolescence. Although the aetiology of BD in adolescence is not known, some factors which have been linked with the development of early-onset BD, include having an immediate family member with a mood disorder, a history of childhood abuse, comorbid substance misuse, stimulant and antidepressant use, and omega-3 fatty acid deficiency (McNamara et al., 2010).

Reviews and practice guidelines recommend a combination of pharmacotherapy and psychosocial intervention for adolescents with BD I (Fristad and MacPherson, 2014). The existing empirical literature disproportionately focuses on the treatment of manic and mixed episodes, at the expense of bipolar depression and prophylactic treatment. Open label studies suggest lamotrigine may be effective, either as monotherapy or adjunctive therapy, for treating depressed bipolar adolescents (Level IV) (Chang et al., 2006).

Acute mania. Second generation antipsychotics, such as olanzapine (Tohen et al., 2007), quetiapine (DelBello et al., 2006), ziprasidone (DelBello et al., 2008), risperidone (Haas et al., 2009) and aripiprazole monotherapy (Findling et al., 2009) and quetiapine and sodium valproate combination therapy (DelBello et al., 2002), have Level II support (McClellan et al., 2007). However, the potential for metabolic side effects with this class of drugs with long term treatment warrants serious consideration (Thomas et al., 2011). Despite common usage, there is a lack of published RCT studies regarding lithium and valproate in acute mania and such use is reliant upon open studies (Level III) (Goldstein et al., 2012).

Maintenance. Currently, there are few well-controlled studies examining the efficacy of pharmacological treatments for prophylaxis in adolescents with BD. Many of these studies did not include a placebo group and have involved antipsychotic comparisons to either lithium or valproate. Overall, these studies suggest that antipsychotics may be more effective than mood stabilizers in acute presentations. Partly, this is the result of lithium receiving FDA approval being grandparented in on the basis of adult data (Goldstein et al., 2012). Further controlled studies are needed to determine the safety and efficacy of these pharmacological treatments in this population.

Recommendation Box 13.

MANAGEMENT OF MAJOR DEPRESSIVE DISORDER IN CHILDREN AND ADOLESCENTS	Grade
13.1. Assessment and treatment planning must go beyond the narrow diagnostic picture to explore family and social context, patient/family preference and potential barriers to engaging with treatment.	CBR
13.2. Optimal management of significant mood symptoms in young people requires specific experience and expertise with this population, and therefore consultation with a specialist child/adolescent/family service should be considered and sought if necessary.	CBR
13.3. Psychological interventions (particularly CBT or IPT) should be used first-line for the treatment of MDD in children and adolescents.	EBR I
13.4. For moderate to severe MDD in children and adolescents who are not responsive to psychological intervention, short-term use of fluoxetine for acute symptom reduction may be trialled.	EBR II
13.5. Children and adolescents prescribed antidepressants must be closely monitored for emergent suicidality, hostility, agitation, mania, and unusual changes in behaviour.	EBR I
13.6. In cases where an antidepressant is used, continuation or commencement of psychological intervention should be considered for additional benefits on global functioning.	EBR I
13.7. ECT should be available for the treatment of severe affective or psychotic illnesses and catatonia in children and adolescents, when pharmacological treatment is ineffective.	EBR IV
13.8. Assessment for ECT should include an adequate assessment by a child, adolescent and family service and an agreement by that service that ECT is indicated and consenting procedures must conform to the legislation requirements of the Mental Health Act in each jurisdiction	CBR

There is support for continuation and/or maintenance use of lithium and valproate from observational and naturalistic studies over 6 to 18 month periods. A direct double blind comparison between lithium and valproate showed no significant difference in median survival time to relapse, which was relatively short (both fewer than 115 days). Notably, when compared with lithium, valproate divalproex was associated with significantly fewer side-effects. Aripiprazole (Findling et al., 2011) and risperidone augmentation of lithium (Pavuluri et al., 2006) have been shown to be efficacious for the treatment of adolescents with BD. However, as with BD in general, the long-term use of atypicals in the treatment strategy for BD should be monitored regularly as medication-emergent side effects are not uncommon. Refer to Malhi and colleagues, 2012b and Ng and colleagues, 2009 for safety monitoring procedures.

The use of ECT in adolescents is rare, but numerous case reports support its efficacy and safety in the treatment of severe affective, psychotic and catatonic conditions. A review of 42 patients aged 14–18 years being treated with ECT in NSW (Walter and Rey, 1997) concluded that ECT was effective in 50% of cases, with mood disorders being the most responsive.

Psychosocial treatments. There has been only limited research into the efficacy of psychosocial treatments for bipolar disorder in adolescents. As with investigations of pharmacotherapy, conclusions must be qualified by ongoing debate about the optimal description of the disorder (ranging from narrow to broad definitions). In terms of specific interventions, a recent systematic review found evidence that family psychoeducation was probably efficacious (Fristad and MacPherson, 2014).

Expert consensus recommends the use of adjunctive psychosocial intervention, and as in the adult case, highlights the overlapping content of the various branded therapies (McClellan et al., 2007). Patients' families should be provided with psychoeducation concerning aetiology, symptoms, course, medications, risk and protective factors, and effective treatments. Adolescents should receive skills training around communication, problem solving, CBT, and emotion regulation skills. Both families and adolescents should be trained in relapse prevention strategies. Important unanswered clinical questions include the matching of treatments to level of severity, particularly the relative cost/benefits of psychosocial and pharmacological intervention across the spectrum of presentations.

Older people. There are multiple issues that will need to be considered when treating depression in older people. The following is designed as a list that may be helpful in clinical practice, but is not necessarily comprehensive.

Evaluation. Late onset depression (onset in adults 60 years or older) should be distinguished from older adults reporting an initial depressive episode at a younger age. Late onset depression is associated with greater neuropsychological deficit, more brain imaging abnormalities and increased risk for dementia (Diniz et al., 2013; Hickie et al., 2005; Salloway et al., 1996). This should prompt more stringent monitoring of cognitive function in older people.

It should be remembered that older people may not declare alcohol use unless specifically asked and that this may be significant (Merrick et al., 2008).

Age is a well-recognised risk factor for suicide. Suicide risk is significant in older people and clinicians should be aware of the possible risk of suicide (Conwell et al., 2011).

Medication issues. Older people may be particularly sensitive to medication for a number of reasons. These include increased sensitivity to the constipating effects of medication, increased risks of falls (Van den Brand et al., 2009), reduced renal function, other medical problems, increased risk of delirium and, for this reason, possibly increased sensitivity to anticholinergic agents (Campanelli, 2012). Drugs that cause falls may give rise to further loss of confidence, which may be a particular issue in older people (Mulsant and Pollock, 2013).

As well as increased sensitivity to medication, older people may be on multiple other drugs giving rise to an increased risk of drug interactions (Mulsant and Pollock, 2013).

For various reasons it may take a longer time for a response to be seen in older people (Calati et al., 2013).

There has been some debate regarding the relative effectiveness of serotonergic compared with noradrenergic drugs in older people with depression (Bose et al., 2008; Navarro et al., 2001). Generally speaking, evidence suggests that there is equivalence between these types of drugs (Calati et al., 2013) and that treatment should be based on symptom and side effect profile and the need to avoid interactions (Coupland et al., 2011).

The combination of antidepressants with antipsychotics for psychotic depression or augmentation of antidepressant response (Steffens et al., 2011) should be approached with more caution in older people given their sensitivity to medication and the evidence that antipsychotics may increase the risk of cardiovascular accidents in patients with dementia (Ray et al., 2009).

Sleep may be a particular issue in older people. The prescription of benzodiazepines (which should only be prescribed short term) should be balanced against the risk of falls (Ray et al., 2000).

There remains a lack of robust high quality evidence for the use of stimulants (Hardy, 2009).

Recommendation Box 14.

MANAGEMENT OF BIPOLAR DISORDER IN ADOLESCENTS	Grade
14.1. Diagnosis of BD in adolescents should be based on satisfying criteria for Bipolar I Disorder – specifically there should be distinct and recognisable episodes of depression and mania.	CBR
14.2. Assessment and treatment planning must go beyond the narrow diagnostic picture to collaboratively explore family and social context, patient/family preference and potential barriers to engaging with treatment.	CBR
14.3. Optimal management of BD in adolescents requires specific experience and expertise with this population, therefore should involve a specialist adolescent/ family service.	CBR
14.4. Adolescents with bipolar I disorder should be offered psychosocial intervention with family involvement, and the costs/benefits of pharmacotherapy should be considered carefully.	CBR
14.5. Adjunctive psychosocial treatment should include psychoeducation for the family, skill development for the young person, and relapse prevention drills.	CBR
14.6. ECT should be available for the treatment of severe affective or psychotic illnesses and catatonia in children and adolescents, when pharmacological treatment is ineffective.	EBR IV
14.7. Assessment for ECT should include an adequate assessment by a child, adolescent and family service and an agreement by that service that ECT is indicated and consenting procedures must conform to the legislation requirements of the Mental Health Act in each jurisdiction.	CBR

Maintenance treatment. Maintenance treatment with antidepressant medication may reduce recurrence compared to maintenance psychotherapy (Reynolds et al., 2006).

Psychotherapy. There are good studies regarding the use of psychological treatments in older people. These should be considered. There is particularly good evidence for the use of cognitive-behavioural therapy (Gould et al., 2012), interpersonal psychotherapy (Van Schaik et al., 2006) and problem-solving therapy (Alexopoulos et al., 2011).

The effect of CBT and IPT may be less in people with physical comorbidity or impaired cognition (Pinquart et al., 2007; Reynolds et al., 2006).

Problem solving therapy is effective for people with impaired cognition (Alexopoulos et al., 2011; Areán et al., 2010).

Lifestyle changes. Structured exercise is helpful for reducing depression severity (Bridle et al., 2012). Improving nutrition, increasing social interactions can also be considered (Solomon and Taylor, 2014).

Māori

Epidemiology. In the 1950s Māori adults were recorded as having lower prevalence of mental disorders than non-Māori (Durie, 1999). However, recent mental health data shows that Māori mental health is now an area of high priority in New Zealand with significant recorded disparities between the mental health of Māori and non-Māori. The rate of diagnosed mood or anxiety disorders in Māori adults at some time in their life has increased to 21.7% in 2013, compared to 17.3% in 2006/07 (Ministry of Health, 2014a).

These changes over time demonstrate the need to develop effective practice guidelines that are responsive to Māori mental health needs and also provide hope that clinicians, health services and researchers can work with Māori to reduce current disparities. An analysis of Māori mental health needs from community and hospital data has been completed and the findings relevant to mood disorders are briefly highlighted in this section (Baxter, 2008).

There are discrepancies between rates of mood disorders in Māori in community samples, primary care and specialist mental health services. Te Rau Hinengaro (The New Zealand Mental Health Survey) measured the prevalence rates of mental disorders using a large nationally representative sample of Māori (n = 2595) (Baxter et al., 2006a, 2006b). This identified higher rate 12-month prevalence of mood disorder in Māori (11.6%) compared to non-Māori/non-Pacific ethnicities (7.5%). One in four Māori (24.3%) had a lifetime mood disorder, the most common lifetime mood disorders being major depressive disorder (15.7%) followed by bipolar disorder (8.3%). Adjusting for contributory factors such as age, gender and socioeconomic status reduced much of the inequity in prevalence. Therefore treatment initiatives for Māori that reduce relative poverty, socioeconomic disadvantage, improve education and physical health outcomes will benefit Māori mental health outcomes. However the unadjusted rates highlight the high health burden associated with mood disorders for Māori. Māori with mood disorders was the most likely group to access a health service compared to other mental disorders. However 3 in 5 (56.9%) Māori with a mood disorder had no contact with any service.

There is consistent evidence of biomedical, social, political and cultural factors that contribute to health inequities of indigenous communities internationally and a broad framework which includes these factors can assist health practitioners working with Māori patients and whānau (families) to contribute to improved Māori health outcomes (King et al., 2009; Pitama et al., 2014).

Major depressive disorder

Community. Te Rau Hinengaro also provides prevalence rates for major depressive disorder (Baxter, 2008). Baxter (2008) This identified marginally higher 12-month prevalence of major depressive disorder in Māori (6.9%) compared to other ethnic groups (5.6%) with the same prevalence after adjustment. Māori females were more likely to have depression than non-Māori in the Youth 2000 survey (Clark et al., 2008). The New Zealand Health Survey also demonstrates Māori experience higher rates of psychological distress than other adults: Māori are 1.6 times as likely to have experienced high levels of psychological distress (indicating a high probability of a depressive or anxiety disorder) as non-Māori (Ministry of Health, 2014a).

Primary care. There is variability in the reported prevalence of depression in Māori in primary care. For example there was no difference in 12-month prevalence of depression by ethnicity in a primary care sample in Auckland, which included 721 Māori participants (Arroll et al., 2009). A smaller study of 81 Māori attending Wellington primary care identified significantly higher rates of depression compared to non-Māori (The MaGPIe Research Group and John Bushnell, 2005). Differences in study methods particularly sampling strategies, sample size and case ascertainment methods may account for much of variation between the studies. Despite the increase in rate of diagnosed mood disorders in recent years, differences between the prevalence of psychological distress and diagnosed mood disorders remain (Ministry of Health, 2014a).This may indicate differences in people's understanding of their own symptoms, health service provision and barriers to health services. Māori continue to be more likely to experience barriers to primary health care (Ministry of Health, 2014a).

Specialist mental health services. Despite the high prevalence of depression identified in the community Māori are less likely to be admitted to hospital for depression (Baxter, 2008; Te Puni Kokiri, 1996). Different pathways to and through care for Māori may influence this discrepancy.

Bipolar disorder. Māori have a higher prevalence of bipolar disorder than other ethnicities with a 12-month prevalence of 4.6% (Baxter et al., 2006b). This discrepancy persisted after adjustment for age, gender and socio-economic status. Māori have a significantly higher hospitalisation rate for bipolar disorder than non-Māori (Robson and Harris, 2007). Manic episodes and bipolar disorder are one of the leading causes of hospitalization among Māori, and 1 in 6 (16.1%) of all hospitalisations in Māori are for these diagnoses (Robson and Harris, 2007).

Suicide and self-harm hospitalisations. Suicide and hospitalisation for intentional self-harm are often associated with mood disorders. In 2011, the total Māori suicide rate was

16.8 per 100,000 Māori population; 1.8 times higher than the non-Māori rate (9.1 per 100,000 non-Māori population) (Ministry of Health, 2014b). The biggest discrepancies were seen in the youth suicide rates with Māori youth 2.4 times higher than the equivalent rate for non-Māori youth. Māori also had higher hospitalisation rates for deliberate self-harm than non-Māori. Unfortunately reductions in non-Māori self-harm between 1996 and 2011 have not been observed in Māori self-harm rates.

Experience of discrimination. There is increasing recognition internationally regarding the adverse effect of discrimination on health and mental health in particular (Paradies, 2006). Māori are more likely to report experiences of self-reported racial discrimination, and are almost ten times more likely to experience discrimination in three or more settings than were Europeans (4.5% [95% CI 3.2–5.8] vs 0.5% [0.3–0.7]) (Harris et al., 2006). After adjustment for discrimination and deprivation, odds ratios comparing Māori and European ethnic groups reduce from 1.30 (1.11–1.54) to 1.02 (0.85–1.22) for low mental health. Māori may experience discriminatory attitudes from clinicians within mental health services, which may contribute to worse outcomes for Māori (Johnstone and Read, 2000).

Specific considerations

Clinical engagement and assessment. There is increasing recognition of need for effective engagement relationship building to work effectively with Māori patients (Mäuri Ora Associates, 2006). There is a range of resources available which aim to provide recommendations for developing clinicians' skills in engaging with Māori (See Appendix 3).

Diagnostic considerations. There are a variety of social and cultural factors that may influence the way some Māori may present. Discussion of this is beyond the scope of these guidelines, but readers are referred to the following resource:

- Recognising and managing mental health disorders in Māori (Best Practice Advocacy Centre New Zealand, 2010).

Developing evidence for best hauora Māori practice for mood disorders. The majority of studies identified in these guidelines have been guided by selecting the highest level and quality of evidence. However this process may come at the cost of reducing the relevance of the evidence for different patient groups including Māori. For example few of the studies referenced in these guidelines include sufficient numbers of Māori participants to allow recommendations specific to Māori to be made. In the following section recent publications involving treatment of Māori with mood disorders are briefly reviewed.

Psychotherapy. In a study investigating ethnic differences in care for all patients admitted to an adult psychiatric inpatient unit Māori were less likely to be referred for psychotherapy in the community (Kumar et al., 2008). However in a primary care study treatment for psychological problems was offered by the GP at similar rates to both Māori and non-Māori (The MaGPIe Research Group and John Bushnell, 2005).

Several Māori adaptions of common psychotherapy approaches have been reported. These include a brief cognitive behavioural therapy based intervention for sub-threshold mental health syndromes in primary care (Mathieson et al., 2012) and cognitive-behavioural therapy

(Bennett, 2009b). Common features of the adaption for Māori include the use of Māori language and imagery and emphasis on relationships. Whilst initial results demonstrate the acceptability of these approaches for Māori larger studies of effectiveness are awaited. Additional resources for psychotherapy for Māori include:

- He rongoa kei te korero. Talking therapies for Māori (Te Pou, 2010).

Medications. Māori may be less likely to receive anti-depressant medication. In a primary care study Māori with depression were significantly less likely to be treated with antidepressant medication although it was uncertain if patient or prescriber factors accounted for this discrepancy (Arroll et al., 2009). In an analysis of national prescription medicine dispensing claims data, Māori have lower age-standardised prescription rates for anti-depressants than non-Māori and non-Pasifika with an estimated shortfall of 46,300 prescriptions of 'newer anti-depressants' after adjusting for population size, age, and disease burden (Metcalfe et al., 2013).

Potential barriers to accessing anti-depressant medication include primary care access, diagnosis, prescribing and collection of prescriptions. Some general practitioners reported beliefs that Māori were less likely to acknowledge depression and had greater stigma towards mental health despite little evidence supporting ethnic differences in stigma towards mental health in New Zealand (Thomas et al., 2010). Prescription costs are another potential barrier with Māori adults 2.4 times as likely not to have collected a prescription due to cost than non-Māori and non-Pacific adults (Ministry of Health, 2014a).

Access to alternative treatments. Clinicians should also be aware Māori may access alternative treatments for mood disorders including traditional healing practices (rongoā rākau-native flora, karakia-prayer, mirimiri/komiri/romiromi-massage). In 2006 10.6% of Māori with a mood disorder saw a non-health service provider with high levels of satisfaction with care reported (Baxter, 2008).

Service delivery models. Both mainstream services and Māori services have a role to play in meeting Māori mental health needs. Mainstream clinical services have been challenged to be more culturally appropriate for Māori and to increase community access to services. Clinical Kaupapa Māori services aim to improve mental health outcomes and recovery through having access to cultural and clinical resources and prioritise a service run by Māori for Māori. Common principles of Kaupapa Māori mental health services include whānaungatanga (emphasis on relationships), whakapapa (genealogy), empowerment of Māori patients and whānau, cultural assessment, Te Reo Māori (Māori language), Tikanga Māori (customs and culture), Kaumātua guidance, access to traditional healing, access to mainstream health services, and quality performance measures relevant to Māori (Ministry of Health, 2002) (te pu). Translating this set of values to service delivery for Māori and their whānau who present with mental illness needs to occur not only with Kaupapa Māori services but also within general community teams, crisis and impatient

Recommendation Box 15.

RECOMMENDATIONS FOR MANAGING MOOD DISORDERS IN MĀORI	Grade
15.1. There are high rates of undetected MDD in Māori populations so health services should routinely investigate potential barriers to Māori accessing quality care pathways.	CBR
15.2. Clinicians should be alert to the increased rate of suicide in Māori.	CBR
15.3. All mental health services and clinicians should provide culturally appropriate and informed care for Māori being assessed or treated for mood disorders. A Māori health worker should be used to assist in a culturally appropriate assessment.	CBR
15.4. Clinicians should be open to presentations involving more physical and spiritual expressions of distress in Māori and ensure the inclusion of these factors in assessment and management.	CBR

Recommendation Box 16.

RECOMMENDATIONS FOR MANAGING MOOD DISORDERS IN ABORIGINAL AND TORRES STRAIT ISLANDER PEOPLES	Grade
16.1. Engagement strategies for managing mood disorders that recognise cultural attitudes to mental illness should be used.	CBR
16.2. When assessing and managing mood disorders, attention should be given to communication, using indirect questioning and including the use of a third person as mediator (family member or cultural consultant).	CBR
16.3. When assessing and treating mood disorders in Aboriginal and Torres Strait Islander peoples the therapeutic style should be adapted, using narrative 'yarning', with open ended questions.	CBR
16.4. The treatment of mood disorders in Aboriginal and Torres Strait Islander peoples should recognise the complicating role of substance use, stress and trauma and take this into consideration when planning management.	CBR
16.5. Careful sharing of knowledge should occur to enable informed choice and enhance engagement with treatment in the management of mood disorders.	CBR
16.6. There should be awareness of the increased risk of side effects especially metabolic syndrome with psychotropic pharmacotherapy.	CBR
16.7. There should be awareness of the elevated risk of suicide in Aboriginal and Torres Strait Islander people with mental illness.	CBR

services and forensic and other specialty areas and requires further development of a Māori mental health workforce.

Aboriginal and Torres Strait Islander peoples. The National Strategic Framework for Aboriginal and Torres Strait islander Peoples' Mental Health and Social and Emotional Wellbeing 2014–2019 will replace the Social and Emotional Wellbeing Framework 2004–2009 as the guiding document informing policy and priorities for Aboriginal and Torres Strait

Islander peoples. It prioritises an holistic approach concordant with the cultural and spiritual beliefs of Australia's first peoples. It is a paradigm that recognises the complex interplay of cultural, historical, social, personal and spiritual factors determining health and mental health outcomes while acknowledging and foregrounding resilience and strength in the face of adversity.

There are a number of important documents including The National Strategic Framework for Aboriginal and Torres Strait Islander People's Mental Health, (Australian Government Department of Health and Ageing, 2005), and The Mental Health and Social and Emotional Wellbeing of Aboriginal and Torres Strait Islander Peoples, Families and Communities (NMHC, 2012b) (which is a supplementary paper to A Contributing Life Closing the Gap) (AHMAC, 2009) that acknowledge the historical context of colonisation, dispossession and displacement and call for a more nuanced understanding of the diversity of the Aboriginal and Torres Strait Islander population with multiple language groups, cultures and traditions. While there are now many learning and practice resources (Commonwealth Australia (collaboration with the University of Western Australia), 2014) there is a lack of comprehensive epidemiological data for the Aboriginal and Torres Strait Islander people for mental health. A number of issues have contributed to this lack of research including methodological issues relating to the need for culturally appropriate tools and research approaches, the diversity of Aboriginal and Torres Strait Islander populations which makes accurate generalisation difficult, and the complicating influence of comorbid conditions and high levels of social adversity, particularly in remote communities. Suffice it to say that *depression is common, may be identified through screening but may also present in culturally informed ways* (Brown et al., 2012; Esler et al., 2008; Lee et al., 2008; Schlesinger et al., 2007). *Practitioners should not presume exotic phenomenology but should be alert to the importance of culture, context and communication in assessment and interventions* (Hunter, 2014).

These recommendations are therefore based on current knowledge base and, for the most part, are not specific to mood disorders but reflect a culturally concordant approach (See Appendix 4).

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See Tables v and vi of Appendix 5.

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RANZCP Project Team.

Ms Rosie Forster, Senior Department Manager, Practice, Policy and Partnerships.

Dr Huseyin Mustafa, Project Manager, Policy Operations and Committees.

Ms Edwina Ward, Project Officer (from October 2014), Practice, Policy and Partnerships.

Ms Helen Walters Project Officer (until December 2014), Practice, Policy and Partnerships.

Ms Claire Leslie, Project Officer (from June – September 2014), Practice, Policy and Partnerships.

Disclaimer

Compiled for the Royal Australian and New Zealand College of Psychiatrists (RANZCP), this information and advice is based on current medical knowledge and practice as at the date of publication. This CPG is intended as a general guide only, not as a substitute for individual medical advice. The RANZCP and its employees accept no responsibility for any consequences arising from relying upon the information contained in this publication.

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Declaration of interest

MDC disclosure of potential conflicts of interest management process.

Members of the Mood Disorders Committee (MDC) signed a deed of undertaking at the time of appointment in which they agreed to declare any conflict, whether actual, potential, perceived or likely to arise. To manage conflicts of interest of the MDC during the CPG development process:

- As a part of the standing items of all meetings, all MDC members were asked to declare their conflicts of interest during each teleconference meeting and these were recorded. If a conflict of interest was declared, the individual(s) concerned was excluded from the discussion and right to vote/contribute.
- The MDC members signed an up-dated COI form at the time of submitting the mood disorders guideline for publication.

Committee member's declarations of interest are listed in *Table iv of Appendix 5*. MDC member disclosure statements will be available at www.ranzcp.org.au.

Notes

1. MDC agreement was in most cases unanimous but allowed for one committee member to abstain.
2. Irritable mood is a primary feature of depression in children and adolescents but not in adults.
3. Adjustment disorder: the development of emotional or behavioural symptoms in response to an identifiable stressor(s) occurring within 3 months of the onset of the stressor(s). It is clinically signification because of (a) marked distress that is out of proportion to the severity or intensity of the stressor, or (b) social, occupational or functional, or other areas of functioning. The stress-related disturbance does not meeting criteria for another mental disorder and is not merely an exacerbation of a prexisting mental disorder. After the termination of the stressor (or its consequences), the symptoms persist for no longer than an additional 6 months. The symptoms do not represent normal bereavement. Six specifiers are used to identify subtypes of adjustment disorder (depressed, anxious, mixed anxiety and depressed, disturbance of conduct and mixed disturbance of emotions and conduct or unspecified).
4. Quality of life (QoL) is an outcome highly valued by patients, and cannot be reduced to the absence of symptoms or adequate objective functioning. Quality of life and symptom measures correlate only moderately, and can diverge with treatment. There is moderate consensus that clinicians should consider both symptom measures (measuring the presumed underlying pathology) and subjective QoL (indexing the state of the person with the disorder) in setting treatment goals and assessing outcomes.
5. Given that many patients are not able to afford private care, the majority are treated via public services. However, in Australia, the in-patient public mental health services are not equipped to handle a high demand of patients; thus, unless patients are at an increased risk of suicide or harm to others, patients are provided outpatient care. Recent research indicates that less than 10% of patients diagnosed with depression or anxiety receive their primary treatment from the public mental health system (Short et al., 2010) which indicates a shift toward private and community-based care. This is likely a result of the introduction of Federal government rebates for psychological and psychiatric treatment in 2006. Nearly all care in NZ is in the public sector.
6. Hepatic P450 and blood brain barrier efflux pump polymorphisms have been associated with differential doses of antidepressants needed clinically, but the evidence base is insufficiently evolved to encourage routine use. It may be appropriate to consider using such genetic information if it happens to be at hand, but clinical value remains unclear at this early stage of the pharmacogenetic evidence base.
7. Efficacy is different from effectiveness. The latter also takes into account tolerability. However, clinical trials are primarily focus on efficacy.
8. Case reports (unpublished) of prolonged QTc interval with doses of citalopram at 60mg or above have prompted the manufacturer and the US FDA to issue a warning about prescribing citalopram above 40mg/day. The seriousness of the risk has been challenged by Vieweg et al. (2012) Vieweg and co-authors reviewed the literature and found no cases of sudden cardiac death or torsade des points in patients treated with up to 60mg/day of citalopram and with no cardiac risk factors. Cases of prolongation of the QTc interval have been reported with other SSRIs in patients with no history of cardiovascular disorders (Moret et al., 2009).
9. Adequate = dose of antidepressant known to be effective.
10. Valproate and lamotrigine have a well-documented interaction that increases the blood levels of both medications and increases the risk of side effects.

11. Persons with BD can have normal fluctuations in mood, such as feeling unhappy when their team loses or relationships breakdown, or feeling happy about achieving something, which does not necessarily imply destabilised mood.
12. Antidepressant induced mood elevation indicates a vulnerability for Bipolar Disorder and in terms of treatment may necessitate similar management.

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Appendix 1

Table i. Levels of evidence for intervention studies*.

Level	Design
I	A systematic review of level II studies
II	A randomised controlled trial (RCT)
III	A pseudo-randomised controlled trial (i.e. alternate allocation or some other method) A comparative study with concurrent controls: Non-randomised, experimental trial Cohort study Case-control study Interrupted time series with a control group A comparative study without concurrent controls: Historical control study Two or more single arm studies Interrupted time series without a parallel control group
IV	A case series with either post-test or pre-test/post-test outcomes

***Adapted** from: NHMRC levels of evidence for intervention studies (NHMRC, 2009).

Appendix 2

Table ii.

Psychotherapy	Depression acute phase[a]		Depression maintenance/relapse[b]		
	Number of studies	NNT versus control (D, 95% CI	Number of studies	NNT versus treatment as usual (RR, 95% CI)	NNT versus ADM (RR, 95% CI)
Cognitive (behavioural) therapy (CBT)	91	2.75 (.87, .60 – 1.15)	16	5 (.64, .53 –.76)	6 (.79, .61 – 1.02)
Interpersonal psychotherapy (IPT)	16	2.91 (.63, .36 – .90)	3	6	n/a
Non-directive supportive therapy	14	3.18 (.57, .37 – .77)	–	–	–
Problem-solving therapy	13	2.26 (.83, .45 – 1.21)	–	–	–
Behavioural activation therapy	10	2.16 (.87, .60 – 1.15)	–	–	–
Self-control therapy	6	4.00 (.45, .11 – .79)	–	–	–

Psychotherapy	Depression acute phase[a]		Depression maintenance/relapse[b]		
	Number of studies	NNT versus control (D, 95% CI	Number of studies	NNT versus treatment as usual (RR, 95% CI)	NNT versus ADM (RR, 95% CI)
Short-term psychodynamic therapy	5	2.67 (.69, .30 – 1.08)	–	–	–
Mindfulness-based cognitive therapy (MBCT)	–	–	3	4 (.66, .53 – .82)	9 (.80, .60 – 1.08)

References: [a]Cuijpers et al. (2011a), [b]Biesheuvel-Leliefeld et al. (2015).
Antidepressant Medication (ADM).
D = pooled mean effect size (Cohen's d).
RR = relative risk.

Appendix 3

Further reading for developing clinicians skills in engaging Māori.

Te Pou. Te Pou works to support and develop the mental health, addiction and disability workforce in New Zealand. They have developed a range of resources and information to improve services, support the workforce, inform outcomes and provide training and funding. Video Resource: Engaging with Tangata Whaiora and Whānau. http://www.tepou.co.nz/supporting-workforce/working-with-Māori
Māori mental health training http://www.psychtraining.org/telho1.html
Medical Council of New Zealand http://www.mcnz.org.nz/news-andpublications/statements-standards-for-doctors/
The Hui Process: a framework to enhance the doctor–patient relationship with Māori (Lacey et al., 2011)
Recommendation for psychiatric assessment of Māori in primary care (Bennett, 2009a)
Recognising and managing mental health disorders in Māori (BPAC TBPACNZ, 2010)

Appendix 4

All mental health staff working in Australia should have mandatory training in Aboriginal and Torres Strait Islander people cultural awareness which should include understanding of the following:

The current relevance of post colonisation history (Hunter, 2014).
The social and emotional well-being paradigm.
A rights based approach with particular reference to self-determination and social justice (Human Rights and Equal Opportunity Commission, 2007).
The principles of 'A Contributing Life' involving 'thriving not just surviving' (NMHC, 2012a) timely and effective care and treatment, meaningful activity, meaningful connections with family, friends, culture and community.
Psychosocial determinants of mental health in Aboriginal and Torres Strait Islander people, particularly unstable poor quality accommodation, unemployment, social exclusion, stress, trauma, violence and substance use.

Appendix 5

Table iii. Mood disorders committee (MDC).

Name	Titles and affiliations
Professor Gin Malhi	Discipline of Psychiatry, Sydney Medical School, University of Sydney, Sydney CADE Clinic, Department of Psychiatry, Royal North Shore Hospital, St Leonards, Sydney
A/Professor Darryl Bassett	Clinical and Adjunct Staff, School of Psychiatry and Clinical Neurosciences, The University of Western Australia, Perth Adjunct Professor, School of Medicine, University of Notre Dame, Perth
Professor Philip Boyce	Discipline of Psychiatry, Sydney Medical School, Westmead Clinical School, University of Sydney, Sydney
Professor Richard Bryant	Scientia Professor, School of Psychology, University of NSW
Professor Paul Fitzgerald	Professor Psychiatry, Deputy Director, Monash Alfred Psychiatry Research Centre, Monash University Central Clinical School and The Alfred, Melbourne
Dr Kristina Fritz	Research Associate, Clinical Assessment Diagnostic Evaluation Clinic, Discipline of Psychiatry, Sydney Medical School – Northern, University of Sydney, Sydney
Professor Malcolm Hopwood	Academic Specialist Department of Psychiatry, University of Melbourne, Melbourne
Dr William Lyndon	Clinical Senior Lecturer, University of Sydney, Sydney Consultant, Mood Disorders Unit, Northside Greenwich Clinic, Greenwich, Sydney Director, ECT Services Northside Group Hospitals, Greenwich, Sydney
Professor Roger Mulder	Professor Department of Psychological Medicine, University of Otago, Christchurch, Christchurch, New Zealand
Professor Greg Murray	Professor of Psychology, Department of Psychological Sciences, Swinburne University of Technology
Professor Richard Porter	Head of Department and Director of the Mental Health Clinical Research Unit, Department of Psychological Medicine University of Otago, Christchurch, Christchurch, New Zealand
Dr Ajeet B Singh	Senior Clinical Lecturer, Deakin Medical School, Deakin University, Melbourne

Table iv. MDC potential conflicts of interest.

Name	Declaration of Interests
Professor Gin Malhi	NHMRC Funding for research: Program Grant and Project Grant Honoraria for lectures/advisory boards: Astrazeneca, Eli-Lilly, Lundbeck, Janseen-Cliag, Sanofi-Aventis, Pfizer, Servier, Wyeth Personal fees for manuscript preparation: Elsevier Grant Non-NHMRC Grants: Ramsay research and Teaching Grant, American Foundation for Suicide prevention.
A/Professor Darryl Bassett	Grant and personal fees: Lundbeck, Servier, Pfizer. Personal fees: Wyeth Grant: Perth Bipolar Disorder Research Conference
Professor Philip Boyce	Consultation fees, sponsorship and speaker fees: Servier Member of advisory board: Lundbeck, Eli Lilly, Astra Zeneca and Janseen Seaker fees: Lundbeck, Astra Zeneca and Janseen Funding for clinical trial: Brain Resource Company
Professor Richard Bryant	NHMRC Funding for research: Program Grant and Project Grant
Professor Paul Fitzgerald	Advisory board membership: Bionomics Ltd. Grants for provision of equipment for research: Brainsway, Medtronic, and MaVenture Study funds: Cervel neurotech
Dr Kristina Fritz	No conflict of interest.
Professor Malcolm Hopwood	Grant and personal fees: Servier Personal fees: Lundberk, Eli Lilly and Astra Zeneca
Dr William Lyndon	Personal fees: Lundbeck Australia, Astra Zeneca, Eli Lilly Australia.
Professor Roger Mulder	No conflict of interests
Professor Greg Murray	NHMRC Funding for research: Project Grant. Personal fees: Servier, CSL biotherapies,
Professor Richard Porter	Patent: Antidepressant Pharmacogenetic Report
Associate Professor Ajeet Singh	Personal fees: Servier Australia, Lundbeck Australia Grants: Pfizer Australia Equity: LifeLetters.com Founder and owner of CNSdose.com website Patent (Pending): Antidepressant Pharmacogenetics Report

Table v. National and international academic and clinical advisers who provided comment*.

Academic Advisers (Australia and New Zealand)	Affiliation/Organisation
Professor Marie-Paule Austin	Chair and Director Perinatal and Women's Mental Health Unit (PWMHU), University of New South Wales and St John of God Health Care, Burwood
Professor Michael Berk	Alfred Deakin Chair in Psychiatry at Barwon Health | IMPACT SRC (Innovation in Mental and Physical Health and Clinical Treatment – Strategic Research Centre) | Barwon Health and Deakin University
Dr Yulisha Byrow	CADE Clinic, RNSH, NSLHD, Sydney, Australia
Professor Helen Christensen	Chief Scientist and Director of the Black Dog Institute
Professor Marie-Paule Austin	Chair and Director Perinatal and Women's Mental Health Unit (PWMHU), University of New South Wales and St John of God Health Care, Burwood
Professor Michael Berk	Alfred Deakin Chair in Psychiatry at Barwon Health | IMPACT SRC (Innovation in Mental and Physical Health and Clinical Treatment – Strategic Research Centre) | Barwon Health and Deakin University
Dr Yulisha Byrow	CADE Clinic, RNSH, NSLHD, Sydney, Australia
Professor Helen Christensen	Chief Scientist and Director of the Black Dog Institute
A/Professor Seetal Dodd	Clinical A/Professor, School of Medicine, Deakin University
A/Professor Megan Galbally	Consultant Psychiatrist and Head of Unit, Perinatal Mental Health at Mercy Hospital for Women
Professor Philip Hazell	Professor, Conjoint Professor of Child and Adolescent Psychiatry with the Sydney Medical School, The University of Sydney
A/Professor Felice Jacka	Principal Research Fellow, IMPACT Strategic Research Centre, Barwon Health
Professor Gordon Johnson	Emeritus Professor of Psychological Medicine at the University of Sydney and Director Mood Disorders Unit Northside Clinic
Professor Anthony Jorm	Professorial Fellow in Melbourne School of Population and Global Health, University of Melbourne
Dr Jon-Paul Khoo	Psychiatrist, Toowong Specialist Clinic
Professor Jayashri Kulkarni	Professor, Psychiatry, The Alfred and Monash University
Dr Cameron Lacey	Senior Lecturer, Māori/Indigenous Health Institute (MIHI), University of Otago, Christchurch, NZ

Dr Noeline Latt	Clinical Lecturer, Psychiatry, Northern Clinical School Senior Staff Specialist, Northern Sydney LHD Addiction Medicine Service
Professor Florence Levy	Professor, Psychiatry, Medicine, School of Psychiatry, The University of Sydney
A/Professor Andrew Lewis	Research Academic, Faculty of Health, School of Psychology, Deakin University
Professor Colleen Loo	Professor, School of Psychiatry, University of NSW
Professor Philip Mitchell	Head of the School of Psychiatry at the University of New South Wales
Professor Daniel O'Connor	Head of the Aged Mental Health Research Unit based at Kingston Centre, Monash University
Dr Tim Outhred	Sydney Medical School Northern, University of Sydney, Australia.
Dr Narelle Shadbolt	Senior Lecturer, General Practice, Northern Clinical School Joint Head of the Discipline of General Practice Sydney Medical School
Dr Martien Snellen	Consultant Psychiatrist, Albert Road Clinic
Professor John Tiller	Professor Emeritus of Psychiatry, The University of Melbourne
Academic Advisers (International)	**Affiliation/Organisation**
Professor Carlo Altamura	Professor of Psychiatry, University of Milan, Italy
Dr Francesco Colom	Head of Psychoeducation and Psychological Treatments Area, Barcelona Bipolar Disorders Unit, Barcelona
Professor Mark George	Distinguished Professor of Psychiatry, Radiology, Medical University of South Carolina
Professor Guy Goodwin	Emeritus Professor of Psychiatry, University, Department of Psychiatry, University of Oxford, Warneford Hospital
Professor Roger McIntyre	Professor, Psychiatry and Pharmacology, University of Toronto
Dr Roger Ng	Consultant Psychiatrist, Department of Psychiatry, Kowloon Hospital
Professor John O'Brien	Foundation Professor of Old Age Psychiatry, Department of Psychiatry, University of Cambridge School of Clinical Medicine
Professor Harold Sackeim	Professor, Psychiatry and Radiology, Columbia University
Professor Jan Scott	Professor, Psychological Medicine, University of Newcastle, United Kingdom
Dr Nobuhiro Sugiyama	Doctor, Department of Psychiatry, School of Medicine Shinshu University, Matsumoto, Nagano, Japan
Professor Eduard Vieta	Professor, Psychiatry. University of Barcelona, Spain
Professor Lakshmi Yatham	Professor, Psychiatry, University of British Columbia, Canada

Clinical Advisers (Australia and New Zealand)	Affiliation/Organisation
Dr Nick De Felice	Psychiatrist, Western Australia
Dr Josh Geffen	Psychiatrist, Toowong Private Hospital, Queensland
A/Professor David Horgan	Clinical Associate Professor, Department of Psychiatry, University of Melbourne
Dr Thomas Mayze	Psychiatrist, Brisbane Clinic
Dr Linton Meagher	Psychiatrist, Northside Cremorne Clinic
Dr Nick O'Connor	Northern Sydney Local Health District. Department of Psychiatry, University of Sydney
Dr Mark Rowe	Psychiatrist, Northside Clinic
Dr Bill Watkins	Clinical Head, Child and Family Unit, The Princess Margaret Hospital, New Zealand
Dr Raymond Wu	Psychiatrist, Perth Clinic

***Expert** advisors provided comment and feedback on a voluntary basis with no remuneration and their declarations of interest are documented.

Table vi. External consultation specialist groups approached.

Key stakeholders, professional bodies, special groups and interested parties
Internal College committees, fellows and trainees: Community Collaboration Committee Aboriginal and Torres Straight Islanders Committee Te Kaunihera Committee Fellows and trainees
Australia and New Zealand Mental Health and Disability Commissions
Mental Health Council of Australia
Committee of Presidents of Medical Colleges Council of Medical Colleges New Zealand
Australian and New Zealand Colleges of Nurses and Mental Health Nurses
Australian Psychological Society New Zealand Psychological Society New Zealand College of Clinical Psychologists Australian Clinical Psychology Association
Australian Association of Social Workers Aotearoa New Zealand Association of Social Workers
Occupational Therapy Australia New Zealand Association of Occupational Therapists
Mental Health Foundation NZ
SANE
Mental Illness Fellowship of Australia
Mental Health Professionals' Network

During the consultation period, the draft guideline was publicly available for review and comment on the RANZCP website. Participants were asked to review the guideline and answer four key questions related to each section of the guideline via Survey Monkey. Question criteria were:

Are there any significant gaps (of topic, literature, other)?

Are there errors in the content?

Is the structure logical and easy to use?

Do you have any other comments?

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Review

REVIEW

The International College of Neuro-Psychopharmacology (CINP) Treatment Guidelines for Bipolar Disorder in Adults (CINP-BD-2017), Part 2: Review, Grading of the Evidence, and a Precise Algorithm

Konstantinos N. Fountoulakis, MD; Lakshmi Yatham, MD; Heinz Grunze, MD; Eduard Vieta, MD; Allan Young, MD; Pierre Blier, MD; Siegfried Kasper, MD; Hans Jurgen Moeller, MD

3rd Department of Psychiatry, School of Medicine, Aristotle University, Thessaloniki, Greece (Dr Fountoulakis); Department of Psychiatry, University of British Columbia, Mood Disorders Centre of Excellence, Djavad Mowafaghian Centre for Brain Health, Canada (Dr Yatham); Paracelsus Medical University, Salzburg, Austria (Dr Grunze); Hospital Clinic, Institute of Neuroscience, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalonia, Spain (Dr Vieta); Centre for Affective Disorders, Institute of Psychiatry, Psychology and Neuroscience, King's College, London, United Kingdom (Dr Young); The Royal Institute of Mental Health Research, Department of Psychiatry, University of Ottawa, Ottawa, Canada (Dr Blier); Department of Psychiatry and Psychotherapy, Medical University Vienna, MUV, AKH, Vienna, Austria (Dr Kasper); Psychiatric Department Ludwig Maximilians University, Munich, Germany (Dr Moeller).

Correspondence: Konstantinos N. Fountoulakis, MD, 6, Odysseos str (1st Parodos Ampelonon str.), 55535 Pylaia Thessaloniki, Greece (kfount@med.auth.gr).

Abstract

Background: The current paper includes a systematic search of the literature, a detailed presentation of the results, and a grading of treatment options in terms of efficacy and tolerability/safety.
Material and Methods: The PRISMA method was used in the literature search with the combination of the words 'bipolar,' 'manic,' 'mania,' 'manic depression,' and 'manic depressive' with 'randomized,' and 'algorithms' with 'mania,' 'manic,' 'bipolar,' 'manic-depressive,' or 'manic depression.' Relevant web pages and review articles were also reviewed.
Results: The current report is based on the analysis of 57 guideline papers and 531 published papers related to RCTs, reviews, posthoc, or meta-analysis papers to March 25, 2016. The specific treatment options for acute mania, mixed episodes, acute bipolar depression, maintenance phase, psychotic and mixed features, anxiety, and rapid cycling were evaluated with regards to efficacy. Existing treatment guidelines were also reviewed. Finally, Tables reflecting efficacy and recommendation levels were created that led to the development of a precise algorithm that still has to prove its feasibility in everyday clinical practice.
Conclusions: A systematic literature search was conducted on the pharmacological treatment of bipolar disorder to identify all relevant random controlled trials pertaining to all aspects of bipolar disorder and graded the data according to a predetermined

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method to develop a precise treatment algorithm for management of various phases of bipolar disorder. It is important to note that the some of the recommendations in the treatment algorithm were based on the secondary outcome data from posthoc analyses.

Keywords: bipolar disorder, anticonvulsants, antidepressants, antipsychotics, evidence-based guidelines, lithium, mania, bipolar depression, mood stabilizers, treatment, clinical trials

Introduction

The current paper is the second in the series of The International College of Neuro-Psychopharmacology papers concerning the development of a precise algorithm and clinical guidelines for the treatment of bipolar disorder (BD) in adults for use in primary and secondary care. It includes a systematic search of the literature and a detailed presentation of the results concerning placebo-controlled randomized trials for all phases and aspects of BD. It also includes the grading of treatment options in terms of efficacy and tolerability/safety as well as a precise algorithm that still has to prove its feasibility in everyday clinical practice.

Materials and Methods

As described in the first paper concerning the CINP treatment guidelines for BD, the workgroup decided that the PRISMA method (Hopewell et al., 2008; Liberati et al., 2009; Moher et al., 2009) should be followed in the search of the literature. The method included the search for 3 kinds of papers:

a. Randomized controlled trials (RCTs; placebo controlled as well as clinical trials with an active comparator with the compounds used as monotherapy or add-on therapy).
b. Posthoc analyses of RCTs.
c. Meta-analyses and review papers.
d. Treatment guidelines papers.

For this purpose, MEDLINE was searched to March 25, 2016 with the following search strategies:

1. To locate RCTs, the combination of the words 'bipolar,' 'manic,' 'mania,' 'manic depression,' and 'manic depressive' and 'randomized' was used.
2. Web pages containing lists of clinical trials were scanned. These sites included http://clinicaltrials.gov and http://www.clinicalstudyresults.org as well as the official sites of all the pharmaceutical companies with products used for the treatment of BP.
3. Relevant review articles were scanned and their reference lists were utilized (Srisurapanont et al., 1995; Yatham et al., 1997; Davis et al., 1999; Burgess et al., 2001; Macritchie et al., 2001, 2003; Bech, 2002, 2006; Rendell et al., 2003; Gijsman et al., 2004; Fountoulakis et al., 2005; Gao et al., 2005; Cipriani et al., 2006a, 2006b, 2011; Rendell et al., 2006; Smith et al., 2007; Fountoulakis, 2008, 2012, 2015a, 2015b, 2015c; Fountoulakis et al., 2008a, 2009b, 2012a, 2012d; Fountoulakis and Vieta, 2008; Yildiz et al., 2010; Nivoli et al., 2011; Tarr et al., 2011; Nivoli et al., 2012).
4. The MEDLINE was searched with the combination of keywords 'guidelines' or 'algorithm' with 'mania,' 'manic,' 'bipolar,' 'manic-depressive,' or 'manic depression.'
5. The treatment guidelines were also scanned and their reference lists were utilized.

It is difficult to locate unpublished studies, especially old ones, and even more difficult to retrieve their results. Thus, the main focus of this paper was on published studies that would have been peer-reviewed, are typically of higher quality, and provide more details than meeting abstracts or conference reports. However, whenever an unpublished trial was located, it is mentioned in that specific part of the manuscript. The authors decided not to seek additional information concerning unpublished trials from manufacturers as this might increase the retrieval bias.

Eventually the efficacy data were graded on the basis of a method developed by the authors and described in the first paper of the CINP guidelines for BD, that is also shown in Table 1. Agents were graded on the basis of safety and tolerability, and these grades are also shown in Table 1.

The PRISMA chart of the search process is shown in Figure 1 concerning RCTs and in Figure 2 concerning guidelines. Ultimately the current report was based on the analysis of 57 papers related to guidelines and 569 published papers concerning RCTs or other relevant papers (reviews, posthoc, or meta-analyses).

Efficacy Data

Acute Mania

The data on monotherapy and combination treatment for acute mania are shown in Table 2. As well, the table also includes grading of efficacy data for various features of mania such as psychotic features, mixed features, agitation, etc., most of that was based on the posthoc analyses of RCTs.

Monotherapy

Lithium. The first study investigating the efficacy of lithium against acute mania was conducted in 1971, but it did not follow a methodology that is accepted today as scientific standard (Stokes et al., 1971). Since then 4 placebo-controlled RCTs using modern clinical trial methodology starting in 1994 have been published. All of them utilized a period of 3 weeks vs placebo, and if a comparator was included, there was an extension phase without placebo (Bowden et al., 1994, 2005b; Kushner et al., 2006; Keck et al., 2009).

Overall there are 5 RCTs supporting the efficacy of lithium in comparison with placebo in acutely manic or mixed BD patients. All 5 are positive and the results are consistent. The overall response rate suggests a rough number needed to treat (NNT) around 5 to 6. The therapeutic effect appears after 7 days of treatment, that is, later in comparison with antipsychotics. There are limited data about the effect of lithium on the core symptoms of mania, but there are some suggestive of an effect on psychotic features (Bowden et al., 2005b). Its effect specifically on mixed episodes is unknown, and a posthoc analysis (Swann et al., 1997) of one of these RCTs (Bowden et al., 1994) confirmed the efficacy of lithium only in classic manic but not mixed patients albeit the number of mixed patients was too small to allow firm conclusion.

Table 1. The Method for the Grading of Data on the Basis of Efficacy and Tolerability

Grading on Basis of Efficacy	
Level 1	Good research-based evidence, supported by at least 2 placebo controlled studies of sufficient magnitude and good quality. In case of the presence of negative RCTs, positive RCTs should outnumber negative ones.
Level 2	Fair research-based evidence, from one randomized, double-blind placebo controlled trial. Also in case one or more trials exist, however, they fail to fulfil all the criteria above (e.g., very small sample size or no placebo control) as well as in case of positive meta-analysis alone.
Level 3	Some evidence from comparative studies without placebo arm or from posthoc analyses.
Level 4	Inconclusive data or poor quality of RCTs
Level 5	Negative data
Grading on the basis of safety and tolerability	
Level 1	Very good tolerability, few side effects that are not enduring, they do not cause significant distress, and are not life-threatening and they do not compromise the overall somatic health of the patient.
Level 2	Moderate tolerability, many side effects that could be enduring and cause significant distress, but they are not life-threatening although they could compromise the overall somatic health of the patient. Agents with very good overall tolerability but with rare life-threatening adverse events, could be classified here only if the lethality risk can be essentially considered to be negligible with the application of procedures and protocols (e.g., laboratory testing, titration schedules etc.).
Level 3	Poor tolerability, many side effects that are enduring, cause significant distress, compromise the overall somatic health of the patient, or are life-threatening. Agents with moderate overall tolerability and rare life-threatening adverse events should be classified here even in cases the lethality risk can be essentially considered to be negligible with the application of procedures and protocols (e.g., laboratory testing, titration schedules etc.)..
Recommendations for treatment (combination of efficacy and safety/tolerability)	
Level 1	Level 1 or 2 for efficacy and 1 for safety/tolerability
Level 2	Level 1 or 2 for efficacy and 2 for safety/tolerability
Level 3	Level 3 for efficacy and 1 or 2 for safety/tolerability
Level 4	Level 4 for efficacy or 3 for safety/tolerability
Level 5	Level 5 for efficacy (not recommended)

It exerts a therapeutic effect on manic-psychotic symptoms, but probably there is no therapeutic effect on concomitant depressive symptoms. The drop-out rate in these trials was comparable with placebo with probably more patients on placebo withdrawing from the study because of lack of efficacy, while side effects were the more common reasons for withdrawal in patients taking lithium. The most common adverse events with lithium were nausea, vomiting, dizziness headache, insomnia, asthenia, constipation, diarrhoea, tremor, and weight gain.

Antiepileptics. Valproate—Limited data concerning the efficacy of valproate in acute mania exist from earlier studies (Emrich et al., 1980, 1981; McElroy et al., 1989). The first study with modern methodology on the efficacy and safety of valproate in the treatment of acute mania was published in 1991 (Pope et al., 1991). Since then 3 positive (Pope et al., 1991; Bowden et al., 1994, 2006) and 2 failed RCTs (Tohen et al., 2008b; Hirschfeld et al., 2010) were published. Another study on a heterogeneous sample consisting of bipolar spectrum disorder patients was negative (McElroy et al., 2010a). A posthoc analysis of one of the RCTs (Bowden et al., 1994) did not find any preferential effect for divalproex in classic vs mixed manic patients (Swann et al., 1997). Overall the data support the usefulness of valproate against acute mania, although a number of issues need clarification. Its effect on psychotic symptoms is unknown and there seems to be no effect on concomitant depressive symptoms. The NNT for response is probably around 10 and the therapeutic effect is present after 5 to 15 days. Although the dosages utilized in these studies were higher than those usually used in everyday clinical practice (15–30 mg/kg/d), they hardly achieved the target serum concentrations (50–100 microg/mL). The most frequent adverse events were somnolence, nausea, dizziness, asthenia, constipation, twitching, and vomiting.

Carbamazepine—The earlier studies demonstrating the efficacy of carbamazepine in acute mania were published in the 1980s (Ballenger and Post, 1980; Post et al., 1987). Three large clinical trials using modern methodology have been published since 2000, all of that have confirmed the efficacy of carbamazepine (Weisler et al., 2004, 2005; Zhang et al., 2007).

Thus, the data concerning the efficacy and safety of carbamazepine at dosages 400 to 1600 mg/d and a mean plasma level of 8.9 μg/mL are robust. The reported NNT is approximately 5 for response, that starts around week 2. It is unknown whether carbamazepine has a beneficial effect on the core manic symptoms, in mixed patients, or against psychotic symptoms. There seems to be a beneficial effect on concomitant depressive symptoms only in mixed patients but not in manic patients (Weisler et al., 2005). The most frequent adverse events related to carbamazepine treatment were dizziness, nausea, somnolence, and an increase in total cholesterol that was composed of increases in both high-density and low-density lipoproteins.

Other antiepileptics—There is one negative (BIA-2093–203) and one fixed-dosage failed (BIA-2093–204) trial for eslicarbazepine (Robertson et al., 2010). Three unpublished RCTs (NCT00107926, NCT00107939, and NCT00099229) concerning the racemic mixture licarbazepine were also negative. There are 2 unpublished negative trials concerning lamotrigine in treating acute manic episodes (SCAA2008/GW609 and SCAA2009/GW610) (Goldsmith et al., 2003). Four trials con-

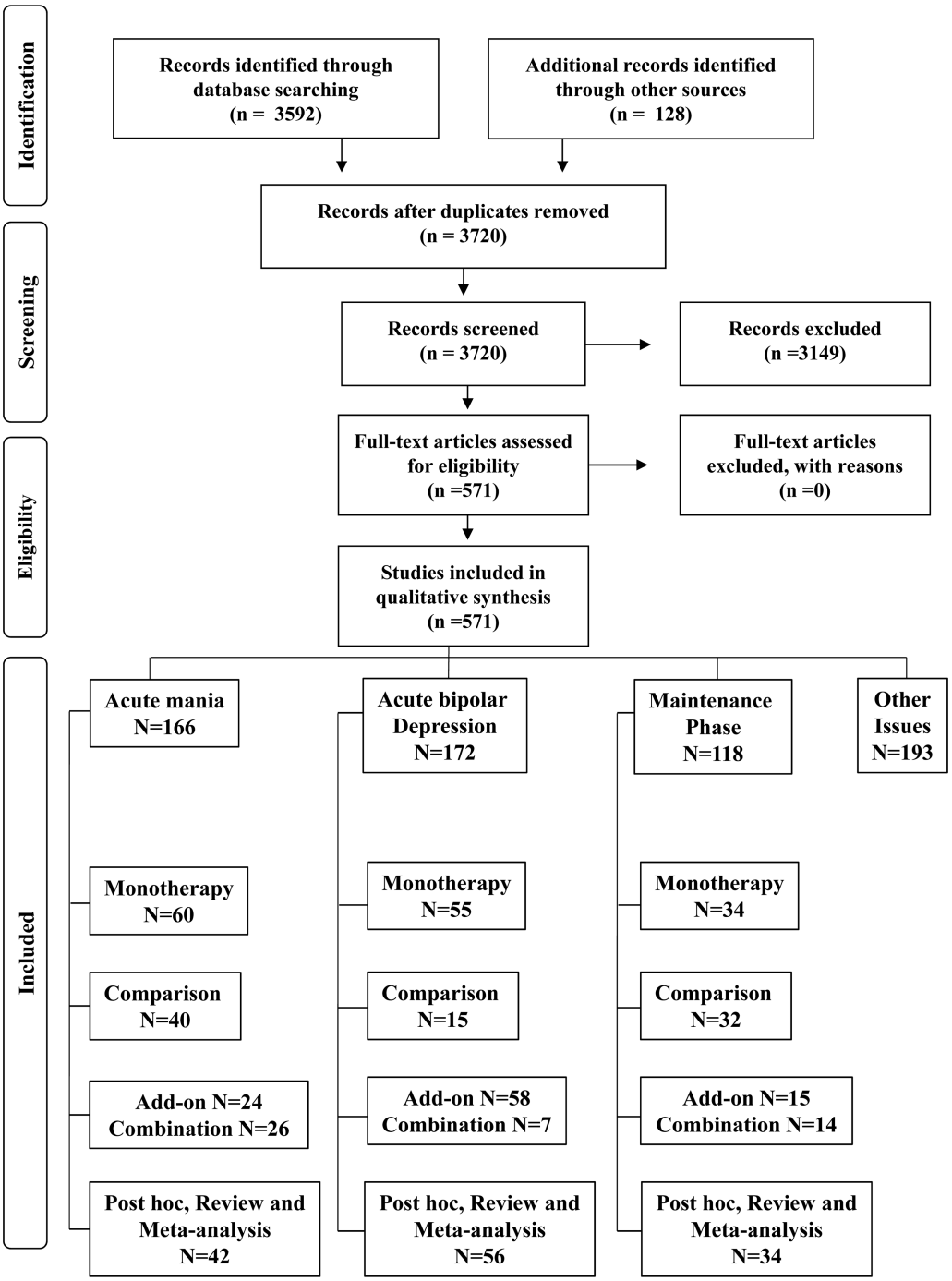


Figure 1. PRISMA flowchart for RCTs literature search.

cerning topiramate were all negative (Kushner et al., 2006). One small RCT evaluated the efficacy and safety of lamotrigine and gabapentin monotherapy vs placebo in 31 patients with refractory bipolar and unipolar mood disorders. Although lamotrigine differed significantly from placebo, gabapentin did not (Frye et al., 2000). Thus the data are negative for all other antiepileptics except for valproic acid and carbamazepine, that suggests that there is no class effect concerning antiepileptics in the treatment of BD (Rosa et al., 2009; Fountoulakis et al., 2011b).

Antipsychotics. The earlier studies on antipsychotics supported the efficacy of chlorpromazine (Klein, 1967) and suggested that antipsychotics acted more rapidly, although lithium was more globally effective (Shopsin et al., 1975).

Haloperidol—The efficacy and safety of haloperidol (up to 30 mg/d) was studied in 5 RCTs and all were positive (McIntyre et al., 2005; Smulevich et al., 2005; Young et al., 2009; Vieta et al., 2010a; Katagiri et al., 2012). The results suggest a NNT roughly equal to 5 to 8 for response. The therapeutic effect is apparent as early as day 4 (Goikolea et al., 2013a). However it is important to note that there is a signal for the induction of depression in the short term (Goikolea et al., 2013b). One study reported no effect on the core symptoms of mania. However, although haloperidol

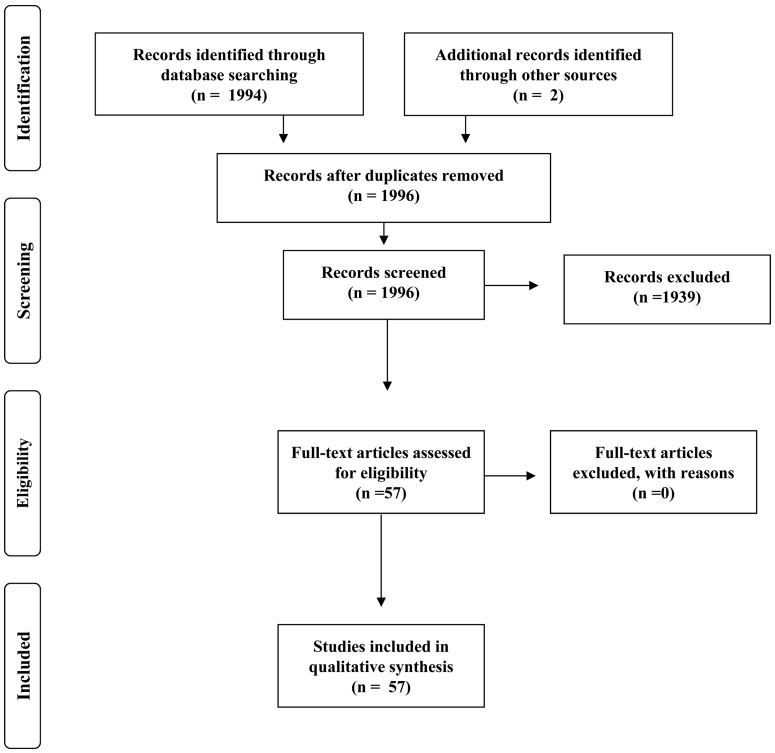


Figure 2. PRISMA flowchart for treatment guidelines literature search

might be particularly efficacious in psychotic patients, its effect on mixed patients is unknown. Adverse events most commonly reported with haloperidol treatment were somnolence, extrapyramidal symptoms (EPS), weight gain, and constipation.

Olanzapine—There are 6 positive trials supporting the efficacy of olanzapine (5–20 mg/d) for the treatment of manic or mixed episodes and concomitant psychotic features (Tohen et al., 1999, 2000, 2008b; McIntyre et al., 2009a, 2010b; Katagiri et al., 2012). The NNT is approximately around 5 for response (defined as a 50% drop in Young Mania Rating Scale [YMRS]). Olanzapine seems to have a beneficial effect on the core symptoms of mania and on psychotic symptoms, treats mixed patients as well as rapid cycling, possibly improves coexisting depressive symptoms, and response occurs as early as days 2 to 7. Olanzapine does not seem to induce a switch to depression. The most common adverse events related with olanzapine treatment were somnolence, dizziness, dry mouth, thirst, and weight gain. EPS occur but at a lower rate than with haloperidol.

Quetiapine—There exist 4 positive studies supporting the efficacy of quetiapine up to 800 mg/d for the treatment of acute mania (Bowden et al., 2005b; McIntyre et al., 2005; Vieta et al., 2010b; Cutler et al., 2011). Quetiapine does not seem to induce depression; on the contrary there is a clear beneficial effect on concomitant depressive symptoms. However, there is some doubt concerning its efficacy against mixed episodes (such patients were excluded in most quetiapine trials), concomitant psychotic features, and in rapid cycling patients. The NNT is around 4 to 6 for response. The most common adverse events associated with quetiapine treatment included sedation, dry mouth, somnolence, headache, dizziness, and postural hypotension.

Aripiprazole—There are 5 positive (Keck et al., 2003b, 2009; Sachs et al., 2006; Young et al., 2009; Kanba et al., 2014) and one negative fixed dosage study (El Mallakh et al., 2010) concerning the efficacy of aripiprazole 15 to 30 mg/d for the treatment of acute manic and mixed episodes. One study was not completed and reported no results. Again the effect on the core symptoms of mania is unknown. There is a significant effect in mixed and rapid cycling patients, and it also treats concomitant positive psychotic features and agitation. Aripiprazole does not seem to induce depression, but it does not seem to have any effect on concomitant depressive symptoms either. The NNT is approximately around 5 to 10 for response. Nausea, dyspepsia, somnolence, anxiety, vomiting, insomnia, light-headedness, constipation, and akathisia were the most common adverse events. There were no significant effects on body weight, serum prolactin, or QTc prolongation.

Risperidone—The efficacy of risperidone 1 to 6 mg/d for the treatment of acute manic and mixed episodes is supported by 3 positive studies (Hirschfeld et al., 2004; Khanna et al., 2005; Smulevich et al., 2005). The therapeutic effect is evident from day 3 onwards. It seems also effective in the treatment of positive psychotic symptoms and agitation and concomitant depressive symptoms. The NNT is approximately around 3 to 5 for response. It is unknown whether risperidone has an effect on the core symptoms of mania or whether it is beneficial for rapid cycling patients. It does not seem to induce a switch to depression. Somnolence, dyspepsia, nausea, and EPS were the most common adverse events.

Ziprasidone—Three positive studies (Keck et al., 2003a; Potkin et al., 2005; Vieta et al., 2010a) support the efficacy of ziprasidone 80 to 160 mg/d for the treatment of acute manic and mixed episodes. It has a treatment effect on the core symptoms of mania and on concomitant positive psychotic symptoms. It does not seem to have any significant effect on depressive symptoms, but it also does not seem to induce a switch to depression. Its effect

Table 2. Acute Mania/Mixed Treatment Phase, Grading on Basis of Efficacy (Treatment Phase up to 12 Weeks)

	Acute Manic Episodes											
		Monotherapy					Combination with					
Agent/modality (alphabetical order)	Effect start day	Overall	Core manic	Depressive	Psychotic	Agitation	MS	Cbz	Lam	Li	Val	FGAs
Allopurinol	-	-	-	-	-	-	5	-	-	3	-	5
Aripiprazole	2–4	1	-	5	3	-	2	-	-	-	-	-
Asenapine	2	1	-	4	-	-	2	-	-	-	-	-
Carbamazepine	14	1	-	5	-	-	-	-	-	-	-	-
Cariprazine	4	1	3	5	-	-	-	-	-	-	-	-
Celecoxib	-	-	-	-	-	-	-	-	-	-	2	-
Chlorpromazine	-	4	-	-	-	-	-	-	-	-	-	-
Clozapine	-	-	-	-	-	-	-	-	-	-	-	-
ECT	-	3	-	-	-	-	-	-	-	-	-	-
Eslicarbazepine	-	5	-	-	-	-	-	-	-	-	-	-
Gabapentin	-	5	-	-	-	-	5	-	-	-	-	-
Haloperidol	4	1	5	5	3	3	2	2	-	2	2	-
Lamotrigine	-	5	-	-	-	-	-	-	-	-	-	-
Levetiracetam	-	-	-	-	-	-	-	-	-	-	-	-
Licarbazepine	-	5	-	-	-	-	-	-	-	-	-	-
Lithium	7	1	4	5	2	-	-	2	-	-	-	-
Loxapine inhalant	-	-	-	-	-	2	-	-	-	-	-	-
Medroxyprogesterone	-	-	-	-	-	-	5	-	-	-	-	-
Olanzapine	2–7	1	3	3	3	2	1	5	-	-	1	-
Oxcarbazepine	-	4	-	-	-	-	-	-	-	4	-	-
Paliperidone	2	1	-	-	-	-	5	-	-	-	-	-
Pimozide	-	4	-	-	-	-	-	-	-	-	-	-
Quetiapine	4	1	-	3	3	-	3	-	-	2	-	-
Risperidone	3	1	-	3	3	-	3	-	-	-	5	-
Tamoxifen	5	2	3	5	3	-	2	-	-	2	-	-
TMS	-	5	-	-	-	-	-	-	-	-	-	-
Topiramate	-	5	-	-	-	-	5	-	-	-	-	-
Valproate	5–15	1	5	5	-	3	-	-	-	-	-	2
Verapamil	-	5	-	-	-	-	-	-	-	-	-	-
Ziprasidone	2	1	3	5	3	-	5	-	-	-	-	-

Abbreviations: -, no data; Cbz, carbamazepine; ECT, electroconvulsive therapy; FGA, first generation antipsychotic; Lam, lamotrigine; Li, lithium; MS, mood stabilizer; TMS, transcranial magnetic stimulation; Val, valproate.
The treatment options are rated according to the rating system shown in Table 1.

in rapid cycling patients is unknown. The NNT is approximately 6 for response. The most common adverse events with ziprasidone treatment were EPS, somnolence, dizziness, anxiety, and dyspepsia. There were no significant effects on body weight or serum lipids. There was a small and clinically not significant QTc prolongation reported

Asenapine—Three positive trials (McIntyre et al., 2009a, 2010b; Landbloom et al., 2016) support the efficacy of asenapine 10 to 20 mg/d for the treatment of acute manic and mixed episodes with efficacy as early as day 2. It is unknown whether it has a treatment effect on the core symptoms of mania, and while in one of the studies a positive effect on the total Possitive and Negative Symptoms Scale (PANSS) score is reported, the specific effect on concomitant positive or negative psychotic features is unknown. Also unknown is the efficacy in rapid cycling patients. The data are equivocal concerning the effect on depressive symptoms, but also it does not seem to induce depression. The NNT is between 6 and 12 for response. The most common adverse events related with asenapine treatment were EPS, somnolence, dizziness, sedation, fatigue, oral hypesthesia, dry mouth, weight gain, and EPS.

Paliperidone—Two studies (Vieta et al., 2010b; Berwaerts et al., 2012b) provide support for the efficacy of 12 mg/d of paliperidone ER for the treatment of acute manic and mixed episodes, while the data for lower dosages is conflicting. Paliperidone is effective as early as day 2. It is not reported whether it has a treatment effect on the core symptoms of mania, positive psychotic symptoms, and depression and the effect in rapid cycling patients is unknown. It is unclear whether paliperidone ER can induce switches to depression. The most common adverse events related with paliperidone ER treatment were headache, somnolence, EPS, and prolactin elevation.

Cariprazine—Three studies (Calabrese et al., 2015; Durgam et al., 2015, 2016; Sachs et al., 2015) confirmed the efficacy of cariprazine (3–12 mg daily) vs placebo in the treatment of acute manic or mixed episodes. The NNT for response or remission is approximately 4 to 7. Cariprazine is reported to improve the core symptoms of mania but had no effect on the Mondgomery Asberg Depression Rating Scale (MADRS). It improves the total PANSS but the specific effect on the PANSS positive subscale is unknown. Its efficacy in mixed and rapid cycling patients is unknown.

Other agents and treatment modalities. Overall, the data for tamoxifen are positive; however, the total patient sample is still small (Zarate et al., 2007; Yildiz et al., 2008). One NIMH-sponsored clinical trial (NCT00026585) has not reported results yet. One small 3-week study was negative for verapamil (Janicak et al., 1998). The data concerning repetitive Transcranial Magnetic Stimulation (rTMS) are conflicting. There are two RCTs, one negative (Kaptsan et al., 2003) and one positive (Praharaj et al., 2009).

Summary of monotherapy trials for acute mania. Overall there are sufficient data in the literature to support the general efficacy of a number of agents in the treatment of acute mania; however, many details remain to be explored concerning many of the agents. Lithium, valproate, carbamazepine, haloperidol, olanzapine, quetiapine, aripiprazole, risperidone, ziprasidone, asenapine, paliperidone, cariprazine, and probably tamoxifen are efficacious in the treatment of acute manic episodes. It should be mentioned that haloperidol probably induces depression. It is unsatisfactory that there are no controlled data concerning the usefulness of electrocunvulsive treatment (ECT).

A significant problem for the everyday clinical practice is that the average clinician often utilizes the so-called "class effect" to easily navigate among therapeutic options. However, what needs to be stressed is that while antipsychotics seem to possess a class effect specific to the treatment of acute mania (possibly an antidopaminergic effect; Brugue and Vieta, 2007), there is no such effect in anticonvulsants concerning any phase of BD (Rosa et al., 2009; Fountoulakis et al., 2011b).

Comparison of Agents

Lithium vs others. In 2 studies comparing lithium with valproate, the 2 agents were found to be equivalent. There was a tendency of valproate to manifest fewer adverse events and dropouts, but its signal for efficacy in RCTs might be driven by its effect in patients with mixed features (Freeman et al., 1992; Bowden et al., 1994). A similar finding restricting the efficacy of carbamazepine to an undefined subgroup of patients in contrast to a wider efficacy of lithium was reported by another study as well (Lerer et al., 1987). Overall the efficacy was similar to carbamazepine but with fewer adverse events (Okuma et al., 1990; Small et al., 1991). There has been a comparison of carbamazepine with lamotrigine that should be considered to be a failed study (Ichim et al., 2000). It should be noted however that lamotrigine is not an effective antimanic agent.

The comparison of lithium to chlorpromazine suggested that although chlorpromazine acts faster and might be more efficacious in more agitated patients, this might be due to sedation alone, while lithium has again a broader effect on the core manic symptomatology (Platman, 1970; Prien et al., 1972; Shopsin et al., 1975). In contrast, the comparison of haloperidol and lithium suggested that haloperidol had a stronger and more rapid effect, especially on behavior and motor activity but without sedation, while lithium acted more evenly and comprehensively on the entire range of manic symptomatology (Shopsin et al., 1975; Garfinkel et al., 1980).

Lithium was found to have equal efficacy to carbamazepine (Lerer et al., 1987; Okuma et al., 1990; Small et al., 1991), olanzapine (Berk et al., 1999; Niufan et al., 2008; Shafti, 2010), quetiapine (Bowden et al., 2005b; Li et al., 2008), and aripiprazole (Keck et al., 2009). In severely psychotic patients, it seems inferior to haloperidol (Shopsin et al., 1975; Garfinkel et al., 1980). Overall, lithium has a wider antimanic effect than valproate and carbamazepine but a weaker effect on psychotic symptoms and a slower onset of action in comparison with antipsychotics. Overall, lithium demonstrated a more favorable adverse effect profile in comparison with all other agents except aripiprazole and valproate.

Valproate vs others. In comparison with lithium, valproate was less efficacious and with a tendency to cause fewer adverse events and dropouts, but its efficacy might be restricted to that specific group of patients with mixed features (Freeman et al., 1992; Bowden et al., 1994). In one small study, it was superior to carbamazepine and had a faster onset of action (Vasudev et al., 2000). In another study, it was superior to oxcarbazepine but with more frequent adverse events (Kakkar et al., 2009). It might be less efficacious in comparison with olanzapine and with a slower onset of action, but also with fewer adverse events (Tohen et al., 2002a, 2008b; Zajecka et al., 2002).

Carbamazepine vs others. Carbamazepine was reported to be equally effective in comparison with lithium but with a higher rate of adverse events. Its efficacy appeared somewhat restricted to an undefined subgroup of patients in contrast to a broader spectrum of efficacy of lithium (Lerer et al., 1987; Okuma et al., 1990; Small et al., 1991). In another study carbamazepine was inferior to valproate and had a slower onset of action (Vasudev et al., 2000). In 2 other studies carbamazepine was found equal to chlorpromazine but with fewer adverse events (Okuma et al., 1979) and equal to haloperidol but with a slower onset of action (Brown et al., 1989).

Other antiepileptics. There is one study on lamotrigine vs lithium that should be considered as failed probably because it was underpowered (Ichim et al., 2000). In another study, oxcarbazepine was found to be inferior to valproate but with fewer adverse events (Kakkar et al., 2009).

Haloperidol vs others. The comparison of haloperidol with lithium suggested that haloperidol is more efficacious in severely psychotic patients and exerts its effect earlier, especially on behavior and motor activity but without sedation, while lithium acted more evenly and comprehensively on the entire range of manic symptomatology (Shopsin et al., 1975; Garfinkel et al., 1980). Haloperidol was found equally effective to carbamazepine but with a faster onset of action (Brown et al., 1989). Haloperidol had a faster onset of action than olanzapine but with more dropouts, and olanzapine was superior in the nonpsychotic patients. Both agents were equally effective in reducing the HDRS score in mixed patients and in patients with higher depressive scores. Switch to depression occurred significantly more rapidly with haloperidol than with olanzapine. More EPS were reported with haloperidol and more weight gain with olanzapine (Tohen et al., 2003b; Katagiri et al., 2012). Haloperidol was reported to be overall superior to quetiapine and more efficacious in psychotic patients. In contrast to quetiapine it had no effect on depressive symptoms. Haloperidol-treated patients had more dropouts and more EPS (McIntyre et al., 2005). It was reported as not superior to aripiprazole and did not improve the depressive symptoms measured with the MADRS. In comparison with aripiprazole, more haloperidol-treated patients switched to depression, more dropped out, and EPSs were more frequent with haloperidol (Vieta et al., 2005b; Young et al., 2009). Haloperidol was found similarly efficacious to risperidone (Segal et al., 1998; Smulevich et al., 2005) and superior to ziprasidone but also with more drop outs and adverse events (Vieta et al., 2010a). The comparison of 25 mg/d vs 5 mg/d haloperidol revealed that the higher haloperidol dosage produced greater improvement than did the low dose but with more side effects (Chou et al., 1999).

In summary, haloperidol was similar in efficacy as carbamazepine (Brown et al., 1989) and olanzapine (Tohen et al., 2003b; Katagiri et al., 2012), risperidone (Segal et al., 1998; Smulevich et al., 2005), and aripiprazole (Vieta et al., 2005b; Young et al., 2009). It was found to be superior to quetiapine (McIntyre et al., 2005) and ziprasidone (Vieta et al., 2010a) and in severely psychotic patients to lithium (Shopsin et al., 1975; Garfinkel et al., 1980). It acted faster in comparison with lithium (Shopsin et al., 1975; Garfinkel et al., 1980), carbamazepine (Brown et al., 1989), and olanzapine (Tohen et al., 2003b; Katagiri et al., 2012). Overall it demonstrated superior efficacy in psychotic patients but less improvement (if any) on depressive symptoms. It also showed more adverse events (especially EPS), switching to depression and dropouts more than the comparators.

Olanzapine vs others. Olanzapine was reported to be equally effective to lithium but with more adverse events, mainly weight gain (Berk et al., 1999; Niufan et al., 2008; Shafti, 2010). It might be superior and faster acting in comparison with valproate (although this could be a function of dosage) but again with more adverse events (Tohen et al., 2002a, 2008b; Zajecka et al., 2002). It was found to be similar in efficacy to haloperidol but with a slower onset of action and fewer dropouts. The data suggest that during the acute phase both agents were equally effective in reducing the HDRS score in mixed patients and in patients with higher depressive scores. More EPSs were registered with haloperidol and more weight gain with olanzapine (Tohen et al., 2003b; Katagiri et al., 2012). Olanzapine was found superior to asenapine in manic and mixed patients and also significantly improved the MADRS score, that asenapine did not. Olanzapine-treated patients had more weight gain (McIntyre et al., 2009a, 2010b).

Olanzapine was found to have similar efficacy as risperidone in patients without psychotic features in terms of YMRS, HAM-D, and MADRS change. The 2 agents were also equal in the subgroup of rapid cycling patients. Fewer olanzapine-treated patients dropped out of the head-to-head comparison but there was more weight gain in the olanzapine group (Perlis et al., 2006b). Finally, an unpublished study of olanzapine vs ziprasidone (NCT00329108) was stopped prematurely due to poor recruitment (2009).

Quetiapine vs others. Quetiapine is reported to be comparable with lithium but with more dropouts and adverse events (Bowden et al., 2005b; Li et al., 2008). Also it is reported to be inferior to haloperidol, with fewer dropouts and less frequent EPS, and also less efficacious in psychotic patients. In contrast to haloperidol it had an effect on depressive symptoms (McIntyre et al., 2005).

Quetiapine is reported to be equal to paliperidone and both agents had a similar effect in manic and mixed patients. Body weight increase was more frequent in the quetiapine group, but more patients with paliperidone switched to depression (Vieta et al., 2010b).

Other antipsychotics. Chlorpromazine was found equal to pimozide with faster action, probably due to its greater sedative effect. Sedation was the side effect most frequent with chlorpromazine and EPS were more frequent with pimozide (Cookson et al., 1981).

The following studies have already been reported and discussed above; however, it is important to consider them again from a reverse angle. Risperidone was found equal to haloperidol (Segal et al., 1998; Smulevich et al., 2005) and olanzapine (Perlis et al., 2006b). Aripiprazole was found equal to lithium (Keck et al., 2009) and haloperidol (Vieta et al., 2005b; Young et al., 2009). Asenapine was found inferior to olanzapine (McIntyre et al., 2009a, 2010b) and paliperidone equal to quetiapine (Vieta et al., 2010b). There is one unpublished study comparing ziprasidone with olanzapine that did not report any results (2009) and another one finding it inferior to haloperidol (Vieta et al., 2010a). Finally, there are 2 studies comparing chlorpromazine with lithium (Platman, 1970; Prien et al., 1972) and one with carbamazepine (Okuma et al., 1979), suggesting equal efficacy.

Summary of the comparison of agents. Overall, comparison studies suggest that the greater the efficacy the more frequent the adverse events are. Although there are no sufficient data to support a big difference between agents, it seems that antipsychotics and lithium are more efficacious than valproate and carbamazepine unless a loading strategy for these anticonvulsants is applied. Also it seems clear that antipsychotics act earlier in comparison with the other compounds. The effect on depressive symptoms is unclear, but it seems that haloperidol-treated patients might switch more often to depression.

Earlier studies suggested that lithium could be specifically useful against the more "classic" cases of euphoric mania, while antiepileptics might have a better efficacy for patients with mixed features and those with comorbidity. This is not supported by more recent data (Fountoulakis et al., 2012b). A factor that could have affected the results is the so-called lithium-discontinuation-related refractoriness (Post et al., 1992), because of that patients enrolled in RCTs could constitute a sample more refractory to lithium treatment than expected. However, the assumption for the existence of lithium-discontinuation-related refractoriness is not supported by studies reporting that even when samples enriched for lithium refractoriness were used, no inferiority of lithium to the other agent was documented (Bowden et al., 1994). Also a recent meta-analysis of all published cases concluded that there is not sufficient data to support such a concept (de Vries et al., 2013).

Combination and Add-On Treatment

Several studies examined the efficacy and safety of agents given not as monotherapy but combined treatments. The study samples range from patients being refractory to an initial treatment to drug-naive patients. In the first instance, an agent is used as adjunct or add-on therapy on a preexisting treatment to that the patient has shown unsatisfactory response. In the second instance the study tests a combination treatment against monotherapy and both agents are initiated simultaneously. Although essentially both designs provide information on how to treat patients with an unsatisfactory response to monotherapy, the conclusions and the generalizability might differ.

Combination Treatment

Adding valproate to First Generation Antipsychotics (FGAs; haloperidol or perazine in this study) produced higher response rates in manic patients (70% vs 46%) compared with FGA plus placebo (Muller-Oerlinghausen et al., 2000). Similarly, combination of lithium (600–1800 mg/d) and quetiapine XR (400–800 mg/d) was superior to quetiapine plus placebo (Bourin et al., 2014) in treating acute mania. Three studies that reported on combinations of mood stabilizing agents with haloperidol vs haloperidol monotherapy are equivocal as the outcome depended on the haloperidol dosage (Garfinkel et al., 1980; Klein et al., 1984; Chou et al., 1999).

Other studies reported on the efficacy of an antipsychotic agent and a mood stabilizer in comparison with mood stabilizer alone. In general, antipsychotic and carbamazepine combination is not superior to carbamazepine alone, primarily due to

the effect of carbamazepine inducing the metabolism of antipsychotics in the combination group, thus resulting in lower plasma levels of antipsychotics. One 6-week international trial of olanzapine (10–30 mg/d) vs placebo add on to carbamazepine (400–1200 mg/d) was negative. In the olanzapine group, however, the triglyceride levels were significantly higher and potentially clinically significant weight gain occurred more frequently. Furthermore, carbamazepine significantly reduced olanzapine serum concentrations (Tohen et al., 2008a). Similarly, in another study, carbamazepine significantly reduced the serum levels of risperidone (Yatham et al., 2003) that contributed to the negative findings of this study on the primary efficacy measure.

Overall the data on the combination of lithium with other agents support the conclusion that the combinations of lithium with haloperidol, lorazepam, carbamazepine, tamoxifen, and allopurinol are superior to lithium alone, but not the combination of lithium plus ziprasidone or dipyridamole. Most of these combinations had more adverse events in comparison with monotherapy (Garfinkel et al., 1980; Lenox et al., 1992; Small et al., 1995; Weisler et al., 2003; Bowden, 2005; Machado-Vieira et al., 2008; Amrollahi et al., 2010). Adding allopurinol to treatment as usual was not more effective compared with treatment as usual (Weiser et al., 2014). On the contrary, positive results were reported by the addition of 400 mg/d celecoxib on valproate in nonrapid cycling and nonpsychotic patients (Arabzadeh et al., 2015) but negative when added on ECT (Kargar et al., 2015).

A number of trials investigated the combination of an atypical antipsychotic or other agents with addition of an agent on top of lithium or valproate, since these 2 constituted the backbone of the treatment of BD for decades. Overall the data are in support of combining lithium or valproate with asenapine, olanzapine, risperidone, haloperidol, and tamoxifen but negative concerning gabapentin and medroxyprogesterone (Pande et al., 2000; Sachs et al., 2002; Yatham et al., 2003; Kulkarni et al., 2006; Szegedi et al., 2012; Kulkarni et al., 2014; Xu et al., 2015b). The addition of folic acid to valproate has equivocal support (Behzadi et al., 2009) and the addition of omega-3 fatty acids has negative data (Chiu et al., 2005). Adding the herbal agent Free and Easy Wanderer Plus (FEWP) on carbamazepine was not better than carbamazepine alone, but it was in comparison with placebo while carbamazepine monotherapy was not. Technically it does not support the use of FEWP in acute mania, but a number of other interpretations also exist, for example that adding FEWP compensates for the drop in carbamazepine levels (Zhang et al., 2007). However, that study did not define an a-priori primary outcome and therefore its quality is low. Finally, one study suggested that the valnoctamide plus risperidone combination was more effective than risperidone alone (Bersudsky et al., 2010).

In summary, there are few but still important data suggesting that specific combinations are superior to monotherapy in nonrefractory or otherwise selected samples, although it is difficult to assess the quality of many study samples. Despite the very small number of trials and the problems with the data quality, one could generalize that the combination of an antipsychotic plus lithium or valproate is superior to lithium or valproate alone, with the caveat of greater side-effect burden. Tamoxifen and probably allopurinol are also valuable agents to use in combination with mood stabilizers.

Add-On Treatment

In patients refractory to haloperidol treatment, the addition of phenytoin has been shown to be beneficial (Mishory et al., 2000). In patients refractory to lithium, adding 600 to 1200 mg/d carbamazepine or oxcarbazepine improved the outcome (Juruena et al., 2009), but that study was of poor quality, questionable phase of the disorder and outcome, and without any a-priory defined primary outcome. Adding lovastatin on lithium was negative (Ghanizadeh et al., 2014).

In patients refractory to lithium, valproate, or carbamazepine, it is beneficial to add haloperidol, olanzapine, quetiapine, aripiprazole, or asenapine (Szegedi et al., 2012) (Sachs et al., 2002, 2004; Tohen et al., 2002b; Yatham et al., 2007; Vieta et al., 2008b) but not ziprasidone, topiramate, risperidone, or paliperidone (Roy Chengappa et al., 2006; Berwaerts et al., 2011; Sachs et al., 2012a, 2012b; Moosavi et al., 2014). One study that used a mixed population with some patients entering after a minimum of 2 weeks of mood stabilizer therapy, and others starting a mood stabilizer and risperidone in parallel, provided inconclusive data for risperidone (Yatham et al., 2003) as the results were likely confounded by the effects of carbamazepine on serum levels of risperidone. Allopurinol was not beneficial in patients refractory to lithium, valproic acid, carbamazepine, or atypical antipsychotic medications (Fan et al., 2012), although there are some data suggesting a beneficial effect on patients refractory to valproate (Jahangard et al., 2014). Adding the melatonin agonist ramelteon was also not efficacious in patients refractory to treatment as usual (McElroy et al., 2010b). There is only one sham-controlled trial of ECT as adjunctive treatment to chorpromazine (600 mg/d) in 30 acutely manic patients. That study supported the efficacy of ECT with a faster rate of improvement (Sikdar et al., 1994)

A recent placebo-controlled 4-week RCT in 180 acutely manic patients supported the efficacy and safety of the purinergic agents allopurinol (600 mg/d) and dipyridamole (200 mg/d) as adjunctive to lithium in acute bipolar mania (Machado-Vieira et al., 2008). Folic acid was also found to be useful as an adjunct to valproate in treating acute mania (Behzadi et al., 2009). There is one 5-week trial from Israel on 32 recently admitted manic inpatients that compared valnoctamide (600–1200 mg/d; n=15) vs placebo (n=17) on top of risperidone (1–6 mg/d). All medications were started at day 1. In all efficacy measures the valnoctamide plus risperidone combination was more effective than risperidone plus placebo from week 3 to week 5. Valnoctamide is an anticonvulsant analogue of valproate that does not undergo biotransformation to the corresponding free acid, and in mice it has been shown to be distinctly less teratogenic than valproate (Bersudsky et al., 2010). A pilot 8-week study in 21 acutely manic outpatients on the usefulness of adjunctive ramelteon in acute mania/mixed states failed (McElroy et al., 2010b), while another 2 on the cholinesterase inhibitor donepezil were negative (Eden Evins et al., 2006a; Chen et al., 2013).

Overall, the data in partial responders or refractory patients support the addition of specific antipsychotics to lithium or valproate and also the use of allopurinol and the combination of lithium with carbamazepine or maybe oxcarbazepine.

Posthoc Analyses and Meta-Analytic Studies

A very important posthoc analysis of individual patient data reported that patients with impaired insight (as measured with the use of item 11 of the YMRS) responded better; therefore treatment should be initiated immediately and the therapist should not wait until the patient gains sufficient insight (Welten et al., 2016).

Overall, posthoc and meta-analytic studies confirm the efficacy of specific agents vs placebo (Emilien et al., 1996; Yatham et al., 2004; Perlis et al., 2006a; Scherk et al., 2007; Tamayo et al., 2010) and also confirm the superiority of antipsychotics vs lithium, valproate, and carbamazepine both in terms of faster onset of action but also in terms of the overall outcome in the short-term treatment of acute mania. However, they also confirm that this higher efficacy comes with the cost of more frequent adverse events, mainly EPS, weight gain, and somnolence (Correll et al., 2010; Tarr et al., 2010). These conclusions should be received with

caution, taking into consideration both the limitations of meta-analytical methods and the frequent conflicting results.

Haloperidol might be the fastest acting of all (Goikolea et al., 2013a) but also the most likely one to induce depression (Goikolea et al., 2013b). Olanzapine was efficacious against mixed episodes, depressive symptoms, and psychotic features as well as in rapid cycling patients (Baker et al., 2002; Baldessarini et al., 2003b; Chengappa et al., 2003; Suppes et al., 2005, 2008b). Quetiapine was proven efficacious for all YMRS individual items, depressive symptoms, and also against psychotic features (Vieta et al., 2005a). Risperidone vs placebo caused higher remission rate and the drop-out rate because lack of efficacy was lower, while the drop-out rate because of adverse events was similar to that of placebo (Gopal et al., 2005). Asenapine was efficacious against depressive symptoms (Szegedi et al., 2011) and mixed episodes (Azorin et al., 2013; McIntyre et al., 2013) and has an effect on the core symptoms of mania (Cazorla et al., 2013). Aripiprazole had no effect in patients aged >55 years but was effective against psychotic symptoms (Suppes et al., 2008b; Fountoulakis et al., 2009a; Sayyaparaju et al., 2014). Aripiprazole, lithium, and haloperidol overall are not efficacious against concomitant depressive features (Ostacher et al., 2015b). Ziprasidone was efficacious against dysphoric mania (Ketter et al., 2010; Stahl et al., 2010). The data of oxcarbazepine appear to be insufficient (Vasudev et al., 2011). A posthoc analysis of a lithium study (Bowden et al., 1994) confirmed the efficacy of lithium in classic manic but not mixed patients (Swann et al., 1997), while another posthoc study confirmed the lack of efficacy of eslicarbazepine although there seems to be some signal in the secondary outcomes (Grunze et al., 2015).

Meta-analytic studies also suggest that combination treatment is superior to monotherapy at the cost of more frequent adverse events; however, these meta-analyses do not distinguish between add-on and combination studies and populations (Scherk et al., 2007; Smith et al., 2007; Tarr et al., 2011; Ogawa et al., 2014). One meta-analysis reported that studies outside the United States had higher effect size and the baseline YMRS predicted the outcome (Tarr et al., 2011), probably because of a mathematical structural coupling effect (Fountoulakis and Kontis, 2012). Year of study publication was not associated with YMRS score change. Furthermore, the study size, number of study sites, YMRS score required for study entry, inclusion of patients with mixed mania or treatment resistance, and inclusion of inpatients vs outpatients had no significant influence on the outcome (Tarr et al., 2011).

Two recent meta-analyses attempted to rank antimanic agents according to efficacy. The first one utilized the method of multiple-treatments meta-analysis and reported that the ranking in terms of efficacy was haloperidol, risperidone, olanzapine, lithium, quetiapine, aripiprazole, carbamazepine, asenapine, valproate, and ziprasidone. According to that meta-analysis, overall, antipsychotics were significantly more effective than mood stabilizers; however, the results of that analysis do not fully support such a conclusion (Cipriani et al., 2011). This meta-analysis has been criticized both concerning the overall methodology but also concerning the incomplete list of RCTs that was utilized (Fountoulakis and Siamouli, 2012). A more balanced meta-analysis confirmed that the response to antipsychotics was greater and more rapid in comparison with lithium, valproate, or carbamazepine, but it did not confirm any difference between haloperidol and second generation antipsychotics (Yildiz et al., 2010). A more recent network meta analysis did not support the superiority of any agent vs another except for risperidone vs aripiprazole and valproate (Yildiz et al., 2015).

A meta-analysis that pooled data from 9 randomized, double-blind, placebo-controlled, acute studies of ziprasidone reported that the discontinuation rate due to adverse events or 7% or greater weight gain between ziprasidone and placebo was not significant for all psychiatric conditions. In acute mania the risk for akathisia with ziprasidone had a number needed to harm (NNH) = 12, the risk for overall EPS had a NNH = 12, and the reported somnolence had NNH = 7 (Gao et al., 2013). Finally, a recent network meta-analysis reported that aripiprazole, olanzapine, quetiapine, risperidone, and valproate had less all-cause discontinuation rates than placebo and that there is a similar efficacy profile for haloperidol, second-generation antipsychotics, and mood stabilizers (Yildiz et al., 2014) while a meta-analysis of combination studies confirmed the higher rate of adverse events in comparison with monotherapy (Galling et al., 2015).

The analysis of the data concerning the usefulness of the cholinesterase inhibitors galantamine and donepezil as well as the glutamate receptor antagonist memantine was negative (Veronese et al., 2016).

Acute Bipolar Depression

Bipolar depression is not well studied, and the common practice among clinicians is to extrapolate the clinical data and wisdom from the treatment of unipolar to bipolar depression. However, the clinical trials that examined the efficacy of various agents have raised questions about the validity of such strategy.

The agents are listed below in a historical sequence with lithium and anticonvulsants first, then antidepressants, and finally with antipsychotics on the basis of the year of the first study they were investigated.

The data on monotherapy and combination treatment for acute bipolar depression and its special characteristics are shown in Table 3.

Monotherapy

Lithium. The earlier studies on the efficacy of lithium against bipolar depression provided some positive data but are difficult to interpret (Goodwin et al., 1969, 1972; Greenspan et al., 1970; Stokes et al., 1971; Noyes and Dempsey, 1974; Noyes et al., 1974; Baron et al., 1975; Mendels, 1976; Donnelly et al., 1978; Srisurapanont et al., 1995). There is only one modern and rigorously conducted RCT (EMBOLDEN I) and it was negative for lithium while positive for quetiapine. While in this particular study the mean lithium serum levels were 0.61 mEq/lt, with 34.9% of patients having levels <0.6 mEq/lt, a posthoc analysis reported that the results were negative also in patients with lithium levels >0.8 mEq/lt and also in patients who completed the study. Furthermore, lithium level did not correlate with change in depression rating scores (Young et al., 2010).

Antiepileptics. Valproate—There are 3 small positive trials (Davis et al., 2005; Ghaemi et al., 2007; Muzina et al., 2010) and one failed (Sachs et al., 2001), that is not published and can be assessed only through 2 meta-analytic papers (Bond et al., 2010; Smith et al., 2010). Taken together, these studies suggest that there are some data (though somewhat inconsistent and not sufficient), coming from small trials supporting the efficacy of valproate (titrated up to 2500 mg/d) in bipolar depression, especially in BD-I patients and on the core symptoms of depression. There is possibly some efficacy against concomitant anxiety.

Carbamazepine—The old, small withdrawal studies concerning carbamazepine efficacy against bipolar depression were positive (Ballenger and Post, 1980; Post et al., 1983, 1986) but also suggested that plasma levels do not correlate with the treatment effect

Table 3. Acute Depression Treatment Phase, Grading on Basis of Efficacy (Treatment Phase up to 12 Weeks)

	Monotherapy				Combination					
Agent/modality (alphabetical order)	Overall	BD-I	BD-II	Depressive core	MS	Cbz	Lam	Li	Val	Anxiety
Agomelatine	-	-	-	-	5	-	-	5	5	-
Aripiprazole	3	3	-	-	-	-	-	5	-	-
Armodafinil	-	-	-	-	4	-	-	-	-	-
Bupropion	-	-	-	-	5	-	-	-	-	-
Carbamazepine	3	-	-	-	-	-	-	-	-	-
Celecoxib	-	-	-	-	5	-	-	-	-	-
Donepezil	5	-	-	-	-	-	-	5	-	-
Escitalopram	-	-	2	-	-	-	-	-	-	-
Fluoxetine	2	-	3	-	-	-	-	4	-	-
FEWP	-	-	-	-	-	4	-	-	-	-
Gabapentin	5	-	-	-	-	-	-	-	-	-
Imipramine	3	-	-	-	-	-	-	5	-	-
Ketamine	-	-	-	-	2	-	-	-	-	-
Lamotrigine	3	3	3	3	-	-	-	2	-	-
Levetiracetam	-	-	-	-	5	-	-	-	-	-
Levothyroxine (L-T4)	-	-	-	-	4	-	-	-	-	-
Lisdexamfetamine	-	-	-	-	5	-	-	-	-	-
Lithium	4	-	-	-	-	-	2	-	-	5
L-sulpiride	-	-	-	-	-	-	-	3	-	-
Lurasidone	2	2	-	3	2	-	-	-	-	3
Memantine	-	-	-	-	-	-	5	-	-	-
Modafinil	-	-	-	-	2	-	-	-	-	-
OFC	2	2	-	3	-	-	-	-	-	-
Olanzapine	1	1	-	3	-	-	-	-	-	-
Oxcarbazepine	-	-	-	-	-	-	-	4	-	-
Paroxetine	5	5	5	-	5	Neg	-	5	5	3
Phenelzin	3	-	-	-	-	-	-	-	-	-
Pioglitazone	-	-	-	-	-	-	-	2	-	-
Pramipexole	-	-	-	-	2	-	-	-	-	-
Pregnenolone	-	-	-	-	5	-	-	-	-	-
Quetiapine	1	3	3	3	-	-	-	-	-	3
Risperidone	-	-	-	-	5	-	-	-	-	5
TMS	5	-	-	-	-	-	-	-	-	-
Tranylcypromine	4	4	4	-	-	-	-	-	-	-
Valproate	3	3	5	3	-	-	-	-	-	3
Venlafaxine	4	4	4	-	-	-	-	-	-	-
Ziprasidone	5	5	-	-	5	-	5	5	5	5

Abbreviations: -, no data; Cbz, carbamazepine; ECT, electroconvulsive therapy; FEWP, Free and Easy Wanderer Plus; Lam, lamotrigine; Li, lithium; MS, Mood Stabilizer; OFC, Olanzapine Fluoxetine Combination; TMS, transcranial magnetic stimulation; Val, valproate.
The treatment options are rated according to the rating system shown in Table 1.

(Post et al., 1983). A more recent 12-week double-blind, randomized, placebo-controlled study from China had equivocal results (Zhang et al., 2007).

Lamotrigine—There are 5 trials that investigated the efficacy and safety of lamotrigine in the treatment of acute bipolar depression (SCA100223/NCT00274677, SCA30924/NCT00056277, SCA40910, SCAA2010, and SCAB2001). One included BD-II patients alone and one a mixed population of BD-I and BD-II patients. All were negative concerning the primary outcome (Calabrese et al., 1999; Goldsmith et al., 2003; Ostacher et al., 2008), although in one study lamotrigine separated from placebo on MADRS, an important secondary outcome measure (Calabrese et al., 1999). A small double-blind, randomized study with crossover series of three 6-week monotherapy evaluations in a mixed unipolar-bipolar population reported that lamotrigine was superior to placebo (Frye et al., 2000). Overall the data are negative concerning the efficacy of lamotrigine in acute bipolar depression, although the presence of a weak signal cannot be ruled out.

Antidepressant Monotherapy

Despite the fact that antidepressants have established efficacy in unipolar depression, that defines them as a class of drugs that includes different kinds of molecules, such a "class effect" does not appear to be present for bipolar depression (Fountoulakis et al., 2011b). Although the data are problematic, the use of antidepressants is neither encouraged nor prohibited by all treatment algorithms, that however consistently advise the concomitant use of an antimanic agent. The current view is that antidepressant monotherapy should not be used in bipolar depression (Vieta, 2014). Older placebo-controlled studies were mostly positive but difficult to judge on the basis of modern criteria and understanding of methodology.

An early study reported superiority of tranylcypromine vs placebo in anergically depressed patients and suggested that

tranylcypromine could be efficacious against bipolar depression since anergic depression most typically occurs in BD and in pseudounipolar affective illnesses (Himmelhoch et al., 1982). However, the methodology of this study has been criticized.

The first trial reported that fluoxetine and imipramine were efficacious vs placebo, but the interpretation of the results of this study is complicated by the concomitant use of lithium, especially in the fluoxetine group (Cohn et al., 1989). A second small trial was negative for fluoxetine and olanzapine monotherapy and also for the olanzapine-fluoxetine combination (OFC) (Amsterdam and Shults, 2005a). Another small placebo-controlled, cross-over study lasting 9 months in 10 BD-II depressed patients suggested that escitalopram might be better than placebo as monotherapy for depression and without worsening of illness course (Parker et al., 2006). The only properly conducted study on a sample of adequate size was an international trial on 740 patients with bipolar depression (both BD-I and BD-II). This study was negative for paroxetine 20 mg/d while it was positive for quetiapine. However, paroxetine produced a significant improvement in anxiety in terms of change of HAM-A scale score from baseline but was not efficacious concerning depressive symptoms in any subgroup of patients. The most frequent adverse events were dry mouth, sedation, headache, insomnia, and nausea with paroxetine treatment (McElroy et al., 2010c).

In conclusion, given that the efficacy data are conflicting along with concerns about manic/hypomanic switch, the use of antidepressant monotherapy is strongly discouraged.

Antipsychotics

Olanzapine. An international trial supported the superiority of olanzapine (5–20 mg/d) vs placebo in the treatment of bipolar depression. However, olanzapine monotherapy was proven inferior to OFC and furthermore, the analysis of individual MADRS items suggested that in contrast with OFC, olanzapine monotherapy had no effect on the core symptoms of depression (Tohen et al., 2003c). Also, a further small study was underpowered and negative (Amsterdam and Shults, 2005a). Another small study was positive (Wang et al., 2014). It is important to note that to demonstrate a true antidepressive effect, an effect on the "core items" of depression should be demonstrated (Bech, 2001; Lecrubier and Bech, 2007). To answer this question, another trial was conducted and the results again suggested that olanzapine (5–20 mg/d) was superior to placebo, but again no effect of olanzapine was observed on the core depressive symptoms according to LOCF analysis but surprisingly MMRM analysis showed a significant effect on core symptoms (Tohen et al., 2012). Overall, while olanzapine separated from placebo in 2 large clinical trials of bipolar depression, the data concerning its efficacy on the core symptoms of depression are equivocal.

Quetiapine. Overall, there are 6 studies concerning the efficacy of quetiapine in bipolar depression. All of them were positive. Quetiapine IR or XR is reported to be efficacious at dosages of both 300 and 600 mg/d. It is important to note that quetiapine had a similar efficacy in BD-I and BD-II patients as well as in rapid cycling, and it significantly improved all the MADRS items corresponding to the core symptoms of depression and also improved concomitant anxiety (Calabrese et al., 2005b; Thase et al., 2006; McElroy et al., 2010c; Suppes et al., 2010; Young et al., 2010; Li et al., 2016)

Aripiprazole. Two identically designed, 8-week, multicentre, randomized, double-blind, placebo-controlled studies (CN138-096 and CN138-146) to evaluate the efficacy and safety of aripiprazole monotherapy in depressed BD-I outpatients without psychotic features were both negative for aripiprazole (Thase et al., 2008). It has been argued that the failure of these 2 trials was due to the "catching up" of the placebo group after week 6 rather than because of a lack of efficacy of aripiprazole; however, at endpoint the placebo response in terms of MADRS score change in the aripiprazole studies (-10.6 and -11.5) was similar to what was observed also in the quetiapine studies (from -10.3 to -11.9), while the aripiprazole response (-11.9 and -12.3) was clearly lower to the response observed with quetiapine (from -15.4 to -17.4). Another confounding factor in these studies was that transient use of hypnotics was permitted but not after 4 weeks into the trial.

Ziprasidone. There are 2 negative trials (NCT00141271 and (NCT00282464) concerning ziprasidone, that were published in a single paper (Lombardo et al., 2012). The placebo responses in these trials were >50%, that might have contributed to negative results. One trial of ziprasidone in bipolar spectrum depressed patients was negative (Patkar et al., 2015).

Lurasidone. One 6-week trial in bipolar depressed patients without psychotic features reported that lurasidone (20–60 mg/d or 80–120 mg/d) was superior to placebo. Lurasidone had an effect on the core symptoms of depression. Both lurasidone groups also experienced significant improvements compared with placebo in anxiety symptoms and in patient-reported measures of quality of life and functional impairment (Loebel et al., 2014a). As this was a 6-week study, and having in mind the negative findings at endpoint (week 8) for aripiprazole while the data was positive at week 6, one might be cautious concerning the interpretation of the lurasidone data. However, the magnitude of improvement and the absolute values of lurasidone and placebo-induced change in the MADRS score argue in favor of lurasidone.

Other agents and treatment options. There is a small number of early studies on very small samples concerning the α2-adrenergic agonist clonidine, the α2-adrenergic antagonist idazoxan, and Thyrotropin-releasing hormone (Kastin et al., 1972; Jimerson et al., 1980; Osman et al., 1989). A trial concerning the usefulness of ECT has been announced (Kessler et al., 2010), but its results have not been published until now. Three other uncontrolled trials suggested that bipolar depressives respond to ECT, and conflicting results exist as to whether unipolar or bipolar depression respond better although probably to a lesser extent in comparison with unipolars (Daly et al., 2001; Medda et al., 2009; Bailine et al., 2010). A recent study showed ECT to be superior to a pharmacotherapy algorithm (Schoeyen et al., 2015). There is one negative study of rTMS (Nahas et al., 2003). There is a small positive study on the usefulness of cranial electrotherapy stimulation in BD-II depression (McClure et al., 2015).

Comparison of Treatment Options

Since only a limited number of options for the treatment of bipolar depression exist, comparison studies are limited and often they compare agents with unproven efficacy. Some early studies were too small and are problematic concerning their methodology (Coppen et al., 1972; Kessell and Holt, 1975; Aberg-Wistedt, 1982). Overall the comparison data are sparse and they suggest antidepressants are equal in efficacy but with a different adverse events profile (Baumhackl et al., 1989; Cohn et al., 1989; Himmelhoch et al., 1991; Grossman et al., 1999; Amsterdam and Garcia-Espana, 2000; Silverstone, 2001; Vieta et al., 2002). Clomipramine might be more efficacious than imipramine in refractory BD depressed patients (Thase et al., 1992).

However, the efficacy of antidepressants should be considered in combination with the negative monotherapy data for paroxetine. The frequent use of concomitant mood stabilizers as "background" medication complicates the interpretation of results. OFC is superior to olanzapine alone (Tohen et al., 2003c) and to lamotrigine (Brown et al., 2006) and has an effect on the core symptoms of depression. The comparison of paroxetine with venlafaxine suggests a higher switching risk for patients treated with venlafaxine (Vieta et al., 2002). The relatively higher risk of treatment emergent affective switches with venlafaxine compared with sertraline or bupropion has also been reported (Post et al., 2006). However, a more recent study reported that venlafaxine was equal to lithium and without any increase in the switch rate (Lorenzo-Luaces et al., 2016).

Combination and add-on treatment. Combination treatment—There is one trial in BD-I depressed patients that suggested that the OFC (6 and 25, 6 and 50, or 12 and 50 mg/d) was superior both to olanzapine monotherapy and to placebo. The OFC arm was relatively small (only 86 patients) and this was one of the limitations of the study. The analysis of individual MADRS items suggested that OFC had an effect on the core symptoms of depression. In comparison with placebo and olanzapine, the OFC arm also had a lower number of inpatients, less frequent psychotic features, more rapid cycling (that may translate in higher rates of "spontaneous remission"), and lower number of centers. All these could translate into better response and limit interpretation (Tohen et al., 2003c). Another small study was negative but also underpowered to detect any treatment effect (Amsterdam and Shults, 2005a). A second study from the United States (STEP-BD) utilized a combination treatment by adding paroxetine or bupropion or placebo to a mood stabilizer. The results suggested that the 2 antidepressant arms did not perform significantly better than placebo on top of a mood stabilizer after 26 weeks in terms of recovery rates or transient remission. The switch rates were similar as was the drop-out rate (Sachs et al., 2007), and neither response to treatment nor switching were dose dependent (Tada et al., 2015). The third trial was a 12-week double-blind, randomized, placebo-controlled study from China that reported that carbamazepine plus the herbal FEWP (36 g/d) was superior to carbamazepine alone and to placebo, but the quality of this study is considered to be low because there was no a-priori defined primary outcome (Zhang et al., 2007).

In a small study, 21 patients with acute BD-II depression, being on therapeutic levels of lithium or valproate, were randomly assigned to treatment with the dopamine D2/D3 antagonist pramipexole (n = 10) or placebo (n = 11) for 6 weeks. All subjects except for one in each group completed the study. There was a superiority of pramipexole in terms of response (60% vs 9%; $P = .02$). One subject on pramipexole and 2 on placebo developed hypomanic symptoms (Zarate et al., 2004). Another small study randomized 17 BD depressed patients to receive adjunctive inositol or placebo for 6 weeks on lithium or valproate. The results were numerically in favor of inositol in terms of response rates (44% vs 0%; $P = .053$) (Eden Evins et al., 2006b).

Add-on treatment—Overall, the data suggest that in bipolar depressed patients who experience depression while under lithium treatment, it is appropriate to add lamotrigine (van der Loos et al., 2009, 2010, 2011), the D2 antagonist L-sulpiride (Bocchetta et al., 1993), or maybe oxcarbazepine (Juruena et al., 2009) but not imipramine (Nemeroff et al., 2001). The data on adding paroxetine and amitriptyline are equivocal (Bocchetta et al., 1993; Bauer et al., 1999a; Pilhatsch et al., 2010; van der Loos et al., 2010). Imipramine and venlafaxine might pose the patients at an increased risk of switching to the opposite pole without any visible therapeutic benefit in comparison with other antidepressants (Nemeroff et al., 2001; Vieta et al., 2002)

In BD patients experiencing depression during treatment with lithium or valproate, ketamine or lurasidone could be added. Lurasidone also improves anxiety and ketamine improves suicidality in these patients. Response to a single ketamine infusion appears within minutes but does not last more than 3 to 4 days (Young et al., 2000; Diazgranados et al., 2010; Zarate et al., 2012; Loebel et al., 2014b; Xu et al., 2015a). However, there is one unpublished failed study with lurasidone as add-on to lithum or valproate (Suppes et al., 2013; Sanford and Dhillon, 2015). A small placebo-controlled adjunctive study of aripiprazole to lithium and citalopram was negative. However, the study was underpowered and the study sample was too small to detect any differences (Quante et al., 2010).

The data on the options to treat BD patients who experience a depressed episode during treatment with mood stabilizers suggest that it is not appropriate to add ziprasidone (Sachs et al., 2011), and the data are also negative also concerning bipolar spectrum depressed patients (Patkar et al., 2015). The antiepileptic agent topiramate and levitiracetam should be avoided because there is a risk of worsening depression and inducing suicidality (Fountoulakis et al., 2012c, 2015; Siamouli et al., 2014). Imipramine and venlafaxine increased the risk of switching to the opposite pole without any visible therapeutic benefits in comparison with other antidepressants (Sachs et al., 1994, 2011; Post et al., 2001, 2006; Shelton and Stahl, 2004; Schaffer et al., 2006; Altshuler et al., 2009; Saricicek et al., 2010).

The data are negative concerning the addition of memantine to lamotrigine (Anand et al., 2012) or valproate (Lee et al., 2014a, 2014b), ketamine to ECT (Abdallah et al., 2012), lisdexamfetamine to treatment as usual (McElroy et al., 2015), and the melatonergic antidepressant agomelatine to lithium or valproate (Yatham et al., 2016).

Another placebo-controlled study in 85 bipolar depressive patients with adjunctive modafinil (a wake-promoting agent; mean dose 177 mg/d) demonstrated improved outcomes of bipolar depression without switching to mania or hypomania. Both the response and remission rates were significantly higher in the modafinil group (44% and 39%) compared with the placebo group (23% and 18%) (Frye et al., 2007). Although that study did not report a higher risk for manic switches, it has been reported that modafinil could cause subclinical switches (Fountoulakis et al., 2008c). One published study for the treatment of acute BD-I depression with adjunct armodafinil (the longer lasting isomer of modafinil; dosage 150 mg/d; n = 128) on lithium, valproate, or olanzapine was positive (Calabrese et al., 2010, 2014). However 2 other studies were reported to be negative (Ostacher, 2014; Ketter et al., 2015). One small study on the efficacy of the antidiabetic agent pioglitazone as add-on to lithium in bipolar patients without diabetes mellitus was positive (Zeinoddini et al., 2015). A trial of celecoxib (400 mg/d) did not support its efficacy as an adjunct in the treatment of depressive or mixed episodes (Nery et al., 2008). One study with add-on pregnenolone (titrated to 500 mg/d) was negative (Brown et al., 2014), while a very small placebo controlled trial without an a-priori defined primary outcome suggested that adding supraphysiologic doses of levothyroxine (L-T4) to a mood stabilizer improves the outcome (Bauer et al., 2016).

Some data support the usefulness of omega-3 fatty acids as adjunctive therapy in bipolar depression but not mania, but the data are conflicting and inconclusive (Stoll et al., 1999; Chiu et al.,

2005; Frangou et al., 2006; Keck et al., 2006b; Frangou et al., 2007; Murphy et al., 2012; Sarris et al., 2012; Sylvia et al., 2013)

Although there is a wide consensus on the usefulness of ECT both against acute mania and acute bipolar depression and in refractory cases, controlled hard data are scant (Loo et al., 2010). A recent study suggests that ECT may be more effective than pharmacotherapy for treatment-resistant bipolar depression (Schoeyen et al., 2015). Another potential tool could be TMS; however, it has been poorly investigated in bipolar depression (Dell'Osso et al., 2009). Sleep deprivation and other noninvasive circadian-related interventions could be useful add-on treatments to accelerate and sustain the antidepressant response (Wu et al., 2009). One study on bright light therapy in bipolar depression was negative (Dauphinais et al., 2012).

Posthoc, Review, and Meta-Analytic Studies

Posthoc analyses of controlled trials. A posthoc analysis of the OFC and olanzapine data (Tohen et al., 2003c) reported patients with bipolar depression receiving olanzapine or OFC had greater improvement in health-related quality of life than those receiving placebo, and additionally OFC treatment is superior to olanzapine alone (Shi et al., 2004b). A second posthoc analysis of the same data set data reported that the beneficial effect was already present at day 7. A number of alternative methods of analysis of the data (pattern analysis, survival analysis, and mixed-effects regression analysis) confirmed the superiority of both olanzapine and OFC vs placebo (Dube et al., 2007). A subanalysis of Japanese subpopulation from the second olanzapine study (Tohen et al., 2012) further supported the efficacy of olanzapine in the treatment of bipolar depression (Katagiri et al., 2013). A pooled analysis of the 2 olanzapine studies (Tohen et al., 2003c, 2012) that utilized last observation carried forward data supported the efficacy of olanzapine on the core depressive items (Tohen et al., 2013).

One posthoc analysis included 2 quetiapine trials (Calabrese et al., 2005b; Thase et al., 2006) and confirmed the efficacy of quetiapine as monotherapy, in comparison with placebo, for the treatment of acute depressive episodes in BD-II disorder (Suppes et al., 2008a). Another posthoc analysis of only one of these trials (Calabrese et al., 2005b) concluded that quetiapine significantly improved quality of life from week 4 onwards as well as quality of sleep (Endicott et al., 2007). A further posthoc analysis of the same study reported that the NNT was 5 for both response and remission for quetiapine (600 and 300 mg/d) compared with placebo (Cookson et al., 2007). Another posthoc analysis of these 2 quetiapine trials reported that quetiapine was effective in BD-I depressed patients already from week 1 onwards (Weisler et al., 2008).

One posthoc analysis of pooled data from 2 similarly designed trials who assessed the impact of aripiprazole monotherapy (Thase et al., 2008) reported that at endpoint aripiprazole was not efficacious in the more severely depressed patients (Thase et al., 2012). The posthoc analysis of the 2 negative unpublished ziprasidone monotherapy trials confirmed that ziprasidone did not show superiority over placebo at week 6 in the treatment of bipolar depression and was not efficacious in the more or less severely depressed patients (Lombardo et al., 2012).

A posthoc analysis of a 6-week trial of imipramine, phenelzine or placebo reported that BD-II depressive patients respond in a similar way to unipolar patients (Agosti and Stewart, 2007).

An interesting posthoc analysis of the lurasidone studies developed a mathematical model for the drug and placebo responses and trajectories (Chapel et al., 2016), while a meta-analysis of combination studies confirmed the higher rate of adverse events in comparison with monotherapy (Galling et al., 2015). A third analysis suggested a beneficial effect of lurasidone on functioning that was partially mediated through the improvement of depressive symptoms and partially a direct effect (Rajagopalan et al., 2016).

The meta-analysis of ketamine studies support its efficacy but suggest the data are conflicting as to whether the therapeutic effect extends beyond day 4 and up to day 7 (Lee et al., 2015; Romeo et al., 2015).

Review and meta-analytic studies. A review confirmed that lamotrigine had only negative data concerning the primary outcome in acute bipolar depression (Amann et al., 2010); however, there was some kind of positive signal in some of the secondary outcomes. The pooling of raw data from the lamotrigine studies found a significant effect in terms of response (HAM-D score, RR=1.27, 95% CI 1.09–1.47, $P=.002$) and remission rates (MADRS score, RR=1.21, 95% CI 1.03–1.42, $P=.021$). There was a significant change in the MADRS total score from baseline ($P=.04$) but not in the HAM-D ($P=.08$). Baseline severity of depression seemed to play a significant role, and lamotrigine was superior to placebo in patients with HAM-D score >24 (RR=1.47, $P=.001$) but not in those with HAM-D score ≤24 (RR=1.07, $P=.445$). This meta-analysis reported an admixture of contradictory results, with lamotrigine being efficacious according to one outcome but not according to another (e.g., according to MADRS but not to HAM-D and vice versa). Also the interaction by severity was because of a higher response rate in the placebo group in the moderately ill patients, while the response rate to lamotrigine was independent of severity (Geddes et al., 2009). The efficacy of carbamazepine was supported by 2 other reviews (Srisurapanont et al., 1995; Yatham et al., 1997).

A number of meta-analyses that were published later reported that only quetiapine, OFC, lurasidone, and to a lesser extend olanzapine monotherapy exert efficacy in the treatment of bipolar depression. They also reported negative results for lamotrigine and aripiprazole, lithium as well as for adjunctive inositol (Cruz et al., 2010; Kemp et al., 2010; Tamayo et al., 2010; Vieta et al., 2010c; De Fruyt et al., 2011, 2012; Gao et al., 2011; Silva et al., 2013; Citrome et al., 2014; Mukai et al., 2014; Suttajit et al., 2014). Also, it was reported that patients who do not respond in the first 2 weeks of treatment are unlikely to respond eventually and would benefit from a change in treatment (Kemp et al., 2010).

Two meta-analyses using identical studies suggested there is some weak efficacy for valproate (Bond et al., 2010; Smith et al., 2010) and one suggested the same for aripiprazole (Fountoulakis et al., 2011a). Another one suggested that treatment with ziprasidone increases the risk for akathisia and reported somnolence that seemed to be dose dependent (Gao et al., 2013). There are 3 meta-analysis with conflicting conclusions concerning the efficacy of antidepressants (Gijsman et al., 2004; Sidor and Macqueen, 2010, 2012; Vazquez et al., 2013) However, it is clear that a class effect is not present concerning antidepressants in bipolar depression (Fountoulakis et al., 2011b). Another meta-analysis suggested that mood stabilizer monotherapy is efficacious but the addition of an antidepressant does not increase efficacy (Van Lieshout and MacQueen, 2010).

One meta-analysis that focused on depressed patients with BD-II reported that quetiapine had compelling evidence supporting its efficacy, while there was some support for the efficacy of lithium, antidepressants, and pramipexole. The data for lamotrigine were equivocal (Swartz and Thase, 2011), while some data suggest the efficacy of stimulants, especially modafinil (Corp et al., 2014), ketamine (Fond et al., 2014; McGirr et al., 2014), and antiinflammatory agents compared with

conventional therapy alone in the treatment of bipolar depression (Rosenblat et al., 2016).

Two reviews investigated the issue of the treatment of refractory bipolar depression and concluded that the available hard data are extremely scarce and most of the strategies remain essentially experimental; however, there seem to be some that are potentially efficacious and promising (Aan Het Rot et al., 2012; Sienaert et al., 2013).

One meta-analysis compared the efficacy of ECT in unipolar vs bipolar depression and identified 6 relevant studies. It reported a similar rate of response in both disorders (50.9% vs 53.2%) (Dierckx et al., 2012).

Finally, a meta-analysis reported that the probability of receiving placebo, baseline illness severity, and trial duration correlate with placebo response rates and/or clinical trial outcome in RCTs of pharmacotherapy for bipolar depression (Nierenberg et al., 2015), while another one was negative concerning the usefulness of galantamine, donepezil, and memantine (Veronese et al., 2016).

Maintenance Treatment

The efficacy data for monotherapy for the maintenance treatment phase are shown in Table 4. The data concerning the combination treatment are shown in Table 5.

Monotherapy

Lithium. There are a number of historic small studies that investigated the usefulness of lithium in the maintenance treatment of BD (Baastrup et al., 1970; Melia, 1970; Small et al., 1971; Cundall et al., 1972; Hullin et al., 1972; Persson, 1972; Prien et al., 1973b; Prien et al., 1973a; Dunner et al., 1976; Fieve et al., 1976; Fyro and Petterson, 1977; Klein et al., 1981; Christodoulou and Lykouras, 1982; Kane et al., 1982; Margo and McMahon, 1982; Mander and Loudon, 1988; Post et al., 1992). All of them reported positive findings; however, a number of drawbacks including the obsolete methodological approach and the utilization of mixed and small samples make the results of these trials difficult to interpret.

Overall there are 4 randomized placebo controlled studies concerning the efficacy of lithium in the maintenance treatment of BD. One is negative/failed (Bowden et al., 2000) and 3 are positive (Bowden et al., 2003; Calabrese et al., 2003b; Weisler et al., 2011). The fourth is a small discontinuation study (Kafantaris et al., 2004). Two of the positive studies support the usefulness of lithium in the prevention of manic but not depressive episodes irrespective of the polarity of the index episodes (Bowden et al., 2003; Calabrese et al., 2003b). The third study also supports its usefulness in the prevention of depressive episodes (Weisler et al., 2011). There are no data on the efficacy concerning the prevention of mixed episodes or for rapid cycling patients. It is important to note that the study samples were not enriched for response to lithium. On the contrary, one study had a sample enriched for response to quetiapine (Weisler et al., 2011), while 2 others had samples enriched for lamotrigine (Bowden et al., 2003; Calabrese et al., 2003b), that, however, is not efficacious against acute mania. There are some problems with the design of the studies, especially concerning the magnitude of improvement during the acute treatment phase and the duration the patients were required to be stable before entering the double-blind phase. With a few exceptions, most are essentially relapse prevention, not maintenance studies.

Antiepileptics. Valproate—As mentioned above, there is one properly conducted trial (Bowden et al., 2000) in that valproate was the agent under investigation. Lithium served as active control, and since, as shown above, lithium has proven efficacy during the maintenance phase of BD, this specific trial is best considered to be a failed study and not negative for valproate.

Carbamazepine—Concerning carbamazepine, there is only one small placebo controlled study. Although carbamazepine was effective in 60% of cases relative to 22% in the placebo group, the differences were not significant likely due to lack of power. Further, there were methodological issues with the study design and hence, the data are difficult to interpret (Okuma et al., 1981).

Lamotrigine—Overall there are 3 placebo controlled RCTs concerning the efficacy of lamotrigine in the maintenance treatment of BD. Two of them suggest lamotrigine is efficacious in the prevention of depressive but not manic episodes irrespective of the polarity of the index episodes (Bowden et al., 2003; Calabrese et al., 2003b). There are no data concerning index mixed episodes. The only study in rapid cycling patients was negative concerning the primary outcome (Calabrese et al., 2000). All studies were enriched for tolerability to lamotrigine, but one should keep in mind that lamotrigine is neither efficacious against acute mania nor acute bipolar depression. There were some problems with the design of the studies, particularly concerning the magnitude of improvement during the acute treatment phase and the dura-

Table 4. Monotherapy Treatment during the Maintenance Phase, Grading on Basis of Efficacy

Agent/modality (alphabetical order)	Index episode	Enriched sample	Any episode	Manic	Depressive
Aripiprazole	m*	Yes	-	1	5
Carbamazepine	-	-	4	4	4
Fluoxetine	d	Yes	-	-	2
Imipramine	d	?	5	5	5
Lamotrigine	m/d	Yes	1	3	1
Lithium	m/d	No	1	1	3
Olanzapine	m	Yes/No	1	1	1
Paliperidone	m	Yes	1	2	5
Quetiapine	m/d	Yes	2	2	2
Risperidone, LAI	m	Yes	1	1	5
Valproate	m	Yes	4	4	3

Abbreviations: -, no data; m, mania/mixed; d, depression; m/d, both mania and depression.
The treatment options are rated according to the rating system shown in Table 1. Enriched sample: the sample is enriched on the basis of remission after treatment with the agent under consideration during the acute phase (index episode).

Table 5. Combination treatment during the maintenance phase, grading on basis of efficacy.

			Overall				Manic			Depressive			
Agent/modality (alphabetical order)	Index episode	Enriched sample	MS	Lam	Li	Val	MS	Lam	Li	MS	Lam	Li	Val
Aripiprazole	m*	Yes	2	5	-	5	2	5	-	5	5	-	-
CBT	D	No	2	-	-	-	-	-	-	-	-	-	-
Gabapentin	-	-	-	-	-	-	4	-	-	-	-	-	-
Imipramine	D	?	-	-	5		-	-	-	-	-	-	-
Lamotrigine	m/d	Yes	-	-	4		-	-	-	-	-	-	5
Lithium	m/d	No	-	4	-	-	-	-	-	-	-	-	-
Memantine	-	-	-	-	-	5	-	-	-	-	-	-	-
N-acetyl cysteine	D	Yes	4	-	-	-	-	-	-	-	-	-	-
Olanzapine	M	Yes/No	4	-	-	-	-	-	-	-	-	-	-
Oxcarbazepine	-	-	-	-	5	-	-	-	5	-	-	5	-
Paroxetine	-	-	3	-	-	-	-	-	-	3	-	-	-
Perphenazine	m	Yes	5	-	-	-	-	-	-	-	-	-	-
Phenytoin	euth	No	2	-	-	-	-	-	-	-	-	-	-
Quetiapine	m/d	Yes	1	-	-	-	1	-	-	1	-	-	-
Risperidone, long-acting injectable	m	Yes	2	-	-	-	2	-	-	-	-	-	-
Valproate	m	yes	-	-	-	-	-	-	-	-	5	-	-
Ziprasidone	m	yes	2	-	-	-	-	-	-	-	-	-	-

Abbreviations: -, no data; CBT, cognitive behavioral therapy; Cbz, carbamazepine; d, depression; Lam: Lamotrigine; Li: Lithium; m, mania/mixed; m/d, both mania and depression; MS, mood stabilizer; Val, valproate.
The treatment options are rated according to the rating system shown in Table 1. Enriched sample: the sample is enriched on the basis of remission after treatment with the agent under consideration during the acute phase (index episode).

tion the patients were stable before entering the double-blind phase. Essentially they were relapse prevention, not maintenance studies.

Antidepressants. There are 2 small, old negative studies concerning the efficacy of imipramine (Prien et al., 1973a; Kane et al., 1982), while on the contrary, 3 other small studies in BD-II patients provide some support for the usefulness of fluoxetine monotherapy in the prevention of depressive episodes (Amsterdam et al., 1998; Amsterdam and Shults, 2005b, 2010).

Antipsychotics. Olanzapine—Three trials provide suport for the efficacy of olanzapine in the prevention of manic, depressive, or mixed episodes in patients with an index manic or mixed episode that responded to olanzapine treatment during the acute phase (Tohen et al., 2006; Berwaerts et al., 2012a; Vieta et al., 2012). There are some data to support the notion that the efficacy of olanzapine is not restricted to those patients who responded to olanzapine during the acute phase. Its long-term effects in rapid cycling patients are unknown.

Aripiprazole—There are 2 trials that support the efficacy of aripiprazole in the prevention of manic but not depressive episodes in BD patients after an index manic or mixed episode who responded to aripiprazole during the acute phase (Keck et al., 2006a; Keck et al., 2007). These 2 trials utilize a methodology that satisfies stringent criteria concerning the definition of "maintenance" treatment.

Quetiapine—There is one published positive study that investigated the efficacy and safety of quetiapine IR monotherapy (300–800 mg/d) as maintenance treatment in BD-I patients compared with switching to placebo or lithium. The time to recurrence of any mood event was significantly longer for both quetiapine and lithium vs placebo. Both quetiapine and lithium significantly increased time to recurrence of both manic and depressive episodes compared with placebo (Weisler et al., 2011). A second study in patients who had recovered from bipolar depression reported that quetiapine prevented depressive but not manic episodes (Young et al., 2014).

Paliperidone—There is one positive study that supports the usefulness of paliperidone in the prevention of manic but not depressive recurrences in patients with index manic or mixed episodes who responded to paliperidone during the acute phase (Berwaerts et al., 2012a).

Risperidone long-acting injectable (RLAI)—Two studies support the efficacy of RLAI in the prevention of manic but not depressive episodes in BD-I patients with a manic or mixed index episode who responded to oral risperidone or RLAI during the acute phase (Quiroz et al., 2010; Vieta et al., 2012).

Conclusion of monotherapy trials. Lithium, olanzapine, quetiapine, aripiprazole, paliperidone, and RLAI are efficacious in the prevention of manic episodes in patients who recovered from an index manic or mixed episode. Olanzapine and quetiapine are also efficacious in the prevention of depressive episodes. Quetiapine was efficacious irrespective of the index episode. Olanzapine was also efficacious in the prevention of mixed episodes. There is a lack of data concerning carbamazepine or valproate.

Lamotrigine is efficacious in the prevention of depressive but not manic episodes irrespective of index episode. It was not efficacious in the prevention of mixed episodes or in rapid cycling patients. The literature does not support the efficacy of imipramine, while, on the contrary, it gives some support for the efficacy of fluoxetine but only in BD-II patients.

All except lithium and olanzapine were proven efficacious only in samples enriched for response or tolerability during the acute phase. Except from the negative data for lamotrigine there are no data concerning rapid cycling patients. Also, except from the data concerning olanzapine, there are no data concerning

specifically the prevention of mixed episodes or the response of patients with an index mixed episode.

Comparison of Treatments

Lithium vs others. There are a number of studies comparing lithium with carbamazepine (Placidi et al., 1986; Watkins et al., 1987; Lusznat et al., 1988; Stoll et al., 1989; Small et al., 1991; Coxhead et al., 1992; Simhandl et al., 1993; Denicoff et al., 1997; Hartong et al., 2003) including the MAP study (Greil et al., 1997; Greil and Kleindienst, 1999a, 199b; Kleindienst and Greil, 2000, 2002), and overall the data suggested that both agents are comparable in terms of efficacy. There are some data in favor of a superiority of lithium in the treatment of more "classic" patients, but in the rest of patients the 2 agents seem to be comparable. Lithium was also comparable to valproate in terms of prevention of mood episodes (Bowden et al., 2000; Calabrese et al., 2005a) and suicidality (Oquendo et al., 2011) to olanzapine (Tohen et al., 2005) and also to aripiprazole (El-Mallakh et al., 2012)

Furthermore, there was a difference in the clinical profiles of lithium and lamotrigine. As mentioned before, 3 placebo-controlled RCTs suggest that lamotrigine was more efficacious in the prevention of depressive episodes and lithium in the prevention of manic, hypomanic, and mixed episodes (Bowden et al., 2003; Calabrese et al., 2003b).

When compared with antidepressants, the available data suggest that lithium is superior to imipramine for the prevention of depression in BD-I patients episodes (Prien et al., 1973a; Prien et al., 1984) but inferior to fluoxetine in BD-II patients (Amsterdam and Shults, 2010).

A maintenance study reported equal efficacy between venlafaxine and lithium in the prevention of depressive relapses, although there was a tendency of better performance for venlafaxine (Amsterdam et al., 2015)

Antiepileptics vs others. The studies comparing valproate with lithium have already been discussed above (Bowden et al., 2000; Calabrese et al., 2005a; Oquendo et al., 2011). Two trials suggested valproate is comparable with olanzapine (Tohen et al., 2003a) and with a similar cost to healthcare system (Zhu et al., 2005). Carbamazepine has been studied only in comparison with lithium, and these studies have been discussed previously in the paragraph concerning lithium (Placidi et al., 1986; Watkins et al., 1987; Lusznat et al., 1988; Small et al., 1991; Coxhead et al., 1992; Simhandl et al., 1993; Denicoff et al., 1997; Greil et al., 1997; Greil and Kleindienst, 1999a; Kleindienst and Greil, 2000, 2002; Hartong et al., 2003).

Olanzapine vs others. The comparison of olanzapine with lithium (Tohen et al., 2005) and valproate (Tohen et al., 2003a; Zhu et al., 2005) has been discussed above.

One study that constituted the extension of an acute phase trial suggested that olanzapine is comparable with asenapine (McIntyre et al., 2010a), while another suggested that it is superior to paliperidone ER (Berwaerts et al., 2012a) and to long-acting risperidone (Vieta et al., 2012).

Other comparisons. The comparisons of aripiprazole (El-Mallakh et al., 2012), fluoxetine (Amsterdam and Shults, 2010), imipramine (Prien et al., 1984), and lamotrigine (Bowden et al., 2003; Calabrese et al., 2003b) with lithium, and of asenapine (McIntyre et al., 2010a), paliperidone, and risperidone with olanzapine (Berwaerts et al., 2012a; Vieta et al., 2012) have been discussed previously.

One 25-week RCT comparing the OFC vs lamotrigine in the prevention of bipolar depression reported that bipolar depressive patients who responded to OFC do better on long-term OFC in comparison with spontaneously improved patients on long-term lamotrigine (Brown et al., 2009). The result is difficult to interpret as there was an enrichment of the OFC arm, but not the lamotrigine arm. Finally, one study compared the efficacy of venlafaxine in the prevention of bipolar vs unipolar depression and reported no difference between groups (Amsterdam and Garcia-Espana, 2000).

Combination and Add-On Treatment

Combination treatment. There are 3 early studies that investigated the combination of lithium with another agent. The lithium plus imipramine combination was not more efficacious than lithium monotherapy (Kane et al., 1982; Prien et al., 1984) and lithium or carbamazepine monotherapy was not inferior to their combination that, however, was more efficacious in rapid cycling patients (Denicoff et al., 1997). Also the combination of lithium, carbamazepine, or valproate with perphenazine was not better than mood stabilizer monotherapy; on the contrary, combination treatment was associated with a shorter time to depressive relapse, more drop-outs, and increased rates of dysphoria and depressive symptoms (Zarate and Tohen, 2004). Similarly negative were the results for the lithium or valproate combination with olanzapine (Tohen et al., 2004) while, on the contrary, the combination with quetiapine had significant advantages irrespective of index episode, mood stabilizer and rapid cycling status (Vieta et al., 2008a; Suppes et al., 2009). Positive results were also reported for their combination with ziprasidone (Bowden et al., 2010). Results were negative for aripiprazole plus valproate (Woo et al., 2011) or lamotrigine (Carlson et al., 2012).

The OFC was similar to lamotrigine in terms of incidence of relapse, but overall bipolar depressive patients who responded to OFC do better on long-term OFC in comparison with spontaneously improved patients on long-term lamotrigine (Brown et al., 2009). Lamotrigine plus divalproex was not superior to lamotrigine alone concerning the time to depressive episode (Bowden et al., 2012).

The open-label BALANCE study results neither reliably confirmed nor refuted a benefit of valproate-lithium combination therapy compared with lithium monotherapy, but clearly demonstrated that it is superior to valproate alone (Geddes et al., 2010). Another study reported that risperidone or olanzapine adjunctive therapy for 24 weeks is beneficial but continuation of risperidone beyond this period does not reduce the risk of relapse. Whether continuation of olanzapine beyond this period reduces relapse risk remains unclear but the potential benefit needs to be weighed against an increased risk of weight gain (Yatham et al., 2015).

Overall, there is no compelling data that combination treatment in general does better than monotherapy. Patients stabilized on combination treatment might, however, do worse if shifted to monotherapy, and combination treatment with quetiapine or ziprasidone plus a mood stabilizer might work better than a mood stabilizer alone.

Add-on treatment. A small study supported the adding of phenytoin to treatment as usual (Mishory et al., 2003) as did another small one for gabapentin (but not on top of antipsychotics) (Vieta et al., 2006). The data are negative for the addition of oxcarbazepine (Vieta et al., 2008c) and equivocal for lamotrigine (van der Loos et al., 2011) to lithium. Negative data were also reported from a trial of adjunctive pramipexole to treatment as usual (TAU) in stabilized BD patients with the aim to improve neurocognition (Burdick et al., 2011), and from a trial of N-acetyl cysteine on TAU in patients after an index episode of bipolar depression (Berk et al., 2012). It is interesting that adjunctive

RLAI on TAU significantly prolongs the time to relapse in rapid cycling patients (Macfadden et al., 2009). Adding aripiprazole to lithium or valproate also supplied positive results (Marcus et al., 2011).

It is reported that patients who respond to treatment with lithium, valproate, or carbamazepine plus antidepressants are more likely to maintain response with continuation of the combined treatment; however, those patients who manifest only a partial acute response are unlikely to further improve when the same treatment is continued (Altshuler et al., 2009). Also adjunctive asenapine to lithium or valproate was well tolerated for up to 52 weeks, but no efficacy data were reported from that trial (Szegedi et al., 2012).

Two trials investigated the efficacy of adjunctive N-acetyl cysteine (NAC). The first one randomized 75 BD patients during the maintenance phase and reported that NAC treatment caused a significant improvement on the MADRS score in comparison with placebo ($P = .002$). Improvements were lost after washout. There was no effect of NAC on time to a mood episode and no significant between-group differences in adverse events (Berk et al., 2008). The second randomized 14 patients (not all of them with high depression scores) and reported a superiority of the NAC group vs placebo in terms of remission ($P = .031$) (Magalhaes et al., 2011b). One maintenance study supported the usefulness of ramelteon in the prevention of relapse in BD patients (Norris et al., 2013). Negative results have been reported for the usefulness of memantine in patients on valproate treatment (Lee et al., 2014b).

There are some studies suggesting that there is a role for various nutritional supplements such as n-3 fatty acids, chromium, choline, magnesium, and tryptophan alone or in combination with pharmacotherapies for the treatment of BD, but the data are of low quality (Sylvia et al., 2013).

Posthoc, Reviews, and Meta-Analytic Studies

Posthoc analyses. A number of posthoc analyses exist and attempt to answer questions that the original papers did not address. Posthoc analysis can be informative but can also be a major source of publication bias (Vieta, 2007). A subanalysis of the MAP study reported that lithium was superior in classical BD-I patients and comparable with carbamazepine in the rest. An additional subanalysis including mixed states as an additional nonclassical feature confirmed the results (Greil et al., 1998).

Concerning the usefulness of antidepressants, one posthoc analysis suggested that the discontinuation rate for any reason was lower among patients in the divalproex group taking a selective serotonin re-uptake inhibitor (SSRI) than among patients in the placebo group taking an SSRI (Gyulai et al., 2003b), while the application of 4 different remission criteria suggested that the application of different definitions of remission does not make any significant difference concerning the results (Pae et al., 2012). The addition of an atypical antipsychotic-antimanic agent in some BD patients might help to reduce suicidal ideation (Houston et al., 2006). Olanzapine might be more beneficial if started at an earlier stage of the disease (Ketter et al., 2006), and it is also efficacious in patients with an index mixed episode (Tohen et al., 2009).

Concerning lithium, it has been reported that only at plasma levels between 0.6 and 1.2 mEq/lt it is efficacious in the prevention of both manic and depressive episodes (Nolen and Weisler, 2013). Another posthoc analysis did not confirm its efficacy in the prevention of depressive episodes while it confirmed the efficacy of lamotrigine in the prevention of both manic and depressive episodes irrespective of index episode (Calabrese et al., 2003a; Goodwin et al., 2004). These results still held true when early relapses that occurred in the first 90 or 180 days were excluded from the analysis (Calabrese et al., 2006). The lack of efficacy of lithium in a subgroup of patients might be due to lithium induced thyroid function abnormalities in a subpopulation of patients (Frye et al., 2009). Overall, lamotrigine performed better in comparison with lithium in terms of remission and the persistence of subsyndromal symptoms (Frye et al., 2006). Some positive results for NAC were also suggested by 2 posthoc analysis (Magalhaes et al., 2011a, 2013).

Review and meta-analyses. One review confirmed the efficacy of lithium but reported that there is no definitive evidence as to whether or not lithium has an anti-suicidal effect (Burgess et al., 2001). A more recent meta-analysis confirmed the antisuicidal effect of lithium vs placebo but not its superiority over other agents except carbamazepine (Cipriani et al., 2013). Two other studies support the usefulness of RLAI (Bobo and Shelton, 2010) and of ziprasidone for the maintenance treatment of BD-I disorder in adults as an adjunct to lithium or valproate (Citrome, 2010). Another review identified 4 issues that limit the interpretation of trials (insufficient duration, enriched sample, possible conflation with iatrogenic adverse effects by abrupt medication discontinuation with beneficial effects on treatment, and a low overall completion rate) (Tsai et al., 2011).

Concerning meta-analysis, the first one for carbamazepine failed to prove the prophylactic efficacy (Dardennes et al., 1995). A second one concluded that the data for oxcarbazepine are of very low quality not allowing firm conclusions (Vasudev et al., 2008). A fair number of meta-analyses focused on lithium. One confirmed its efficacy but failed to find sufficient evidence to prove that a lithium-withdrawal relapse phenomenon exists, that is patients relapse soon after stopping lithium and the symptomatology turns refractory to treatment (Davis et al., 1999). Another one supported an antisuicidal efficacy of lithium (Tondo et al., 2001). Three others confirmed the prophylactic antimanic efficacy of lithium but were equivocal for the prophylactic efficacy against depressive episodes (Burgess et al., 2001; Geddes et al., 2004; Severus et al., 2014).

Furthermore, a number of meta-analytic studies confirmed the prophylactic antimanic efficacy of specific agents and the antidepressant of others. It is important to mention that among other more or less expected results, the antidepressant efficacy of valproate and imipramine was supported (Beynon et al., 2009) as well as of lithium (Popovic et al., 2010), while the prophylactic antidepressant efficacy of olanzapine was questioned (Cipriani et al., 2010). Antipsychotics might be superior to lithium and anticonvulsants but with more adverse effects (Vazquez et al., 2015a, 2015b).

The issue of combination treatment has been the focus of 2 meta-analyses. They both reported negative conclusions for the addition of antidepressants (Ghaemi et al., 2008; Beynon et al., 2009). A third analysis suggested that no monotherapy was associated with a significantly reduced risk for both manic/mixed and depressive relapse, and only quetiapine plus lithium or divalproex was associated with a significantly reduced risk for relapse towards both the manic/mixed and depressive pole (Vieta et al., 2011). This specific meta-analysis also pointed out that the majority of studies included samples enriched for response to a specific agent during the acute phase.

Finally, pharmaco-epidemiological data suggest that valproate and lithium might have a protective effect against any psychiatric hospitalization for patients with BD in a real world setting, while lamotrigine and carbamazepine might exert

protective effects solely against depressive and manic episodes, respectively (Joas et al., 2015).

Treatment of Mixed Episodes

Mixed episodes are no longer accepted as a diagnostic entity by DSM-5; instead "mixed features" is included as a specifier and this creates a degree of confusion for future treatment recommendations, since the 2 concepts differ significantly (Fountoulakis, 2015d). So far, mixed episodes have been combined with pure manic episodes in RCTs and results have been reported together. Only a few papers, usually posthoc analyses, report the results concerning mixed episodes separately. Unfortunately all data on mixed episodes stem from trials of acute mania and only one trial reports on the efficacy of lurasidone in bipolar depressive patients with mixed features. That trial supported the efficacy of lurasidone in these patients for the improvement of both depressive and manic symptoms (McIntyre et al., 2015; Suppes et al., 2015). Another important limitation is that the results reported usually concern only the manic but not the depressive component of the mixed episode (Fountoulakis et al., 2012b). The ranking of the data for the treatment of mixed episodes is shown in Table 6.

Treatment of Acute Mixed Episodes

Aripiprazole and carbamazepine were found efficacious in the treatment of both the manic and the depressive component of acute mixed episodes (Keck et al., 2003b; Weisler et al., 2004, 2005, 2006; Sachs et al., 2006; Suppes et al., 2008b). Ziprasidone was also found to be efficacious against both components, but the definition of mixed states was different from the DSM.

Olanzapine and valproate were reported to be efficacious against mania but the data are inconclusive concerning the depressive component (Tohen et al., 1999, 2000; Baker et al., 2003; Baldessarini et al., 2003b; Shi et al., 2004a; Bowden et al., 2006; Ghaemi et al., 2007; McIntyre et al., 2009b). The posthoc analysis of the 2 bipolar depressive trials suggested that olanzapine was efficacious in those patients with mixed features suggesting an effect also on the depressive component (Tohen et al., 2014). Furthermore, risperidone but not asenapine is reported to be efficacious against the manic component, but no data exist concerning their efficacy on the depressive component (Khanna et al., 2005; McIntyre et al., 2009b). A posthoc analysis suggested that asenapine but not olanzapine improved the quality of life in mixed patients (Michalak et al., 2014), and another 2 suggested that asenapine improved both the manic and depressive component in comparison with placebo and was also found superior to olanzapine concerning the manic but not the depressive component (McIntyre et al., 2013; Berk et al., 2015). However, a more recent trial was negative (Landbloom et al., 2016). Paliperidone was efficacious only against the manic component (Vieta et al., 2010c; Berwaerts et al., 2012b). One study for quetiapine was a failed one (Cutler et al., 2011).

The combination of olanzapine olanzapine plus lithium or valproate have positive data concerning both components (Tohen et al., 2002b; Baker et al., 2004; Houston et al., 2006, 2009, 2011). In mixed depression the OFC was comparable with olanzapine and both were superior to placebo, but due to the small number of subjects the report does not permit to derive conclusions (Tohen et al., 2003c; Benazzi et al., 2009). The data concerning the combination of haloperidol or risperidone plus lithium or valproate were negative (Sachs et al., 2002). Overall it seems that second generation antipsychotics (SGAs) are effective in treating acute mixed episodes of BD, with predominant manic symptoms. Their efficacy in treating depressed mixed episodes remains unclear (Muralidharan et al., 2013).

The only trial in patients in bipolar depressive episode with mixed features supported the efficacy of lurasidone in these patients for the improvement of both depressive and manic symptoms (McIntyre et al., 2015; Suppes et al., 2015).

Maintenance Treatment of Mixed Bipolar Episodes

The data so far suggest that olanzapine prolongs time to relapse into any episode in patients with an index mixed episode (Tohen et al., 2006, 2009) while on the contrary, lithium and valproate had negative results in patients with a dysphoric manic index episode (Bowden et al., 2005a). Additionally, the data are in support of the combination of quetiapine plus lithium or valproate (Vieta et al., 2008a; Suppes et al., 2009) but are negative concerning aripiprazole in patients with an index mixed episode (Yatham et al., 2013a).

Table 6. Treatment of Mixed Episodes

	Acute Phase				Maintenance Phase					
	Monotherapy		Combination with MS			Combination				
Agent/modality (alphabetical order)	Manic component	Depressive component	Manic component	Depressive component	Monotherapy	MS	Cbz	Lam	Li	Val
Aripiprazole	3	3	-	-	-	2	-	5	-	-
Asenapine	4	4	-	-	-	-	-	-	-	-
Carbamazepine	3	3	-	-	-	-	-	-	-	-
Celecoxib	-	-	5	5	-	-	-	-	-	-
Haloperidol	-	-	5	5	-	-	-	-	-	-
Lithium	5	-	-	-	-	-	-	-	-	-
OFC	4	4	-	-	-	-	-	-	-	-
Olanzapine	3	3	2	2	1	-	-	-	-	-
Paliperidone	3	5	-	-	-	-	-	-	-	-
Quetiapine	5	-	-	-	-	-	-	-	-	-
Risperidone	3	-	5	5	-	-	-	-	-	-
Valproate	3	4	-	-	-	-	-	-	-	-
Ziprasidone	4	4	-	-	-	-	-	-	-	-

Abbreviations: -, no data; Cbz, carbamazepine; Lam, lamotrigine; Li, lithium; MS, mood stabilizer; OFC, olanzapine-fluoxetine combination; Val, valproate.
The treatment options are rated on the basis of efficacy according to the rating system shown in Table 1.

Treatment of Rapid Cycling Patients

The treatment of rapid cycling patients constitutes a challenge. Often their course frustrates the therapist and the evaluation of treatment is difficult because of the rapid switching from one pole to another (Fountoulakis et al., 2013). The ranking of the treatment of rapid cycling patients is shown in Table 7.

Treatment of Acute Episodes in Rapid Cycling Patients

Olanzapine is effective in reducing symptoms of mania and was well tolerated in rapid cycling BD-I patients as shown by a secondary analysis (Sanger et al., 2003). The pooling of data from 2 RCTs reported that improvement of mania with olanzapine was similar in rapid cyclers and non-rapid cyclers. However, rapid cyclers showed an earlier response (Vieta et al., 2004). One trial was also positive concerning aripiprazole in acutely manic rapid cycling patients (Sachs et al., 2006).

Although one study on acute mania in rapid cycling patients was a failed one (Cutler et al., 2011), one a priori planned subanalysis of data from rapid cycling patients with acute BD-I or BD-II depression suggested that quetiapine monotherapy (300–600 mg/d) was effective and well tolerated (Vieta et al., 2007). The posthoc analysis of the rapid cycling subsample of bipolar depressives from the BOLDER study confirmed this (Cookson et al., 2007), and finally the subanalysis of the data from a small number of depressed rapid cycling BD patients again suggested that 300 mg of quetiapine monotherapy was superior to placebo (Suppes et al., 2010).

It seems that lithium has a week but positive effect (Young et al., 2010) and also there are some positive but equivocal data for valproate (Muzina et al., 2010). On the other hand, the data are clearly negative for paroxetine (McElroy et al., 2010c).

The combination of lithium and divalproex was not effective and the further addition of lamotrigine did not seem to add anything in Terms of efficacy (Kemp et al., 2012b)

Relapse Prevention in Rapid Cycling Patients

For the prevention phase, the data so far suggest that divalproex is not more effective than lithium (Calabrese et al., 2005a) and also that the combination of lithium plus divalproex is not better than lithium alone (Kemp et al., 2009). One small study reported that the combination of lithium plus carbamazepine did better than either agent alone (Denicoff et al., 1997). It is interesting that the data are negative for lamotrigine, although in some secondary outcomes there was a beneficial signal especially in BD-II patients (Calabrese et al., 2000). Overall, the widely believed concept among clinicians that divalproex is more effective than lithium in the long-term management of rapid-cycling BD was not supported by a trial on 139 patients (Findling et al., 2005).

One posthoc analysis suggested that aripiprazole was efficacious (Muzina et al., 2008). There are no data on other antipsychotics in monotherapy concerning the maintenance phase. A posthoc analysis reported that rapid cycling patients did less well during the extended observation period than nonrapid cycling patients, regardless of treatment and that overall olanzapine and divalproex appeared comparable (Suppes et al., 2005).

Another study confirmed the efficacy and safety of quetiapine add-on to lithium or divalproex in the prevention of mood episodes in rapid cycling BD-I patients with most recent episode manic/mixed or depressive (Vieta et al., 2008a). There was a North American study with a similar design as the previous one reporting similar results (Suppes et al., 2009). A large controlled trial that evaluated adjunctive maintenance treatment with RLAI on TAU in 240 BD-I patients with at least 4 mood episodes in the 12 months prior to study entry yielded positive results (Macfadden et al., 2009).

The results of the STEP-BD support a role of antidepressants in the development of rapid cycling in a subpopulation of BD patients (Schneck et al., 2008; Ghaemi et al., 2010). A similar conclusion came from earlier randomized controlled study of rapid cycling patients using a double-blind on-off-on-off design with the use of tricyclic antidepressants (Wehr et al., 1988)

Finally, the data are negative concerning the administration of 6 g/d of ethyl-eicosapentanoate as augmentation of treatment with mood stabilizers in rapid cycling patients with bipolar depression (Keck et al., 2006b).

One meta-analysis suggested that lithium is at least partially efficacious in rapid cycling patients (Kupka et al., 2003), another one suggested there is no clear advantage of any treatment option vs the others (Tondo et al., 2003), while a third one proposed that some atypical antipsychotics (especially quetiapine and olanzapine) may be considered as the first-line treatment options (Cruz et al., 2010). The meta-analysis of 20 studies published from 1974 to 2002 comparing subjects with rapid and nonrapid cycling BD reported that in contrast to common beliefs, lithium prophylaxis has at least partial efficacy in a considerable number of rapid cyclers, especially when antidepressants are avoided. Hypothyroidism may be associated with mood destabilization in vulnerable patients (Kupka et al., 2003).

Table 7. Treatment of Rapid Cycling Patients during the Different Phases of BD

Agent/modality (alphabetical order)	ACUTE mania	Depression	Maintenance
Aripiprazole	3	-	3
Carbamazepine	-	-	2 (Li + Cbz)
Lamotrigine	-	-	5
Lithium	4	3	2 (Li, Li + Cbz)
Olanzapine	3	-	-
Paroxetine	-	5	-
Quetiapine	3	2	2 (Quet+ Val/Li)
Risperidone, long-acting injectable	-	-	2 (RLAI+TAU)
Valproate	4	4	-

Abbreviations: -, no data; Cbz, carbamazepine; Li, lithium; Quet, quetiapine; RLAI, risperidone long-acting injectable; TAU, treatment as usual; Val, valproate. The treatment options are rated on the basis of efficacy according to the rating system shown in Table 1.

Treatment of Special Conditions

Treatment of Comorbid Conditions

Comorbidities are common in bipolar patients and often need more elaborated therapeutic interventions (Fountoulakis, 2015e, 2015f, 2015g).

Treatment of comorbid substance abuse disorder (SUD). There are 2 placebo controlled trials suggesting that the combination of valproate and lithium in BD patients with co-occurring alcohol dependence improves both mood and alcohol use symptoms (Salloum et al., 2005, 2007) and that lithium treatment in BD adolescents improves mood and substance use symptoms (Cerullo and Strakowski, 2007). Lithium can be used for the treatment of concomitant substance and polysubstance abuse (Geller et al., 1992, 1998), and quetiapine and risperidone can reduce drug craving

(Nejtek et al., 2008). On the contrary, the data concerning quetiapine for alcohol abuse are negative (Brown et al., 2008; Sherwood Brown et al., 2014). For bipolar patients with alcohol dependence, the opiate receptor antagonist naltrexone could be useful (Sherwood Brown et al., 2009), and a preliminary report is positive for acamprosate (Tolliver et al., 2012) but negative concerning the treatment of any substance use with NAC (Bernardo et al., 2009). One trial on the usefulness of citicoline in the treatment of cocaine use was inconclusive (Brown et al., 2015) as was one study with the use of topiramate in alcohol dependence (Sylvia et al., 2016).

There are open-label medication trials that provide limited support to quetiapine, aripiprazole, bupropion, and lamotrigine for the treatment of BD patients with cocaine dependence. Also, aripiprazole might be helpful in patients with alcohol use disorders (Cerullo and Strakowski, 2007; Sepede et al., 2014).

Overall, while some data are available for alcohol, cannabis, and cocaine use comorbid with BD, the evidence is sparse concerning heroin, amphetamine, methamphetamine, and polysubstance SUD comorbid with BD (Beaulieu et al., 2012).

Treatment of comorbid anxiety and disorders. A posthoc analysis of anxiety symptoms with data from 2 RCTs of 8-week duration of quetiapine (300 or 600 mg/d) (Calabrese et al., 2005b; Thase et al., 2006) reported that at endpoint there was no difference between treatment groups and placebo concerning the total HAM-A score, but there was a difference both for the psychic and the somatic anxiety subscale scores in comparison with placebo ($P < .001$) (Lydiard et al., 2009). Also, quetiapine XR (50–300 mg/d) was superior both to divalproex ER (500–3000 mg/d) and placebo in the improvement of anxiety in BD patients with comorbid panic attacks or generalized anxiety disorder (GAD) (Sheehan et al., 2013). In another study, again quetiapine (300 or 600 mg/d) and paroxetine (20 mg/d) produced a significant improvement in anxiety in terms of change of HAM-A scale score from baseline in acutely depressed BD patients (McElroy et al., 2010c). Of note, quetiapine (300–600 mg/d) also significantly improved the HAM-D score from baseline, while this was not the case with paroxetine (600–1800 mg/d; $P = .279$) (Young et al., 2010). However, another study was negative for quetiapine concerning its effect on depression in BD patients with GAD (Gao et al., 2014).

Lurasidone (20–60 mg/d; n = 166 or 80–120 mg/d) also significantly improved anxiety symptoms in comparison with placebo (Loebel et al., 2014a). On the contrary, risperidone monotherapy was not an effective anxiolytic for BD patients with comorbid panic disorder or GAD in doses of 0.5–4 mg/d over 8 weeks of treatment (Sheehan et al., 2009), and similar results were obtained with ziprasidone (Suppes et al., 2014).

The data concerning divalproex (rapidly titrated up to 2500 mg/d, as tolerated, to a target serum level of 50–100 mg/dL) are equivocal, because the only positive study was based on a very small study sample (25 outpatients with BD-I depression) (Davis et al., 2005).

It is reasonable to suggest that also benzodiazepines can be used as adjunctive medication for sedation or for the treatment of anxiety, although abuse, tolerance, and dependence constitute important problems. Although approved for the treatment of GAD, pregabalin has no data in BD. However, again it is reasonable to suggest it might be a useful agent for the treatment of anxiety disorders that commonly accompany BD and could substitute for benzodiazepines. A significant advantage is that it is not metabolized by the liver.

There is one study suggesting that adjunctive topiramate could be beneficial in the treatment of BD with comorbid obsessive compulsive disorder, but the overall design and reporting of results does not permit reliable conclusions (Sahraian et al., 2014).

The ranking of the treatment of comorbid anxiety is shown in Table 3.

Weight gain. Topiramate is not effective in the treatment of BD per se; however, it is unique because of its ability to cause weight loss at dosages of 50 to 200 mg/d. A review reported that more than 70% of patients taking topiramate for a mean duration of 5 months lost a mean of 5 to 6 kilograms (Arnone, 2005). However, topiramate might cause de novo depression and suicidality in some patients, although no completed suicides related to topiramate have been reported (Fountoulakis et al., 2012c).

Treatment of agitation. Probably most clinicians would choose antipsychotics in severely agitated bipolar patients, and this option is supported by a double blind clinical trial that reported that intramuscular haloperidol (5–10 mg) was equal in efficacy but faster acting in comparison with intramuscular clonazepam (1–2 mg) in agitated mania at 0, 30, and 60 minutes (Chouinard et al., 1993). Similarly, i.m. olanzapine (10 mg, first 2 injections; 5 mg, third injection) was reported to be superior to lorazepam (2 mg, first 2 injections; 1 mg, third injection) for the control of agitation in manic patients. Already 2 hours after the first injection, patients treated with olanzapine showed a significantly greater reduction in scores on all agitation scales compared with patients treated with either placebo or lorazepam (Meehan et al., 2001).

Valproate oral loading of 20 mg/kg/d was reported to be comparable with haloperidol 0.2 mg/kg/d for the treatment of exited manic patients in a single blind study and the effect was evident within 3 days from starting (McElroy et al., 1996). Overall, valproate loading up to 30 mg/kg/d was reported to be safe and well tolerated (Hirschfeld et al., 1999).

Inhaled loxapine exerted an antiagitation effect at 10 minutes at both the 5- and 10-mg doses and was superior to placebo at all time points measured. For safety reasons it has been recommended that inhaled loxapine should be restricted to a single dose in 24 hours and needs to be subject to a Risk Evaluation and Mitigation Strategy program (Citrome, 2012; Kwentus et al., 2012). In Europe, 2 doses are allowed (the second must be given 2 hours after the initial inhalation) (Popovic et al., 2015).

The issue of agitation with aripiprazole is controversial. As an adverse event it is not reported in the dataset and on the contrary, aripiprazole is a recommended evidence based treatment against agitation associated with schizophrenia or bipolar mania (Sanford and Scott, 2008; Gonzalez et al., 2013; Citrome et al., 2016). However, it has been reported under naturalistic conditions (Di Lorenzo et al., 2007) and especially in vulnerable populations such as elderly patients (Coley et al., 2009). Agitation has also been described when initiating aripiprazole in patients after prolonged treatment with potent D2 blocking agents that may result in an upregulation of postsynaptic dopamine receptors (Lea et al., 2007). However, a major obstacle for a fair estimate of the rate of agitation with aripiprazole is that akathisia can easily be mistaken as agitation (Thomas et al., 2015), especially by less experienced raters.

Treatment of Neurocognitive Deficits

The presence of a significant neurocognitive deficit in BD patients has been solidly shown and it concerns all phases of the disorder, including periods of euthymia (Tsitsipa and Fountoulakis, 2015). Galantamine may have specific benefits for episodic memory, but not processing speed, in patients with cognitive impairment as part of BD (Ghaemi et al., 2009). One study reported that pramipexole

may improve neurocognition in euthymic patients only (Burdick et al., 2012) while the data are negative for NAC (Dean et al., 2012).

Adjunctive intranasal insulin (40 IU q.i.d.; n = 34) had a beneficial effect on executive function but not on the other neurocognitive measures in euthymic patients (McIntyre et al., 2012a). Also adjunctive mifepristone, which is a synthetic steroid, at 600 mg/d improved spatial working memory in BD depressed patients, and this was evident also 7 weeks after the cessation of treatment (Watson et al., 2012)

ECT was reported to produce an improvement in neurocognitive function similar to that of algorithm-based pharmacological treatment (Kessler et al., 2014).

Suicide

There is much discussion concerning the potential antisuicidal efficacy of specific drugs and especially of lithium. However, almost all the data come from studies of naturalistic and epidemiological nature and no controlled studies exist.

There is only one posthoc analysis that investigated suicidality in BD-I patients during treatment with olanzapine in combination with lithium or divalproex. In mixed patients with residual suicidality, suicidal thoughts were associated with somatic discomfort, agitated depression, and psychosis. It seems that combination therapy with olanzapine plus lithium (n = 36) vs lithium alone (n = 22) significanlty reduced the score in the suicidal item of the HAM-D by 58% vs 29% ($P < .05$) within 1 week and all associated symptoms within 2 weeks by averages of 31% vs 12% ($P < .05$) (Houston et al., 2006). The analysis of pharmaco-epidemiological data suggests that treatment with lithium but not with valproate is associated with lower suicidality (Goodwin et al., 2003; Song et al., 2015).

Nonbiological Treatment Options

There are some but overall limited data concerning the usefulness of specific adjunctive psychotherapies (Reinares et al., 2014; Miziou et al., 2015). Research so far has focused on acute depression and the maintenance phase but not on acute mania. These studies suffer from the same limitations and methodological problems as all psychotherapy trials do. There is no universally accepted standardized method to conduct this kind of study and blinding and the nature of the control intervention are unresolved limitations. The grading of these treatment options is shown in Table 8.

Cognitive-Behavioral Therapy (CBT)

The overall data for the long-term efficacy of CBT either as monotherapy or as add on to psychoeducation and in comparison with TAU are negative concerning relapse prevention. However, there are some positive results for the acute depressive phase in BD (Ball et al., 2006; Scott et al., 2006; Zaretsky et al., 2008; Costa et al., 2011; Gomes et al., 2011; Meyer and Hautzinger, 2012; Gonzalez Isasi et al., 2014). A posthoc analysis suggested that CBT could be more effective than TAU in patients with <12 previous episodes, but less effective in those with more episodes (Scott et al., 2006). In BD patiens with insomnia, CBT for insomnia was superior to psychoeducation concerning manic relapses (Harvey et al., 2015).

Psychoeducation

The data on adjunctive psychoeducation suggest that in comparison with TAU or nonspecific intervention, it prevents relapse to both poles if administered to patients in clinical remission (Perry et al., 1999; Colom et al., 2003, 2009; Lobban et al., 2010; de Barros et al., 2013) but it has no effect on biological rhythms (Cardoso Tde et al., 2015). Again a posthoc analysis suggested that patients with more than 7 episodes did not show significant improvement with group psychoeducation for time to recurrence, and those with more than 14 episodes did not benefit from the treatment in terms of time spent ill (Colom et al., 2010). A systematic review confirmed the above (Bond and Anderson, 2015).

Interpersonal and Social Rhythm Therapy (IPSRT)

Overall there are no convincing data on the usefulness of IPSRT during the maintenance phase of BD; however, there are some data suggesting that if applied early and particularly already during the acute phase, it might prolong the time to relapse (Frank et al., 2005, 2008; Swartz et al., 2012; Inder et al., 2015).

Family Focus Treatment

Overall the literature supports the idea that interventions that focus on families and caregivers exert a beneficial impact especially on family members, but the effect on the patients themselves is controversial and uncontrolled. Probably it improves issues like treatment adherence and family dynamics (Miklowitz et al., 2000, 2003; Rea et al., 2003; Reinares et al., 2004, 2008; D'Souza et al., 2010)

Intensive Psychosocial Intervention

"Intensive" psychotherapy is another option but it is of unknown efficacy with limited research support (Miklowitz et al., 2007a, 2007b). The term refers to up to 30 sessions of CBT, IPSRT, or family focus treatment within 9 months.

Cognitive Remediation and Functional Remediation

The data are positive in improving functioning, that is the critical endpoint, but mostly negative concerning cognitive outcomes

Table 8. Grading of the Evidence for the Efficacy of Nonbiological Treatment Options

	Efficacy					
Intervention	Relapse/ recurrence	Manic symptoms	Depressive symptoms	Anxiety	Neurocognition	Overall functioning
CBT	5	-	3	-	-	-
Psychoeducation	3	5	5	-	-	3
IPSRT	4	-	-	-	-	-
Family intervention	5	5	5	-	-	5
Intensive psychosocial intervention	-	-	-	-	-	-
Cognitive remediation	5	5	5	-	5	5
Mindfulness based interventions	5	5	5	3	-	-

Abbreviations: -, no data; CBT, cognitive behavioral treatment; IPSRT, InterPersonal and Social Rhythms Therapy.
The treatment options are rated according to the rating system shown in Table 1.

when using cognitive remediation techniques as add on to TAU in BD patients (Martinez-Aran et al., 2011; Lahera et al., 2013; Torrent et al., 2013), although a more recent posthoc analysis was promising (Sole et al., 2014).

Mindfulness-Based Interventions (MBCT)

Overall the data do not support a beneficial effect of MBCT on the core symptoms of BD but also suggest that MBCT could be useful in the reduction of anxiety in BD patients. So far there are no data supporting its efficacy in the prevention of recurrences (Williams et al., 2008; Ives-Deliperi et al., 2013; Perich et al., 2013a, 2013b).

Internet-Based Interventions

There is only one randomized trial that compared a completely Internet-based preventive program for BD, adjunctive to usual pharmacological management vs a control intervention. The results suggested no differences between treatment groups (Barnes et al., 2015). The design of the study precludes deriving general conclusions for the efficacy of web-based approaches. Another study that combined psychoeducation with mobile phone technology did not show any benefit vs paper and pencil method, however this could mean that a mobile phone approach could be an important alternative without compromising the outcome (Depp et al., 2015).

Safety Issues With Pharmacotherapy of BD

A comprehensive grading of all agents in terms of their safety and tolerability profile is shown in Table 9.

Lithium

Lithium has a narrow therapeutic window concerning its dosage and plasma levels (recommended plasma level 0.6–1.2 mmol/L), and laboratory testing and thorough investigation before starting lithium treatment (ECG; kidney function etc.) is necessary. Unfortunately this often delays the initiation of treatment. Adverse events are more frequent with higher doses, while "rebound mania" has been described upon withdrawal. The most frequent adverse events include neurological, endocrinological (more often from the thyroid), cardiovascular, renal, gastrointestinal, hematological, and dermatological manifestations, and lithium intoxication is not rare. In clinical practice patients often complain of sedation and tremor and sometimes a decline in creative thinking (Shaw et al., 1986; Engelsmann et al., 1988; Stoll et al., 1996). A general negative impact of lithium on neurocognitive function has been reported (Karniol et al., 1978; Kropf and Muller-Oerlinghausen, 1979; Reus et al., 1979; Squire et al., 1980; Connelly et al., 1982; Lund et al., 1982; Shaw et al., 1987; Engelsmann et al., 1988; Maarbjerg et al., 1988; Kocsis et al., 1993; Kessing, 1998; Honig et al., 1999; Bora et al., 2007; Senturk et al., 2007; Goldberg, 2008). It seems that there is a complex relationship between lithium treatment, female gender, hypothyroidism, and rapid cycling (Cowdry et al., 1983; Bauer and Whybrow, 1990; Bauer et al., 1990; Gyulai et al., 2003a; Fountoulakis et al., 2008b). While most authors argue that lithium is neuroprotective, a neurotoxic effect is also possible in the long term, even at therapeutic levels, especially in combination with antipsychotics (Fountoulakis et al., 2008b). Comprehensive guidelines concerning lithium treatment and optimal therapeutic serum levels are available and should be applied (Malhi et al., 2011), and a recent review provides up-to-date information on its safety (Murru et al., 2015).

Antiepileptics

The recommended therapeutic valproate serum concentration is 50 to 150 mg/mL. It is not recommended to be used in women of childbearing age because of the high frequency of unplanned pregnancies in bipolar females and the relatively high teratogenicity of valproate. Other potential acute side effects are weight gain and hair loss. Its use has been associated with polycystic ovary syndrome (PCOS). It is to be noted however, that similar to epilepsy, there is an association between PCOS and major psychiatric disorders, including BD. An increased risk can also be demonstrated in their siblings suggestive of shared familial factors between PCOS and psychiatric disorders (Cesta et al., 2016).

The typical dosage of carbamazepine in the treatment of acute mania is 600 to 1800 mg/d (serum concentration 4–12 mg/mL). After several weeks under carbamazepine, an induction of hepatic enzymes (CYP 3A4) occurs and the drug levels drop and may require additional upward dose titration (Bertilsson and Tomson, 1986). The dosage-related adverse effects include double or blurred vision, dizziness, sedation, ataxia, vertigo, gastrointestinal disturbances, cognitive impairment, hematological effects, and Stevens-Johnson syndrome including its related dermatologic effects (Tohen et al., 1991, 1995; Blackburn et al., 1998).

The most significant drawback of lamotrigine treatment is the need to initiate it at 25 mg/d for 2 weeks, then 50 mg/d for another 2 weeks and then by increments of 25 to 50 mg/d thereafter to avoid a moderately high incidence of rash (Seo et al., 2010).

Carbamazepine decreases lamotrigine concentrations by approximately 50%, and in combination therapy, lamotrigine can be started with higher dosages and faster titration. Vice versa, when combined with valproate a slower titration scheme is needed for lamotrigine, carbamazepine induces the metabolism of other agents as well, for example, risperidone (Ono et al., 2002).

It is also important to note the adverse effects of topiramate because although it is not used in the treatment of BD per se, it is often administered in BD patients in order to lose weight or to treat a comorbid substance abuse disorder. It is reported that topiramate impairs attention, verbal memory, psychomotor speed, and word-finding even at very low dosages (25–50 mg/d). This impairment is reversible after discontinuation of the drug (Salinsky et al., 2005; Goldberg, 2008).

An important recent development was the safety warning by the FDA after a meta analysis that suggested that antiepileptics might double the suicidal risk (FDA, 2008). The field remains uncertain, with some reports and authors supporting the FDA warning (Nilsson et al., 2002; Mula and Sander, 2007; Gibbons et al., 2009; Andersohn et al., 2010; Arana et al., 2010; Olesen et al., 2010; Patorno et al., 2010; VanCott et al., 2010; Ziemba et al., 2010; Wen et al., 2011; Fountoulakis et al., 2012c; Pugh et al., 2012; Siamouli et al., 2014). It is important to note that suicidality data came from the registration of adverse events rather than from systematically collected data (Hesdorffer and Kanner, 2009). However, it seems clear that topiramate, lamotrigine, and levetiracetam are related to increased suicidality in nonpsychiatric patients and this should be the focus of further research.

Antipsychotics

The adverse effects of FGAs include EPS, tardive dyskinesia, and hyperprolactinaemia and the life-threatening but rather rare

Table 9. Grading of Treatment Options According to Safety Issues (According to the System Shown in Table 1)

Agent/modality (alphabetical order)	Grade	Comments
Agomelatine	2	Liver enzymes induction
Allopurinol	2	Swelling of mouth and lips, severe skin rashes, infections, eye irritation, hepatitis, appetite and weight loss, and painful or bloody urination
Aripiprazole	1	
Armodafinil/modafinil	2	Stimulant, risk for abuse
Asenapine	1	
Bupropion	1	
Carbamazepine	2	Hepatic enzymes induction, many adverse effects
Cariprazine	1	
Celecoxib	1	
Chlorpromazine	1	
Clozapine	3	Potentially lethal agranulocytosis, metabolic syndrome
Donepezil	1	
ECT	2	Not preferred by patients, mild cognitive problems
Escitalopram	1	
Eslicarbazepine	1	
Fluoxetine	1	
FEWP	1	
Gabapentin	1	
Haloperidol	2	EPS, Tardive dyskinesia, neuroleptic malignant syndrome, switch risk
Imipramine	2	Cardiac side effects, many adverse effects, switch risk
Ketamine	3	Stimulant
L-sulpiride	1	
Lamotrigine	2	Good overall tolerability but potentially lethal skin reaction that can be avoided by slow titration
Levetiracetam	3	Induction of suicidality
levothyroxine (L-T4)	2	Mild cardiovascular, skin and bone adverse effects
Licarbazepine	1	
Lisdexamfetamine	3	High risk for abuse and dependence
Lithium	2	Many adverse effects, weight gain, toxicity
Loxapine inhalant	1	
Lurasidone	1	
N-acetyl cysteine	1	
Memantine	1	
Medroxyprogesterone	1	
Modafinil	2	Stimulant, risk for abuse
Olanzapine	2	Metabolic syndrome
Oxcarbazepine	1	
Paliperidone	1	
Paroxetine	1	
Perphenazine	2	Switch risk, EPS, tardive dyskinesia, neuroleptic malignant syndrome
Phenytoin	2	Many adverse effects
Phenelzin	2	Many adverse effects
Pimozide	2	EPS, tardive dyskinesia, neuroleptic malignant syndrome
Pioglitazone	2	Not recommended in patients with diabetes mellitus type I and in liver disease. Absolute contraindication in heart failure patients
Pramipexole	2	Adverse effects include the induction of problematic behaviours and psychotic symptoms
Pregnenolone	2	Not well studied
Quetiapine	1	
Risperidone	1	
RLAI	1	
Sertraline	1	
Tamoxifen	3	Deep vein thrombosis, cognitive disorder
TMS	1	
Topiramate	3	Induction of depression and suicidality
Tranylcypromine	2	Many adverse effects
Valproate	1	Cautious use in women of childbearing age
Venlafaxine	2	Switch risk
Verapamil	1	
Ziprasidone	2	QTc prolongation, patients should undergo cardiologic examination before receiving ziprasidone

Abbreviations: ECT, electroconvulsive therapy; EPS, extrapyramidal signs; FEWP, Free and Easy Wanderer Plus; RLAI, risperidone long-acting injectable; TMS, transcranial magnetic stimulation.

neuroleptic malignant syndrome, while the most frequent side effects of chlorpromazine are EPS, tardive dyskinesia, postural hypotension, and hepatotoxicity.

On the other hand, the most significant problem with some of the SGAs is weight gain, hyperlipidaemia, and diabetes mellitus. The treatment of these somatic conditions is difficult and the methods proposed have produced rather unsatisfactory results so far. Hyperprolactinaemia and EPS are the most frequent adverse effects with amisulpride. Akathisia and EPS are the adverse effects most often reported with aripiprazole.

Concerning olanzapine, the most frequent adverse effects include dry mouth, weight gain, increased appetite, diabetes mellitus and metabolic syndrome, and somnolence. The main adverse effects of quetiapine are persistent sedation and weight gain, however, to a lower extent than olanzapine. Maybe the XR formulation of quetiapine induces less sedation in comparison with the IR formulation (Riesenberg et al., 2012). The main side effects of risperidone are dose-related EPS, weight gain, sedation, and hyperprolactinemia. Somnolence, akathisia, and EPS as well as a significant QTc prolongation are the main adverse effects of ziprasidone treatment; however, ziprasidone is not associated with the metabolic syndrome (Kemp et al., 2012a).

Reports on antipsychotics concerning adverse effects on neurocognition are rare and conflicting (Holmes et al., 2008; Goldberg and Chengappa, 2009; Pan et al., 2011). There are data suggesting that an executive function deficit is correlated with years of exposure to antipsychotic drugs (Zubieta et al., 2001). This latter finding could reflect either the toxic effect of chronic psychosis, the toxic effect of long-term medication, or both. Current antipsychotic treatment in BD patients is reported to relate to worse performance in sustained attention and visuomotor speed, across all executive function tests as well as in semantic fluency, verbal learning, and recognition memory, even when studies were controlled for differences in clinical features (King, 1994; Altshuler et al., 2004; Frangou et al., 2005; Jamrozinski et al., 2009).

Antidepressants

There is a number of different adverse effects caused by antidepressants. Most of them are not severe and may cause significant burden to the patients but usually improve with time (NHS, 2014).

The adverse effects of SSRIs and serotonin and norepinephrine re-uptake inhibitors include agitation, shakiness, anxiety or feeling of being sick, indigestion, stomach aches, diarrhoea or constipation, loss of appetite, dizziness, insomnia and other sleep disorders, or, on the contrary, hypersomnia and sedation, headache, loss of libido, weight gain, excessive sweating, hyponatriaemia (especially in the elderly), and sexual dysfunction. The adverse effects of tricyclic antidepressants include: dry mouth, blurred vision, constipation, dysuria, drowsiness, dizziness, weight gain, excessive sweating, and heart rhythm problems. A rare but potentially life-threatening adverse event is the serotonin syndrome whose symptoms include confusion, agitation, muscle twitching, sweating, shivering, and diarrhea. Rare but serious cases may manifest with very high fever, epileptic fits, arrhythmia, and coma. All classes of antidepressants have been linked to an increased risk of developing type 2 diabetes, but the causality is uncertain.

There is a warning issued by the FDA (black box warning) concerning the risk of suicidality in pediatric patients taking SSRIs for depression (Libby et al., 2007), and a number of papers suggest that antidepressants are related to an increased risk for suicidal behavior (Rouillon et al., 1991; Khan et al., 2000, 2001, 2003; Luoma et al., 2002; Baldessarini et al., 2003a; Healy, 2003) but not for completed suicide (Whittington et al., 2004). This might constitute one of the most interesting paradoxes of our contemporary psychiatry, since antidepressants prevent suicidal behavior among severely ill, frequently suicidal "real life" unipolar depressives but may provoke such behavior sometimes in less severe, actually nonsuicidal unipolar depressives (Leon et al., 1999; Angst et al., 2002; Yerevanian et al., 2004; Simon et al., 2006; Gibbons et al., 2007). It has been suggested that antidepressants induce suicidality essentially only in pseudo-unipolar patients (Akiskal and Benazzi, 2005; Rihmer and Akiskal, 2006; Perlis et al., 2007b), while the data from the STAR*D trial suggest the presence of a genetic vulnerability predisposing to the manifestation of new suicidal ideation after antidepressant treatment (Laje et al., 2007; Perlis et al., 2007a, 2007b).

Switching to the Opposite Pole

It is widely accepted among psychiatrists that both antidepressants and FGAs can induce a mood switch to the opposite pole, or a chronic, dysphoric, mixed, or irritable state in BD patients and may accelerate episode frequency and/or may cause other forms of course destabilization in patients with BD. However, hard evidence is limited and the bulk of evidence comes from chart reviews and retrospective and open studies. A comprehensive summary of the risk to induce switching for all agents during the 3 phases of treatment is shown in Table 10.

The literature suggests that without the concomitant use of an antimanic agent the switch rate to mania or hypomania is around 20 to 40% (Bottlender et al., 2001, 2004; Goldberg and Truman, 2003), while with the concomintant use of an antimanic

Table 10. Risk of Various Agents to Induce the Opposite Mood Pole (Switch Risk)

	Treatment phase		
Agent/modality (alphabetical order)	**Acute mania**	**Depression**	**Maintenance**
Aripiprazole	5	5	5
Asenapine	5	-	5
Bupropion	-	5	-
Carbamazepine	5	-	5
ECT	-	4	-
Escitalopram	-	5	-
Fluoxetine	-	-	5
Haloperidol	4	-	4
Imipramine	-	3	2
Lamotrigine	5	-	5
Lithium	5	-	5
OFC	-	5	5
Olanzapine	5	5	5
Paliperidone	5	-	5
Paroxetine	-	5	5
Perphenazine	4	-	2
Quetiapine	5	5	5
RLAI	5	-	5
Sertraline	-	-	5
Valproate	5	-	5
Venlafaxine	-	3	-
Ziprasidone	5	-	5

Abbreviations: -, no data; ECT, electroconvulsive therapy; OFC, olanzapine-fluoxetine combination; RLAI, risperidone long-acting injectable.
The treatment options are rated in an analogous way to the rating system shown in Table 1 as "efficacy to induce the opposite pole."

Table 11. Levels of Recommendation Concerning Monotherapy in Acute Mania and Recommended Dosages for Medication Options

Agent/modality	Recommendation level	Recommended dosage (mg/d)
Aripiprazole	1	15–30 mg/d
Asenapine	1	10–20 mg/d
Cariprazine	1	3–12 mg/d
Paliperidone	1	3–12 mg/d
Quetiapine	1	400–800 mg/d
Risperidone	1	2–6 mg/d
Valproate	1	1200–3000 mg/d (loading dose 20–30 mg/kg body weight; serum level 75–150 mg)
Carbamazepine	2	600–1200 mg/d (serum level 4–15 mg/L)
Haloperidol	2	5–20 mg/d
Lithium	2	600–1200 mg/d (serum level 0.8–1.3 mmol)
Olanzapine	2	10–20 mg/d
ECT	3	
Oxcarbazepine	4	900–1800 mg/d
Chlorpromazine	4	300–1000 mg/d
Pimozide	4	2–16 mg/d
Tamoxifen	4	40–80 mg/d
Ziprasidone	4	80–160 mg/d`
Eslicarbazepine	5	
Gabapentin	5	
Lamotrigine	5	
Licarbazepine	5	
TMS	5	
Topiramate	5	
Verapamil	5	

Abbreviations: ECT, electroconvulsive therapy; NR: not recommended; TMS, transcranial magnetic stimulation.

Table 12. Recommendation levels for combination treatment for acute mania

Agent/modality	MS	Li	Val	Cbz	FGAs
Asenapine	1	-	-	-	-
Haloperidol	2	2	2	2	-
Olanzapine	2	-	2	5	-
Aripiprazole	2	-	-	-	-
Medroxyprogesterone	5	-	-	-	-
Celecoxib	-	-	2	-	-
Quetiapine	3	3	-	-	-
Risperidone	3	-	5	-	-
Tamoxifen	4	4	-	-	-
Allopurinol	5	2	-	-	5
Paliperidone	5	-	-	-	-
Ziprasidone	5	-	-	-	-
Gabapentin	5	-	-	-	-
Topiramate	5	-	-	-	-
Lamotrigine	-	-	-	-	-
Lithium	-	-	-	2	-
Oxcarbazepine	-	4	-	-	-
Valproate	-	-	-	-	2

Abbreviaitons: Cbz, carbamazepine; FGA, first generation antipsychotic; Li, lithium; MS, mood stabilizer; Val, valproate.

agent the rate is reduced to 14% or below (Nemeroff et al., 2001; Post et al., 2001, 2006; Harel and Levkovitz, 2008; Licht et al., 2008; Tondo et al., 2010). More recent reports suggest that switching

Table 13. Recommendation Levels for Monotherapy in Rapid Cycling Patients in an Acute Manic Episode

Agent/modality	Recommendation level
Quetiapine	3
Aripiprazole	3
Olanzapine	3
Valproate	4
Lithium	4

Table 14. Recommendation Levels for Monotherapy in Patients in an Acute Manic Episode and the Specific Effect on Concomitant Depressive Symptoms (Mixed Features) and Psychotic Features

	Therapeutic effect on		
Agent/modality	Overall on manic episode	Concomitant Depressive symptoms	Psychotic symptoms
Quetiapine	1	3	3
Risperidone	1	3	3
Aripiprazole	1	5	3
Asenapine	1	5	-
Olanzapine	2	3	3
Carbamazepine	2	5	-
Cariprazine	1	5	-
Haloperidol	2	5	3
Lithium	2	5	3
Tamoxifen	4	5	4
Valproate	1	5	-
Ziprasidone	2	5	3

is exclusively related to antidepressant monotherapy, while the concomitant use of an antimanic agent has a robust protective effect (Viktorin et al., 2014). The results of the STEP-BD support the potentially harmful role of antidepressants in the long-term course of BD (Truman et al., 2007; El-Mallakh et al., 2008, 2015). According to that study switching to the opposite pole was not dose dependent (Tada et al., 2015). However, a number of larger RCTs reported negative data concerning switching with paroxetine and bupropion (Sachs et al., 2007), fluoxetine, even as monotherapy in BD-II patients (Amsterdam et al., 2004), and citalopram (Schaffer et al., 2006). There are some data suggesting a higher risk of switching while on treatment with venlafaxine (Amsterdam and Garcia-Espana, 2000; Vieta et al., 2002; Altshuler et al., 2006, 2009; Leverich et al., 2006; Post et al., 2006) and imipramine (Himmelhoch et al., 1991; Nemeroff et al., 2001; Silverstone, 2001), but a more recent study reported that venlafaxine was equal to lithium and without any increase in the switch rate (Lorenzo-Luaces et al., 2016).

It is important to mention that switching to mania or hypomania during treatment of comorbid OCD (White et al., 1986; Steiner, 1991; Vieta and Bernardo, 1992; Rihmer et al., 1996; Perugi et al., 2002) or panic disorder with antidepressants have been reported (Pecknold and Fleury, 1986; Sholomskas, 1990).

The switch risk is probably as high as 18.2% in the short term and 35.6% during the continuation phase (Post et al., 2003) and is higher in BD-I patients in comparison with BD-II (14.2% vs 7.1% in acute trials and 23.4% vs 13.9% in maintenance studies). The rates of switching in unipolar patients are lower than those of bipolar (1.5% in acute trials and 6.0% in maintenance studies) (Bond et al., 2008; Tondo et al., 2010).

Table 15. Recommendation Levels for Monotherapy and Combination Treatment in Patients in a DSM-IV-TR Mixed Episode and the Specific Effect on the Manic and the Depressive Component

	Monotherapy		Combination with MS	
Agent/modality	Manic component	Depressive component	Manic component	Depressive component
Olanzapine	3	3	2	2
Asenapine	3	3	-	-
Aripiprazole	3	3	-	-
Carbamazepine	3	3	-	-
Valproate	3	4	-	-
Paliperidone	3	5	-	-
Risperidone	3	-	5	5
OFC	4	4	-	-
Ziprasidone	4	4	-	-
Lithium	5	-	-	-
Quetiapine	5	-	-	-
Celecoxib	-	-	5	5
Haloperidol	-	-	5	5

Abbreviations: MS, mood stabilizer; OFC, olanzapine-fluoxetine combination.

Haloperidol and perphenazine treatment have been associated with the development of dysphoria and depression, although the data are inconclusive for haloperidol (Tohen et al., 2003b; Zarate and Tohen, 2004). On the contrary, SGAs do not appear to induce depression, while some authors suggest they possess a mild protective property against switching (Tohen et al., 2003c; Amsterdam and Shults, 2005a; Calabrese et al., 2005b; Keck et al., 2005; Thase et al., 2006; Benazzi et al., 2009). A recent meta-analysis reported that treating acute mania with SGAs is associated with a 42% lower risk of switch to depression than with haloperidol. Nevertheless, caution should be taken when considering this to be a class effect, as only olanzapine, quetiapine, and ziprasidone may show these advantages (Goikolea et al., 2013b).

Overall there are no data to suggest a generalized and class effect for antidepressants or FGAs concerning the induction of an affective switch. There are negative data concerning all SSRIs and SGAs studied and positive data only concerning venlafaxine, imipramine, and perphenazine. Some authors believe that at least the switch risk and perhaps also the risk for rapid cycling and new-onset suicidality have been overinterpreted (Grunze, 2008), and thus the issue of switching is still open and further research is needed. Also negative for the presence of a treatment-induced switch are the longitudinal data of Jules Angst (Angst, 1985). For a safe use of antidepressants in BD, clinicians may follow the recommendations of the International Society for Bipolar Disorders Task Force (Pacchiarotti et al., 2013).

Review of Existing Guidelines for BD

A number of treatment guidelines were identified and their reference lists were utilized (APA, 1994, 1995, 2002; Suppes et al., 1995, 2001, 2002, 2003; Frances et al., 1996; 1997; AACAP, 1997; Goodwin et al., 1997, 2003, 2009, 2016; Jobson, 1997; Kusumakar et al., 1997; McClellan and Werry, 1997; Gilbert et al., 1998; Barreira et al., 1999; Bauer et al., 1999b; Rush et al., 1999, 2003; Dennehy, 2000; Goldberg, 2000; Sachs et al., 2000; Allen et al., 2001; Montgomery, 2001; Grunze et al., 2002, 2003, 2004, 2009, 2010, 2011, 2013; Licht et al., 2003; Hirschfeld, 2005; Yatham et al., 2005, 2006, 2008, 2009, 2013b, 2013c; National Collaborating Centre for Mental Health, 2006; O'Dowd, 2006; Nolen et al., 2008; Jon et al., 2009; Ng et al., 2009; Beaulieu et al., 2012; Bond et al., 2012; McIntyre et al., 2012b; Rosenbluth et al., 2012; Schaffer et al., 2012; Mohammad and Osser, 2014; Malhi et al., 2015; Ostacher et al., 2015a; Woo et al., 2015). An additional source was the National Institute of Clinical Excellence (NICE) guideline concerning BD (NICE, 2014), while the latest version of the guidelines of the British Association of Psychopharmacology (Goodwin et al., 2016) were included, although they were published after the date of last literature search.

A description of the most important and most recent guidelines (after 2005) will be included in the text that follows. In Tables 17, 21, and 25 there is a detailed description of difference between the current CINP guidelines and previously developed guidelines by other bodies.

American Psychiatric Association Treatment Guidelines for BD

In 2008 the APA developed a draft of new guidelines after a thorough review of the literature. However, they were never published because of unresolved issues pertaining to the conflict of interest.

The Canadian Network for Mood and Anxiety Treatments and International Society on Bipolar Disorder Guidelines

The most recent 2013 version of the Canadian Network for Mood and Anxiety Treatments and International Society on Bipolar Disorder guidelines (Yatham et al., 2013c) suggests that for the treatment of acute manic episodes the first line recommendation is monotherapy with lithium, divalproex, divalproex ER, olanzapine, risperidone, quetiapine, quetiapine XR, aripiprazole, ziprasidone, asenapine, or paliperidone ER, and adjunctive therapy with risperidone, quetiapine, olanzapine, aripiprazole, asenapine on lithium, or divalproex. The second line includes monotherapy with carbamazepine, carbamazepine ER, ECT, or haloperidol and combination therapy with lithium plus divalproex. The third line of treatment includes monotherapy with chlorpromazine, clozapine, oxcarbazepine, tamoxifen, or cariprazine and combination therapy with lithium or divalproex plus haloperidol, lithium plus carbamazepine, or adjunctive tamoxifen. They do not recommend monotherapy with gabapentin, topiramate, lamotrigine, verapamil, or tiagabine and combination therapy with risperidone or olanzapine plus carbamazepine.

Table 16. Precise Evidence-Based Alrogithm to Treat Acute Manic Episodes on the Basis of Specific Clinical Characteristics

Step	First	Second	Third	Fourth	Fifth
All cases	Discontinue treatment with antidepressants				
Rapid cycling	Start with aripiprazole or quetiapine monotherapy. In nonpsychotic cases valproate is also an option Take into consideration the previous history of psychotic features.	Olanzapine or lithium monotherapy	Combination treatment of lithium or valproate with quetiapine, or risperidone.	Apply ECT on top of pharmacological treatment. Monotherapy with chlorpromazine, pimozide, or tamoxifen. Options are also combination treatments of lithium or valproate plus tamoxifen or the combination of risperidone or oxcarbazepine plus lithium	Various combinations of medication according to anecdotal knowledge or the personal experience of the therapist, ECT if not applied earlier
Nonrapid cycling with psychotic features	Start with aripiprazole, cariprazine, paliperidone, quetiapine, or risperidone monotherapy.	Monotherapy with haloperidol, lithium, olanzapine or ziprasidone or combination treatment of lithium or valproate with aripiprazole, haloperidol or olanzapine. Lithium combinations with allopurinol* is also an option. Another combination is valproate plus an FGA.			
Nonrapid cycling without psychotic features	All options that are suitable in the presence of psychotic features and also valproate and asenapine monotherapy are a choice. Take into consideration the previous history of psychotic features.	All options that are suiTable in the presence of psychotic features and also monotherapy with carbamazepine or valproate plus celecoxib* are an option Take into consideration the previous history of psychotic features.			
Mixed Features	Start with quetiapine or risperidone monotherapy.	Olanzapine monotherapy			
All other cases	If the patient is already under one of the above 'first step' monotherapy or under combination therapy of any kind and response is unsatisfactory, switch into another 'first step' monotherapy.				

Table 16. *Continued*

Step	First	Second	Third	Fourth	Fifth
In case the personal history of the patient suggests this is not an option, proceed to next step and switch to the closest second step treatment option.	Proceed to next step				
Mixed episode	Start with combination of olanzapine plus valproate or maybe lithium	Monotherapy with olanzapine, aripiprazole, or carbamazepine.	Valproate monotherapy	OFC or ziprasidone monotherapy.	

Abbreviations: CBT, cognitive behavioral treatment; Cbz, carbamazepine; ECT, electroconvulsive therapy; IPSRT, InterPersonal and Social Rhythms Therapy; Lam, lamotrigine; Li, lithium; MS, mood stabilizer; OFC, olanzapine fluoxetine combination; rTMS, repetitive Transcranial Magnetic Stimulation; Val, valproate.
* No wide clinical experience.

Table 17. Comparison of the Detailed Algorithm to Previously Developed Guidelines for Acute Mania

	CINP 2016	WFSBP 2013[a]	CANMAT and ISBD 2013	NICE 2014[b]	BAP 2016[b]
Aripiprazole	1	1	1	-	3
Asenapine	1	3	1	-	3
Cariprazine	1	-	3	-	3
Paliperidone	1	3	1	-	3
Quetiapine	1	3	1	1	1
Risperidone	1	1	1	1	1
Valproate	1	1	1	1	2
Carbamazepine	2	3	2	-	3
Haloperidol	2	3	2	1	1
Lithium	2	3	1	1	3
Olanzapine	2	3	1	1	1
Ziprasidone	2	1	1	-	3
ECT	3	4	2	-	3
Oxcarbazepine	4	4	3	-	-
Chlorpromazine	4	3	3	-	3
Pimozide	4	3	-	-	3
Tamoxifen	4	3	3	-	-
Eslicarbazepine	NR	-	-	-	-
Gabapentin	NR	NR	NR	NR	-
Lamotrigine	NR	NR	NR	NR	-
Licarbazepine	NR	-	-	-	-
rTMS	NR	-	-	-	-
Topiramate	NR	NR	NR	NR	-
Verapamil	NR	-	-	-	-
Phenytoin	-	3	-	-	-
Clozapine	-	4	3	-	3
Amisulpride	-	4	-	-	3
Clonazepam	-	4	-	-	-
Levіracetam	-	4	-	-	-
Lorazepam	-	4	-	-	-

Abbreviations: ECT, electroconvulsive treatment; NR, not recommended;
rTMS, repetitive Transcranial Magnetic Stimulation.
The grading is not uniform; instead it reflects the grading utilized by individual guidelines and the table aims only to give an image of how different guidelines prioritize treatment options.
Numbers correspond to steps not to efficacy ranking.
[a] NICE and BAP ordering is on the basis of line of treatment.
[b] Step 2 in the WFSBP guideline would be a combination of 2 grade "1" recommended medication, or switch from one grade "1" medication to another.

Table 18. Level of Recommendation Concerning Monotherapy in Acute Bipolar Depression, in Comorbid Conditions and Rapid Cycling Patients, and Recommended Dosages for Medication Options

Agent/modality	Overall	BD-I	BD-II	Depressive core	Comorbid anxiety	Rapid cycling	Recommended dosage (mg/d)
Quetiapine	1	3	3	3	3	2	300–600 mg/d
Lurasidone	1	-	-	3	3	-	20–120 mg/d
OFC	2	2	-	3	-	-	6 + 25; 6 + 50; 12 + 50 mg/d
Escitalopram	-	-	1	-	-	-	10 mg/d
Fluoxetine	2	-	3	-	-	-	20–80 mg/d
Olanzapine	2	4	-	3	-	-	5–20 mg/d
Carbamazepine	3	-	-	-	-	-	300–800 mg/d
Valproate	3	3	5	3	3	4	500–2500 mg/d (50–100 mcg/mL)
Aripiprazole	3	3	-	-	-	-	5–30 mg/d
Imipramine	3	-	-	-	-	-	75–300 mg/d
Lamotrigine	3	3	3	3	-	-	50–200 mg/d
Phenelzine	3	-	-	-	-	-	15–90 mg/d
Lithium	4	-	4	-	5	3	600–1800 mg/d
Tranylcypromine	4	4	4	-	-	-	20–30 mg/d
Venlafaxine	4	4	4	-	-	-	75–225 mg/d
Paroxetine	5	5	5	-	3	5	20 mg/d
Ziprasidone	5	5	-	-	5	-	
Gabapentin	5	-	-	-	-	-	
rTMS	5	-	-	-	-	-	
Risperidone	-	-	-	-	5	-	

Abbreviations: NR, not recommended; OFC, olanzapine-fluoxetine combination; rTMS, repetitive Transcranial Magnetic Stimulation.

Table 19. Level of Recommendation Concerning Combination Treatment in Acute Bipolar Depression

Agent/modality	MS	Cbz	Lam	Li	Val
Lurasidone	2	-	-	-	-
Modafinil	2	-	-	-	-
Pramipexole	2	-	-	-	-
Pioglitazone	-	-	-	2	-
Armodafinil	4	-	-	-	-
Ketamine	4	-	-	-	-
Paroxetine	5	5	-	5	5
Ziprasidone	5	-	5	5	5
Bupropion	5	-	-	-	-
Celecoxib	5	-	-	-	-
Levetiracetam	5	-	-	-	-
Levothyroxine (L-T4)	4	-	-	-	-
Risperidone	5	-	-	-	-
Lithium	-	-	2	-	-
Memantine	-	-	5	-	-
FEWP	-	4	-	-	-
Oxcarbazepine	-	-	-	4	-
Lamotrigine	-	-	-	2	-
L-sulpiride	-	-	-	3	-
Fluoxetine	-	-	-	4	-
Agomelatine	5	-	-	5	5
Aripiprazole	-	-	-	5	-
Imipramine	-	-	-	5	-

Abbreviations: Cbz, carbamazepine; FEWP, Free and Easy Wanderer Plus (herbal agent); Lam, lamotrigine; MS, mood stabilizer; Val, valproate.

For the treatment of acute BD-I depression as first line option they recommend monotherapy with lithium, lamotrigine, quetiapine, or quetiapine XR and combination therapy with lithium or divalproex or olanzapine plus an SSRI, lithium plus divalproex and lithium, or divalproex plus bupropion. The second line includes monotherapy with divalproex or lurasidone and combination therapy with quetiapine plus an SSRI, adjunctive modafinil, and lithium or divalproex plus lamotrigine or lurasidone. The third line includes monotherapy with carbamazepine, olanzapine, or ECT or combination therapy with lithium plus carbamazepine or pramipexole, lithium or divalproex plus venlafaxine, lithium plus MAOI, lithium or divalproex or atypical antipsychotic plus a TCA, lithium or divalproex or carbamazepine plus an SSRI plus lamotrigine, and quetiapine plus lamotrigine. They do not recommend monotherapy with gabapentin, aripiprazole, or ziprasidone and combination therapy with adjunctive ziprasidone or levetiracetam.

For the maintenance treatment, the first line recommendation includes monotherapy with lithium, lamotrigine, divalproex, olanzapine, quetiapine, risperidone LAI, and aripiprazole and adjunctive therapy with quetiapine, risperidone LAI, aripiprazole,e or ziprasidone on lithium or divalproex. The second line monotherapy includes carbamazepine and paliperidone ER and combination therapy with lithium plus divalproex or carbamazepine, lithium or divalproex plus olanzapine, risperidone or lamotrigine, and olanzapine plus fluoxetine. The third line monotherapy includes asenapine and the adjunctive therapy includes phenytoin, clozapine, ECT, topiramate, omega-3-fatty acids, oxcarbazepine, gabapentin, and asenapine. They do not recommend monotherapy with gabapentin, topiramate, or antidepressants and adjunctive therapy with flupenthixol.

The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of BD

The latest WFSBP guidelines utilized a modified version of the PORT method to grade the data concerning efficacy (Grunze et al., 2009, 2010, 2013) and afterwards utilized a secondary classification to include also safety and tolerability.

For the treatment of acute mania, as first choice agents are ranked aripiprazole, valproate, risperidone, and ziprasidone. As second choice, olanzapine, quetiapine, asenapine,

Table 20. Precise Algorithm to Treat Acute Bipolar Depressive Episodes on the Basis of Specific Clinical Characteristics

Steps	First	Second	Third	Fourth	Fifth
Overall	Start with quetiapine or lurasidone Consider CBT as add-on to medication and according to the patient preference and to availability.	Add a mood stabilizer on lurasidone, modafinil or pramipexole Lithium plus lamotrigine, or pioglitazone* Olanzapine monotherapy or OFC	Valproate, aripiprazole, imipramine, phenelzin, carbamazepine or lamotrigine monotherapy Lithium plus L-sulpiride	Tranylcypromine or lithium monotherapy Venlafaxine preferably in combination with an antimanic agent Armodafinil or ketamine on a mood stabilizer	ECT or various combinations of medication according to anecdotal knowledge or the personal experience of the therapist
Rapid cycling	Never consider CBT as monotherapy	If BD-I start with valproate, in BD-II with lithium		Lithium plus fluoxetine Carbamazepine plus FEWP Mood stabilizer plus levothyroxine (L-T4) Lithium plus oxcarbazepine	
No rapid cycling		If BD-II start with escitalopram or fluoxetine monotherapy			
Comorbid anxiety		Add paroxetine, quetiapine, valproate or lurasidone and consider Mindfulness based interventions as add-on to these agents			

Abbreviations: CBT, cognitive behavioral treatment; Cbz, carbamazepine; ECT, electroconvulsive therapy; FEWP, Free and Easy Wanderer Plus (herbal agent); IPSRT, InterPersonal and Social Rhythms Therapy; Lam, lamotrigine; Li, lithium; MS, mood stabilizer
OFC, olanzapine fluoxetine combination; rTMS, repetitive Transcranial Magnetic Stimulation; Val, valproate.
* No wide clinical experience.

Table 21. Comparison of the Presise Algorithm to Previously Developed Guidelines for Acute Bipolar Depression Concerning Monotherapy

	CINP 2016	WFSBP 2013[a]	CANMAT and ISBD 2013	NICE 2014[b]	BAP 2016[b]
Lurasidone	1	-	2	-	1
Quetiapine	1	1	1	1	1
Escitalopram	2[c]	-	-	-	3
Fluoxetine	2[c]	1	-	-	3
Olanzapine	2	1	3	1	1
OFC	2	1	1	1	1
Aripiprazole	3	NR	NR	-	-
Imipramine	3				4
Lamotrigine	3	1	1	1	2
Phenelzin	3				-
Valproate	3	1	2	1	-
Carbamazepine	3	1	3	-	-
Lithium	4	1	1	1	3
Tranylcypromine	4	-	-	-	4
ECT	5	-	3	-	5
Gabapentin	NR	-	NR	-	-
Leviracetam	-	-	NR	-	-
L-thyroxine	-	-	-	-	-
Paroxetine	NR	NR	-	-	3
Risperidone	-	-	NR	-	-
rTMS	NR	-	-	-	-
Ziprasidone	NR	NR	NR	-	-

Abbreviations: ECT, electroconvulsive treatment; NR, not recommended;
OFC, olanzapine-fluoxetine combination; rTMS, repetitive Transcranial Magnetic Stimulation.
The grading is not uniform; instead it reflects the grading utilized by individual guidelines and the table aims only to give an image of how different guidelines prioritize treatment options. Numbers correspond to steps not to efficacy ranking.
[a] WFSBP: Recommendation only reflects monotherapy not considering evidence derived from combination treatment (except OFC).
[b] NICE and BAP ordering is on the basis of line of treatment.
[c] Against BD-II depression.
NICE ordering is on the basis of line of treatment.

carbamazepine, haloperidol, and lithium were recommended. The third choice includes chlorpromazine, paliperidone, phenytoin, pimozide, and tamoxifen. The fourth includes amisulpride, clonazepam, clozapine, levetiracetam, lorazepam, nimodipine, oxcarbazepine, retigabine, zonisamide, zotepine, and ECT. The fifth and final choice includes verapamil. With the utilization of this classification, the WFSBP suggests that concerning the treatment of acute mania the first step includes

Table 22. Level of Recommendation Concerning Monotherapy during the Maintenance Phase and in Relationship to Index Episode, Composition of the sample, Presence of Rapid Cycling and the Efficacy in the Prevention of Mainic, Mixed or Depressive Episodes as Well as Recommended Dosages

Agent/modality	Index episode	Enriched sample	Manic	Depressive	Mixed	Rapid cycling	Recommended dosage
Quetiapine	m/d	Yes	2	2	-	Quet+ Val/Li (3)	300–800 mg/d
Olanzapine	m	Yes/No	2	2	2	-	5–20 mg/d
Lithium	m/d	No	2	3	-	Li, Li + Cbz (3)	0.6–1.2 mEq/L
Lamotrigine	m/d	Yes	3	2	-	5	50–400 mg/d
Aripiprazole	m	Yes	1	5	-	3	10–30 mg/d
RLAI	m	Yes	1	5	-	RLAI+TAU (3)	25–50 mg/biweekly
Paliperidone	m	Yes	2	5	-	-	3–12 mg/d
Valproate	m	Yes	4	3	-	-	45–100 mg/L
Ziprasidone	m	Yes	-	-	-	-	80–160 mg/d
Perphenazine	m	Yes	-	-	-	-	
Imipramine	d	?	5	5	-	-	
Fluoxetine	d	Yes	-	2	-	-	10–40 mg/d
CBT	d	No	-	-	-	-	
N-acetyl cysteine	d	Yes	-	-	-	-	
Carbamazepine	-	-	4	4	-	Li + Cbz (3)	4–12 mg/L

Abbreviations: CBT, cognitive behavioral therapy; Cbz, carbamazepine; Li, lithium; Quet, quetiapine; RLAI, Risperidone Long Acting Injection; TAU, treatment as usual; Val, valproate.
Enriched sample: the sample is enriched on the basis of remission after treatment with the agent under consideration during the acute phase (index episode).

Table 23. Level of Recommendation Concerning Combination Treatment during the Maintenance Phase

Agent/modality	MS	Cbz	Lam	Li	Val
Quetiapine	1	-	-	-	-
Aripiprazole	2	-	5	-	5
RLAI	2	-	-	-	-
CBT	2	-	-	-	-
Phenytoin	2	-	-	-	-
Paroxetine	3	-	-	-	-
Psychoeducation	3	-	-	-	-
Olanzapine	4	-	-	-	-
Ziprasidone	4	-	-	-	-
N-acetyl cysteine	4	-	-	-	-
Imipramine	-	-	-	5	-
Memantine	5	-	-	-	-
Oxcarbazepine	-	-	-	5	-
Lithium	-	-	4	-	-
Perphenazine	5	-	-	-	-

Abbreviations: CBT, cognitive behavioral therapy; Cbz, carbamazepine; Lam, lamotrigine; Li, lithium; MS, mood stabilizer; RLAI, Risperidone Long Acting Injection; Val, valproate.

monotherapy with first choice agents. The second step would be switching to another first-choice agent or combine 2 first choice agents. Similarly the third step includes combination of 2 first-choice agents. The fourth and fifth steps include combinations of agents essentially according to the judgement of the therapist.

For the treatment of acute bipolar depression, the WFSBP guidelines suggest that first choice agent is only quetiapine, while the next-best option includes olanzapine, fluoxetine, lamotrigine, valproate, OFC, lithium plus lamotrigine, adjunctive modafinil, NAC on lithium or valproate, and FEWP plus carbamazepine. A variety of combinations are proposed as next steps.

For the treatment during the maintenance phase the guidance is more complex and on the basis of the available data the WFSBP guidelines suggest the use of aripiprazole, lamotrigine, lithium, quetiapine, olanzapine, and risperidone, but they note that not all of them prevent both mania and depression. They also note the problems because of the metabolic syndrome induced by some of these agents when used for prolonged periods of time. They also suggest the avoidance of typical antipsychotics because of the risk to induce tardive dyskinesia.

British Association for Psychopharmacology

The 2016 British Association for Psychopharmacology guidelines for the treatment of BD (Goodwin et al., 2016) recommend for acute mania antidopaminergic agents, lithium, or valproate. For acute bipolar depression they recommend quetiapine, olanzapine, olanzapine plus fluoxetine, antidepressants, lurasidone, and lamotrigine as combination. It also recommends family focused therapy, IPSRT, and CBT as add-on to medication but also CBT as monotherapy as an extrapolation of unipolar depression studies. For the maintenance phase they recommend lithium (for mania, depression, and suicide), dopamine antagonists, and partial agonists as well as valproate (mainly for mania), lamotrigine (for depression), and family focused therapy, CBT, and IPSRT as add-on to medication.

The UK NICE Treatment Guidelines for BD

Concerning acute mania, the 2014 NICE (NICE, 2014) guidelines recommend the use of olanzapine, risperidone, quetiapine, or haloperidol. If the patient does not respond it is recommended to change to another antipsychotic, and the choice should be made also on the basis of previous response if it exists. If the patient is already under treatment with lithium or valproate then the recommendation is to increase dosage to the highest permitted, and reassessment should follow before the changing of medication. If an antidepressant is in place, it should be discontinued. The second step includes combination of lithium or valproate plus an antipsychotic and the third step demands hospitalization. The NICE warns against the use of gabapentin, lamotrigine, and topiramate in acute mania.

For acute bipolar depression, the NICE recommends olanzapine, OFC, quetiapine, lamotrigine, lithium, and valproate. If the patient is already under treatment with lithium or valproate then the recommendation is to increase the dosage to the highest permitted, and reassessment should follow before the changing of medication. The next step includes combination of lithium or valproate plus quetiapine or OFC. The third step includes lithium plus lamotrigine or olanzapine and valproate plus lamotrigine. The NICE warns against the use of gabapentin and topiramate.

During the maintenance phase, the NICE guidelines recommend as first line treatment the continuation of the treatment the patient received during the acute phase and led to the resolution of the symptoms. Irrespective of predominant polarity the continuation of this treatment should be done for at least 3 to 6 months. In case the patient does not wish to follow this, it is recommended to change treatment to lithium, olanzapine, quetiapine, valproate, or lithium plus valproate. Again, NICE warns against the use of gabapentin and topiramate.

The procedure and the interpretation of evidence as presented in the NICE guidelines have been criticized (Jauhar et al., 2016).

Efficacy, Recommendation Level, and Precise Treatment Algorithm

The detailed table of the efficacy level for all treatment options during all phases and against specific features of BD is shown in web appendix 1. The detailed table of the recommendation level for all treatment options during all phases and against specific features of BD is shown in web appendix 2. Add-on and combination data were merged for the sake of simplicity. Additionally, the detailed precise algorithm that was developed is shown in web appendix 3.

The levels of recommendation concerning monotherapy in acute mania and recommended dosages for medication options are shown in Table 11, while the recommendation levels for combination treatment are shown in Table 12. Recommendation levels concerning treatment options for rapid cycling patients are shown in Table 13 and the effects on concomitant depressive and psychotic features are shown in Table 14. The recommendation levels for monotherapy and combination treatment in patients with a DSM-IV-TR mixed episode and the specific effects on the manic and the depressive component are shown in Table 15 (provided here for academic reasons).

The chart of the algorithm for acute mania/hypomania on the basis of strict evidence and by taking into consideration specific clinical features is shown in Table 16. The comparison of this algorithm to previously developed guidelines for acute mania is shown in Table 17.

The levels of recommendation concerning monotherapy in acute bipolar depression, in comorbid conditions, and rapid cycling patients and recommended dosages for medication options are shown in Table 18, while the levels of recommendation concerning combination treatment are shown in Table 19.

The chart of the algorithm for acute bipolar depression is shown in Table 20. The comparison of this algorithm to previously developed guidelines for acute bipolar depression is shown in Table 21.

The levels of recommendation concerning monotherapy during the maintenance phase and in relationship to index episode, composition of the sample, presence of rapid cycling, and the efficacy in the prevention of manic, mixed, or depressive episodes as well as recommended dosages are shown in Table 22, while the levels of recommendation concerning combination treatment during the maintenance phase are shown in Table 23.

The chart of the algorithm for the maintenance phase is shown in Table 24. The comparison of this algorithm to previously developed guidelines for the maintenance phase is shown in Table 25.

Overall the algorithm consists of the stepwise approach in Tables 16, 20, and 24 and in web appendix 3. However, a more fundamental approach would be to utilize web appendix 2 that includes a table with the recommendation levels by clinical indication for all the treatment options. The utilization of this table could be more precise and accurate in comparison with the stepwise description. Until then, the clinician can handle the table in a manual way. First he or she should decide on the phase of the disorder (acute manic vs mixed vs depressive episode vs maintenance phase). Then he or she should choose the combination of the clinical features under the specific phase and finally he or she will identify that treatment options best fit the clinical syndrome. For example, if the patient is in an acute manic episode with some accompanying depressive symptoms (mixed features) and psychotic symptoms and his or her history suggests he or she is also a rapid cycling, then the only agents that treats all these conditions are olanzapine and quetiapine followed by lithium that is second choice. If the patient is BD-II in a depressive episode with anxiety, then the only suitable agent is quetiapine. Of course such an algorithm might be too restrictive; however, the clinician can use the table to produce combinations of treatment options to satisfy all clinical needs on the basis on research data.

Discussion

The current paper represents a systematic search of the literature on the treatment of BD. By using an established approach we identified all relevant RCTs pertaining to all faces and special issues of BD and graded the data according to a predetermined method. Finally, a recommendation level was assigned to all treatment options depending on the clinical situation.

It was interesting to see that except for rare cases, the concept of mood stabilizers is not supported by the available data, especially for those agents traditionally considered as such.

It is obvious that, by far, the body of evidence originates from RCTs that were conducted with agents that have been launched in the last 2 decades. This constitutes a significant bias in the literature, and one should be cautious in the way that the accumulated clinical experience concerning those agents and treatment modalities with poor evidence-based support should also be taken into account.

A low grade of evidence for these old and poorly studied agents and modalities (e.g., carbamazepine, clozapine, ECT, etc.) does not necessarily mean a lower effectiveness and safety in comparison with other drugs, but it still implies that the clinicians should be cautious in their application in patients with BD. Yet it is irrational to use different standards; on the one hand to study carefully and seek flaws in the design of major RCTs and on the other hand to accept a wide recommendation of agents with poor evidence-based support because of historical reasons. The authors of the current paper spent much time and effort to grade the agents on the basis of quantitative but also qualitative characteristics of the data available. This effort resulted in the development of a precise algorithm on the basis of a reproducible methodology.

Also, the results on those areas of interest that are not targeted as primary outcomes are reported in a nonsystematic way and therefore the grading of evidence is lower. Unfortunately these areas constitute the overwhelming clinical picture of BD.

As with many other guidelines, the inherent limitations of the literature as well as the unavoidable subjectivity of experts when

Table 24. Precise Algorithm to Treatment during the Maintenance Phase for BD on the Basis of Specific Clinical Characteristics

Step	First	Second	Third	Fourth	Fifth
Depressive predominant polarity or No predominant polarity	Quetiapine or olanzapine monotherapy	Add fluoxetine or lamotrigine	Add N-acetylcysteine	If depressive episodes keep emerging add an agent with proven efficacy against acute bipolar depression no matter whether it has proven maintenance efficacy. Consider adding venlafaxine or lithium plus lamotrigine.	Consider any combinations from steps 1–4 that have not been tried. Consider maintenance ECT Various combinations of medication according to anecdotal knowledge or the personal experience of the therapist
Manic predominant polarity	Start with lithium, aripiprazole, olanzapine, paliperidone, quetiapine or risperidone (including RLAI) monotherapy	Add lithium on the first step option Lithium plus carbamazepine Quetiapine plus lithium or valproate	If manic episodes keep emerging add RLAI on current treatment if not already in place Add N-acetylcysteine	If manic episodes keep emerging add an agent that has proven efficacy against acute mania no matter whether it has proven maintenance efficacy. Consider haloperidol or lithium plus lamotrigine	Consider IPSRT as add-on to medication on the basis of clinical judgement of the therapist and according to the patient preference and to availability. Never consider IPSRT as monotherapy
Mixed episodes are frequent	Olanzapine or aripiprazole plus a mood stabilizer		Add valproate, carbamazepine, or lamotrigine on second step treatment	Proceed to next step	
Rapid cycling	Lithium monotherapy				
All cases	Consider CBT or psychoeducation as add-on to medication on the basis of clinical judgement of the therapist and according to the patient preference and to availability. Never consider CBT or psychoeducation as monotherapy				

Abbreviations: CBT, cognitive behavioral treatment; Cbz, carbamazepine; ECT, electroconvulsive therapy; IPSRT, InterPersonal and Social Rhythms Therapy; Lam, lamotrigine; Li, lithium; MS, mood stabilizer.

Table 25. Comparison of the Presise Algorithm to Previously Developed Guidelines for Maintenance Phase Concerning Monotherapy

	CINP 2016	WFSBP 2013[a]	CANMAT and ISBD 2013	NICE 2014[b]	BAP 2016[b]
Aripiprazole	1	1	1	-	3
Lithium	1	1	1	1	1
Olanzapine	1	2	1	1	2
Paliperidone	1	3	2	-	3
Quetiapine	1	1	1	1	2
Risperidone	1	2	-	-	3
RLAI	1	-	1	-	2
OFC	2	-	2	-	-
Lamotrigine	2	1	1	-	2
Carbamazepine	3	4	2	-	2
Valproate	3	3	1	1	2
Haloperidol	4	-	-	-	3
Venlafaxine	4	-	-	-	-
ECT	5	4	3	-	-
Ziprasidone	5	3	-	-	3
Continue most recent episode treatment	NR	-	-	1	-
Antidepressants	-	3	NR	-	4
Asenapine	-	4	3	-	3
Gabapentine	-	4	NR	NR	-
Topiramate	-	4	NR	-	-

Abbreviations: ECT, electroconvulsive treatment; NR, not recommended; OFC, olanzapine-fluoxetine combination; RLAI, Risperidone Long-Acting Injectable.
The grading is not uniform; instead it reflects the grading utilized by individual guidelines and the Table aims only to give an image of how different guidelines prioritize treatment options.
Numbers correspond to steps not to efficacy ranking.
[a] WFSBP: Recommendation grades and subsequent positioning could be either based on efficacy in the prevention of mania, depression or any episode. Thus, numbers do not reflect the sequence of treatment in an individual patient.
[b] NICE and BAP ordering is on the basis of line of treatment.

making a recommendation (even when based on evidence) should be taken seriously into consideration by the clinicians when reading the current paper. Also negative results (level 5) should be taken very seriously into consideration, as they should be considered to be scientifically stronger in comparison with positive ones.

Further limitations include the heterogeneity of the RCTs that served as basis for the recommendations and the lack of trials assessing specific subpopulations, following the rules of stratified medicine (Schumann et al., 2014), or applying staging methods to psychopharmacology (Grande et al., 2015), in search of more precision when treating individual patients (Vieta, 2015). However, these CINP guidelines represent the most up-to-date effort to condense the current knowledge on the management of BD from an international perspective.

Statement of Interest

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A.H.Y. is employed by King's College London, is Honorary Consultant SLaM (NHS UK), has paid lectures by and participated in advisory boards for all major pharmaceutical companies with drugs used in affective and related disorders, and has no share holdings in pharmaceutical companies. He was lead investigator for Embolden Study (AZ), BCI Neuroplasticity Study, and Aripiprazole Mania Study; investigator-initiated studies from AZ, Eli Lilly, Lundbeck, and Wyeth; and has received grant funding (past and present) from NIHR-BRC (UK); NIMH (USA); CIHR (Canada); NARSAD (USA); Stanley Medical Research Institute (USA); MRC (UK); Wellcome Trust (UK); Royal College of Physicians (Edin); BMA (UK); UBC-VGH Foundation (Canada); WEDC (Canada); CCS Depression Research Fund (Canada); MSFHR (Canada); and NIHR (UK).

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