



# **Clinician Summary Atypical Antipsychotics**

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## Category: Atypical Antipsychotics

### Drugs included

Clozapine, olanzapine, quetiapine, risperidone, asenapine ziprasidone, iloperidone, aripiprazole

### Limitations of the evidence:

1. Commercial sponsorship of most trials may bias results. Nonequivalent mean doses of compared drugs were common. Blinding is easily compromised in studies with dosage titrations. Outcomes were a wide variety of rating scales that are not comparable and involve subjectivity on the part of the assessor.
2. The CATIE study, a large, widely referenced, federally funded study, uses a surrogate endpoint of all cause discontinuation. This is not measure of efficacy.
3. For Children and Adolescents with Autism or Disruptive Behavior Disorders, the comparative evidence is poor: no head-to-head trials, no effectiveness trials.

### Schizophrenia:

- 1) **Good evidence:** No differences in efficacy among clozapine, olanzapine, quetiapine, risperidone, asenapine ziprasidone, iloperidone, or aripiprazole in short-term trials of inpatients or outpatients.
- 2) **Good evidence:** olanzapine is superior to quetiapine for reduction in relapse rate. Evidence for olanzapine vs. risperidone was mixed for relapse rate. No evidence was found for the other included drugs
- 3) There is insufficient evidence to draw conclusions about the impact of these drugs on:
  - Global assessment of functioning, quality of life, social functioning, employment
  - Violent behavior, aggressive behavior, suicide death.
  - Time to onset of efficacy, rates or time to discontinuation,
  - Inpatient outcome, length of stay, nursing burden for inpatients, or rehospitalization
  - Subgroups of race, age, and gender
- 4) **Good evidence:** No difference for response rates. Asenapine and iloperidone: no studies.
- 5) **One good quality** study of first episode schizophrenia (n=400) found no statistically significant differences in overall discontinuation rates (primary outcome) or symptom response for olanzapine, immediate release quetiapine, and risperidone.

### Bipolar Disorder

1. There is insufficient evidence to determine a clinically meaningful difference between drugs in this class for bipolar disorder.
2. The strength of evidence for efficacy and comparative difference between drugs in this category is low

### Major Depressive Disorder

**Fair evidence:** No atypical antipsychotic had evidence of providing a significant long-term benefit when used as an adjunctive treatment for augmentation of antidepressant therapy in adults with treatment resistant depression.

### Dementia **Fair evidence:**

1. There was no evidence that any atypical antipsychotic was superior to haloperidol for treating behavioral and psychological symptoms of dementia.
2. There were no differences between drugs and placebo on a variety of evaluation scales.
3. The incidence of Parkinsonism is higher with olanzapine and risperidone compared to immediate release quetiapine and placebo in patients with dementia.

### Children with Pervasive Developmental Disorder or Disruptive Behavior Disorder

There is **insufficient evidence** of to prove benefit of medications in this class on patients with pervasive developmental disorder or disruptive behavior disorder.

### Harms and adverse effects

1. Clozapine is associated with an increased risk of seizures (2,9% and 4.2% in two separate studies) and agranulocytosis (13 studies reported incidence of 0-2.4%),
2. No differences among the drugs in other serious harms.
3. No differences in extrapyramidal symptoms, metabolic syndrome, or sexual dysfunction.
4. Weight gain was 6 to 13 pounds greater with olanzapine than the other atypical antipsychotics over periods up to 18 months of treatment.
5. Clozapine is more sedating than risperidone and olanzapine.

For more information see complete HRC report at: [http://www.oregon.gov/OHPPR/HRC/Evidence\\_Based\\_Reports.shtml](http://www.oregon.gov/OHPPR/HRC/Evidence_Based_Reports.shtml)

**Table 1. Atypical antipsychotic drug indications, doses, and mechanisms of action**

Generic Name/ Approval Date	Trade Name	FDA Approved Indications	Pharmacodynamics	Black Box Warnings*
Aripiprazole 2002	Abilify® Tablet Abilify® Discmelt ODT Abilify® Liquid	Schizophrenia Manic and mixed episodes associated with bipolar I disorder Adjunctive treatment to antidepressants for MDD Treatment of irritability associated with autistic disorder	Partial agonist at D2 and 5-HT1A receptors, antagonist at 5-HT2A receptors.  High affinity for D2, D3, 5-HT1A, and 5-HT2A receptors. Moderate affinity for D4, 5-HT2C, 5-HT7, - $\alpha$ -adrenergic and H1 receptors.  Moderate affinity for the serotonin reuptake site and no appreciable affinity for cholinergic muscarinic receptors.	Y
	Abilify® IM Injection	Agitation associated with schizophrenia or bipolar disorder, manic or mixed		Y
Asenapine 2009	Saphris® Tablet	Acute treatment of schizophrenia in adults. Acute treatment of manic or mixed episodes associated with bipolar I disorder with or without psychotic features in adults	High affinity for serotonin 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT5-7 receptors, dopamine D1-4 receptors, $\alpha$ 1 and $\alpha$ 2-adrenergic receptors, and histamine H1 receptors Moderate affinity for H2 receptors	Y
Clozapine 1989	Clozaril® Tablet  Fazaclor® ODT	Treatment-resistant schizophrenia Reduction in risk of recurrent suicidal behavior in schizophrenia or schizoaffective disorder in adults	Antagonist at D1-5 receptors, with high affinity for D4 receptors. Also antagonist at serotonergic, adrenergic, cholinergic, and histaminergic receptors.	
Iloperidone 2009	Fanapt™ Tablet	Schizophrenia in adults	High affinity to serotonin 5-HT2A and dopamine D2 and D3 receptors Moderate affinity for dopamine D4, serotonin 5-HT6 and 5-HT7, and norepinephrine NE $\alpha$ 1 receptors	Y
Olanzapine 1996	Zyprexa® Tablet  Zyprexa® Zydis® ODT	Schizophrenia Monotherapy or in combination therapy for acute mixed or manic episodes associated with bipolar I disorder Maintenance monotherapy of bipolar I disorder	Selective monoaminergic antagonist with high affinity binding to 5-HT2A/2C, 5-HT6, D1-4, histamine H1, and $\alpha$ 1-adrenergic receptors.	Y
	Zyprexa® Intramuscular Injection	Agitation associated with schizophrenia or bipolar I disorder		
Paliperidone 2006	Invega® ER Tablet	Acute and maintenance treatment of schizophrenia in adults	Antagonist at D2 receptors and 5-HT2A receptors.	Y

	Invega® Sustenna® ER Intramuscular	Mono or adjunctive therapy for schizoaffective disorder in adults	Also antagonist at $\alpha$ 1-2 and H1 receptors.	
Quetiapine 1997	Seroquel® Tablet	Schizophrenia in adults and adolescents (13-17 years) Acute treatment of manic episodes associated with bipolar disorder, both as monotherapy and as an adjunct to lithium or divalproex in adults and as monotherapy in pediatric patients (10-17 years) Acute treatment of depressive episodes associated with bipolar disorder in adults Maintenance treatment of bipolar disorder as an adjunct to lithium or divalproex in adults	Antagonist at D1-2, 5HT 1A-2A, norepinephrine transporter (NET), H1, M1, and $\alpha$ 1b-2 receptors	Y
	Seroquel XR® Tablet	Acute and maintenance treatment of schizophrenia in adults Acute treatment of manic or mixed episodes associated with bipolar disorder, both as monotherapy and as an adjunct to lithium or divalproex in adults Acute treatment of depressive episodes associated with bipolar disorder in adults Maintenance treatment of bipolar disorder as an adjunct to lithium or divalproex in adults Adjunctive treatment of major depressive disorder in adults		Y
Risperidone 1993	Risperdal® Tab, Liquid Risperdal® M-TAB® ODT	Acute and maintenance treatment of schizophrenia in adults and acute treatment in adolescents (13-17 years) Monotherapy (for adults and children 10-17 years) or combination therapy (for adults) for acute mixed or manic episodes associated with bipolar I disorder	Antagonist with high affinity binding to 5-HT2 and D2 receptors. Antagonist at H1, and $\alpha$ 1-2 receptors	Y
	Risperdal® Consta® Long-acting IM Injection	Treatment of irritability associated with autistic disorder in children and adolescents aged 5-16 years		Y
Ziprasidone 2001	Geodon® Capsule	Schizophrenia Acute mixed or manic episodes associated with bipolar I disorder	Antagonist with high affinity binding to 5-HT2 and D2 receptors.	Y
	Geodon® IM Injection	Acute agitation in schizophrenia		Y
	Geodon® Suspension	Schizophrenia in adults Acute manic and mixed episodes associated with bipolar disorder in adults		Y

\* See Appendix in HRC report on page 84 for complete list of Black Box Warnings:

<http://www.oregon.gov/OHPPR/HRC/Evidence Based Reports.shtml>