

MENTAL HEALTH CLINICAL ADVISORY GROUP AGENDA

SPECIAL MEETING

Thursday, October 18, 2018 (10:00am-12:00pm)

Portland State Office Building

800 NE Oregon St, Room 710

Portland, OR 97232

TYPE OF MEETING	Advisory Board
FACILITATOR	Presiding officer
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
	Mark Helm, MD, MBA, FAAP		Jonnaliz Corbett
Chris Bouneff	Bob Joondeph, JD		
Mark Bradshaw, MD	Nick Kashey, MD		
Keith Cheng, MD	Lori Martin, MSN, PMHNP		
Neil Falk, MD	Kara Shirley, Pharm.D., BCCP, BCPS, BCACP		
George Fussell, MD			

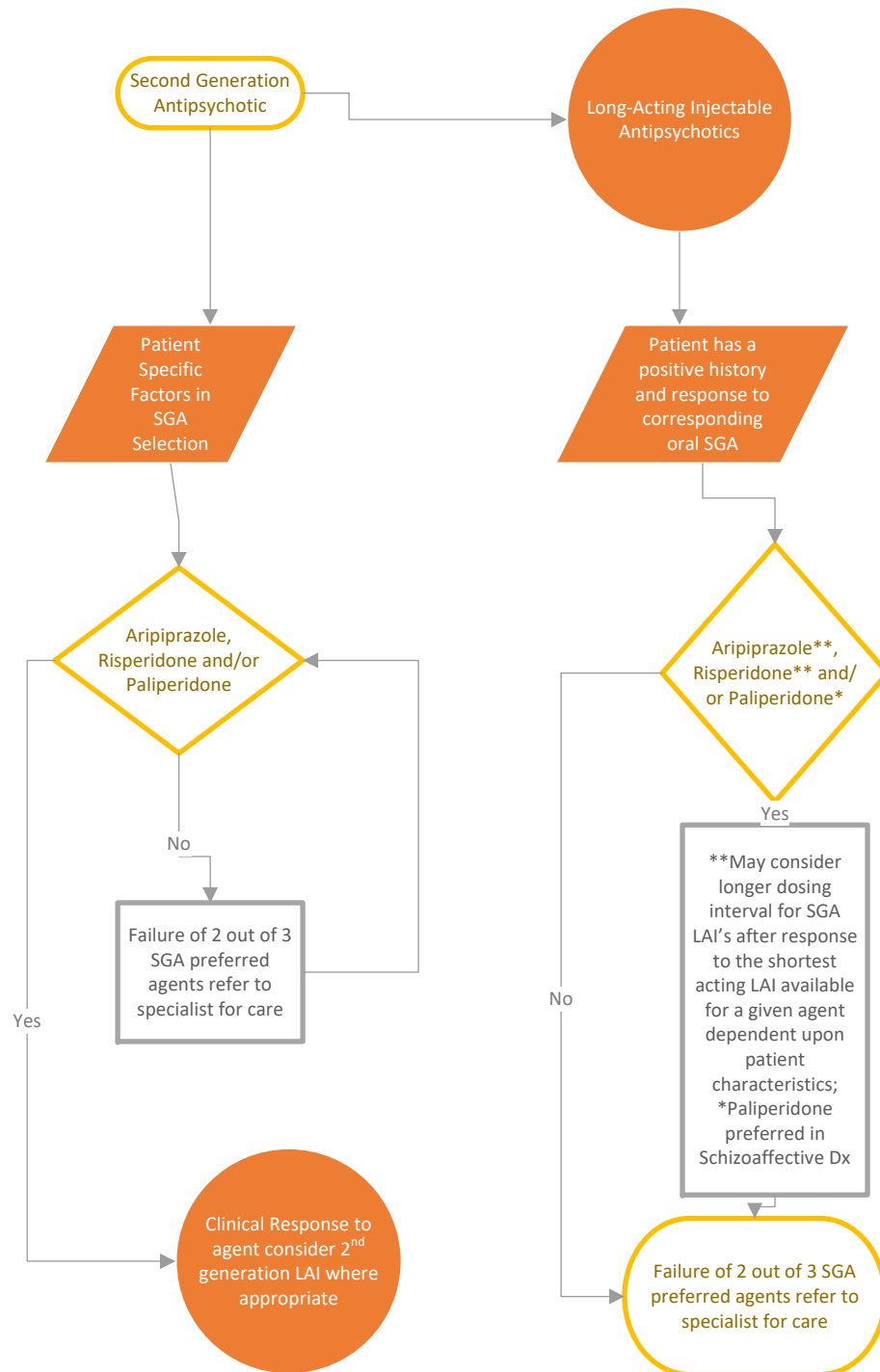
DISCUSSION TOPICS	TIME	RESPONSIBLE PARTY
Call to order	5 min	Presiding officer
Section 1.3, Treatment guidelines for medication use	105 min	All
Public comment	10 min	Presiding officer
Adjournment	-----	Presiding officer

Schizophrenia PCP Rx Treatment Pathway

Stage 1

Stage 2

Stage 3



Schizophrenia Treatment
Pathway (after and/or
conjunction with OPAL referral)

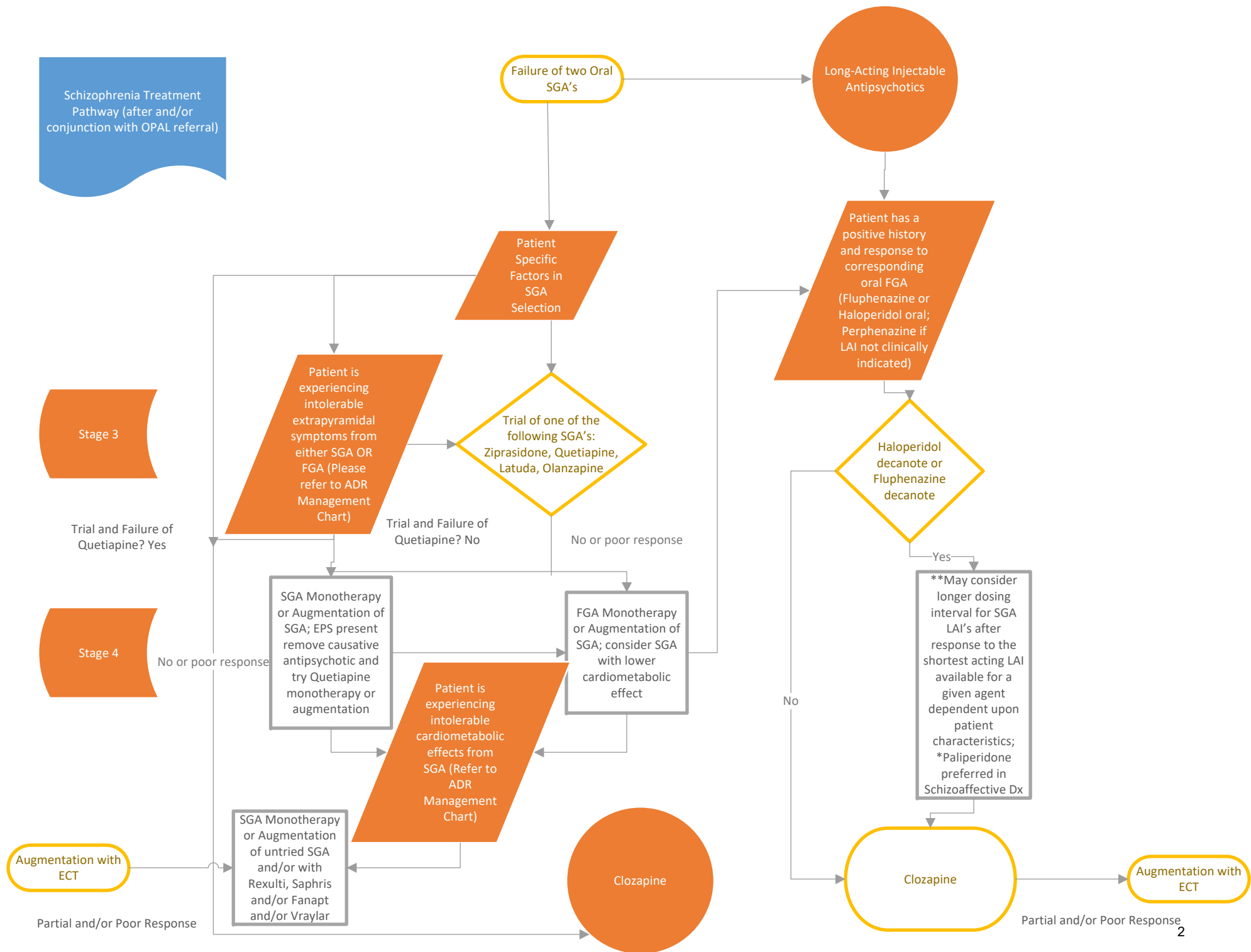


Table 1. Mood stabilizers and Miscellaneous agents

Drug	Form	t _{1/2}	Dosing	FDA Indication	Pediatric approval	Side Effects (>10%) and Drug Specific Considerations	Cost
Mood Stabilizers							
Carbamazepine (Tegretol)	Oral, ER caps, Susp, Chew	25-65 ER: 35-40 MD: 12-17 ~34	200 mg BID (>1600 mg/day not studied)	Bipolar I Disorder, Acute manic or mixed	No	Side Effects: Dizziness, Somnolence, Nausea, Vomiting, Xerostomia, Ataxia CYP3A4 Inducer and inhibitor Box Warnings: Aplastic Anemia and Agranulocytosis AND Serious dermatologic reaction for patients with HLA-B*1502 allele	\$
				Epilepsy	Yes (Oral form only)		
Lamotrigine (Lamictal)	Oral, Chew, ODT	25-70 ^13-58 ^^46-100	Target: 200 mg/d (see table 2)	Bipolar I Disorder (IR only) Maintenance	No	Side Effects: Diplopia, Headache, Rash, Dizziness, Nausea Box Warning: Life-threatening rash, typically occur within 2-8 weeks of therapy	\$
				Bipolar Depression, Acute (Off-Label)	No		
Lithium (Lithobid)	Oral, Sol.	14-24 ^36	900-1200 mg/d: Goal level of 0.6-1.2 mEq/L	Bipolar Disorder, Maintenance	≥ 12 yr	Side Effects: Hypothyroidism, Weight gain, Hyponatremia, Cardiac dysrhythmia, Nausea, Xerostomia Possible Toxicity: Polyuria, increased thirst	\$
				Bipolar Disorder, manic episodes	≥ 12 yr		
Valproic acid Divluproex Na (Depakote)	Oral, Syrup, IV	9-16 ^^12-18	750 mg/d Titrate to effect Max 60 mg/kg/d	Manic Bipolar I Disorder	No	Side Effects: Nausea, Headache, Diplopia, Dizziness, Diarrhea, Dose-related thrombocytopenia (27% at 50 mg/kg/d) Box Warning: Hepatotoxicity*, Fetal Risk, Pancreatitis	\$
				Bipolar I Disorder, Maintenance (Off-label)	No		
				Bipolar II Disorder, Maintenance (Off-label)	No		
Levetiracetam (Keppra)	Oral, ODT, Sol., IV	6-8	Max 3 g/day QD-BID	No indication or off-label dosing for bipolar or mood disorders	No	Side Effects: Reduced bone mineral density, somnolence, fatigue, vomiting, infections, headache	\$\$
Oxcarbazepine (Trileptal) (Oxtellar XR)	Oral, ER, Susp.	2-11 ~9-11 ^~19	Max 2400 mg/day	No indication or off-label dosing for bipolar or mood disorders	No	Side Effects: Dizziness, Drowsiness, headache, ataxia, Nausea/vomiting, diplopia, abdominal pain Serious dermatologic reaction for patients with HLA-B*1502 allele No Autoinduction	\$

Drug	Form	t _{1/2}	Dosing	FDA Indication	Pediatric approval	Side Effects (>10%) and Drug Specific Considerations	Cost
Miscellaneous							
Prazosin (Minipress)	Oral	2-3	1-15 mg/d	PTSD-related nightmares (off-label)	No	Side Effects: <i>Dizziness, Lethargy, Headache, Somnolence, Hypotension</i>	\$
Hydroxyzine HCl – (Atarax) Pam – (Vistaril)	Oral, IM, Sol.	20 ^e 29 [^] 37 ^{^^}	50-100 mg QID	Anxiety	Yes	Side Effects: <i>Xerostomia, Somnolence, QT Prolongation</i>	\$
Clonidine	Oral, Epidural, Patch	12.5-16 [^] 41 [^] Epi: 22	0.1-0.2 mg BID-QID max 1 mg/d	Opioid Withdrawal (off-label)	No	Side Effects: <i>Hypotension, Xerostomia, Nausea, Abdominal Pain, Fatigue</i>	\$
			N/A	Anxiety (off-label)	No		

Legend: t_{1/2} = half-life; ER = Extended Release; Susp = suspension; caps = capsules; MD = Multiple Doses; ODT = Orally Disintegrating Tablets; Sol. = Solution

*Increased risk for hepatotoxicity in patients with DNA mutation of mitochondrial DNA polymerase gamma (POLG), use is contraindicated

t_{1/2} reported in hours unless otherwise specified; ~ = active metabolite half-life; ^ = half-life in renal failure; ^^ half-life in hepatic failure,

^e = elderly; Na = Sodium

Estimated Average Monthly Cost based on AWP:

\$ 250 - 500

\$ 0-250

Table 2. Pharmacokinetics

Drug	Form	t _{1/2}	Tmax	%PB	Metabolism	Oral BA	Dosing Consideration
Mood Stabilizers							
Carbamazepine (Tegretol)	Oral, ER caps, Susp, Chew	25-65 ER: 35-40 MD: 12-17 ~34	IR: 4-5 ER tab: 3-12 ER Caps: 6 Susp: 1.5	75-90	Induces CYP3A4 and shortens half-life over time CYP3A4 substrate CYP1A2 Inducer	75-85% (Susp 89%)	May sprinkle contents of capsule over soft food Slow absorption in GI tract t _{1/2} decrease with prolonged use of carbamazepine (induces own metabolism)
Lamotrigine (Lamictal)	Oral, Chew, ODT	25-70 ^13-58 ^^46-100	1.4-5 ER: 4-11	55	Liver UGT1A4 Substrate	98%	Dosing Schedule: 25 mg/d x 2 wk; 50 mg/d x 2 wk; 100 mg/d x 1 wk; 200mg/d maintenance With Valproic acid: start 25mg/qod x 2 wk; 25mg/d x 2 wk; 50 mg/d x 1wk; 100 mg/d maintenance Double doses for enzyme inducer without valproic acid
Lithium (Lithobid)	Oral, Sol.	14-24 ^36	IR: 0.5-3 ER: 2-6 Sol: 0.25-1	None	Kidney	80-100%	Long term therapy t _{1/2} = 2.4 days 8 mEq of solution (5 mL) is equivalent to 300 mg of Lithium Carbonate
Valproic acid (Depakote)	Oral, Syrup, IV	9-16 ^^12-18	4-17 Sprinkle 3.3	74-93	Hepatic Glucuronidation	89%	Sprinkle on food delays Tmax to 4.8 Unbound doubles with liver damage
Levetiracetam (Keppra)	Oral, ODT, Solution, IV	6-8	1 hr ER: 4 hr	3.4	No CYP metabolism, not extensively metabolized (66% excreted unchanged)	100%	Max 3 grams per day (1500 mg BID)
Oxcarbazepine (Trileptal) (Oxtellar XR)	Oral, ER, Susp.	2-11 ~9-11 ^~19	IR: 4.5 Susp: 6 ER: 7	39.5	Rapid and extensive hepatic metabolism Active metabolite	90%	Food increases Tmax of ER formulation by 60% and reaches Tmax 2 hr sooner (not IR form) No enzyme autoinduction

%PB = Percent Protein Binding

t_{1/2} and Tmax are reported in hours unless otherwise specifiedt_{1/2}: ~ = active metabolite half-life; ^ = half-life in renal failure; ^^ half-life in hepatic failure, ° = elderly

Drug	Form	t _{1/2}	Tmax	%PB	Metabolism	Oral BA	Dosing Consideration
Miscellaneous							
Prazosin (Minipress)	Oral	2-3	0.5-3	92-97	Extensive liver metabolism via demethylation and conjugation	56-63%	Sudden discontinuation can cause rebound hypertension
Hydroxyzine HCl – (Atarax) Pam – (Vistaril)	Oral, IM, Sol.	20 °29 ^^37	2 4-12*	NA	Extensive hepatic metabolism ~Active metabolite cetirizine	Rapid	IM and solution both HCl formulation
Clonidine (Catapres)	Oral, Epidural, Patch	12.5-16 ^41 Epi: 22	2-5 ER:6.5 Epi: 19-26 min	20-40	Hepatic 40-60% excreted unchanged	75-100	Dose-related hypotension May exacerbate depression Withdrawal symptoms with abrupt discontinuation

%PB = Percent Protein Binding

t_{1/2} and Tmax are reported in hours unless otherwise specified

t_{1/2}: ~ = active metabolite half-life; ^ = half-life in renal failure; ^^ half-life in hepatic failure, ° = elderly

* Hydroxyzine Tmax for antihistamine effect

References:

1. Lexi-drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at <http://online.lexi.com.liboff.ohsu.edu/lco/action/home>. Updated April 2018
2. Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. Available at <http://www.micromedexsolutions.com>. Updated April 2018.

Table 1. Tardive Dyskinesia

Drug	Form	t _{1/2}	Dosing	FDA Indication	Pediatric Approval	Side Effects (>10%) and Drug Specific Considerations	Cost
Central Monoamine-Depleting Agents and Vesicular Monoamine Transporter 2 (VMAT2) Inhibitors							
Valbenazine (Ingrezza)	Oral	15-22	40 mg QD x 1 wk; 80 mg QD	Tardive Dyskinesia	No	Side Effects: <i>Somnolence, Akathisia, Sedation</i> QT Prolongation (especially with CYP2D6 or CYP3A4 inhibitors)	\$\$\$\$\$
Deutetrabenazine (Austedo)	Oral	~9-10	6-48 mg/d BID	Tardive Dyskinesia	No	Side Effects: <i>Somnolence, Diarrhea, Xerostomia, Fatigue</i> QT Prolongation	\$\$\$\$\$
Tetrabenazine (Xenazine)	Oral	~A: 7 ~B: 5 ^^ 17.5 ^^~A: 10 ^^~B: 8	50-200 mg/d	Tardive Dyskinesia (off-label)	No	Side Effects: <i>Insomnia, Fatigue, Anxiety, Nausea, Depression, Dysphagia, Sedated</i> QT Prolongation Highest rates of adverse effects	\$\$\$\$\$\$\$

Legend: t_{1/2} = half-life

t_{1/2} reported in hours unless otherwise specified; ~ = active metabolite half-life; ^ = half-life in renal failure; ^^ half-life in hepatic failure

Estimated Average Monthly Cost based on AWP: \$\$\$\$\$ = 2,500-5,000; \$\$\$\$\$\$ = 5,000-10,000; \$\$\$\$\$\$\$\$ > 10,000

Table 2. Pharmacokinetics

Drug	Form	t _{1/2}	Tmax	%PB	Metabolism	Oral BA	Dosing Consideration
Central Monoamine-Depleting Agents and Vesicular Monoamine Transporter 2 (VMAT2) Inhibitors							
Valbenazine (Ingrezza)	Oral	15-22 ~15-22	0.5-1	>99% ~A:60-68	CYP3A4 – extensive CYP2D6: Alpha-HTBZ active metabolite	49	CrCl < 30: use not recommended Hepatic impairment (Mod-Sev): 40 mg/d CYP3A4 Inhibitors: 40 mg/d CYPD3A4 inducers: Not recommended
Deutetrabenazine (Austedo)	Oral	~9-10	3-4	~A: 60-68 ~B: 59-63	CYP2D6 Alpha-HTBZ (~A) and Beta-HTBZ (~B) active metabolites	80%	CYP2D6 Poor metabolizer or strong inhibitors MAX 36 mg/d CI in hepatic impairment Miss > 1wk restart at initial dose
Tetrabenazine (Xenazine)	Oral	~A: 7 ~B: 5 ^^ 17.5 ^^~A: 10 ^^~B: 8	1-1.5	82-85 ~A: 60-68 ~B: 59-63	CYP2D6: extensive Alpha-HTBZ (~A) and Beta-HTBZ (~B) active metabolites	75%	CYP2D6 inhibitor: MAX 50 mg per day and 25 mg per dose

%PB = Percent Protein Binding; t_{1/2} and Tmax are reported in hours unless otherwise specified

t_{1/2}: ~ = active metabolite half-life; ^ = half-life in renal failure; ^^ half-life in hepatic failure, ^e = elderly

References:

1. Tardive Dyskinesia. Rae-Grant A, Shaughnessy A, Ehrlich A. Dynamed. Available at <http://www.dynamed.com/topics/dmp~AN~T113751/Tardive-dyskinesia#Dopamine-depleting-medications>. Updated May 4, 2017.
2. Lexi-drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at <http://online.lexi.com.liboff.ohsu.edu/lco/action/home>. Updated April 2018
3. Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, MI. Available at <http://www.micromedexsolutions.com>. Updated April 2018.

Table 1: Antipsychotic Drugs, Indications, and General Information

Drug	Form.	t _{1/2} *	Adult Dose	FDA Indications	Pediatric Approval	Drug Specific Considerations	Cost
First Generation (typical) Antipsychotics							
Chlorpromazine (Thorazine)	Oral, IM	6 ~30	10mg TID-QID or 25 mg BID-TID	Bipolar disorder, manic episodes	No	Most weight gain of any first-generation antipsychotic Use caution in elderly due to relatively high sedation and anticholinergic side effects	\$\$\$
				Schizophrenia	No		
				Severe Problem Behavior	6 mo-12 yr		
			10-25mg Q6H PRN	Nausea and Vomiting	6 mo-12 yr		
Fluphenazine (Prolixin)	Oral, IM, Elix.	12.2	PO: 2.5-40 mg/d Q6-8hr IM: 1.25-10 mg/d Q6-8hr	Schizophrenia	No	Contraindicated with large doses of hypnotics, liver damage and subcortical brain damage	\$
LAI - (Prolixin Decanoate)	LAI	14-26 days	12.5-100 mg SubQ Q4-6 weeks	Schizophrenia, Chronic	No	12.5 mg Q3weeks = 10mg Oral daily Titrate to effectiveness (max 100mg)	\$
Haloperidol (Haldol)	Oral	14-37	2-5 mg BID-TID	Schizophrenia	≥ 3 yr	Not approved for IV administration, monitor EKG if given IV (higher risk of QT prolongation)	\$
			0.5-5 mg BID-TID, No Max established	Severe problematic behavior in children	≥ 3 yr		
			0.5-5mg BID-TID	Tourette's syndrome	≥ 3 yr		
LAI - (Haldol Decanoate)	LAI	21 d	10-20 x PO dose monthly	Schizophrenia, Chronic	No	Doses over 450mg per month have limited clinic evidence	\$
Loxapine (Loxitane)	Oral, IM	5-19	10-250 mg/day BID-QID	Schizophrenia	No	Dose above 250mg/day is not recommended	\$\$
Inh - (Adasuve)	Inh	7.6	10 mg within 24 hr	Bipolar I Disorder	No	REMS for asthma and bronchospasms	\$\$\$\$
Molindone (Moban)	Oral, IM	1.5	50-225 mg/day TID-QID	Schizophrenia	≥12 yr	36 Active metabolites	\$\$
Perphenazine (Trilafon)	Oral, IM	9-12 ~10-19	8-64mg/day BID-QID	Schizophrenia	≥ 12 yr	Active metabolites	\$
			8-32mg/day	Nausea and Vomiting	≥ 12 yr		
Pimozide (Orap)	Oral	55	1-10mg/day in divided doses	Tourette's syndrome	≥ 12 yr	CYP2D6 genotyping recommended for dose > 4mg in adults Contraindicated with other QTc prolonging medications	\$
Prochlorperazine (Compazine) (Procot) Rectal - (Compro)	Oral, IM, Rectal	6-22	5-10mg TID-QID	Nausea and Vomiting	≥ 2 yr	Contraindicated in children ≤ 9 kg	\$
			IM:10-20 mg Q2-4hr PO: 100-150mg/day TID-QID	Schizophrenia	≥ 2 yr		

Drug	Form.	t _{1/2} *	Adult Dose	FDA Indications	Pediatric Approval	Drug Specific Considerations	Cost
Thioridazine (Mefaril)	Oral	21-24	100-800 mg/day BID-QID	Schizophrenia, refractory	Yes	Contraindicated with other QTc prolonging medications or medications that prevent metabolism (fluvoxamine, propranolol, pindolol, fluoxetine and paroxetine)	\$\$
Thiothixene (Navane)	Oral	34	20-60 mg/day TID	Schizophrenia	≥ 12 yr		\$\$\$
Trifluoperazine (Stelazine)	Oral	3-12	1-2 mg BID	Anxiety, non-psychotic	No	Max 6 mg and no longer than 12 weeks	\$
			15-40 mg/day BID	Schizophrenia	6-12 yr		
Second Generation (Atypical) Antipsychotics							
Aripiprazole (Abilify)	Oral	75 ~94	2-15 mg/day QD	Autistic Disorder	≥ 6 yr	Schizophrenia: efficacy not significantly greater for doses > 15mg/day	\$\$
			10-30 mg/day QD	Bipolar disorder, maintenance and acute treatment +/- Lithium or valproate	≥ 10 yr		
			2-20 mg/day QD	Tourette's Syndrome	≥ 6		
			2-15 mg/day QD	Major Depressive Disorder (Adjunct)	No		
			10-30 mg/day QD	Schizophrenia	≥ 13 yr		
(Abilify Maintena)	LAI Maintena	29.9-46.5 d	400 mg once monthly (≥ 26 days)	Schizophrenia	No	~Missed Dose Schedule 2 nd /3 rd dose: > 5 wk since last dose, restart oral aripiprazole for 14 days ≥4 doses: > 6 wk since last dose, restart oral aripiprazole for 14 days	\$\$\$\$\$
(Aristada)	LAI Aristada	53-57 days	300 mg once monthly for adverse effects	Bipolar I Disorder, maintenance	No		
Asenapine (Saphris)	Oral (SL)	24	5-10 mg BID	Bipolar I Disorder	≥ 10 yr	Pediatric: Use for ≥10 yr for Bipolar I disorder as acute monotherapy Contraindicated severe hepatic disease	\$\$\$\$
				Schizophrenia	No		
Brexipiprazole (Rexulti)	Oral	91	0.5-3 mg QD	Major Depressive Disorder (Adjunct)	No	Dose adjustments recommended with CYP2D6 and/or CYP3A4 Inhibitors	\$\$\$\$
			1-4 mg QD	Schizophrenia	No		
Cariprazine (Vraylar)	Oral	2-4 d ~1-2 d ~1-3 wks	1.5-6 mg/day QD	Bipolar I Disorder	No	Use not recommended in severe renal (CrCl ≤ 30) or severe hepatic (Child-Pugh Class C) impairment	\$\$\$\$
				Schizophrenia	No		

Drug	Form.	t _{1/2} *	Adult Dose	FDA Indications	Pediatric Approval	Drug Specific Considerations	Cost
Clozapine (Clozaril)	Oral, Susp., ODT	12 (4-66)	25-900 mg/day -Dose based on tolerability and CBC	Treatment resistant schizophrenia	No	Black Box Warnings for Severe Neutropenia, Orthostatic Hypotension, Seizures, Myocarditis, Cardiomyopathy and mitral valve incompetence	\$\$
				Schizophrenia, recurrent suicidal behavior	No		
Iloperidone (Fanapt)	Oral	18-33 ~26-37 ~23-31	1-12 mg BID	Schizophrenia	No	Slow titration due to hypotension concerns QT Prolongation concern	\$\$\$\$\$
Lurasidone (Latuda)	Oral	18	40-160 mg QD	Schizophrenia	≥ 10 yr	Take with food, at least 350 Calories Renal and Hepatic adjustments (specified in Table 3)	\$\$\$\$\$
			20-120 mg QD	Bipolar Disorder	≥ 10 yr		
Olanzapine (Zyprexa)	Oral, IM ODT	30	5-20 mg/day	Bipolar I Disorder	≥ 13 yr, Acute only	Sedating with significant metabolic side effects	\$\$\$
			5-20 mg/day	Schizophrenia	≥ 13 yr		
			5-18 mg/day Flu: 20-50 mg/day	Major Depressive Disorder, with Fluoxetine	≥ 10 yr		
LAI – (Zyprexa Relprevv)	LAI	30 d	150 mg, 210 mg, 300 mg every 2 wks OR 300 mg or 405 mg every 4 wks	Schizophrenia	No	REMS: Post-injection delirium/sedation syndrome (PDSS). Continuous observation of patients for ≥ 3 hr in certified healthcare facilities	\$\$\$\$
Paliperidone (Invega)	Oral, IM	23	3-12 mg/day QD	Schizoaffective Disorder	No	Mild Renal Impairment t _{1/2} = 24 hr Moderate Renal Impairment t _{1/2} = 40 hr Severe Renal Impairment: t _{1/2} = 51 hr	\$\$\$\$
				Schizophrenia	≥ 12 yr		
LAI – (Invega Sustenna)[1 mo.]	LAI (sustenna)	25-49 d	39-234 mg Once monthly	Schizoaffective Disorder	No	Oral → LAI dose: 3 mg/day → 39-78 mg monthly 6 mg/day → 117 mg monthly 9 mg/day → 156 mg monthly 12 mg/day → 234 mg monthly	\$\$\$\$\$
(Invega Trinza) [3 mo.]	LAI (trinza)	84-95 d, 118-139 d	273-819 mg every 3 months	Schizophrenia	No		
Pimavanserin (Nuplazid)	Oral	57 ~200	34 mg QD	Parkinson's Disease, psychotic disorder	No	Strong CYP3A4 inhibitors = 17 mg QD	\$\$\$\$\$
Quetiapine (Seroquel)	Oral	6 (IR) 7 (ER) ~12	25-750mg/day QD- BID	Schizophrenia	≥ 13 yr	QT Prolongation Hepatic impairment: initiate dose at 25 mg IR and 50 mg ER. Titrate dose up as tolerated Schizophrenia: Max 800 mg/day for ER	\$\$\$ ER: \$\$\$\$
			50-300 mg/day QD	Major Depressive Disorder	No		
			50-300 mg/day QD	Bipolar Disorder	≥ 10 Acute for mania		

Drug	Form.	t _{1/2} *	Adult Dose	FDA Indications	Pediatric Approval	Drug Specific Considerations	Cost
Risperidone (Risperdal)	Oral, Solution ODT	3-20 ~21-30	0.25-3mg/day QD (initial 0.5 mg when ≥ 20 kg)	Autistic Disorder, irritability	≥ 5 yr and ≥ 15 kg	Renal: CrCl ≤ 30 mL/min initiate at 0.5 mg BID for Bipolar and Schizophrenia Hepatic: Child-Pugh Class C initiate at 0.5 mg BID for Bipolar and Schizophrenia	\$\$
			2-6 mg/day QD	Bipolar I Disorder	≥ 10 yr		
			2-8 mg/day QD	Schizophrenia	≥ 13 yr		
LAI – (Risperdal Consta)	LAI	3-6 d ~8 d	25-50 mg IM every 2 weeks	Bipolar I Disorder	No		\$\$\$\$
				Schizophrenia	No		
Ziprasidone (Gedon)	Oral, IM	7	20-80 mg BID	Bipolar I Disorder	No	Contraindicated in uncompensated heart failure, myocardial infarction (acute and recent), and QT Prolongation (history of)	\$\$\$
				Schizophrenia	No		

* Half-life reported in hours unless otherwise specified; ~ = active metabolite

Legend: t_{1/2} = half-life; LAI = Long-Acting Injectable; IM = Intramuscular; Inh = Inhalation; SL = Sublingual

Cost based on average AWP for average monthly maintenance dose

Estimated Average Monthly Cost based on AWP:

\$\$\$\$\$ ≥ 1500

\$\$\$\$ 1000 - 1500

\$\$\$ 500 - 1000

\$\$ 250 - 500

\$ 0-250

IR = Immediate Release; ER = Extended-Release

Table 2: Side Effects:

Drug	Trade Name	Weight Gain	Hyper-cholesterolemia	EPS/TD	Prolactin	Sedation	Anticholinergic Effects	Hypotension	QTc Prolongation
First Generation Antipsychotics									
Chlorpromazine	Thorazine	+++	+	+	++	+++	+++	+++	+
Fluphenazine*	Prolixin	+	+	+++	+++	+	-/+	-	ND
Haloperidol*	Haldol	+	+	++	+++	++	-/+	-	+
Loxapine	Loxitane	++	ND	++	++	++	+	+	+
Perphenazine	Trilafon	++	ND	++	++	++	+	-	ND
Pimozide	Orap	+	ND	+++	++	+	+	+	++
Thioridazine	Melfaril	++	ND	+	+++	+++	++++	++++	+++
Thiothixene	Navane	++	ND	+++	++	+	+	+	+
Trifluoperazine	Stelazine	++	ND	+++	++	+	+	+	ND
Second Generation Antipsychotics									
Aripiprazole*	Abilify	+	-	+	-	+	-	-	-/+
Asenapine	Saphris	++	-	++	++	++	-	+	+
Brexpiprazole	Rexulti	+	+	+	-/+	+	-/+	-/+	-/+
Cariprazine	Vraylar	+	-/+	++	-/+	+	-/+	-/+	-/+
Clozapine	Clozaril	++++	++++	-/+	-/+	+++	+++	+++	+
Iloperidone	Fanapt	++	++	-/+	-/+	+	+	+++	++
Lurasidone	Latuda	-/+	-/+	++	-/+	++	-	+	-/+
Olanzapine*	Zyprexa	++++	++++	+	+	++	++	+	+
Paliperidone*	Invega	+++	+	+++	+++	+	-	++	+
Pimavanserin	Nuplazid	+	-	-/+	-	+	+	++	+
Quetiapine	Seroquel	+++	+++	-/+	-/+	++	++	++	+
Risperidone*	Risperdal	+++	+	+++	+++	+	+	+	+
Ziprasidone	Geodon	-/+	-/+	+	+	+	-	+	++

Legend: * = Long acting injectable agent available

Table 3. Pharmacokinetics and Dosing consideration

Drug	Form.	$t_{1/2}$ *	Tmax	Metabolism	Oral BA	Dosing Considerations
First Generation Antipsychotics						
Chlorpromazine (Thorazine)	Oral, IM, IV	6 ~30	PO: 2.8 IM: 1-4 IV: 2-4	Extensive Hepatic metabolism: glucuronidation and CYP2D6	32%	No renal or hepatic dose adjustments
Fluphenazine (Prolixin) LAI - (Prolixin Decanoate)	Oral	12.2	PO: 2 IM: 1.5-2	No well-defined metabolic pathway	20-50%	High Volume of distribution: 10,580- 61,924 L/kg Variable oral absorption Contraindicated with liver damage
	LAI	14-26 days	34-65			
Haloperidol (Haldol) LAI - (Haldol Decanoate)	Oral	PO: 14-37 IM: 20	PO: 3-6 IM: 20min	50-60% Glucuronidation CYP2D6 and CYP3A4 activity	60-86%	Do not administer IV due to high risk of QT prolongation resulting in Torsades de Pointes Administer initial doses > 100 mg 3-7 days apart
	LAI	21 days	6 days			
Loxapine (Loxitane) Inh - (Adasuve)	Oral	Initial: 5 Final: 19	1.5-3	Extensive Liver Metabolism: CYP1A2, CYP2D6, CYP3A4 substrates.	100%	Inhibitor of P-glycoprotein Active and inactive metabolites Contraindicated for asthma or COPD
	Inh	7.6	1.1 min			
Molindone (Moban)	Oral, IM	1.5	1.5	Hepatic (36 active metabolites)	-	Duration of action: 24-36 hours
Perphenazine (Trilafon)	Oral, IM	9-12 ~10-19	1-3	CYP2D6, glucuronidation and sulfoxidation	-	Poor CYP2D6 metabolizers may have prolonged half-life
Pimozide (Orap)	Oral	55	6-8	CYP2D6, CYP3A4, CYP1A2	≥50%	CYP2D6 Poor metabolizers increase dose in 14-day intervals Contraindicated with other QT prolonging medications or strong CYP2D6 Inhibitors
Prochlorperazine (Compazine) (Procot) Rectal - (Compro)	Oral, IM, Rectal	6-22	0.5-1	Hepatic (active metabolite)	12.5%	No renal or hepatic dose adjustments
Thioridazine (Mefaril)	Oral	21-24	1-4	Extensive Hepatic metabolism	25-33%	Do not use with QT prolonging medications or inhibitors of thioridazine metabolism (see table 1)
Thiothixene (Navane)	Oral	34	-	CYP1A2 metabolism	Erratic	High lipophilicity
Trifluoperazine (Stelazine)	Oral	3-12	1.5-6	In the gut and liver (active)	Erratic	Onset 2-4 weeks

Drug	Form.	t _{1/2} *	Tmax	Metabolism	Oral BA	Dosing Considerations
Second Generation Antipsychotics						
Aripiprazole (Abilify)	Oral	75 ~94	3-5	Extensive Hepatic metabolism via CYP2D6 and CYP3A4	87%	See table 1 for LAI missed dose schedule Concurrent strong CYP2D6 or CYP3A4 inhibitors reduce dose by 50% -For LAI 400 mg → 200 mg and 300 mg → 160 mg
(Abilify Maintena)	LAI (Maintena)	29.9-46.5 days	4-7 days			
(Aristada)	LAI (Aristada)	53-57 days	4-7 days			
Asenapine (Saphris)	Oral (SL)	24	0.5-1.5	Hepatic via CYP1A2 and UGT1A4	35%	Use contraindicate in severe hepatic impairment (Child-Pugh Class C)
Brexpiprazole (Rexulti)	Oral	91	4	Hepatic via CYP3A4 and CYP2D6	95%	CYP2D6 poor metabolizers reduce dose to 50% (reduce to 25% if concomitant strong inhibitors of CYP3A4 as well)
Cariprazine (Vraylar)	Oral	2-4 days ~1-2 days ~1-3 wks	3-6	Extensive Hepatic metabolism via CYP 3A4	50%	Reduce dose to 50% with concurrent strong inhibitor of CYP3A4
Clozapine (Clozaril)	Oral	12 (4-66)	2.2-2.5	Extensive Hepatic metabolism via CYP1A2 (primary), CYP2C19, CYP3A4, CYP2D6	27-60%	Monitoring: REMS for severe neutropenia. ANC > 1500/mcL (>1000/mcL with benign ethnic neutropenia) required for initiation CBC: weekly for 6 months, then every other week for 6 months, then monthly thereafter
Iloperidone (Fanapt)	Oral	18-33 ~26-37 ~13-31	2-4	Extensively Hepatic metabolism via CYP2D6 and CYP3A4	96%	Weak inhibitor of P-glycoprotein Use not recommended in severe hepatic impairment: Child-Pugh Class C
Lurasidone (Latuda)	Oral	18	1-3	Hepatic Via CYP3A4 (active metabolite)	9-19%	Take with food, at least 350 Calories Renal: CrCl ≤ 50 mL/min = Max 80 mg/day Hepatic: Class B Max 80 mg/day Hepatic: Class C Max 40 mg/day
Olanzapine (Zyprexa)	Oral, IM	30	1-8	Hepatic via CYP1A2 and CYP2D6	Rapid	40% removed via first pass metabolism
LAI – (Zyprexa Relprevv)	LAI	30 days	7 days			

Drug	Form.	t _{1/2} *	Tmax	Metabolism	Oral BA	Dosing Considerations
Paliperidone (Invega) LAI – (Invega Sustenna)[1 mo.] (Invega Trinza) [3 mo.]	Oral, IM	23	24	P-glycoprotein Limited Hepatic Metabolism	28%	Mild Renal Impairment t _{1/2} = 24 hr Moderate Renal Impairment t _{1/2} = 40 hr Severe Renal Impairment: t _{1/2} = 51 hr
	LAI (Sustenna)	25-49 days	13 days			
	LAI (Trinza)	84-95 d, 118-139 d	30-33 days			
Pimavanserin (Nuplazid)	Oral	57 ~200	6	Primarily CYP3A4 and CYP3A5 Some CYP2J2 and CYP2D6	-	Strong CYP3A4 inhibitors = 17 mg QD
Quetiapine (Seroquel)	Oral	6 (IR) 7 (ER) ~12	1.5 (IR) 6 (ER)	Primarily CYP3A4 (active metabolite)	100%	Rapid absorption with high fat meals (800-1000 Cal) increase C _{max} 8% and AUC 2% of ER formulation
Risperidone (Risperdal) LAI – (Risperdal Consta)	Oral	3-20 ~21-30	1 17 (PM)	Extensive Hepatic metabolism via CYP2D6	70% 94% (ODT)	Dose adjustments with renal or hepatic impairment or with concomitant use of CYP3A4 inducers or CYP2D6 inhibitors
	LAI	3-6 d ~8 d	29-31 d			
Ziprasidone (Gedon)	Oral	7	6-8	Hepatic metabolism via CYP3A4 and CYP1A2	60%	Take with ≥ 500 calories of food. Increase Oral BA up to 2-fold

* t_{1/2} = Half-life reported in hours unless otherwise specified; ~ = active metabolite; wks = weeks

**Paliperidone 3-month extended release LAI

^ Active Metabolite Half-life

CYP = Cytochrome P540; UGT = UDP-Glucuronosyltransferase

Oral BA = Oral Bioavailability

IR = Immediate Release; ER = Extended-Release

PM = Poor metabolizer

AUC = Area Under the curve; C_{max} = Maximum Concentration

T_{max} = Time to maximum concentration (absorption), reported in hours unless otherwise specified

Inh = Inhalation; SL = Sublingual

CBC = Complete Blood Count; ANC = Absolute Neutrophil Count

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OLD TOWN RECOVERY CENTER

Pharmacist Collaborative Drug Therapy Management Protocol for the Initiation, Titration and Management of Clozapine

DATE OF APPROVAL: _____

DATE OF IMPLEMENTATION: _____

DATES BI-ANNUAL REVIEW COMPLETED: _____

The Pharmacy Practice Act allows pharmacists to practice under a collaborative practice agreement with individual healthcare providers (HCPs) or groups of HCPs. Pharmacists may participate in the practice of managing, modifying, and monitoring drug therapy, and provide education related to therapy according to a written protocol between the specific pharmacist(s) and the healthcare provider(s) who is/are responsible for the patient's care and authorized to prescribe drugs. This collaborative drug therapy management (CDTM) protocol is to be considered as standard of professional practice or as rules of conduct. The established protocol(s) are to be used as guidelines only and allow for professional discretion and deviation where the individual healthcare provider deems to be appropriate.

By signing this document, the named physicians agree that the named pharmacists may enter into a collaborative practice for their patients.

CLINICAL PHARMACIST(S):

Print Name	Signature	Date
Petrus Oliphant, PharmD – <i>principle practicing pharmacist</i>		
Adam Day, PharmD		
Jazz Valencia, PharmD		

PHYSICIAN(S):

Print Name	Signature	Date
John Bischof, MD Psychiatric Medical Director, Old Town Recovery Center (OTRC) – <i>principle practitioner</i>		
Shauna Hahn, Psychiatric Mental Health Nurse Practitioner (PMHNP), OTRC		
Tracy Bitz, PMHNP		

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1. Introduction

Clozapine (Trade name “Clozaril”) is an effective antipsychotic medication indicated in treatment resistant schizophrenia (TRS), schizoaffective disorder (especially with suicidality or intermittent suicidality) and/or treatment-resistant bipolar depression (TRBD) which has failed at least 2-3 combinations of antipsychotics, mood stabilizers and other neuroleptics (e.g., lithium, valproic acid, carbamazepine, oxcarbazepine).^{1,2}

Clozapine is the only antipsychotic proven to be more effective than alternative agents for the treatment of refractory schizophrenia, bipolar disorder and schizoaffective disorder.¹ However, the administrative burden of prescribing, monitoring and appropriate follow-up has limited practitioners at Old Town Recovery Center (OTRC) from initiating clozapine to only those patients that will benefit most from therapy.

The standardization of practices in the prescribing, administering and monitoring of clozapine by practitioners and collaborating pharmacists will ensure good evidence-based practice if followed by staff, enhancing patient care and reducing the potential for error. Additionally, it will increase the availability of clozapine therapy to a wider range of treatment-resistant patients who may greatly benefit from its use.

1.1. Aims

The purpose of this document is to establish guidelines for participating pharmacists managing clozapine therapy for patients under the care of participating providers at OTRC. These guidelines define the roles and responsibilities of participating prescribers and collaborating pharmacists caring for patients currently taking clozapine or initiating therapy on clozapine.

1.2. Objectives

To ensure that monitoring procedures for safe and effective prescribing of clozapine are followed by participating practitioners/pharmacists in a timely/appropriate manner and to expand availability of clozapine therapy to all patients who may benefit from use.

1.3. Scope

These guidelines are to be used by participating pharmacists who are actively managing patients of participating providers to direct the safe and effective use of clozapine therapy. These guidelines are in no way intended to replace clinical judgement.

The decision to initiate clozapine therapy may only be made by the assigned psychiatric provider (Psychiatrist, Psych NP, etc).

1.4. Key Stakeholders

Participating psychiatric providers, pharmacists, psychiatric nurses, pharmacy technicians and all others involved in the prescribing, dispensing, and administration of clozapine to patients enrolled at OTRC.

1.5. Quality

The principle pharmacist and practitioner will meet on a bi-annual basis to review and revise the CDTM protocol.

Participating pharmacists and practitioners may meet to discuss patient outcomes.

1.6. Documentation

All activities will be documented in the patient electronic medical record and a copy will be forwarded to the patient’s psychiatric provider for review and signature.

Psychiatric providers are required to review the documentation of each visit conducted by the clinical pharmacists and document their review.

Any questions or concerns should be addressed to the clinical pharmacist as soon as possible.

1.7. Acknowledgements

This collaborative practice agreement was developed using already developed guidelines for clozapine management including: Veterans Health Administration “Clozapine Patient Management Protocol,” National Health Service Wales “Protocol for the Use and Administration of Clozapine” and California Correctional Health Care Services/Division of Health Care Services “Care Guide: Clozapine.”

2. Before Starting Clozapine

2.1. Provider Visit

Provider provides the pharmacist with patient's diagnosis and goal of care.

Provider refers patient to clinic pharmacist for brief (approximately 10-15 minute) meeting

2.2. Initial, Brief Pharmacist Meeting (10-15 minutes)

2.2.1. Patient Education

2.2.2. Baseline Labs/Monitoring

Pharmacist obtains/orders the following vitals/labs for baseline and continuous monitoring:

- Initial, plus 25 weekly standing CBC orders post-dated for future monitoring
- Lipid panel if fasting/direct LDL if not fasting
- HbA1c
- CMP
- EKG (if clinically indicated)
- CRP and troponin I – initial, plus 4 weekly standing orders post-dated for the first 4 weeks of therapy
- Height (if not recorded previously)
- Weight
- Blood pressure
- Clozapine level post-dated for expected date patient will reach 100mg per day in titration schedule

Baseline, continuous monitoring schedule can be found in **Appendix A: Table 1.**

30 minute clozapine initiation visit scheduled with pharmacist the following business day

3. Clozapine Initiation

3.1. Initial Clozapine Order Placed by Pharmacist

3.1.1. Baseline CBC

- If Absolute Neutrophil Count (ANC) $\geq 1500/\mu\text{L}$, pharmacist may enter and fill initial clozapine order
- If Absolute Neutrophil Count (ANC) $\leq 1500/\mu\text{L}$, pharmacist must inform psychiatric provider and primary care provider. Pharmacist must also communicate to patient that clozapine may not be dispensed

3.1.2. Constipation Prophylaxis

Consider prophylactic bowel regimen to prevent potentially serious or life-threatening constipation, especially in patients with history of constipation or on other medications known to cause constipation (see Treatment Options for Clozapine-Induced Constipation **Appendix B: Table 2**)

3.1.3. Clozapine Initiation Dose

Initial dose and titration of clozapine to be determined by (but not limited to):

- Baseline vitals/labs
- History of orthostasis/falls
- Concurrent medications, smoking history, caffeine intake or any other factors that may interfere with clozapine metabolism or result in additive side effects that increase the risk of dose-dependent clozapine effects
- Clinical judgement must be used in initial titration schedule as there is no uniform dosing strategy
- See **Appendix A: Table 4** for common titration schedule

3.2. First Clozapine Dispense (20-30 minute visit)

Pharmacist may only dispense enough clozapine to last until next CBC result is due (e.g. 7 days if CBC drawn the day before clozapine is dispensed and results are within acceptable range)

3.2.1. Patient Education

Pharmacist reviews pertinent baseline vitals/labs with patient

Pharmacist reviews common side effects, signs/symptoms of less common/serious side effects and counsels patient on preventive measures that reduce fall risk, constipation, and metabolic risk

Pharmacist reviews patient's goals of therapy and usual time to both initial and full benefit

Patient provided with the following informational handouts (**Appendix C**):

- *Clozapine – Reducing Side Effects and Drug Interactions*
- Clozapine patient information (from Pharmacy dispensing system)
- *Heart Disease: Frequently Asked Questions*

3.2.2. Pharmacist reviews past medical history/lab data for the following:

- Liver disease
- Renal function
- Seizure disorder
- Heart disease or congenital long-qt syndrome or multiple qt prolonging medications
 - o EKG indicated – EKG prior to initiation is largely based on clinical judgement
- Constipation/medications that may cause constipation
- HbA1c
- Lipid panel
- Weight/vitals must be obtained if not already done so

The pharmacist will obtain the above lab information the following week if not completed within the last 3 months

3.2.3. Referrals

Referral to OTRC Wellness group and/or OTC Nicotine Dependence Program for current smokers are encouraged to reduce cardiovascular risk

- OTRC Wellness Referral Contact: Alex Romer (ext. 6137) or Jade Adams (ext. 6138)
- OTC Smoking Cessation Contact: Kerith Hartmann (ext. 6049)

4. Follow-up

4.1. Frequency

Pharmacist will follow-up weekly with patient until

- The lowest effective clozapine dose has been reached
- Side effects are controlled to a level that is acceptable to the patient

4.2. Evaluation of Response to Clozapine

Response to clozapine occurs within 6 months on average.

Every effort should be made to achieve an adequate therapeutic trial for any patient placed on clozapine. An adequate therapeutic trial is a 6 month period during which the patient has a therapeutic level of clozapine at least 250ng/ml.³

4.3. Interruption of Clozapine Therapy

If clozapine therapy is interrupted for more than 48 hours, therapy should be restarted at the initial starting dose to minimize risks of hypotension, bradycardia, and syncope.

If clozapine therapy is interrupted, the frequency of ANC monitoring must be evaluated using the guidelines for ANC monitoring **Appendix A: Table 1**

4.4. Re-challenge or Retreatment with Clozapine After Treatment Interruption

Patients may be re-challenged with clozapine if benefits of treatment outweigh the risk of neutropenia. However, generally patients with clozapine related myocarditis or cardiomyopathy should not be re-challenged with clozapine, see guidelines for ANC monitoring **Appendix A: Table 1**
Patients with any neutropenia must have ANC monitored more frequently until levels reach target or baseline.

4.5. Management of Adverse Clozapine Side Effects

Monitoring for common clozapine-associated side effects must occur at each weekly visit according to **Appendix A: Table 5** until tolerable at stable dose of clozapine. Patient should then be screened for side effects as indicated

For management of common clozapine-associated side effects, refer to **Appendix B: Clozapine Adverse Effects Management**

4.6. Monitoring

4.6.1. Routine Labs and Diagnostics

Refer to **Appendix A: Table 1** for details on routine lab and diagnostic monitoring

4.6.2. CBC Monitoring

Refer to **Appendix A: Tables 2 and 3** for specific details regarding CBC monitoring

4.7. Cross-Tapering medications

The pharmacist may cross-taper and discontinue other psychiatric medications prescribed by patient's psychiatric provider.

The pharmacist will prioritize taper & discontinuation of psychiatric medications based on the following considerations:

- Patient preference
- Side effect profile and tolerability issues related to other medications
- Drug-drug interactions
- Drug-smoking/caffeine interactions
- Clozapine-related tolerability issues
- Efficacy of other medications
- Efficacy of clozapine

The pharmacist will use best clinical judgement and consult with overseeing provider if any doubt regarding dose optimization of clozapine and/or other psychiatric medications

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Appendix A: Monitoring Tables and Sample Titration Schedule

TABLE 1: PHARMACIST CLOZAPINE MONITORING*¹

EVALUATION	BASELINE OR AS INDICATED	EVERY 3 MONTHS/MORE FREQUENTLY	ANNUAL OR AS INDICATED
HEIGHT / WEIGHT / BMI	BASELINE Height only necessary if not previously recorded	Weight, from initiation date: 4 weeks 8 weeks 12 weeks 6 months	ANNUAL
BLOOD PRESSURE VITAL SIGNS	BASELINE • Before initiation of clozapine • At least monthly during titration. More frequently if clinically indicated	YES WHEN STABLE DOSE ACHIEVED x2 WEEKS OR MORE	ANNUAL
BOWEL FUNCTION ASSESSMENT	BASELINE Weekly during first 3 months of therapy		At every MH provider visit while on therapy
EKG	AS INDICATED (SEE APPENDIX B, TABLE 1)		ANNUAL
ANC (absolute neutrophil count) -see tables 2 and 3 for more detailed information	BASELINE • Weekly for first 6 months and • Every two weeks for second 6 months or as indicated based on ANC • Monthly after 1 year	SEE BASELINE COMMENT	MONTHLY AFTER ONE YEAR OF THERAPY
CMP	BASELINE		ANNUAL
FASTING GLUCOSE / A1C	BASELINE	3 MONTHS AFTER INITIATION, THEN ANNUALLY	ANNUAL
LIPID PANEL AND DIRECT LDL	BASELINE	3 MONTHS AFTER INITIATION, THEN ANNUALLY	ANNUAL
C-Reactive Protein (CRP) and Troponin I	BASELINE, THEN WEEKLY FOR FIRST 4 WEEKS	AS INDICATED	
ECHOCARDIOGRAM	AS INDICATED (SEE APPENDIX B, TABLE 1)		
CLOZAPINE PLASMA LEVELS	5-7 DAYS FOLLOWING TITRATION TO 100 MG A DAY	AS INDICATED	

* Adapted from California Division of Health Care Services “*Care Guide: Clozapine*,” American Psychiatric Association metabolic monitoring guidelines for patients taking second generation antipsychotics, Veteran’s Affairs Pharmacist Scope of Practice Agreement for Clozapine Therapy, Australian Guidelines for Monitoring Myocarditis and Clozapine REMS monitoring guidelines

Table 2: ANC Monitoring Guidelines in Clozapine Initiation and Maintenance in the General Population

ANC Level		Treatment Recommendation	AN
Normal Range (New Patient)	>1500	• Initiate treatment • If treatment interrupted: ◦ <30 days, continue monitoring as before ◦ ≥30 days, monitor as if new patient • Discontinuation for reasons other than neutropenia	• Weekly from initiation to 6 months • Every 2 weeks from 6-12 months • Monthly after 12 months
Mild Neutropenia*	1000-1499	• Continue treatment	• Three times weekly until ANC ≥1500/microliter • Once ANC ≥1500/microliter, return to patient's last "Normal Range" ANC monitoring interval, if clinically appropriate
Moderate Neutropenia*	500-999	• Recommend hematology consultation • Interrupt treatment for suspected clozapine induced neutropenia • Resume treatment once ANC normalizes to ≥1000/microliter	• Daily until ANC ≥1000/microliter, then • Three times weekly until ANC ≥1500/microliter • Once ANC ≥1500/microliter, check ANC weekly for 4 weeks, then return to patient's last "Normal Range" ANC monitoring interval, if clinically appropriate
Severe Neutropenia*	<500	• Recommend hematology consultation • Interrupt treatment for suspected clozapine induced neutropenia • Do not rechallenge unless prescribed determines benefits outweigh risks	• Daily until ANC ≥1000/microliter • Three times weekly until ANC ≥1500/microliter • If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥1500/microliter

**Confirm all initial reports of ANC<1500/microliter with a repeat ANC measurement within 24 hours*

Table 3: ANC Monitoring Guidelines in Clozapine Initiation and Maintenance in the Benign Ethnic Neutropenia (BEN) Population		
ANC Level	Treatment Recommendation	ANC Monitoring
Normal Range ≥ 1000 (Mild Neutropenia – New Patient)*	- Obtain at least 2 baseline ANC levels before initiating treatment - If treatment interrupted: <30 days, continue monitoring as before ≥ 30 days, monitor as if new patient - Discontinuation for reasons other than neutropenia	- Weekly from initiation to 6 months - Every 2 weeks from 6-12 months - Monthly after 12 months
Moderate Neutropenia* 500-999	- Recommend hematology consultation - Continue treatment	- Three times weekly until ANC ≥ 1000/microliter or $\geq$patient's known baseline - Once ANC ≥ 1000/microliter or patient's known baseline, then check ANC weekly for 4 weeks, then return to patient's last "Normal BEN Range" ANC monitoring interval, if clinically appropriate
Severe Neutropenia* <500	- Recommend hematology consultation - Interrupt treatment for suspected clozapine induced neutropenia - Do not rechallenge unless prescriber determines benefits outweigh risks	- Daily until ANC ≥ 500/microliter - Three times weekly until ANC $\geq$patient's established baseline - If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥ 1000/microliter or at patient's baseline
*Confirm all initial reports of ANC <1000/microliter with a repeat ANC measurement within 24 hours		

Table 4: Sample Clozapine Initiation and Titration Schedule (with dose increases every 3 days)*		
Week 1	AM Dose (mg)	PM dose (mg)
Day 1 Initiate	0	12.5
Day 2	0	12.5
Day 3	0	12.5
Day 4	12.5	12.5
Day 5	12.5	12.5
Day 6	12.5	12.5
Day 7	12.5	12.5
Week 2	AM Dose (mg)	PM Dose (mg)
Day 8	12.5	25
Day 9	12.5	25
Day 10	12.5	25
Day 11	25	25
Day 12	25	25
Day 13	25	25
Day 14	25	25
Week 3	AM Dose (mg)	PM Dose (mg)
Day 15	25	37.5
Day 16	25	37.5
Day 17	25	37.5
Day 18	37.5	37.5
Day 19	37.5	37.5
Day 20	37.5	37.5
Day 21	37.5	37.5
Week 4	AM Dose (mg)	PM Dose (mg)
Day 22	37.5	50
Day 23	37.5	50
Day 24	37.5	50
Day 25	50	50
Day 26	50	50
Day 27	50	50
Day 28	50	50
<i>* Sample titration schedule is relatively conservative and dose increases of 50 mg a week may be utilized in patients showing good tolerability. Initial dose and titration of clozapine to be determined by baseline vitals/labs, history of orthostasis/falls and concurrent medications that may interfere with clozapine metabolism or result in additive side effects that increase the risk of dose-dependent clozapine effects. Clinical judgement must be used in initial titration schedule as there is no uniform dosing strategy in the outpatient setting.</i>		

0 = none 1 = mild 2 = moderate 3 = severe

Table 5: Clozapine side effects screening checklist		
Side Effect	0-3	Comments
Appetite/weight increase		
Hyper salivation		
Excessive sweating		
Postural hypotension		BP-Sitting Standing
Blurred vision		
Confusion		
Constipation		
Diarrhea		
Fluctuating temperature		
Sore Muscles/Joints		
Nausea/vomiting		
Sedation/fatigue/drowsiness		
Jerky movements/fits/seizures		
Rapid pulse		Pulse <u> </u>
Tremor		
Urinary incontinence/retention		
Other		

Appendix B: Clozapine Side Effects Management

Table 1: CLOZAPINE ADVERSE EFFECTS AND SUGGESTED MANAGEMENT

Adverse Effect	Clinical Presentation/ Diagnostic Features	Action/Comments
ABNORMAL¹ INVOLUNTARY MOVEMENTS	Abnormal movements caused by clozapine are very rare. When seen, they are primarily mild and orolingual	- Clozapine has been shown to improve tardive dyskinesia (TD) symptoms. - Clozapine has rarely been reported to cause TD symptoms. - Evaluate medication regimen to identify more likely causes if TD present
AGRANULOCYTOSIS/ LEUKOPENIA²	Fever, weakness, lethargy, and/or sore throat	- Fatal agranulocytosis: - Occurs in 1-2% of patients. - Incidence increases with age. - Incidence higher in Jewish population. - Monitoring and reporting CBC/ANC to clozapine registry is critical. - Some patients will require interruption or permanent discontinuation of clozapine. Rechallenge may be considered in some cases based on degree of ANC reduction. (Benefits must outweigh risks). - Results must be reviewed promptly and indicated treatment adjustments ordered.
CONSTIPATION	Abdominal discomfort, distension, cramping, slow or absent bowel movements or intestinal obstruction and paralytic ileus which may be fatal	See Prevention and Management of Bowel Dysfunction, Appendix B: Table 2
CARDIOMYOPATHY^{3, 4}	New onset systolic dysfunction on any echocardiogram in the follow-up period characterized as: LVEF < 50% AND At least a 10% reduction in LVEF from baseline OR most recent echocardiogram LVEF = Left ventricular ejection fraction.	- Symptoms consistent with heart failure and include fatigue, dyspnea, palpitations, chest pain, tachycardia - Many cases are asymptomatic - Symptom onset has been noted from 6 to 66 months - Refer to PCP and/or cardiology as indicated
ECG CHANGES⁵	QT prolongation, syncope, pre-syncope, dizziness, palpitations, arrhythmias, cardiac arrest	- QT prolongation and life-threatening arrhythmias may occur. - Discontinue and/or refer to cardiologist if QTc > 500 msec. - Risk is increased with other QT prolonging agents, electrolyte abnormalities, significant arrhythmia, recent MI, uncompensated CHF. - Monitor for other signs of myocarditis or ischemia closely, especially if ECG changes are occurring within the first month of therapy. - ECG changes typically normalize when drug discontinued.
EOSINOPHILIA⁶	Eosinophil count > 700/μl	- Eosinophilia develops in about 1% of patient. If eosinophilia occurs, evaluate patient for signs of rash or other allergic symptoms. - Eosinophilia from clozapine without organ involvement can resolve without intervention and clozapine may be continued with careful monitoring. - If clinically indicated, obtain ECG and look for sign/symptoms of myocarditis or other organ specific disease (pancreatitis, hepatitis, colitis, nephritis). Fatal organ injury may occur. - Treat underlying cause of eosinophilia unrelated to clozapine (e.g., asthma, allergies, parasites, specific neoplasms).
HYPERTHERMIA (BENIGN)⁷	Transient clozapine-related fever may occur (up to 100.4°F)	- Reduce speed of dose titration and decrease dose of clozapine if any hyperthermia develops. - Peak incidence of transient benign fever occurs in first 3 weeks of treatment. - Benign hyperthermia resolves over time and responds to antipyretics. - Discontinue clozapine if temperature exceeds 101°F. - Gradually restart when hyperthermia subsides. - Fever may be associated with increase or decrease in WBC. Infection and agranulocytosis should be ruled out. Also consider possibility of myocarditis or neuroleptic malignant syndrome.

Table 1: CLOZAPINE ADVERSE EFFECTS AND SUGGESTED MANAGEMENT

Adverse Effect	Clinical Presentation/Diagnostic Features	Action/Comments
ORTHOSTATIC HYPOTENSION	Dizziness, orthostatic hypotension and/or bradycardia	- Risk highest during initial titration period, initial dose should not exceed 12.5 mg once or twice daily. - Monitor orthostatics closely upon initiation and with dose increases - Use cautious titration and divided dosage schedule to minimize risk of serious cardiovascular reactions. - Use with caution in patients with ASCVD, cerebrovascular disease, and those receiving antihypertensive agents. See Appendix B: Table 4 for treatment recommendations.
METABOLIC CHANGES⁸	Signs of insulin resistance: ☐Hyperglycemia ☐Dyslipidemia ☐Weight gain	- Monitor weight/BMI: clozapine can cause significant weight gain (average of 30 lbs in a 10 year cohort study). Most weight gain occurs in first 6-12 months of therapy. - DM developed in 34% of 96 patients followed up to 10 years. - Monitor BP, lipids - Increased risk of cardiovascular and cerebrovascular events from obesity, DM, dyslipidemia, hypertension.
MYOCARDITIS⁴	At least ONE symptom AND/OR sign of cardiac dysfunction: - Chest pain - Flu-like symptoms - Persistent tachycardia (heart rate > 100 beats per minute) - Signs of heart failure (3rd heart sound, basal crepitations, peripheral edema) PLUS At least ONE of the following diagnostic abnormalities: - Elevated troponin I (>2 ULN) - Echocardiographic evidence of systolic dysfunction - Evolutionary ECG changes involving T-wave inversion or >1 mm ST-segment deviation in at least 2 contiguous leads	- Immediately discontinue clozapine and refer to TTA. - Monitor closely, especially during first 4 weeks of therapy. Myocarditis is associated with elevated eosinophils, CRP, ESR, CPK, troponin, and brain natriuretic peptide (BNP). - Clozapine-induced myocarditis is an absolute contraindication to clozapine therapy.
NEUROLEPTIC MALIGNANT SYNDROME (NMS)⁹	Hyperpyrexia, muscle rigidity, altered mental status, autonomic instability, unstable blood pressure, stupor	- Although clozapine has only a weak affinity for dopamine receptors, NMS, which is potentially fatal, can develop during clozapine monotherapy or when used concomitantly with other CNS active agents. - Management includes: - Immediate discontinuation of antipsychotic drugs and other nonessential medications. - Intensive symptomatic treatment and medical monitoring, and/or treatment of comorbid conditions.
PULMONARY EMBOLISM¹⁰	Dyspnea, pleuritic pain, orthopnea, cough, calf or thigh pain with or without swelling, hemoptysis, wheezing	- There have been cases of deep vein thrombosis and pulmonary embolism associated with the use of clozapine, in some cases fatal. - Clozapine should be withdrawn promptly under the supervision of a psychiatrist in the case of venous thromboembolic events, and alternative antipsychotic therapy should be commenced to avoid recurrence of target symptoms. - In order to minimize risk of DVT or PE: - Minimize weight gain. - Avoid sedentary lifestyle (encourage frequent movement/exercise).

Table 1: CLOZAPINE ADVERSE EFFECTS AND SUGGESTED MANAGEMENT

Adverse Effect	Clinical Presentation/ Diagnostic Features	Action/Comments
SALIVATION¹¹	Excessive salivation, drooling	- May be treatment limiting as excessive drooling is stigmatizing and may interfere with sleep. - May respond to dose reduction. - See Appendix B: Table 3 for treatment recommendations
SEIZURE^{12, 13, 14}	Seizures	- Prophylactic therapy should be considered in patients previously treated for seizures who are currently not on anticonvulsants. - Obtain an EEG if patient seizes during clozapine treatment as an underlying seizure focus may be unmasked. - Seizure risk is dose related. Initiate treatment at low dose, titrate slowly, use divided dosing. Patients on doses ≥ 600 mg/day have four times more seizures than those on ≤ 300 mg/day. - Seizure risk increases in relation to the rapidity of dose titration (faster than 25mg/day), or in relation to the total daily dose.
TACHYCARDIA, SUSTAINED¹⁵	HR increase ≥ 10 -15 bpm	- Monitor for other signs of cardiotoxicity closely, especially if resting tachycardia persists during the first two months of therapy. - Tachycardia is a common side effect of clozapine, occurs in about 25% of users, especially during initiation and dose titration.
ENURESIS	Repeated involuntary voiding of urine into bed or clothes	- Least invasive treatment options are preferred initially. Pharmacological treatment may be considered after non-pharmacological treatment is unsuccessful - May respond to dose reduction - See Appendix B: Table 5 for treatment recommendations

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Table 2: Treatment Options for Clozapine-induced Constipation^{1,2}**Therapy goals**

- Maintain normal bowel function.
- Minimize polypharmacy in constipation management.
- Prevent acute constipation, ileus, and bowel obstruction.

For all clozapine patients

- Discontinue other constipating medications (especially other anticholinergics), if possible.
- Increase daily fluid and fiber intake (cereals, wheat bran, fruits and vegetables).
- Encourage regular exercise.

ACUTE CONSTIPATION TREATMENT*— “RESCUE”

Interventions to evacuate colon and provide symptom relief include:

- ✓ Milk of Magnesia (osmotic agent), 2 tbsp orally, may repeat every 6-8 hours
- ✓ Magnesium Citrate (osmotic agent), 150-300 ml orally
- ✓ Bisacodyl (Dulcolax), 10 mg suppository
- ✓ Large volume enema

LAXATIVE MEDICATION	DOSE	ACTION ONSET	COMMENTS/ADVERSE EFFECTS
BULK-FORMING			
Polycarbophil (Fiber-Lax®) Tablet: 625 mg	2 tablets 1 to 4 times a day with at least 8 ounces of fluid Max: 8 tabs/24 hours Separate from other drugs by at least 2 hours	24 to 48 hours	• Increases frequency and softens consistency of stool. Dose must be increased slowly to minimize bloating. • Effect on bowel function will not be seen for several weeks. • Contraindicated in patients with difficulty swallowing. • May cause epigastric fullness, flatulence.
Psyllium husk (Reguloid®)	½ tbsp once daily. Titrating up ½ tbsp every week to reach total recommended daily allowance. Adults 19-50 YO: males: 38/ g/day; females: 25 g/day Adults ≥ 51 YO: males: 30 g/day; females 21 g/day	12 to 72 hours	• Increases frequency and softens consistency of stool. Dose must be increased slowly to minimize bloating. • Effect on bowel function will not be seen for several weeks. • Contraindicated in patients with difficulty swallowing. • May cause epigastric fullness, flatulence.
SURFACTANTS (SOFTENERS)			
Docusate Sodium (Doc-Q-Lace®) Softgel: 100 mg Capsule: 250 mg	100-250 mg 2 times per day (Max dose 500 mg/day)	24 to 72 hours	• No laxative effect alone, use with another laxative. • Shown to be ineffective with long term use. • Not useful in patients with mushy or soft stools. • <i>More effective in preventing constipation in patients who should avoid straining rather than treating acute episodes.</i> • Rarely causes nausea, abnormal taste in mouth, cramping.

Table 2: Treatment Options for Clozapine-induced Constipation^{1,2}

LAXATIVE MEDICATION	DOSE	ACTION ONSET	COMMENTS/ADVERSE EFFECTS
STIMULANTS			
Chronic use of stimulant laxatives has not been shown to cause structural or functional impairment of the colon or increased risk of colon cancer or other tumors.			
Bisacodyl EC (Dulcolax) Tablets: 5 mg	10 to 30 mg as enteric coated tabs orally once daily Separate administration of oral tabs with antacids or milk by at least 1 hour	6 to 10 hours	Very infrequent: - Mild abdominal cramps. - Electrolyte disturbances (acidosis, alkalosis, or hypocalcemia). - Nausea or vomiting. - Vertigo.
Bisacodyl (Bisac-Evac®) Suppository: 10 mg	10 mg suppository per rectum once daily Separate administration of oral tabs with antacids or milk by at least 1 hour	15 to 60 min	Infrequent cause of rectal irritation (burning).
Senna (Senokot®), Senna/Docusate (Senexon-S) Tablets: 8.6 mg, 8.6/50mg	For constipation (senna): 2 to 4 tabs as a single daily dose or divided dose twice daily (Max dose: 70-100 mg sennosides/day divided Q 12 hours) Senna/docusate: Two tablets (17.2 mg sennosides plus 100 mg docusate) once daily (maximum: 4 tablets twice daily)	6 to 12 hours	- Abdominal cramps, diarrhea, nausea, or vomiting. Contraindications: - Intestinal obstruction, nausea/vomiting, abdominal pain of unknown origin, appendicitis, Crohn's disease, sudden change in BM lasting more than 2 weeks.
OSMOTIC AGENTS			
Lactulose (Enulose®) Oral solution: 10 g/15 ml)	10 to 20 grams (15 to 30 ml) once daily. May increase up to 2 times per day. May mix with fruit juice, water, or milk.	24 to 48 hours	- Avoid if patient is lactose intolerant (contains galactose and lactose). - Potential electrolyte imbalance when used > 6 months or in patients predisposed to electrolyte imbalance (elderly). - Caution in diabetics due to lactose/galactose content. - May cause abdominal bloating, flatulence, belching, cramping, diarrhea (excessive dose), nausea/vomiting.
Polyethylene glycol 3350 (Miralax)	8.5 to 34 grams in 240 ml (8 ounces) liquid daily Typical dose 17g (1 heaping tablespoonful, or one measuring cap)	1 to 4 days	- Use with caution in older adults and those with renal impairment. - Requires dissolving powder in 8 ounces of liquid before administration. <i>May make nurse administration more complicated than lactulose.</i> - Nausea, bloating, cramping.
Glycerin (Fleet Glycerin®, Glycerin suppositories Gnp, Sani-Supp) Suppository:	Insert 1 suppository or unit/day into rectum and retain for about 15 minutes	10 to 30 min	- Use with caution in patients with cardiac, renal, or hepatic disease. - May cause rectal discomfort or a burning sensation.
Magnesium Hydroxide (milk of magnesia) Suspension: 400 mg/5 ml	2400-4800 mg (30-60 ml) with 8 ounces of liquid once daily at bedtime or in divided doses 400 mg Mg hydroxide = 166.7 mg (13.7 mEq) elemental Mg	30 min to 3 hours	- Use with caution in renal impairment (possible hypermagnesemia). - Avoid in renal failure. - Nausea, vomiting, cramping.
Magnesium citrate (Citroma®) Solution: 1.75 g/30 ml	150-300 ml given once or in divided doses with 8 ounces of water 300 ml magnesium citrate = 2.8 g (235 mEq) elemental Mg	0.5 to 3 hours	- Use with caution in renal impairment (possible hypermagnesemia). - Avoid in renal failure. - Nausea, vomiting, cramping.
References			
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Sialorrhea Management¹

Table 3: Treatment Options for Clozapine-induced Sialorrhea

TREATMENT OPTION	MECHANISM FOR REDUCTION OF SALIVA	DOSAGE RANGE	NOTES
ANTICHOLINERGIC MEDICATIONS			
Benztropine Tablet	Muscarinic receptor antagonist	0.5-6 mg daily	Increased risk of constipation
Atropine eye drops		1% place 1-6 drops sublingually daily	Needs multiple daily dosing Minimal systemic absorption Tell patient to swish drops around mouth if possible
Ipratropium Bromide Nasal Spray		0.03-0.06%, 2-6 sprays daily sublingually	Minimal systemic absorption Well tolerated Effect may not be long lasting, requiring multiple daily doses
Hyoscine (scopolamine)		0.4-0.8 mg tablet daily 1.5 mg patch every 72 hours	Patch was studied with greater improvement than that reported with oral treatment
Amitriptyline Tablet		25-100 mg daily	Increased risk of constipation
Glycopyrrolate Tablet or Solution		1-8 mg daily	Does not cross blood-brain barrier and may have less impact on cognitive functioning. Increased risk of constipation
ALPHA ₂ -ADRENERGIC ANTAGONISTS			
Clonidine	Alpha ₂ -adrenergic receptor antagonist	0.05-0.1 mg daily 0.1-0.2 mg patch weekly	Postural hypotension may worsen in combination with clozapine Other side effects: hypotension, sedation, dizziness, urinary retention, bradycardia, constipation
Terazosin Capsule		2 mg at bedtime	
Guanfacine Tablet		1 mg daily	
OTHER TREATMENTS			
Sulpiride Tablet	Unknown, selectively binds D ₂ and D ₂ receptors	150-300 mg daily	Not available in the United States May allow for decrease in clozapine dosage which can reduce hypersalivation
Amisulpride Tablet		400 mg daily	
Botulinum	Inhibits acetylcholine release in salivary glands	150 international units injected into parotid glands	Side effects: pain, tenderness, bleeding RARE: jaw dislocation

NOTE: none of the treatment options are FDA approved for this indication and there are no established doses for this purpose.

Anticholinergic medications:

Contraindications: narrow-angle glaucoma, bladder obstruction, prostatic hypertrophy, and gastrointestinal motility disorders

Adverse effects: dry mouth, urinary retention, blurred vision, impairment in cognitive functioning

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Orthostatic Hypotension^{1,2,3}

Orthostatic hypotension is defined as a drop in blood pressure of 20 mm Hg systolic and 10 mm Hg diastolic when rising from sitting to standing. It usually occurs when initiating clozapine therapy or when increasing dosage. Most patients develop tolerance to hypotension within 4-6 weeks.

Patients should be advised to take their time standing up and to have adequate fluid intake to lessen the impact of hypotension. Tilting the head of the bed upward and wearing supportive stockings are non-pharmacological strategies to help manage this side effect. When non-pharmacological options fail, Fludrocortisone, midodrine, ephedrine, or dihydroergotamine can be considered.

Table 4: Treatment Options for Clozapine-induced Orthostatic Hypotension

TREATMENT OPTION	MECHANISM OF ALLEVIATING HYPOTENSION	DOSAGE RANGE	NOTES
Fludrocortisone	Increasing sodium retention and potassium excretion in the kidney	Starting dose: 0.1 mg/day and can be increased by increments of 0.1 mg every 5-7 days. Maintenance doses range from 0.1 to 1.0 mg/day	May cause hypertension, hypokalemia, marked fluid retention, and congestive heart failure.
Midodrine	Alpha ₁ -agonist; increases vascular tone and elevates blood pressure	10 mg PO q3-4h	May cause hypertension, paresthesia, piloerection, pruritus, urinary retention. Dose adjust for renal impairment
Dihydroergotamine	Activation of 5-HT(1D) receptors found in the intracranial blood vessel and in the arterio-venous anastomoses resulting in vasoconstriction	10 mg/day	Used for short-term or intermittent treatment of severe hypotension. Dose reduction for liver disease suggested.
Ephedrine	Alpha-adrenergic agonist	25 to 150 mg/day	May cause hypertension, palpitations, tachycardia, tremor, anxiety, nausea, and vomiting

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NOTE: none of the treatment options are FDA approved for this indication and there are no established doses for this purpose.

Clozapine-induced Enuresis^{1,2}

There may be several mechanisms by which clozapine induces urinary incontinence. Clozapine has potent anti-alpha-adrenergic effects which leads to the relaxation of the bladder-neck sphincter and may contribute to incontinence. Clozapine also antagonizes the histaminergic, cholinergic, 5-HT_{2A}, 5-HT_{2C}, and D₁-D₅ receptors. Overflow can occur due to urine retention by antagonism at the muscarinic receptors. Antagonism at the 5-HT_{2A} and 5-HT_{2C} receptors can block inhibitory effects of the parasympathetic neurons that innervate the bladder. Bladder hyperactivity may also be induced by antagonism of dopamine D₁-D₅. It is estimated to affect 0.23-44% of those taking clozapine. These numbers may not reflect the true prevalence due to factors not yet determined.

Treatment options should start with the least invasive and progress towards more invasive procedures. These are non-pharmacological options that may be recommended based on empirical evidence.

NON-PHARMACOLOGICAL OPTIONS:

- **Dietary changes:** reduce the amount of alcoholic, caffeinated, and carbonated beverages consumed.
- **Fluid intake:** Consuming large amounts of fluids (>40 ml/kg/day) may be responsible for nocturia. Fluid restriction before bedtime may be recommended. Caution should be taken with elderly patients that may have inadequate fluid intake when recommending fluid restriction.
- **Constipation:** constipation can exacerbate urinary incontinence and should be managed and avoided when possible
- **Pelvic floor muscle exercises (Kegel exercises):** recommended regimen is three sets of 8-12 slow-velocity contractions sustained for 6-12 seconds, 3-4 times per week.

Although evidence has shown efficacy of nonpharmacological options lacking for men, it is still recommended as initial treatment.

Table 5: Treatment Options for Urinary Incontinence

TREATMENT OPTION	MECHANISM	DOSE	COMMENTS
Desmopressin	Reduces the amount of urine produced by the kidneys	10 µg/day in each nostril	May develop hyponatremia. Sodium levels should be monitored within 3 days of initiation. Do not take with food to maximize absorption.
Anticholinergic agents (oxybutynin, trihexyphenidyl)	Causes the relaxation of the bladder muscle therefore increasing bladder capacity, reducing the frequency of uninhibited contractions of the detrusor muscles, and slows the initial desire to void	Oxybutynin: 5-15 mg/day Trihexyphenidyl: 5-6 mg/day	Improvement in symptoms may take up to 4 weeks. Medication may take 12 weeks to reach full efficacy.
Adrenergic agonists (ephedrine, pseudoephedrine)	Contracts the sphincter muscle and relaxes the urinary bladder wall	Ephedrine: 25-150 mg/day Pseudoephedrine: 30 mg QID	Ephedrine: Contraindicated in those with diabetes, hypertension or other cardiovascular disorders, hyperthyroidism Pseudoephedrine: Contraindicated in severe CAD, severe hypertension, and MAOI therapy Evidence is limited in case reports of ephedrine and pseudoephedrine linked to exacerbation of manic episodes in bipolar patients. Caution should be used when administering this therapy.

NOTE: none of the treatment options are FDA approved for this indication and there are no established doses for this purpose.

References:

1. "Treatment Options for Clozapine-Induced Enuresis: A Review of Clinical Effectiveness" Canadian Agency for Drugs and Technologies in Health, 27 Sept. 2010. Web. 11 Oct. 2016.
2. Hanes, Alicia et al. "Pseudoephedrine for the Treatment of Clozapine-Induced Incontinence." *Innovations in Clinical Neuroscience* 10.4 (2013): 33-35. Print.

Appendix C: Patient Handouts

CLOZAPINE: WHAT YOU SHOULD KNOW*

WHAT IS CLOZAPINE?

Clozapine is a highly effective medicine used to treat people with some types of mental illness who have not responded to other treatments or cannot take other treatments.

REQUIREMENTS FOR CLOZAPINE THERAPY

You must agree to have all blood tests required during clozapine therapy. These include:

- Weekly blood tests for the first six months of treatment.
- Every 2 week blood tests for the second 6 months.
- Every 4 week blood tests after one year of therapy.

You must return to the clinic the next business day after your last blood test to receive clozapine refills

WHAT ARE THE POSSIBLE RISKS AND SIDE EFFECTS OF CLOZAPINE?

- | | |
|--|---|
| ☐ Constipation, which may be severe | ☐ Seizures |
| ☐ Weight gain | ☐ Rapid heart rate |
| ☐ Drowsiness | ☐ Potentially serious or life-threatening infections |
| ☐ Dizziness or fainting | ☐ Myocarditis (inflammation of the heart) |
| ☐ Heavy salivation | ☐ Pulmonary Embolism (blood clot in the lungs) |
| ☐ Fever | |

CLOZAPINE: WHAT YOU SHOULD DO?

Take your medications as prescribed, do not miss doses.

Report any of the following symptoms to your treatment team right away:

- Fever
- Change in heartbeat
- Change in bowel pattern
- Shortness of breath
- Abdominal pain
- Dizziness or fainting, especially when you stand
- Fatigue
- Seizures

Be sure you also report any other new symptom that you have while you are taking clozapine to your treatment team right away.

*Adapted from California Division of Health Care Services "Care Guide: Clozapine."

A Guide for Patients and Caregivers

What You Need to Know about Clozapine and Neutropenia

What is clozapine?

Clozapine is a prescription medicine to treat people with schizophrenia who have not responded to other medicines. Clozapine may also reduce the risk of suicidal behavior.

What is the most serious risk information about clozapine treatment?

Clozapine can cause severe neutropenia. Neutropenia is a blood disorder that occurs when a certain type of white blood cells called neutrophils are not made or not enough of them are made. This makes it harder for your body to fight infections.

Before you can start clozapine and during treatment, you must have regular blood tests to measure the number of neutrophils you have in your blood. This test is called absolute neutrophil count (ANC). If the number of neutrophils, or ANC, is too low, you may have to stop clozapine. Your doctor will decide if or when it is safe to restart clozapine. This is not the only serious risk associated with clozapine treatment. Talk to your doctor about the other serious risks.

What are the symptoms of neutropenia?

You might not have any symptoms at all. Getting your blood tested to measure the number of neutrophils is the only way to check for neutropenia. This helps your doctor know if you are more likely to get an infection.

If you have any of these symptoms, talk to your doctor right away

- Infection, including skin, throat, urinary tract, vaginal, pneumonia, or any other infection
- Fever or chills
- Sores or ulcers inside your mouth, gums, or on your skin
- Wounds that take a long time to heal
- Feel like you have the flu
- Pain or burning while urinating
- Unusual vaginal discharge or itching
- Abdominal pain
- Sores or pain in or around your rectal area
- Feel extremely weak or tired

What can I do to help reduce the risk of developing neutropenia?

Three important things you can do:

1. Have your blood tested as instructed by your doctor
2. Tell your doctor about all the medicines you are taking (prescription and over-the-counter), and if you start a new medicine
3. Tell your doctor right away if you get a fever or feel sick

CLOZAPINE REMS

The Single Shared System for Clozapine
No Blood, No Drug™

What is the Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program?

Because of the risk of developing severe neutropenia, the Food and Drug Administration (FDA) has required a special program called a Risk Evaluation and Mitigation Strategy (REMS) for clozapine. The purpose of the Clozapine REMS Program is to make sure that the benefits of clozapine treatment outweigh the risks.

What are the Clozapine REMS Program requirements for me?



To receive clozapine:

1. **Review this Guide** with your doctor, pharmacist, or nurse
2. Ask questions! **Make sure you understand** what you need to do to take part in the Clozapine REMS Program
3. **Get your blood tested** as directed by your doctor. You must get your blood tested before you can receive clozapine from your pharmacy
4. **Pick up your clozapine prescription** from a pharmacy that is part of the Clozapine REMS Program. Your doctor will help you find a pharmacy that participates in the Clozapine REMS Program
5. **Tell your doctor right away** if you suffer any flu-like illness or fever while taking clozapine

What are the blood testing requirements for clozapine?

Get your Blood Tested	• Your doctor will give you an order to have blood tests done • You will need to get your blood tested on the following schedule or as directed by your doctor: - Weekly blood tests for the first 6 months you are taking clozapine - Every 2 weeks for the next 6 months if your ANC stays normal - Every 4 weeks after the first year if your ANC stays normal
Monitoring Results	• If your ANC is too low, your doctor will schedule blood tests more frequently
Stay on clozapine	• The Clozapine REMS Program will keep track of your blood test results so your doctor and pharmacist know if it is safe to fill your clozapine prescription
No Blood, No Drug	• Remember: <i>You must get your blood tested before you can receive clozapine from your pharmacy!</i>

Where can I get more information about clozapine?

If you would like more information, talk to your doctor or visit www.clozapinerems.com.

Report any side effects directly to the Clozapine REMS Program at [844-267-8678](tel:844-267-8678).

You can also report negative side effects to the FDA at www.fda.gov/medwatch, or call [800-FDA-1088](tel:800-FDA-1088).

Heart Disease: Frequently Asked Questions

Our risk of developing heart disease increases as we age. The good news is that heart disease is preventable *and* treatable!

Risk of heart disease is greater for:

- Women over age 55
- Men over age 45
- People with a family history of heart disease (parent, sibling, etc.)

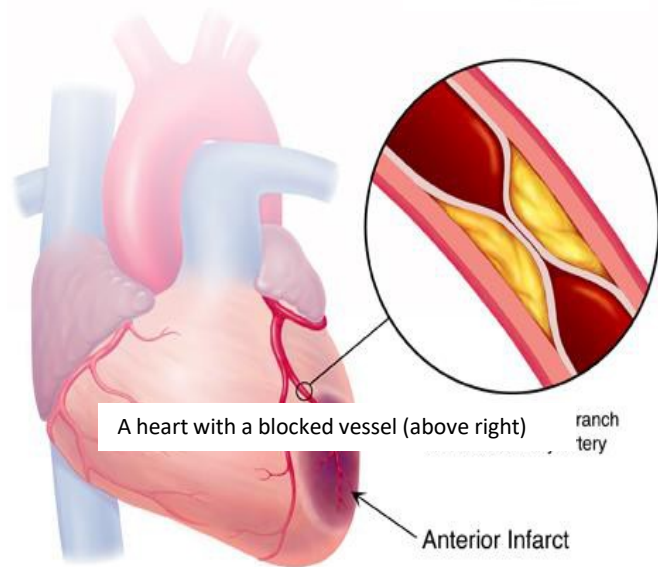


What is Heart Disease?

‘Heart disease’ can refer to different diseases of the heart. Coronary heart disease is the most common kind of heart disease.

When someone has coronary heart disease, the vessels that bring blood from their body to their heart become narrow or blocked.

This is from fatty material and cholesterol called plaques (‘plaks’) building up inside the vessels.



What are ‘plaques’ caused by?

- Fat and cholesterol in the blood
- High Blood Pressure
- Smoking
- Too much sugar in the blood (often due to diabetes)
- When they block an artery, it’s difficult for blood to get from the body to heart. A blocked artery can lead to chest pain or a heart attack.

What can I do?



1. Get screened

Check in with your provider regularly and take heart medication as prescribed. If you are making changes to your diet or exercise routine, let your provider know. Over time, you may be able to reduce or even eliminate the medication you are taking.

2. Quit Smoking

Smoking **can cause** stroke and coronary heart disease. Cigarette smoke damages blood vessels, making them thicken with plaques and grow narrower.

Quitting now can cut your chances of coronary heart disease in half, after one year!

Contact your provider or a health educator to learn more about your options for quitting smoking.

3. Eat Healthy

For heart health:

- Eat foods low in salt.
- Stay away from fried foods.
- Decrease your intake of sugar.

(If you have diabetes, please take the diabetes healthy eating hand-out.)

4. Be Active

Walking 30 minutes a day, five days a week can decrease your blood pressure by **ten points**.

Every 5 points you decrease your blood pressure, risk of stroke is reduced by 34% (one-third!).

Small changes make a big difference

Clozapine – Reducing Side Effects and Drug Interactions

1. *Dizziness, lightheadedness, blurred vision, and weakness when standing up are common side effects when clozapine is started or the dose is increased. These symptoms are signs of an increased risk of falls.*

To reduce the risk of falling down¹

- Stand up slowly and give your body time to adapt. This is especially important when you get out of bed in the morning. Start by sitting up and waiting a few seconds. Then swing your legs over the side of the bed and swing them back and forth. You should also flex the muscles in your lower legs. This helps move blood back up to your head and reduce dizziness.
- Support yourself by holding on to something stable when standing up.
- Wait until dizziness, lightheadedness, blurred vision, weakness stop before you begin walking.
- Avoid running, hiking, or doing anything that takes a lot of energy in hot weather.
- Make sure you drink enough fluids, especially in hot weather.
- Put blocks under the posts at the head of your bed. This will raise your head above your heart slightly.
- Limit the amount of alcohol you drink or quit drinking.

Constipation

To reduce constipation^{2, 3}

- Eat foods that have a lot of fiber. Good choices are fruits, vegetables, prune juice, beans, oatmeal and cereal.
- Drink plenty of water and other fluids.
- When you feel the need to go to the bathroom, go to the bathroom - don't hold it.
- When possible, go on walks. Regular movement helps reduce constipation.

The effectiveness of clozapine is affected by the following^{4,5}

- Caffeine
- Tobacco smoke

Please inform your psychiatric provider or pharmacist if there is a significant increase or decrease in the amount of caffeine you are drinking or cigarettes you are smoking.

In addition, please update your pharmacist or psychiatric provider with any changes to your medications not discussed. This includes over-the-counter medications and herbal supplements/vitamins.

References

1. Mills PB, Fung CK, Travlos A, Krassioukov A. Nonpharmacologic management of orthostatic hypotension: a systematic review. *Arch Phys Med Rehabil* 2015; 96:366
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3. Christine Hsieh, M.D. Thomas Jefferson University, Philadelphia PA. *Am Fam Physician*. 2005 Dec 1;72(11):2277-2284
4. Desai HD, Seabolt J, Jann MW. Smoking in patients receiving psychotropic medications: a pharmacokinetic perspective. *CNS Drugs*. 2001;15(6):469- 94
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Appendix D: Patient Questionnaire



**CENTRAL CITY
CONCERN**

HOMES HEALTH JOBS

THE MOOD DISORDER QUESTIONNAIRE

Instructions: Please answer each question to the best of your ability.

	YES	NO	
1. Has there ever been a period of time when you were not your usual self and...			
...you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?	☐	☐	
...you were so irritable that you shouted at people or started fights or arguments?	☐	☐	
...you felt much more self-confident than usual?	☐	☐	
...you got much less sleep than usual and found you didn't really miss it?	☐	☐	
...you were much more talkative or spoke much faster than usual?	☐	☐	
...thoughts raced through your head or you couldn't slow your mind down?	☐	☐	
...you were so easily distracted by things around you that you had trouble concentrating or staying on track?	☐	☐	
...you had much more energy than usual?	☐	☐	
...you were much more active or did many more things than usual?	☐	☐	
...you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?	☐	☐	
...you were much more interested in sex than usual?	☐	☐	
...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?	☐	☐	
...spending money got you or your family into trouble?	☐	☐	
2. If you checked YES to more than one of the above, have several of these ever happened during the same period of time?	☐	☐	
3. How much of a problem did any of these cause you – like being unable to work; having family, money or legal troubles; getting into arguments or fights? <i>Please circle one response only.</i>			
No Problem	Minor Problem	Moderate Problem	Serious Problem
4. Have any of your blood relatives (i.e. children, siblings, parents, grandparents, aunts, uncles) had manic-depressive illness or bipolar disorder?	☐	☐	
5. Has a health professional every told you that you have manic-depressive illness or bipolar disorder?	☐	☐	

www.goodrx.com- Searchable drug pricing list

www.orpdl.org/drugs- Searchable PDL/OHP

From the Sept 18 Medication Tables Special Mtg:

Considerations for the MHCAG include:

- Providing links within the tables to: www.goodrx.com for pricing for a broad audience and www.orpdl.org/drugs for those on Medicaid fee-for-service instead of listing pricing symbol equivalents which would need to be updated regularly.
- Discuss putting pricing information for MHCAG- recommended drugs at the beginning of the tables, then list remainder of drugs in the appendix.
- Consider including wording in the guide to note that the P & T encourages the use of preferred over non-preferred drugs when safety and efficacy are equivalent among medication options.
- Kara mentioned reorganizing the order of medications within the tables in section 1.4 to prioritize LAI information as well as clozapine

What wording would the group like to use?

Protocol for Pharmacist Management of Mental Health Prescription Refills

Revision: 1.4

Original Approval Date: 4/16/2015

Most Recent Revision Date: 4/2/2018

Prepared By: Petrus Oliphant PharmD; John Bischof MD

Next Annual Review Due: 4/2/2019

CLINICAL PHARMACIST(S):

Print Name	Signature	Date
Petrus Oliphant, PharmD – <i>principle practicing pharmacist</i>		
Adam Day, PharmD		
April Higdon, PharmD – <i>director of pharmacy services Central City Concern (CCC)</i>		

PHYSICIAN(S):

Print Name	Signature	Date
John Bischof, MD Psychiatric Medical Director Old Town Recovery Center (OTRC) – <i>principle practitioner</i>		
Shauna Hahn, PMHNP OTRC		
Tracy Bitz, PMHNP OTRC		

Statement of Policy

This policy is intended to support the Central City Concern (CCC) Mental Health Pharmacy Refill Protocol (hereby referred to as the “refill protocol”) developed to comply with the Oregon Board of Pharmacy Statutes, Division 19; Collaborative Therapy Management. This policy defines the process by which patient refill prescription requests will be completed by Pharmacists, PharmD Residents and Pharmacy Interns in final year of an accredited PharmD program, only when directly supervised by a licensed pharmacist, and in accordance with the rules laid out in the protocol, with final oversight by the Pharmacist in Charge.

Scope

This policy affects the patients and providers of Old Town Clinic (OTC), Old Town Recovery Center (OTRC), and OTC Pharmacy (OTCP) and is effective upon signed approval.

Administration and Oversight: OTRC Psychiatric Medical Director, OTRC Pharmacist

- Only a licensed pharmacist or an OTC or OTRC Mental Health provider may request changes to the CCC Pharmacy Refill Protocol, including addition or subtraction of medications and alteration of refill processing criteria. Requests will be reviewed and approved or denied by the OTRC Psychiatric Medical Director, OTC Psychiatric Medical Director, and OTRC Pharmacist

Administration and implementation: OTRC Psychiatric Medical Director, OTC Psychiatric Medical Director, OTRC Pharmacist

Distributing and overseeing the policy: OTRC Psychiatric Medical Director, OTC Psychiatric Medical Director, OTRC Pharmacist

Procedures

1. Roles and Responsibilities

- a. Pharmacy staff including: pharmacists, PharmD residents, and pharmacy interns will review and approve or place on the provider desktop for further review, refill prescriptions in accordance with the CCC Mental Health Pharmacy Refill Protocol (see Appendix C)
- b. OTC Pharmacist in Charge, OTRC Pharmacist on duty will provide clinical oversight of the execution of this protocol
- c. OTC Pharmacist in Charge, OTRC Pharmacist on duty will train PharmD residents on the appended protocol
- d. In collaboration with the pharmacist, PharmD residents will train and supervise pharmacy interns when approving refills
- e. During the first week of rotation while at OTC Pharmacy, pharmacy interns will participate in an orientation period, during which they will receive direct supervision of refills by PharmDs
- f. Thereafter, students will follow the protocol unobserved once they have achieved a level of confidence in the workflow and have met predetermined competency standards, as evidenced by results of routine audits as part of the CCC Mental Health Pharmacy Refill Protocol Quality Plan (see Appendix C)
- g. Continued supervision will be provided until confidence and competency standards have been achieved
- h. Refills will be reviewed and authorized routinely during normal pharmacy operating hours, as staff are available

2. Refill Requests Faxed to OTRC from Outside Pharmacies

- a. OTRC nursing staff will enter faxed refill requests received from outside pharmacies and route to OTRC Pharmacy desktop for approval provided the medication is included in Appendix A

3. Processing of Refill Requests

- a. Refill requests will be processed first and foremost with the safety and well-being of the patient in mind, while considering the patient experience of medication dispense and management as a close second priority
- b. Under no circumstances will controlled substances be approved for refills by pharmacy staff. Refill requests for controlled substances must be routed to the prescriber for evaluation
 - i. Should the prescribing provider be absent on the day of request for refill, those requests will be routed to another provider on duty so as not to delay the processing of refill orders
- c. This refill protocol may only be implemented by staff described in Section 1
- d. If a prescribing provider other than the patient's assigned psychiatric provider is approving the refill request, the patient's assigned psychiatric provider will also be indicated on the refill form
- e. Refill requests will only be addressed during the 30 day window either prior to or after the intended refill date
 - i. If a refill is requested outside of these parameters, pharmacy staff will communicate as such to the patient's assigned psychiatric provider
 - ii. Refill requests made beyond the 30-day window after the intended refill date that are prescribed "to be taken as needed" may be approved if the refill request meets the criteria outlined in the appended protocol
- f. All refill requests that meet the requirements within the protocol and do not require further review by the prescribing provider will be filled within 48-72 hours after the refill request is received
- g. If patient is due for refill but the authorization is pending, a 3-day emergency fill may be authorized by the dispensing pharmacist
 - i. Dispensing of an emergency fill will be communicated to the patient's assigned provider

4. Exceptions to Immediate Processing of Refill Requests

- a. Given the scope of the pharmacy staff involved in executing this procedure, refill requests will not be immediately processed in the following conditions
 - i. If a medication is not listed as an "active medication" in the patient's chart
 - ii. If the refill request is for a controlled substance or other medication not included in Appendix A
 - iii. If required labs have not been completed (see Section 5 below)
- b. In all conditions above, the pharmacy staff will communicate with the patient's assigned psychiatric provider before proceeding with the refill request

5. Required Labs

- a. Any lab orders required in the refill protocol will be ordered by Pharmacists and Pharmacy Residents granted:
 - i. OTRC: psychiatric provider is alerted and OTRC nursing staff or health assistant is informed for follow-up and/or patient referral to lab
 - ii. OTC: Primary Care or Mental Health provider is alerted and health assistant flagged for follow-up and/or patient referral to lab
 - iii. Alert to dispensing pharmacy is added in "pharmacy notes" section to refer patient to lab or nursing station at medication pickup
 - iv. Pharmacy students/interns may enter labs but must place order on hold for pharmacist sign-off if appropriate
- b. If a refill is noted to have required labs previously, and they were not completed, the date of the previous order will be changed to the current date and a reminder sent to Nurse or HA to re-schedule the patient
- c. For past-due labs, a one month refill will be provided, appropriate labs ordered, and the patient's care team notified for patient follow-up
 - i. If a refill is noted to have required labs for a third time and they were not completed, the refill will be held and the assigned psychiatric provider will be notified

6. Administrative Monitoring of Protocol Implementation

- a. CCC Quality Management will audit the execution of the refill protocol in accordance with the CCC Mental Health Pharmacy Refill Protocol Quality Plan

Appendix A: Mental Health Pharmacy Refill Protocol

Selective Serotonin Reuptake Inhibitors (SSRIs)			
Allow 3 months of refills if the following criteria have been met* • Patient has been evaluated by mental health provider within the past 3 months ◦ If not, allow a one month refill and refer patient to provider • Patient has been stable on same medication and same dose ◦ If recent switch or change with no subsequent provider follow-up, route request to provider • Ensure patient is not suddenly discontinuing - important that patient is adherent with medications. If patient is less than 80% adherent, check if appropriate to resume current dose with pharmacist • Patient should not be taking an MAOI			
Medication	BMP or CMP†	CMP & INR†,§	Comments
Citalopram (Celexa)	-	Hepatic Function Baseline if history of/at risk for hepatic impairment, then as clinically indicated (see Table 1: Child-Turcotte-Pugh Score for Hepatic Impairment for further detail) (see Table 1)	• Recent Myocardial Infarction/Uncompensated Heart Failure: Alert provider • Daily dose not to exceed 40mg (20mg in patients >60 years old) on moderate/strong 2C19 inhibitors)
Escitalopram (Lexapro)			• Recent Myocardial Infarction/Uncompensated Heart Failure: Alert provider • Daily dose not to exceed 20mg (10mg in patients >60 years old, on moderate/strong 2C19 inhibitors)
Fluoxetine (Prozac)			-
Fluvoxamine (Luvox)			
Paroxetine (Paxil)‡	Renal function Baseline, then as clinically indicated		
Sertraline (Zoloft)	-		
* Non-OTRC patients with no dose/therapy changes at last visit: 6 months of refills may be authorized provided patient has met above criteria. * OTRC patients who keep regular visits with psychiatric providers, have good med adherence, and no dose/therapy changes at last visit may receive 6 months of refills provided the above criteria has been met (use clinical judgement) † If the following parameters have not been assessed within specified time period refer patient to nursing/phlebotomy and/or provider ‡ Renal dose adjustment required § Hepatic dose adjustment required for all SSRIs labeling (has not been studied). Use with caution due to extensive hepatic metabolism and risk of increased exposure. A lower dose or less frequent dosing is recommended			

Serotonin/Norepinephrine Reuptake Inhibitors (SNRIs)

Allow 3 months of refills if the following criteria have been met*

- Patient has been evaluated by mental health provider within the past 3 months
 - If not, allow a one month refill and refer patient to provider
- Patient has been stable on same medication and same dose
 - If recent switch or change with no subsequent provider follow-up, route request to provider
- Ensure patient is not suddenly discontinuing - important that patient is adherent with medications. If patient is less than 80% adherent, check if appropriate to resume current dose with pharmacist
- **Patient should not be taking an MAOI**

Medication	Blood Pressure & Pulse [†]	BMP or CMP ^{†,‡}	CMP & INR [†]	Comments
Desvenlafaxine (Pristiq)[§]	Baseline, within 12 weeks of initiation then every 6 months	Renal Function Baseline, then as clinically indicated	Hepatic Function Baseline if history of/at risk for hepatic impairment, then as clinically indicated (see Appendix B, Table 1: Child-Turcotte-Pugh Score for Hepatic Impairment for further detail)	-
Duloxetine (Cymbalta)[§]				
Venlafaxine (Effexor)[§]				
Levomilnacipran (Fetzima)			-	Levomilnacipran in Alcoholism: Alcohol can result in quicker release of medication. Relapsing alcoholics should be referred to provider for consideration of alternate therapy

* **Non-OTRC patients** with no dose/therapy changes at last visit: 6 months of refills may be authorized provided patient has met above criteria.

* **OTRC patients** who keep regular visits with psychiatric providers, have good med adherence, and no dose/therapy changes at last visit may receive 6 months of refills provided the above criteria has been met (use clinical judgement)

[†] If the following parameters have not been assessed within specified time period refer patient to nursing/phlebotomy and/or provider

[‡] Renal dose adjustment required for all SNRIs

[§] Hepatic dose adjustment required

Tricyclic Antidepressants (TCAs)

Allow 3 months of refills if the following criteria have been met*

- Patient has been evaluated by mental health provider within the past 3 months
 - If not, allow a one month refill and refer patient to provider
- Patient has been stable on same medication and same dose
 - If recent switch or change with no subsequent provider follow-up, route request to provider
- Ensure patient is not suddenly discontinuing (excluding prn medications) - important that patient is adherent with medications. If patient is less than 80% adherent, check if appropriate to resume current dose with pharmacist
- **Patient should not be taking an MAOI**

Medication	EKG [†]	Other Anticholinergics [†]	BMP or CMP & INR ^{†,‡}
Amitriptyline (Elavil)	TCAs may increase risk of Torsades de Pointes (TdP). Patients on high dose TCAs or with multiple risk factors for TdP are at highest risk. Annual EKG monitoring should be recommended if patient has multiple risk factors (see Table 3).	Consider alternative therapy if patient is on dual anticholinergic and >65 years old	• Renal Function Baseline, then as clinically indicated • Hepatic Function Baseline if history of/at risk for hepatic impairment, then as clinically indicated
Clomipramine (Anafranil)			
Desipramine (Norpramin)			
Doxepin (Silenor)			
Imipramine (Tofranil)			
Nortriptyline (Pamelor)			

* **Non-OTRC patients** with no dose/therapy changes at last visit: 6 months of refills may be authorized provided patient has met above criteria.

* **OTRC patients** who keep regular visits with psychiatric providers, have good med adherence, and no dose/therapy changes at last visit may receive 6 months of refills provided the above criteria has been met (use clinical judgement)

† If the following parameters have not been assessed within specified time period refer patient to nursing/phlebotomy and/or provider

‡ Many TCAs are eliminated renally and hepatically. However, there are no known studies to guide dose adjustment in patients with impaired clearance. Dose with caution in these patients.

Monoamine Oxidase Inhibitors (MAOIs)

Allow 3 months of refills if the following criteria have been met*

- Patient has been evaluated by mental health provider within the past 3 months
 - If not, allow a one month refill and refer patient to provider
- Patient has been stable on same medication and same dose
 - If recent switch or change with no subsequent provider follow-up, route request to provider
- Ensure patient is not suddenly discontinuing - important that patient is adherent with medications. If patient is less than 80% adherent, check if appropriate to resume current dose with pharmacist
- Patient **should not** be on serotonergics including SSRIs, SNRIs, TCAs, tryptophan, 5-HTP, amphetamines, levodopa, mirtazapine, tramadol, bupropion, cyclobenzaprine, St. John's wort, 5HT₃ antagonists (e.g. ondansetron), dextromethorphan, carbamazepine, valproate, metoclopramide, buspirone, triptans (e.g. sumatriptan), fentanyl, lithium, linezolid

Medication	Blood Pressure [†]	BMP or CMP ^{†,‡}	CMP & INR ^{†,‡}	Comments
Isocarboxazid (Marplan)	Baseline, then every 12 months	Renal Function Baseline, then as clinically indicated	Hepatic Function Baseline if history of/at risk for hepatic impairment, then as clinically indicated	Monitor patient for intake of tyramine-rich foods. Monitor patient for increased intake of tyramine-rich foods
Phenelzine (Nardil)				
Selegiline patch (Emsam)				
Tranylcypromine (Parnate)				

* **Non-OTRC patients** with no dose/therapy changes at last visit: 6 months of refills may be authorized provided patient has met above criteria.

* **OTRC patients** who keep regular visits with psychiatric providers, have good med adherence, and no dose/therapy changes at last visit may receive 6 months of refills provided the above criteria has been met (use clinical judgement)

† If the following parameters have not been assessed within specified time period refer patient to nursing/phlebotomy and/or provider

‡ All MAOIs require dose adjustment for patients with renal and hepatic impairment.!!

Novel Antidepressant Agents

Allow 3 months of refills if the following criteria have been met*

- Patient has been evaluated by mental health provider within the past 3 months
 - If not, allow a one month refill and refer patient to provider
- Patient has been stable on same medication and same dose
 - If recent switch or change with no subsequent provider follow-up, route request to provider
- Ensure patient is not suddenly discontinuing (excluding trazodone) - important that patient is adherent with medications. If patient is less than 80% adherent, check if appropriate to resume current dose with pharmacist
- **Patient should not be taking an MAOI**

Medication	BMP or CMP [†]	CMP & INR [†]	Comments [†]
Bupropion (Wellbutrin IR/SR/XL, Forfivo XL, Aplenzin, Buproban, Zyban) ^{‡,§}	Renal Function Baseline, then as clinically indicated	Hepatic Function Baseline if history of/at risk for hepatic impairment, then as clinically indicated	Contraindicated with: seizure disorder [#] , anorexia
Mirtazapine (Remeron) ^{‡,§}			Lipids (preferred) or direct LDL: Baseline, then every 12 months
Nefazodone (Serzone) [§]	-	-	LFTs: Baseline and periodic; if AST/ALT increase >3x ULN, nefazodone should be discontinued and not reintroduced
Vortioxetine (Trintellix) [§]			
Vilazodone (Viibryd)			
Trazodone (Desyrel) [¶]			

***Non-OTRC patients** with no dose/therapy changes at last visit: 6 months of refills may be authorized provided patient has met above criteria.

* **OTRC patients** who keep regular visits with psychiatric providers, have good med adherence, and no dose/therapy changes at last visit may receive 6 months of refills provided the above criteria has been met (use clinical judgement)

† If the following parameters have not been assessed within specified time period refer patient to nursing/phlebotomy and/or provider

‡Dose adjustment required for patients with renal impairment

§Dose adjustments required for patients with hepatic impairment

¶ Not studied in patients with renal/hepatic impairment. Use with caution in these populations

Other risk factors for seizure include: benzodiazepine and/or alcohol withdrawal and head trauma. Evaluate patient history and use clinical judgment when continuing therapy

First Generation Antipsychotics (FGAs)

Allow 3 months of refills if the following criteria have been met

- Patient has been evaluated by mental health provider within the past 3 months
 - If not, allow a one month refill and refer patient to provider
- Patient has been stable on same medication and same dose
 - If recent switch or change with no subsequent provider follow-up, route request to provider
- Ensure patient is not suddenly discontinuing (excluding prn medications) - important that patient is adherent with medications. If patient is less than 80% adherent, check if appropriate to resume current dose with pharmacist

Medication	EKG*	EPS/TD [†]	CMP & INR*	BMP or CMP*
Chlorpromazine (Thorazine)	Annual EKG monitoring should be recommended if patient has multiple risk factors (see Table 2)	AIMS at baseline, then annually or as clinically indicated	Hepatic Function Baseline if history of/at risk for hepatic impairment, then as clinically indicated [§]	Renal Function Baseline, then as clinically indicated [§]
Fluphenazine (Prolixin, Decanoate) [‡]				
Haloperidol (Haldol, Decanoate)				
Perphenazine (Trilafon) [‡]				
Trifluoperazine (Stelazine) [‡]				

**If the following parameters have not been assessed within specified time period, refer patient to nursing/phlebotomy and/or provider*

† Assessed using Abnormal Involuntary Movement Scale (AIMS)

‡ Contraindicated in patients with hepatic impairment

§ Except where noted, it is unknown to what degree hepatic or renal impairment affect clearance of FGAs. Dose with caution and monitor for dose-related side effects.

Second Generation Antipsychotics (SGAs)

Allow 3 months of refills if the following criteria have been met

- Patient has been evaluated by mental health provider within the past 3 months
 - If not, allow a one month refill and refer patient to provider
- Patient has been stable on same medication and same dose
 - If recent switch or change with no subsequent provider follow-up, route request to provider
- Ensure patient is not suddenly discontinuing (excluding prn medications) - important that patient is adherent with medications. If patient is less than 80% adherent, check if appropriate to resume current dose with pharmacist

Medication	Weight*	Blood Pressure*	HbA1c*	Fasting Lipids (preferred) or Direct LDL*	EPS/TD†	CMP/BMP for Renal Function*,‡	CMP & INR for Hepatic Function*,§	Comments*
Aripiprazole (Abilify, Maintena, Aristada)	Within last month for first 3 months of therapy, then within last 3 months	Within last 3 months	Baseline, within 3 months of initiation x1 then annually		Baseline, then annually or as clinically indicated	-	-	• SGAs alone have low risk of TdP • Annual EKG monitoring should be recommended if pt has multiple risk factors (see Table 2) • Clozapine: requires regular monitoring of complete blood count with differential (CBC w/ Diff). See Tables 3 and 4, refer to CDTM for initiation, titration and management of clozapine
Asenapine (Saphris)						-	✓	
Brexipiprazole (Rexulti)						✓	✓	
Cariprazine (Vraylar)						✓	✓	
Clozapine (Clozaril)						✓	✓	
Iloperidone (Fanapt)						-	✓	
Lurasidone (Latuda)						✓	✓	
Olanzapine (Zyprexa)						-	✓	
Paliperidone (Invega, Sustenna, Trinza)						✓	-	
Quetiapine (Seroquel)						-	✓	
Risperidone (Risperdal, Consta)						✓	✓	
Ziprasidone (Geodon)						-	✓	

*If the following parameters have not been assessed within specified time period, refer patient to nursing/phlebotomy and/or provider

†Assessed using Abnormal Involuntary Movement Scale (AIMS)

‡ Baseline, then as clinically indicated

§ Baseline if history of/at risk for hepatic impairment, then as clinically indicated (see **Appendix B, Table 1: Child-Turcotte-Pugh Score for Hepatic Impairment** for further detail)

Mood Stabilizers				
Allow 3 months of refills if the following criteria have been met				
• Patient has been evaluated by mental health provider within the past 3 months ◦ If not, allow a one month refill and refer patient to provider • Patient has been stable on same medication and same dose ◦ If recent switch or change with no subsequent provider follow-up, route request to provider • Ensure patient is not suddenly discontinuing - important that patient is adherent with medications. If patient is less than 80% adherent, check if appropriate to resume current dose with pharmacist • Check indication – if patient using for epilepsy, refer to OTC refill protocol				
Medication	Therapeutic Drug Level*	BMP or CMP*	CMP & INR*	Comments*
Carbamazepine (Tegretol) [†]	Within 30 days of initiation or dose change, then annually	Renal Function Baseline, then as clinically indicated	LFTs, electrolytes baseline then annually or as clinically indicated	• CBC w/ diff baseline then annually for anemia, neutropenia and/or thrombocytopenia • Therapeutic Level Within 30 days of initiation or dose change
Divalproex/Valproic Acid (Depakote, Depakene, VPA) [‡]		-	Hepatic Function baseline then annually or as clinically indicated	• CBC w/ diff baseline then annually for thrombocytopenia • Therapeutic Level Within 30 days of initiation or dose change
Lithium (Lithobid, Eskalith) [§]		Renal Function & Calcium Baseline, within first 6 months, then annually	-	• Therapeutic Level ◦ Within 30 days of initiation or dose change ◦ Within 30 days of new prescription/dose change of ACEI, ARB, HCTZ, NSAID, K⁺ sparing diuretic, or loop diuretic • TSH at baseline, within first 6 months, then annually
Oxcarbazepine (Trileptal) ^{§,¶}	-	Renal Function Baseline, then as clinically indicated	LFTs baseline, then annually or as clinically indicated Electrolytes baseline, within 12 weeks of initiation then annually or as clinically indicated	-
Topiramate (Topamax) [§]		Renal Function and Serum Bicarbonate Baseline, within first 6 months, then annually	-	
Lamotrigine (Lamictal) [#]		-	Hepatic Function baseline then as clinically indicated	
• Adherence If patient has gone ≥ 4 days without medication, route to provider for re-initiation assessment				
* If the following parameters have not been assessed within specified time period, refer patient to nursing/phlebotomy and/or provider † No renal/hepatic adjustment recommendations; advised to monitor closely and titrate cautiously ‡ No renal dosing guidelines available. Renal impairment may increase free fraction of serum valproate – monitor free plasma levels. Contraindicated in severe hepatic impairment, not recommended for use in hepatic disease § Renal dose adjustment required§CrCl 10-50 mL/minute: Administer 50% to 75% of normal dose; CrCl <10 mL/minute: Administer 25% to 50% of normal dose; dialyzable (50% to 100%); 4-7 times more efficient than peritoneal dialysis ¶ Has not been studied in moderate or severe hepatic impairment # Dose adjustment required for patients with hepatic impairment §§For values above or below therapeutic range, hold refill request to prescriber's desktop for evaluation of dose (see Table 6 for appropriate range)				

Medications for Drug-Induced Movement Disorders (DIMD)

Allow 3 months of refills if the following criteria have been met*

- Patient has been evaluated for the indication within the past 3 months
 - If not, allow a one month refill and refer patient to provider
- Patient has been stable on same medication and same dose
 - If recent switch or change with no subsequent provider follow-up, route request to provider
- Ensure patient is not suddenly discontinuing (excluding prn medications) - important that patient is adherent with medications. If patient is less than 80% adherent, check if appropriate to resume current dose with pharmacist
- Check indication
 - If Parkinson or RLS indication, refer to OTC refill protocol

Medication	BMP or CMP [†]	CMP & INR [†]	Comments [†]
Amantadine (Symmetrel)	Renal Function Baseline, then as clinically indicated	-	• Centrally-acting anticholinergics (benztropine, trihexyphenidyl, diphenhydramine) ◦ Consider alternative therapy if on multiple anticholinergics and >65 years old • All medications for DIMDs ◦ DIMDs rarely occur with clozapine, olanzapine, quetiapine, asenapine, ziprasidone, and iloperidone. If patient prescribed medication for DIMD in the absence of other antipsychotics, discuss appropriateness with prescriber. • Propranolol ◦ Monitor blood pressure/pulse at baseline, following dose increase, then as clinically indicated
Benztropine (Cogentin)	-		
Diphenhydramine (Benadryl)	-		
Propranolol (Inderal)[‡]	Renal Function Baseline, then as clinically indicated	Hepatic Function Baseline if history of/at risk for hepatic impairment, then as clinically indicated	
Trihexyphenidyl (Artane)	-	-	

* **Non-OTRC patients** with no dose/therapy changes at last visit: 6 months of refills may be authorized provided patient has met above criteria.

* **OTRC patients** who keep regular visits with psychiatric providers, have good med adherence, and no dose/therapy changes at last visit may receive 6 months of refills provided the above criteria has been met (use clinical judgement)

[†] If the following parameters have not been assessed within specified time period, refer patient to nursing/phlebotomy and/or provider.

[‡] No dose adjustments provided in manufacturer's labeling; however, hepatic and renal impairment increase exposure. Monitoring and cautious dosing advised.

Anxiety, Post-Traumatic Stress Disorder (PTSD)			
Allow 3 months of refills if the following criteria have been met* • Patient has been evaluated for the indication within the past 3 months ◦ If not, allow a one month refill and refer patient to provider • Patient has been stable on same medication and same dose ◦ If recent switch or change with no subsequent provider follow-up, route request to provider • Ensure patient is not suddenly discontinuing (excluding prn medications) - important that patient is adherent with medications. If patient is less than 80% adherent, check if appropriate to resume current dose with pharmacist • Check indication (only refill if being used for anxiety, PTSD) ◦ If for primary care indication, refer to OTC refill protocol			
Medication	BMP or CMP†	CMP & INR†	Comments
Buspirone (Buspar)	Renal Function at baseline, then as clinically indicated	Hepatic Function Baseline if history of/at risk for hepatic impairment, then as clinically indicated	
Gabapentin (Neurontin)			
Hydroxyzine (Atarax, Vistaril)		Baseline, then as clinically indicated	Primary biliary cirrhosis: change dosing interval to every 24 hrs
Prazosin (Minipress)			Monitor blood pressure at baseline, then as clinically indicated
<i>* Non-OTRC patients with no dose/therapy changes at last visit: 6 months of refills may be authorized provided patient has met above criteria.</i>			
<i>* OTRC patients who keep regular visits with psychiatric providers, have good med adherence, and no dose/therapy changes at last visit may receive 6 months of refills provided the above criteria has been met (use clinical judgement)</i>			
<i>† If the following parameters have not been assessed within specified time period, refer patient to nursing/phlebotomy and/or provider.</i>			

Miscellaneous Products	
Allow 3 months of refills if the following criteria have been met • Patient has been evaluated for the indication within the past 3 months ◦ If not, allow a one month refill and refer patient to provider • Patient has been stable on same medication and same dose ◦ If recent switch or change with no subsequent provider follow-up, route request to provider Ensure patient is not suddenly discontinuing - important that patient is adherent with medications. If patient is less than 80% adherent, check if appropriate to resume current dose with pharmacist	
Medication	Comments*
Strattera	Blood pressure/pulse • Baseline and within 3 months of initiation/dose increase • Every 6 months thereafter CMP/INR for hepatic function at baseline if history/risk of liver disease then as clinically indicated
Nicotine Replacement Therapy (NRT)	-
Varenicline (Chantix)	BMP or CMP for renal function* at baseline or within last year, then as clinically indicated
Levothyroxine (Synthroid, Levoxyl, Levothroid)†	TSH: Baseline, 6-8 weeks after initiation/dose adjustment/change in manufacturer and annually once within range
Liothyronine (Cytomel, Triostat)†	
<i>*If the following parameters have not been assessed within specified time period, refer patient to nursing/phlebotomy and/or provider</i>	
<i>† For OTC patients: may authorize 1 year refills if on stable dose/TSH within range.</i>	
<i>† For OTRC patients: may authorize 6 month refill if on stable dose/TSH within range.</i>	

Vitamins, Supplements, and Other Non-Prescription Items

Allow 6 months of refills if the following criteria have been met

- Patient has seen the prescriber within the past 6 months
 - o If not, allow a one month refill and refer patient to provider

Vitamin B (complex or individual vitamins)	Magnesium
Vitamin D ≤ 5000 IU per day	Melatonin
Vitamin E	Multivitamins
Fish Oil	Docusate Sodium (Colace, DSS)
Fiber products (psyllium husk (Metamucil), partially hydrolyzed guar gum (Benefiber)	Polyethylene Glycol (PEG, Miralax)

Medications for Clozapine-Associated Side Effects

Allow 6 months of refills if the following criteria have been met

- Patient has seen the prescriber within the past 6 months
 - o If not, allow a one month refill and refer patient to provider
- Patient is adherent to clozapine regimen

Refer to *Pharmacist Collaborative Drug Therapy Management Protocol for the Initiation, Titration and Management of Clozapine* for list of medications

Appendix B: Tables

Table 1: Child-Turcotte-Pugh Score for Hepatic Impairment*			
Criteria	+1 point	+2 points	+3 points
Encephalopathy	None	Grade 1: Altered mood/confusion Grade 2: Inappropriate behavior, impending stupor, somnolence	Grade 3: Markedly confused, stuporous but arousable Grade 4: Comatose/unresponsive
Ascites	Absent	Slight	Moderate
Bilirubin	<2mg/dL	2-3mg/dL	>3mg/dL
Albumin	>3.5g/dL	2.8-3.5g/dL	<2.8g/dL
PT/INR	PT: <4 seconds above control INR: <1.7	PT: 4-6 seconds above control INR: 1.7-2.3	PT: >6 seconds above control INR: >2.3
*Child Pugh class A: 5-6 points Child Pugh class B: 7-9 points Child Pugh class C: 10-15 points			

Table 2: Risk Factors for Torsades de Pointes (TdP)	
• Prolonged QT_c >500 msec • Use of QT prolonging medication (an extensive, regularly updated database of QT prolonging medications can be found at crediblemeds.org) • Heart failure • Hypokalemia	• Myocardial infarction • Age >65 years • Female gender • Hypomagnesemia

Table 3: ANC Monitoring Guidelines in Clozapine Initiation and Maintenance in the General Population			
ANC Level	Treatment Recommendation		ANC Monitoring
Normal Range (New Patient)	>1500	• Initiate treatment • If treatment interrupted: ◦ <30 days, continue monitoring as before ◦ ≥30 days, monitor as if new patient • Discontinuation for reasons other than neutropenia	• Weekly from initiation to 6 months • Every 2 weeks from 6-12 months • Monthly after 12 months
Mild Neutropenia*	1000-1499	• Continue treatment	• Three times weekly until ANC ≥1500/microliter • Once ANC ≥1500/microliter, return to patient's last "Normal Range" ANC monitoring interval, if clinically appropriate
Moderate Neutropenia*	500-999	• Recommend hematology consultation • Interrupt treatment for suspected clozapine induced neutropenia • Resume treatment once ANC normalizes to ≥1000/microliter	• Daily until ANC ≥1000/microliter, then • Three times weekly until ANC ≥1500/microliter • Once ANC ≥1500/microliter, check ANC weekly for 4 weeks, then return to patient's last "Normal Range" ANC monitoring interval, if clinically appropriate
Severe Neutropenia*	<500	• Recommend hematology consultation • Interrupt treatment for suspected clozapine induced neutropenia • Do not rechallenge unless prescribed determines benefits outweigh risks	• Daily until ANC ≥1000/microliter • Three times weekly until ANC ≥1500/microliter • If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥1500/microliter

*Confirm all initial reports of ANC<1500/microliter with a repeat ANC measurement within 24 hours

Table 4: ANC Monitoring Guidelines in Clozapine Initiation and Maintenance in the BEN Population
--

ANC Level		Treatment Recommendation		ANC Monitoring
Normal Range (Mild Neutropenia – New Patient)*	≥1000	- Obtain at least 2 baseline ANC levels before initiating treatment - If treatment interrupted: <30 days, continue monitoring as before ≥30 days, monitor as if new patient - Discontinuation for reasons other than neutropenia		- Weekly from initiation to 6 months - Every 2 weeks from 6-12 months - Monthly after 12 months
Moderate Neutropenia*	500-999	- Recommend hematology consultation - Continue treatment		- Three times weekly until ANC ≥1000/microliter or ≥patient's known baseline - Once ANC ≥1000/microliter or patient's known baseline, then check ANC weekly for 4 weeks, then return to patient's last "Normal BEN Range" ANC monitoring interval, if clinically appropriate
Severe Neutropenia*	<500	- Recommend hematology consultation - Interrupt treatment for suspected clozapine induced neutropenia - Do not rechallenge unless prescriber determines benefits outweigh risks		- Daily until ANC ≥500/microliter - Three times weekly until ANC ≥patient's established baseline - If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥1000/microliter or at patient's baseline
*Confirm all initial reports of ANC <1000/microliter with a repeat ANC measurement within 24 hours				

Table 5: Therapeutic Range for Medications Used in Bipolar Depression	
Carbamazepine (Tegretol)	4 – 12mcg/mL
Lithium (Lithobid, Eskalith)	0.4 – 1.2mmol/L
Divalproex/Valproic Acid (Depakote, Depakene, VPA)	40 – 120mcg/mL

Appendix C: CCC Mental Health Pharmacy Refill Protocol Quality Plan

Background:

Recent collaboration of OTC pharmacy services with OTRC mental health services has resulted in a need for expanded policies and procedures defining the scope of Pharmacists working with psychiatric providers to deliver quality mental health care safely and efficiently. Presently, pharmacy staff are only qualified to process refill requests for providers (both mental health and primary care) managing patients at OTC. With several OTRC psychiatric providers scheduled at 0.5 full-time equivalents or less, delays in the approval and therefore, timely filling of medications can occur.

In addition to outlining the policies and procedures that will guide the pharmacy-led refill protocol at OTRC, this refill protocol is also intended to supersede all sections pertaining to the medications in Appendix A, written within the current revision of the OTC Pharmacy Refill Protocol, unless drug is indicated for a non-mental health condition. Combining OTC and OTRC Pharmacy Refill Protocols will benefit both sites by avoiding discrepancies and updating OTCs policy for pharmacy-approved mental health medication refills with procedures that are more consistent with recommendations from current clinical practice guidelines.

The addition of a Pharmacy Refill Protocol specifically designed for mental health medications will improve patient safety and decrease the processing time of medication refills, thus enhancing the quality of mental health services at OTC and OTRC.

Purpose:

The CCC Pharmacy Developed Mental Health Refill Protocol policy outlines the parameters for the pharmacy refilling a range of mental health medications and the conditions under which refill requests will be redirected to the provider for further review. This Quality Plan follows these guiding principles and defines the clear standards to which pharmacy staff and prescribing providers will be held. The plan identifies the process by which adherence to the refill protocol will be routinely evaluated, including periodic audits by OTC and OTRC Quality Coordinators as well as on-going monitoring by the OTC Pharmacist in Charge, OTRC Pharmacist and Psychiatric Medical Director at OTC and OTRC.

Monitoring Procedure:

Most major categories of medications from the current Pharmacy formulary have been included in the developed Refill Protocol, which details the criteria that should be verified and met before processing a refill request. Audits will be conducted by the Quality Coordinator, comparing actual practice to the guidelines outlined in the protocol. Audits will be conducted annually.

Five processed refills from each of the current clinic providers from the previous month period will be selected at random for review. The Quality Coordinator will verify the clinical criteria for refill processing in the patient chart (recent visit with psychiatric provider, blood pressure, lab result, etc) and will review documentation within the refill request comments to verify that appropriate consultation with the pharmacist and/or provider took place when required. This Quality Plan will set the threshold for compliance at 90%.

In addition to the accuracy of execution of these protocols, the timeliness of refill processing will be assessed, to ensure safety to the patient and a positive customer experience. Pharmacy policy requires refills to be processed within 72 hours of receiving the request.

Results of these routine reviews will be shared with the Pharmacist, Director of OTC and OTRC Mental Health Services, Senior Director of Clinical Operations and Quality, and CCC Medical Director. Should compliance to these refill protocols fall below 85% for 3 consecutive audits, this leadership team will convene to identify potential challenges to adherence and propose interventions for performance improvement.

The Quality Plan can be amended to reflect changes in pharmacy practice or other administrative requirements. Amendments should be made in consultation with OTC and OTRC Quality Coordinators, Director of Quality Management, the CCC Pharmacist in Charge, OTRC Pharmacist and the Director of Primary Care.

Guidelines for the Administration of Long Acting Antipsychotic Injections in Adults

(Version 5 – January 2018)

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If you require this document in another format such as large print, audio or other community language please contact the Corporate Governance Team on 01903 843041 or email: policies@sussexpartnership.nhs.uk

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1. INTRODUCTION AND CONTEXT

Long acting antipsychotic injections (LAAs) are indicated for the maintenance treatment in the treatment of Schizophrenia, Mania and other psychoses. They consist of both oil-based depot injections, e.g. fluphenazine, and aqueous based injections, e.g. aripiprazole or paliperidone LAAs. Across the Trust we have a number of clinics and wards where LAAs are administered, and for some of our patients' administration of these medicines will take place in their own home.

In order to ensure that patients receive the best possible standards of care, we need to maintain best evidence based practice and continually review our practices, skills and techniques of our nurses. These guidelines offer clear guidance to practitioners about the appropriate techniques, which are endorsed by the Trust in the light of recent research into LAA medication. It also sets out clear guidance about legal requirements, and guidance on dosage for LAA preparations.

The following Sussex Partnership clinical policies should be read and referred to alongside these clinical guidelines for the intramuscular injection of LAAs:

- Medicines Code
- Infection Control Policy
- Patient Identification Policy
- Resuscitation and Anaphylaxis Policy
- Sharps Policy
- Hand Washing Policy
- Clinical Risk Policy
- Mental Capacity Act 2005 Policy

as well as the Nursing and Midwifery Council Standards for Medicines Management (2015)¹ must also be applied during the handling and administration of these medicines.

2. SCOPE OF THE GUIDELINES

- 2.1 These guidelines are intended for all qualified nurses and other practitioners assessed as competent to administer LAAs, working within Sussex Partnership NHS Foundation Trust, who undertake the administration of LAAs, and for nurses and other practitioners in training supervised by a qualified practitioner. Their aim is to assist staff in their professional practice.
- 2.2 They set out a process to aid effective and informed LAA administration and have been derived from current research evidence where available.
- 2.3 They offer clear guidance on issues such as LAA preparation, consent, how to help prepare the patient, administration and the monitoring and evaluation of possible side effects. They will assist an appropriate decision-making pathway and reflect the degree of expertise the qualified nurse requires in terms of clinical and decision-making skills.

3. LONG ACTING ANTIPSYCHOTIC INJECTIONS

- 3.1 Long acting antipsychotic injections (LAIs) are indicated for the maintenance treatment in the treatment of Schizophrenia, Mania and other psychoses. They are usually prescribed when the patient elects to have treatment administered in this way out of convenience, or where adherence to oral treatment has been unreliable or complicated in some way in the past. As with other antipsychotic medications, however, they may give rise to extrapyramidal and anticholinergic side effects, raised prolactin levels and other symptoms such as sedation. Many adverse events will be dependent on the dose, frequency and the individual's tolerance.
- 3.2 As with oral antipsychotics, patients receiving LAIs should be maintained under regular clinical review, particularly in relation to the risks and benefits of the drug regimen. Whilst in secondary care the clinician responsible will be a consultant psychiatrist or other nominated prescriber. If the patient is discharged to the GP they should take on this role, referring the patient back to secondary care if there are concerns.
- 3.3 If patients on long-acting antipsychotic injections are admitted to a general hospital ward and their dose is due, it is vital that the Trust team and the acute hospital team liaise closely with regard to the action to be taken. Whilst it is permissible for a CPN to visit the ward to administer the LAI, this must only occur following consultation with the ward medical team, in order to establish the physical well-being of the patient and the assessed appropriateness of administering the injection on the date it is due. Once it is agreed that the injection should proceed, the CPN may attend the ward with the medication, (and must also take a copy of the valid prescription). In addition:
- Before administration, the LAI must be prescribed on the acute trust drug chart or e-prescribing system.
 - Before administration, the LAI preparation must be examined and confirmed by the nurse in charge of the ward or by the ward doctor.
 - Administration must be checked / witnessed by a qualified member of the ward nursing team and the administration recorded on the ward drug chart or e-prescribing system by that nurse.
 - Following administration, the CPN must ensure that a full record of administration is also made on the Trust LAI prescription / administration chart and must ensure that an appropriate entry is made in the clinical notes / Care Notes.

Note that it is vitally important that early planning and liaison occur (where possible) with the acute hospital team in order to ensure that the LAI is prescribed on their chart / system on or before the CPN's arrival on the ward. If the LAI is not prescribed on the acute trust chart or e-prescribing system then administration cannot take place.

3.4 In accordance with NICE clinical guidelines for psychosis and schizophrenia (2014)².

- A risk assessment should be performed by the clinician responsible for treatment and the multidisciplinary team regarding concordance with medication, and depot [LAI] preparations should be prescribed when appropriate.
- Depot [LAI] preparations should be a treatment option where a patient expresses a preference for such treatment because of its convenience, or as

part of a treatment plan in which the avoidance of covert non-adherence with antipsychotic drugs is a clinical priority.

- For optimum effectiveness in preventing relapse, depot preparations should be prescribed within the standard recommended dosage and interval range.
- Following full discussion between the responsible clinician and the patient, the decision to initiate depot [LAAI] should take into account the preferences and attitudes of the service user towards the mode of administration and organisational procedures. (For example, home visits and location of clinics)
- Test doses should normally be used as set out in the BNF and full licensed prescribing information on depot antipsychotics is available from the Summary of Product Characteristics, which can be found in the electronic medicines compendium (www.emc.medicines.org.uk). (See also appendix 2 - Long acting antipsychotic injection administration guide)

NOTE - test doses are not used for olanzapine, risperidone, paliperidone or aripiprazole long acting injection. Where a patient is neuroleptic naïve or has not previously been prescribed the active ingredient (orally or IM), a trial of oral aripiprazole, olanzapine or risperidone (for risperidone and paliperidone) is recommended.

4. PATIENT INFORMATION AND CONSENT

- 4.1 Patients and carers must be offered clear and accessible information in a suitable format regarding the use and possible side effects of any injection being considered, to assist in ensuring that full consent has been obtained before commencing treatment. A record should be made in the patient's notes/care plan of any information provided and in what format, and also of any information offered but refused.
- 4.2 Patient information leaflets are available from the medication section of the Trust website:
- 4.3 Additional information resources and other web links are also available from the Royal College of Psychiatrists website.

<http://www.choiceandmedication.org/sussex/>

www.rcpsych.ac.uk/mentalhealthinformation.aspx

A medication information booklet for people with literacy problems or learning disability can be jointly compiled by professionals and carers to provide information and ensure informed consent.

Easy read leaflets and audio pod casts for specific medicines are also available via a link on the Trust's website.

<http://www.sussexpartnership.nhs.uk/medication-information>

- 4.4 In seeking to inform the patient about their proposed treatment consideration should be given to any communication barriers such as the patient's first spoken language, any sensory loss, or learning disability. Where necessary the desired interpreting or advocacy services should be sought prior to the appointment to ensure that informed consent can be obtained. This must be documented in the patient's notes
- 4.5 If information in other formats are required, such as larger print, audio or leaflets in community languages then these can be obtained by contacting the Communications Department on 01903 843129.
- 4.6 Some patients for cultural, religious or personal reasons may be sensitive to the site used for administration and/or the gender of the person administering the injection. Special arrangements will need to be discussed and agreed and these special arrangements documented in the notes and on the prescription.
- 4.7 Where a patient is assessed as lacking capacity using the FACE assessment tool the decision to prescribe a LAAI must be part of a "Best Interests" decision under the Mental Capacity Act 2005. In such circumstances a completed 'medication use form' for carers and next of kin may be useful to demonstrate their involvement in the decision. These forms can be found via the following link to the Trust's website:

<http://www.sussexpartnership.nhs.uk/charts-and-forms>

5. THE PRESCRIPTION

- 5.1 In the community, LAAIs must be prescribed and their administration recorded on the Community Long Acting Injection Prescription Chart. For inpatient units the LAAI must be prescribed on the Drug Prescription and Administration Chart.
- 5.2 The prescription must be legally written and signed by a doctor or non medical prescriber before the LAAI can be administered to the patient.
- 5.3 In an emergency where a patient has arrived at a clinic for the administration of a LAAI and the prescription appears to be out of date, or there is no longer any room to sign that medication has been given on the current prescription chart, then a remote prescription may be sought. This is only appropriate if the patient has previously been prescribed the medicine and had the medicine administered.. (See section 5 Medicines Code).
- 5.4 Prescription details must include:
- The patient's full name, not an assumed name
 - The patient's address
 - The patient's hospital number
 - The patients' date of birth.
 - Any known allergies or sensitivities, including sensitivities to dressings/ plasters. If none, then 'no known drug allergies' must be written. THIS SECTION MUST NOT BE LEFT BLANK
 - Special notes, (ie. only accepts the injection lying down, prefers a particular site)
 - The drug name, dosage, strength and frequency of administration

- The date of review
- The doctor's signature.

5.5 The nurse's signature or two initials must then be added in the relevant section of the prescription / administration chart when the medication has been given, along with details of the site where the medication has been given, indicating

Ven R = Ventrogluteal - right
Ven L = Ventrogluteal - left

Dor R = Dorsogluteal – right
Dor L = Dorsogluteal - left

Del R = Deltoid – right
Del L = Deltoid - left

Oth R = Route not recommended first line - right. Record in the notes the route and the reason why selected.

Oth L = Route not recommended first line - left. Record in the notes the route and the reason why selected.

5.6 On no account may a nurse make alterations to the prescription for LAAs, with regard to type or dosage, unless they are a qualified supplementary prescriber acting within an agreed clinical management plan, or an independent prescriber authorised by the Trust to prescribe in this area of practice.

5.7 In circumstances where a patient is unwilling to accept the prescribed dose, the nurse must then liaise with the prescriber at the earliest opportunity to establish what action to take. If the patient indicates that they would be willing to accept a lower dose and the prescriber agrees then a new prescription is required. If the prescriber is not on site then ideally a fax or email should be used to confirm the change in dose; in exceptional circumstances a text message may be received by a nurse but the dose must be countersigned by the prescriber within one working day (see chapter 5 of the Trust's Medicines Code for more details on dealing with emails, faxes and text messages). The new dose must be either written onto a new Community Long Acting Injection Prescription and the dose reviewed by the prescriber responsible for the care of that patient, or if an inpatient the dose must be recorded in the 'Once only prescriptions' section of the Drug Prescription and Administration Chart and the dose reviewed by the prescriber responsible for the care of the patient. A record of the discussion and decision made must be made in the patient's notes.

5.8 It is preferred that patients only attend for their LAAI medication on the next due date but in reality this does not always happen and occasionally people attend clinics slightly earlier, out of greater convenience. Where patients attend for their injection slightly earlier or later than the next due date, it is considered acceptable for nursing staff to use their discretion as to whether to give the medication slightly out of prescribed schedule, or ask the patient to return on the date the LAAI is actually due. (See 5.9 and 5.10 for further guidance).

5.9 Depots and LAIs can be given early or late, consult the Summary of Product Characteristics (SPC) www.medicines.org.uk on how early or late these can be carried out. SPCs may state a certain number of days for late or early administration and this should be adhered to as outside of this will classified be

unlicensed use. Many of the first generation do not have this advice in their SPC and in this situation it is deemed acceptable to administer one day early if the medication is prescribed weekly, two days early if the medication is fortnightly, three days early if the medication is every three weeks, and four days early if the medication is every four weeks. **This guidance is not based on clinical evidence.**

- 5.10 Administering antipsychotic long acting injections a few days later than scheduled is unlikely to cause any problems, even if normally administered on a weekly or fortnightly basis. With **risperidone long acting injection** (Risperdal Consta®) blood levels drop rapidly shortly after the due day so the likelihood of relapse if not administered on or soon after the due date is greater. Administration less than 4 days later than scheduled should take place as normal and the delay must be clearly documented in the patient's notes. The date of the next injection should be adjusted accordingly and clearly documented. If the patient presents 4 days or more days later than scheduled, this should be brought to the attention of the prescriber, if possible, before administration takes place. The lateness of the administration and the prescriber's instructions to proceed, (or otherwise), must be clearly documented in the patient's notes along with any adjustment to the administration schedule. **This guidance is not based on clinical evidence.**
- 5.11 Prescriptions are only legal for six months and therefore must be reviewed by the responsible prescriber at least every six months or after 13 administrations, whichever is sooner.
- 5.12 A sample of the Community Long-Acting Injection Prescription chart can be found via a link on the Trust's website. Please always ensure that you are using the most recent version of the prescription chart.

<http://www.sussexpartnership.nhs.uk/node/1605/attachment>

6. TEST DOSES PRIOR TO ADMINISTRATION

- 6.1 LAAs are long-acting medications that take a long period to fully wash out of the body. Therefore adverse effects, which result from injection, are likely to be long-lived. With the exception of olanzapine, risperidone, paliperidone and aripiprazole long acting injections, it is recommended that patients are given a small test dose before the onset of the therapeutic dose for treatment, to avoid severe and prolonged adverse effects. (NB the test doses are to ensure there is no reaction to oil based carrier).
- 6.2 A table of LAAI administration guidelines including test doses can be found as Appendix 2 of this guidance.

7. CHOOSING AN APPROPRIATE SITE

- 7.1 Most LAAI are administered by deep intramuscular injection. Although other intramuscular sites are considered possible, the Trust primarily endorses use of the ventrogluteal muscle, which is shown in the figures 1 and 2 below. This is based upon recent literature, which supports the fact that this is a lower risk site in terms of potential harm to the patient, and facilitates the LAAI being effectively given into the muscle, rather than inadvertently into the sub-cutaneous (fatty) tissues from which absorption of the drug will be significantly delayed. Delayed absorption could have a number of consequences, e.g. the dose may be inappropriately increased as the

anticipated response is not seen. Some medications, such as zuclopenthixol decanoate, are only licensed for administration in the dorsogluteal site so in these circumstances practitioners should follow the dorsogluteal site guidance below.

- 7.2 Because historically nurses have predominately used the dorsogluteal route, this route is still approved for use until training in how to administer using the ventrogluteal route has been proved for individuals. It is also recognised that some patients are less likely to be receptive to changes to their injection site, and patient preference must also be considered when selecting a site for injection.
- 7.3 Several LAAs are licensed for deltoid use. In the case of paliperidone LAAI the deltoid route is the licensed method for the loading dose as the pharmacokinetics are more favourable.
- 7.4 **Ventrogluteal site** - research indicates that the ventrogluteal site is a safer site for administration of deep intramuscular injections than other sites. This is because it is well land-marked, allowing the nurse to easily locate it, and it is relatively free of major blood vessels and nerves, thus reducing the risk associated with damaging the sciatic nerve and superior gluteal artery, which are both closely located to the dorsogluteal site. In some circumstances, for example where the patient chooses not to have the injection into this site, another site can be considered for use, this would usually be either the dorsogluteal muscle or lateral thigh.
- 7.5 Women tend to carry more sub-cutaneous (fatty) tissue at this site than men, so this should be considered when choosing the length of needle to use. Greater consideration should be given to using a 50 mm needle as this is preferential in terms of ensuring the medication is delivered in to the muscle, unless the patient is underweight



Figure 1 - Ventrogluteal site

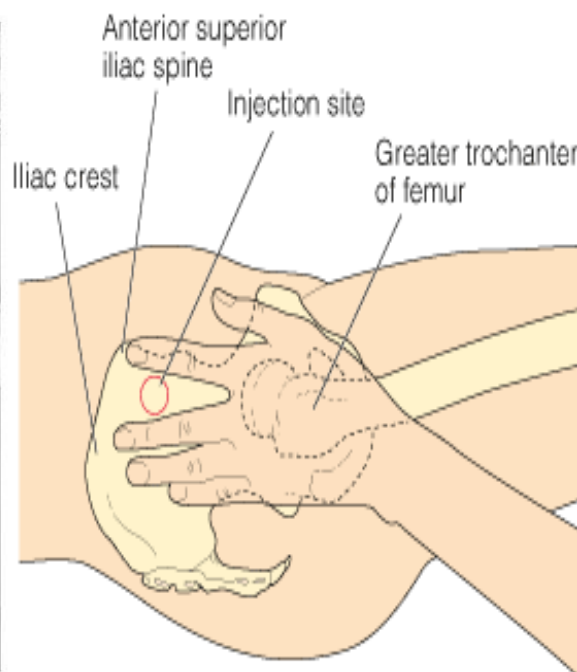


Figure 2 Ventrogluteal muscle

- 7.6 **Dorsogluteal site** - research suggests that for clients receiving deep intramuscular injections into the dorsogluteal site, who have a BMI of in excess of 24.9, a needle of at least 40mm should be used to ensure that medication is delivered into the muscle and not the subcutaneous (fatty) tissue between the muscle and skin.

- 7.7 Woman tend to carry thicker layers of subcutaneous (fatty) tissue in the dorsogluteal area and this should be considered when choosing the site for administration of deep intramuscular injection and choosing needle length.



Figure 3 - Dorsogluteal Site

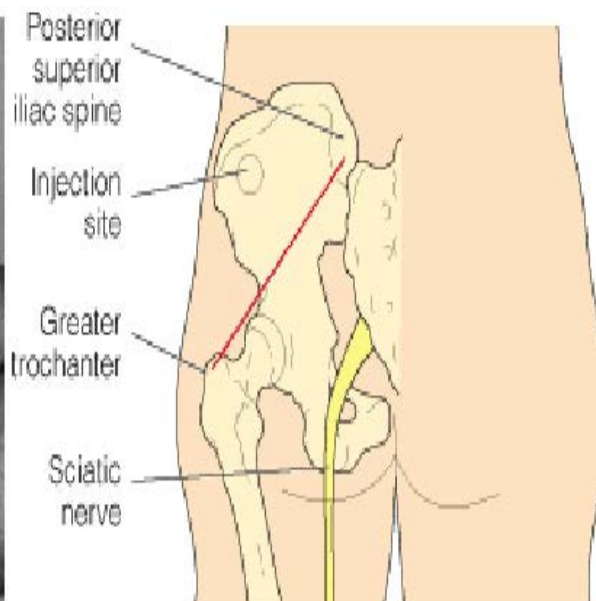


Figure 4 Dorsogluteal muscle

- 7.8 **Tissue Viability** - in circumstances where medication given as a deep intramuscular injection is inadvertently deposited into the subcutaneous (fatty) tissue, there is an increased risk of granuloma, sterile abscess, redness and swelling at injection site, ulceration of tissue and ultimately fat necrosis.
- 7.9 **Deltoid muscle** - The Royal Marsden Guidelines³ state that the maximum limit for administration into this site is 2mls. Reconstituted RLAAI is 2mls in volume. The correct needle for deltoid needs to be chosen (i.e. 25mm, 21 gauge for Risperdal Consta ®) under no circumstances should this be used to administer medication into the dorsogluteal or ventrogluteal site.



Figure 5 Deltoid site

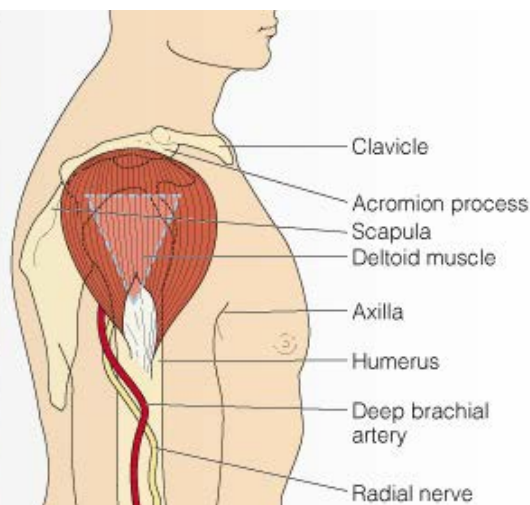


Figure 6 Deltoid muscle

7.10 Recommended maximum volumes of fluid for each muscle group³

- Deltoid 2mL
- Dorsogluteal 4mL
- Ventrogluteal 4mL
- Rectus femoris 5mL
- Vastus lateralis 5mL.

These figures appear to be based on muscle size, with larger muscles tolerating greater volumes. However, the volume of fluid that can be tolerated by the muscle groups is poorly researched and these figures are derived from personal viewpoints or descriptive studies. Patient tolerance is affected by factors associated with the medicine, for example, oil-based formulations, antibiotic or pH of the drug.

Note: In general not more than 2–3 mL of oily injection should be administered at any one site (BNF).

Slow administration can result in a larger volume being tolerated. Hence Trevicta® is recommended at a rate of 10 secs per mL.

7.11 Use of alternative sites to those recommended first-line or sites that are ‘off licence’ - in instances where it appears that the amount of subcutaneous (fatty) tissue is too great for the needle to deposit the medication into the muscle, or where the patient chooses not to have the injection in the clinically preferred site, a full discussion should take place involving the consultant psychiatrist, the prescriber (if not the consultant), the mental health pharmacist and the designated nurse. This discussion and its conclusion should then be fully recorded in the patient's notes. The nurse/doctor should be given the relevant training and supervised practice to equip them to administer into an alternative site safely, and without compromise to patient care or safety.

In such circumstances a completed ‘medication consent form’ for patients may be useful to demonstrate their involvement in the decision. These medication consent forms can be found via the following link to the Trust's website:

<http://www.sussexpartnership.nhs.uk/charts-and-forms>

(Details of licensed and additional alternative unlicensed LAAI sites can be found in Appendix 1 – Long Acting Antipsychotic guide)

8. PREPARATION AND PROCEDURE

8.1 The nurse will need:

- 2 - 5ml syringe
- Green 21 gauge 38mm or 50mm needle (note – RLAAI is provided with special syringes and needles in the pack)
- Needle for drawing up injection – Pink 18 gauge 40mm needle
- Gloves
- Alcohol swab
- Non woven gauze swab (in case of seepage from injection site)
- Small plaster (optional)

- Prescribed medication
 - Prescription chart (community or inpatient)
 - Receptacle for equipment
 - Sharps container
- 8.2 Confirm that the injection is due for the identified patient or has not already been administered before assembling the equipment by checking the prescription, the administration record and whenever possible with the patient.
 - 8.3 Explain to the patient the procedure and which site you will be using. Seek confirmation of patient's consent. If there are problems with communication offer information in another format or consider advocacy or interpreter services documenting what action has been taken in the patient's notes. If the patient does not consent to this site, consider another site, being aware of potential licensing implications.
 - 8.4 Record in the patient's notes that verbal consent has been obtained and if an interpreter was used or information was provided in another format, this should also be recorded in the notes.
 - 8.5 Prior to preparation of medication, it is vital to identify an area where the qualified nurse will not be disturbed, that provides confidentiality for the patient and where there is appropriate facility for the disposal of sharps - either a sharps box within a clinical area or a portable sharps container for use in the community.
 - 8.6 The qualified nurse should wash their hands before preparing the patient and the medication to be administered. Full details of the correct procedure for hand hygiene can be found in the Sussex Partnership's Hand Washing Policy.
 - 8.7 Draw up the prescribed dose of medication immediately prior to the injection, using a wide bore needle.
 - 8.8 Some of the 2nd generation LAAs require vigorous shaking prior to administration which can be for as much as 30 seconds please see appendix 1 for more details.
 - 8.9 Change needle and use the relevant gauge and length needle to administer, ensuring patients who have a higher BMI have the correct length needle. (See section 7 for advice).
 - 8.10 Choose a site for the injection. In general not more than 3mLs of oily injection should be administered at any one time in a gluteal site, and no more than 2 mLs at the deltoid site.
 - 8.11 Ask the patient to expose thigh, buttock or arm for injection, using the opposite side to that of the one injected previously.
 - 8.12 Examine site for evidence of lesions and establish that the site is pain free. Seek clarification again that the patient is happy to have medication given at this site. If the site is not intact or the patient is not happy with another of the clinically preferred sites indicated in this guidance, further discussion with the multi disciplinary care team should be initiated. (See section 7 for guidance).

- 8.13 Wipe the injection site with an alcohol swab (70% Isopropyl Alcohol) and wait 30 seconds until it dries (to avoid the possibility of alcohol entering the site). The use of wipes prior to giving an injection is in keeping with the current recommended infection control measures, and is aimed at reducing the risk of infection at the site of injection.
- 8.14 Administer the injection using the Z-track technique as shown below. Z tracking need not be used in the deltoid site.

Z-Tracking technique

- Stretch/displace the skin by pulling it laterally away from the intended point of injection.
- Insert the needle into the site at a 90° angle, aspirate by pulling back on the plunger for 5 seconds, allowing time for any blood to travel from a penetrated vessel up the bore of the needle. If blood is aspirated withdraw the needle, seal the wound and repeat the procedure at another site with new equipment and medication. If no blood is aspirated administer the injection.
- Wait 10 seconds then withdraw the needle and release the skin allowing the displaced tissue to seal the needle track

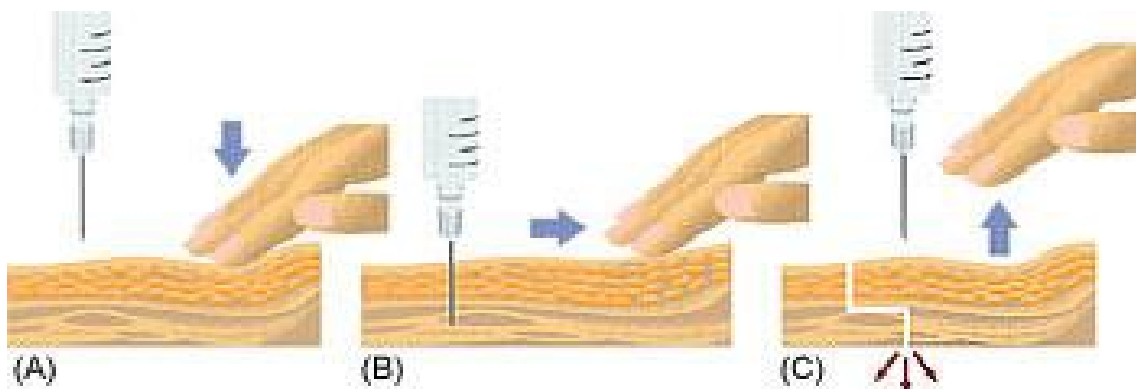


Figure 4 – Z- tracking technique

- 8.15 There is some evidence to suggest that as there are no major blood vessels in the ventrogluteal site, aspiration is not needed. There is however no evidence to suggest that this cautionary practice is in anyway harmful. On this basis the Trust advocates that its nurses continue to use the aspiration technique for all sites until a more substantial body of evidence emerges.
- 8.16 Dispose of sharps and equipment at the point of use in accordance with the Trust's Sharps Policy.
- 8.17 Do not massage the site after the injection as this can promote dispersal into the subcutaneous fatty tissue. Wipe the site with gauze or cotton wool if any medication or blood oozes from it, and if the patient is not allergic to them, apply a plaster (optional).

- 8.18 Immediately record the administration on the community long acting intramuscular injection prescription chart, or the inpatient drug prescription and administration chart, and in the patient's notes. Also, record the next due date in the diary, and inform the patient.

9. CONTRAINDICATIONS AND MONITORING OF SIDE EFFECTS

- 9.1 Throughout treatment, contraindications to the prescribed medication must be considered. Any concerns must be discussed with the prescriber and documented in the patient's notes.
- 9.2 As a benchmark and to establish the impact of side effects, all patients will be offered the opportunity to complete either a Glasgow Antipsychotic Side-effects Scale (GASS) if on an atypical LAAI (e.g. paliperidone) or a Liverpool University Neuroleptic Side Effect rating Scale (LUNSERS) if on an older typical LAAI (e.g. flupentixol), to measure the impact of the side effects of their LAAI. This should be offered routinely at least every 6 months, prior to the prescription's six-monthly review and approximately six weeks after initiation of a LAAI or when there has been dosage alteration.
- 9.3 Completion of the GASS or LUNSERS can be carried out either in the depot clinics, by the care coordinator or on the ward.
- 9.4 If the dose needs to be reduced to alleviate side effects, it is important to recognise that the plasma-drug concentration may not fall for some time after reducing the dose. It may take a month or longer before side effects subside. Side effects should be reassessed by repeating GASS or LUNSERS approximately 6 weeks after the dose alteration.
- 9.5 The GASS and LUNSERS are available by clicking on the icons below or in paper copy as appendices 2 and 3 to this guidance

<http://www.sussexpartnership.nhs.uk/node/2248/attachment>

<http://www.sussexpartnership.nhs.uk/node/2701/attachment>

10. Transportation of LAAI

- 10.1 There is a need for LAAI's to be transported by authorised healthcare practitioners when injections are to be administered in patients' homes.
- 10.2 The practitioner is responsible for ensuring the safe and secure handling of medicines while in transit. This includes ensuring it is safely and securely stored, maintaining temperature control requirements where applicable. The practitioners must also carry an authority to carry stock letter (see the medicines code) if they are carrying an LAAI that is stock, e.g. flupentixol decanote and not previously dispensed e.g. Abilify Maintena[®].

- 10.3 A sharps bin must be carried with the LAAI for the safe and secure disposal of the needles and ampoules or vials following administration of the LAAI. If it is the first or second dose being administered to the patient at home then an anaphylaxis kit must also be carried to the patients' home. See the Medicines Code for more information.
- 10.4 LAAI's should be transported in a Trust approved bag or container that is fit for purpose and should be tamperproof, waterproof, inconspicuous, and spacious enough to hold all the items necessary for the safe and effective administration of an LAAI at a patients home.
- 10.5 Only the LAAI's to be administered on the same day should be carried by authorised practitioners. LAAI's should never be taken home or left in cars overnight and any excess medications should be returned to the base before the practitioner leaves to go home.

11. REFERENCES

1. Standards for Medicines Management. Nursing and Midwifery Council. April 2015.
2. NICE: Clinical Guidelines for Psychosis and Schizophrenia (CG 178). Feb 2014.
3. The Royal Marsden Hospital Manual of Clinical Nursing Procedures, 9th Edition. Lisa Dougherty & Sara Lister, Wiley-Blackwell. March 2015.
4. Nursing Times. Are techniques used for intramuscular injection based on research evidence? 16 December 2008, Vol 104, No 50/51.
5. Summary of Products Characteristics: available from www.medicines.org.uk.

March 2018

Review no later than March 2021

Long acting antipsychotic injection administration guide

Medicine	Recommended first-line route(s)	Test dose ¹	Maintenance dose	Maximum dose	Storage	Pharmaco-kinetics(Bazire)	Examples of volumes ³	Comments
Aripiprazole (Maintena®)	Deep IM into the ventrogluteal or dorsogluteal muscle.	No Test dose (Oral used)	400mg monthly Can be reduced to 300mg monthly	400mg (no sooner than 26 days after the previous injection).		PK = 5-7 days (at SS) T1/2 = 46.5 days (400mg) and 29.9 days (300mg)	400 mg = 2.0 ml of 200mg/mL 300 mg = 1.5 ml of 200mg/mL 200 mg = 1.0 ml of 200mg/mL 160 mg = 0.8 ml of 200mg/mL	See specific Trust guidance. Vertically shake the syringe vigorously for 20 seconds until the reconstituted suspension appears uniform. inject immediately after reconstitution.
Flupentixol decanoate (Depixol®)	Deep IM into the ventrogluteal or dorsogluteal muscle.	20mg (allow 1 wk before re administrating)	50mg every 4wks to 300mg every 2 wks	400mg weekly		DOA = 3-4 wks PK = 7-10 days T1/2 = 8 days (single) 17 days (multiple) SS = 10-12 wks	20mg = 1ml of 20mg/ml 40mg = 2ml of 20mg/ml (2ml vial) 50mg = 0.5ml of 100mg/ml (0.5ml vial) 100mg = 1ml of 100mg/ml 200mg = 2ml of 100mg/ml 400mg = 2ml of 200mg/ml	> 65 years half to quarter of the dose. Can be mixed with other Depixol formulations
Fluphenazine decanoate (Modecate ®)	Deep IM into the ventrogluteal or dorsogluteal muscle.	12.5mg 6.25mg (>60 yrs)	12.5mg to 100mg every 2 to 5 weeks	100mg every 2 weeks	Below 25°C	DOA = 1-3 wks PK = 6-48 hrs T1/2 = 6-10 days (single) 14-100 days (multiple) SS = 6-12 wks	12.5mg = 0.5ml of 25mg/ml 25mg = 1ml of 25mg/ml 50mg = 0.5ml of 100mg/ml (0.5ml vial) 100mg = 1ml of 100mg/ml	
Haloperidol decanoate (Haldol®)	Deep IM into the ventrogluteal or dorsogluteal muscle.	50mg 12.5-25mg (>65 yrs)	50 mg to 300 mg every four weeks	300mg every 4 weeks	Below 25°C	DOA = 6 wks PK = 3-9 days T1/2 = 18-21 (single + multiple) SS = 10-12 wks at monthly dosing	50mg = 1ml of 50mg/ml 100mg = 1ml of 100mg/ml 200mg = 2ml of 100mg/ml 300mg = 3ml of 100mg/ml	
Olanzapine pamoate monohydrate (Zypadhera®)	Deep IM into the ventrogluteal or dorsogluteal muscle.	<u>Initially</u> 210mg every 2 weeks or 405mg every 4 weeks for 2 months (PO Olanzapine 10mg). 300mg every 2 weeks for 2 months (PO Olanzapine 15 or 20mg)	<u>After 2 months</u> 150mg every 2 weeks or 300mg every 4 weeks (PO Olanzapine 10mg). 210mg every 2 weeks or 405mg every 4 weeks (PO Olanzapine 15mg). 300mg every 2 weeks (PO Olanzapine 20mg)	300mg every 2 weeks or 405mg every 4 weeks	Do not refrigerate or freeze.	DOA = 1 day – 4weeks T1/2 = 30 days SS = 5-6 months EP = 6-8 months	150mg = 1.0mL of the 210mg vial 210mg = 1.4mL of the 210mg vial 300mg = 2.0mL of the 300mg vial 405mg = 2.7mL of the 405mg vial	See specific Trust guidance. Shake the vial vigorously until the suspension appears smooth and is consistent in colour and texture. The suspended product will be yellow and opaque.

Paliperidone (Xeplion ®)	First 2 doses into the deltoid (in order to attain therapeutic concentrations rapidly). Maintenance doses can be administered in either the deltoid or gluteal muscle.	No Test dose (Oral used) <u>Initially</u> 150 mg on day 1 and 100 mg one week later (day 8). No loading doses required if currently prescribed a depot (See SPC for further information)	Maintenance dose is range = 25-150mg monthly usually 75mg. Patients who are overweight or obese may require doses in the upper range.	150mg monthly	Do not store above 30°C.	DOA = 1 day – 4 months PK = 13 days T1/2 = 25-49 days	In standard syringes	See specific Trust guidance. Shake the syringe vigorously for a minimum of 10 seconds to ensure a homogeneous suspension.
Paliperidone (Trevicta ®)	Injected slowly, deep into the deltoid or gluteal muscle. Recommended Injection rate is 10 secs per mL.	No test dose required. Only in adult patients who are clinically stable on 1-monthly paliperidone. See trust guidance Initiated on the next schedule 1-monthly dose.	<u>Doses</u> 175mg, 263mg, 350mg or 525mg every 3 months (± 2 weeks) NB The dose is 3.5 fold higher than the monthly dose.	525mg every 3 months (± 2 weeks)		DOA = 1day -18months PK = 30-33 days T1/2 = 84-95 days (deltoid) and 118-139 days (gluteal).		It is important to shake the syringe vigorously with the tip up and a loose wrist for at least 15 seconds to ensure a homogeneous suspension. It should be administered within 5 minutes after shaking.
Pipotiazine palmitate (Piportil ®)	Deep IM into the ventrogluteal or dorsogluteal muscle.	25mg 5-10 mg (>65 yrs of age)	50-100 mg every 4 weeks	200 mg every four weeks.		DOA = 4-6 wks PK = 9-10 days T1/2 = 14-21 days SS = 8-12 wks	25mg = 0.5ml of 50mg/ml 50mg = 1ml of 50mg/ml 75mg = 1.5ml of 50mg/ml (2ml vial) 100mg = 2ml of 50mg/ml (2ml vial) 200mg = 4ml of 50mg/ml (2ml vial) (2 sites⁴)	Product discontinued March 2015 Expiry of last batch: Piportil 100mg - 31/12/2018; Piportil 50mg - 31/01/2018

Risperidone (Risperdal Consta®)	Deep IM into the ventrogluteal, dorsogluteal or deltoid muscle.	No Test dose (Oral used)	25-50mg every 2 wks (For starting doses consider 25mg LAI if on <4mg oral risperidone and 37.5mg LAI if on >4mg oral risperidone)	50 mg every two weeks. 25 mg every two weeks in (>65 years of age)	Store at 2°C to 8°C (fridge) ²	PK = 4-6 wks EP = 7-8 wks (data sheet)	Whole vial used for each strength	See specific Trust guidance. 25 mg to 37.5 mg or from 37.5 mg to 50 mg should be considered after a minimum of four weeks after the previous dose adjustment. NB the trust standard is to increase after six weeks. Continuing to hold down the plunger rod, shake <u>vigorously</u> for at least 10 seconds.
Zuclopenthixol decanoate (Clopixol®)	Deep IM into the ventrogluteal (if trained) or otherwise dorsogluteal (nb. lateral thigh is a licensed route but is not recommended first-line)	100 mg (half to quarter dose >65 yrs)	200-500 mg every one to four weeks	600 mg per week.	Store at or below 25°C	DOA = 2-4 wks PK = 4-9 days T1/2 = 17-21 days (multiple) SS = 10-12 wks	100mg = 0.5ml of 200mg/ml 200mg = 1ml of 200mg/ml 300mg = 1.5ml of 200mg/ml 400mg = 2ml of 200mg/ml 500mg = 1ml of 500mg/ml 600mg = 1ml of 500mg/ml + 1ml of 100mg/ml	This product may be mixed in the same syringe with other products in the Clopixol Injection range, including Clopixol Acuphase Injection (zuclopenthixol acetate 50 mg/ml).

1. Patients who have suffered a relapse following cessation of depot therapy may be restarted on the same dose, although the frequency of injections may need to be increased in the early weeks of treatment until satisfactory control is obtained.
 2. Can be stored at temps not exceeding 25°C for no more than 7 days prior to administration.
 3. This takes into account the cheapest vial, however volume should always be considered and the smallest volume is also recommended.
 4. The BNF recommends 'in general not more than 2-3 ml of an oily injection should be administered in any one site'.
- Key DOA = Duration of action, PK = Peak, T1/2 = Half life, SS = Steady state, EP= Elimination phase

Appendix 2

Glasgow Antipsychotic Side-effect Scale (GASS)

Name:

Age:

Sex: M / F

Please list current medication and total daily doses below:

This questionnaire is about how you have been recently. It is being used to determine if you are suffering from excessive side effects from your antipsychotic medication.

Please place a tick in the column which best indicates the degree to which you have experienced the following side effects. Tick the ☐ box if you found that the side effect distressed you.

fl2007 1\ladde!J&Tavfor

Over the 12.ast week:	Never	Once	A few times	Everyday	Tick/Is box if distressing
1. Ifelt sleepy during the day					
2. Ifelt druggedor like a zombie					
3. Ifelt dizzywhen Istood upand/or have fainted					
4. Ihave feltmy heart beat ng irregularly or unusually fast					
5. My muscles have been tense or jerky					
6. My hands or arms have been shaky					
7. My legs have felt restless and/or Icouldn't sit still					
8. Ihave been drooling					
9. My movements or walking have been slower than usual					
10. Ihave had, or people have noticed uncontrollable movements of mv face or body					
11. My vision has been blurry					
12. My mouth has been dry					
13. Ihave had difficulty passing urine					
14. Ihave felt like Iam going to be sick or have vomtted					
15. Ihave wet the bed					
16. Ihave been very thirsty and/or passing urine frequently					
17. The areas around my nipples have been sore and swollen					
18. Ihave noticed fluid coming from my nipples					
19. Ihave had problems enjoying sex					
20. Men only: Ihave had problems gelling an erection					
Tick yes or no for the following quest ons about thelast throo months					
		No	Yes	Tick/Is box if distressing	
21. Women onl : Ihave noticed a change in my periods					
22. Men andwomen: Ihave been gaining weight					

Staff Information

1. Allow the patient to fill in the questionnaire themselves. Questions 1-20 relate to the previous week and questions 21-22 to the last three months.

2. Scoring

For questions 1-20 award 1 point for the answer "once", 2 points for the answer "a few times" and 3 points for the answer "everyday".
Please note zero points are awarded for an answer of "never".

For questions 21 and 22 award 3 points for a "yes" answer and 0 points for a "no".

Total for all questions=

3. For male and female patients a *total score* of:

0-21 = absent/mild side effects

22-42 = moderate side effects

43 and over = severe side effects

4. Side effects covered by questions 1-2 sedation and CNS side effects

3-4 cardiovascular side effects

5-10 extra-pyramidal side effects

11-13 anticholinergic side effects

14 gastro-intestinal side effects

15 genitourinary side effects

16 screening for diabetes mellitus

17-21 prolactinaemic side effects

22 weight gain

The column relating to the distress experienced with a particular side effect is not scored, but is intended to inform the clinician of the service user's views and condition.

Appendix 3



Name: _____

Assessment No.: _____

Assessment Date: _____

Please indicate how much you have experienced each of the following symptoms in **the last month** by ticking the appropriate boxes.

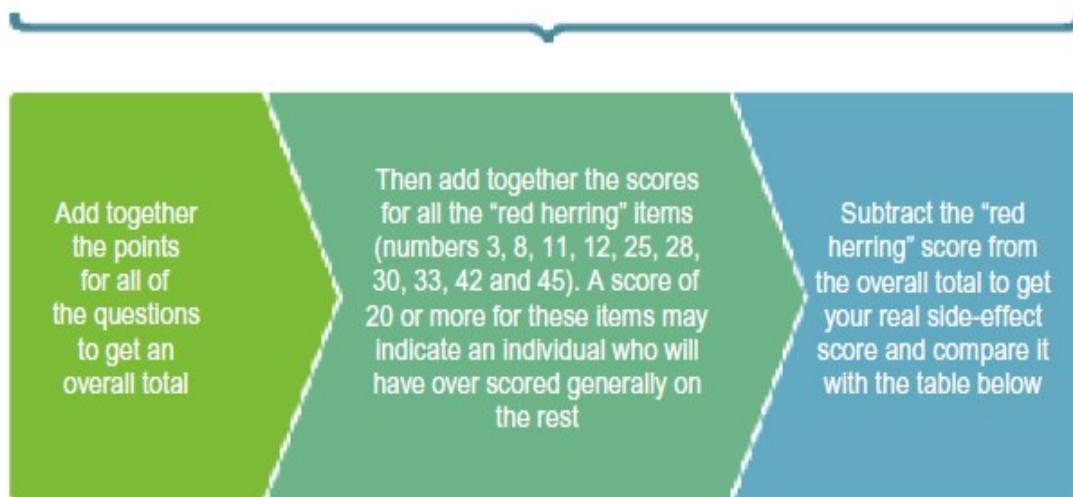
	Not At All	Very Little	A Little	Quite a Lot	Very Much
1.Rash	☐	☐	☐	☐	☐
2.Difficulty staying awake during the day	☐	☐	☐	☐	☐
3.Runny nose	☐	☐	☐	☐	☐
4.Increased dreaming	☐	☐	☐	☐	☐
5.Headaches	☐	☐	☐	☐	☐
6.Dry mouth	☐	☐	☐	☐	☐
7.Swollen or tender chest	☐	☐	☐	☐	☐
8.Chilblains	☐	☐	☐	☐	☐
9.Difficulty in concentrating	☐	☐	☐	☐	☐
10.Constipation	☐	☐	☐	☐	☐
11.Hair loss	☐	☐	☐	☐	☐
12.Urine darker than usual	☐	☐	☐	☐	☐
13.Period problems	☐	☐	☐	☐	☐
14.Tension	☐	☐	☐	☐	☐
15.Dizziness	☐	☐	☐	☐	☐
16.Feeling sick	☐	☐	☐	☐	☐

The Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS)¹

Scoring guide

For all questions

Answers	Score
Not at all	0 points
Very little	1 point
A little	2 points
Quite a lot	3 points
Very much	4 points



For all questions

Overall total	Side-effects rating
0-40	Low
41-80	Medium
81-100	High

Interpreting the results

The range for LUNSERS side-effects scores is:



Female: 0-164



Male: 0-156

You can also split the LUNSER side-effects scores by group as detailed below.

Extra-pyramidal side effects	Psychic side effects
19 muscle stiffness	2 difficulty staying awake during the day
29 slowing of movements	4 increased dreaming
34 muscle spasms	9 difficulty in concentrating
40 restlessness	14 tension
43 shakiness	18 tiredness
48 parts of the body moving of their own accord e.g. Foot moving up and down	21 difficulty in remembering things
37 over wet or drooling mouth	23 lack of emotions
	26 depression
	31 sleeping too much
	41 difficulty getting off to sleep
Possible range 0-28	Possible range 0-40
Anticholinergic side effects	Other autonomic
6 dry mouth	15 dizziness
10 constipation	16 feeling sick
32 difficulty passing water	20 palpitations
38 blurred vision	27 increased sweating
51 passing a lot of water	36 diarrhoea
Possible range 0-28	Possible range 0-40

Allergic reactions	Hormonal side effects
1 rash	7 swollen or tender chest
35 sensitivity to sun	13 period problems – women only
47 new or unusual skin marks	17 increased sex drive
49 itchy skin	24 difficulty in achieving orgasm
	46 reduced sex drive
	50 periods less frequent – women only
Possible range 0-16	Possible range women 0-24, men 0-16
Miscellaneous	Red herrings
5 headaches	3 runny nose
22 losing weight	8 chilblains
39 putting on weight	11 hair loss
44 pins and needles	12 urine darker than usual
	25 weak fingernails
	28 mouth ulcers
	30 greasy skin
	33 flushing of face
	42 neck muscles aching
	45 painful joints
Possible range 0-28	Possible range 0-40



Side Effect Scoring by Group

Patient name:

Pt Id number:

Date:

Effect	Range	Individual Score
Extra pyramidal side effects	0-28	
Other autonomic side effects	0-20	
Psychic side effects	0-40	
Miscellaneous side effects	0-16	
Anticholinergic side effects	0-20	
Allergic reactions	0-16	
Hormonal side effects	0-24	
Red herrings	0-40	
Total female score excl. Red herrings	0-164	
Total female score incl. Red herrings	0-204	
Total male score excl. Red herrings	0-156	
Total male score incl. Red herrings	0-196	

FINDING THE LOWEST EFFECTIVE MEDICATION DOSE IN PSYCHOTIC DISORDERS

Most people who experience a psychotic episode do not develop Schizophrenia, and many will not experience recurrent psychotic symptoms after their first episode resolves (1, 2). In addition, doses of antipsychotic medications can often be lowered after resolution of the acute/initial stages of a psychotic episode. Furthermore, a subset of people who do develop Schizophrenia learn to manage their psychotic symptoms without medication use and/or have a higher quality of life when not taking medications (2, 3, 4). Given the physical health risks of long term antipsychotic use (tardive dyskinesia, weight gain, Diabetes Mellitus, cardiovascular disease, etc.), a trial of tapering down on medications, with a goal of discontinuing medications, should be considered. The goal of this tapering process is not one of decreasing side effects of medications, which is an important but separate issue. The goal of this tapering process is to establish if a lower dose of medication is sufficient to address and manage the patient's symptoms, and if a patient needs to continue medications at all.

A thorough cost/benefit analysis of tapering medications, conducted jointly by the provider and the patient, is highly recommended before starting such a process. This analysis needs to be considered carefully in individuals with a history of high risk symptoms/behaviors, as the sequelae of recurrent symptoms for these individuals can bring significant social and/or legal consequences. Regardless of risks, the provider and patient should create a list of shared goals (e.g. - decreased side effects, improved energy and concentration, maintenance or improvement of work / academic performance, minimal to no recurrent symptoms, etc.), to better assess the effectiveness of the medication taper.

The potential risks and benefits of a medication taper will vary by individual, but generally include the following concerns:

Potential Benefits	Potential Risks
Decreased side effect burden	Recurrent symptoms
Decreased long term health risks	Potential social dysfunction related to recurrent symptoms
Decreased polypharmacy (if applicable)	Potential academic/employment issues related to recurrent symptoms
Decreased potential for medication interactions (if applicable)	

Such a trial of tapering off medications can be considered after 6-12 months of clinical stability (5), even if medications were modified or changed during this 6-12 month period of clinical

stability. Tapering can be considered sooner than 6 months in cases where the psychosis appears related to exogenous etiologies, such as substance induced psychosis.

No clear guidelines exist for how to conduct such a taper, but general recommendations are to slowly and consistently decrease the medication dose over 1-3 months, depending on the initial medication dose (lower initial doses can be tapered off over a shorter period of time). The taper should continue apace until the medication is discontinued, or psychotic symptoms recur/worsen. Should psychotic symptoms recur/worsen, all attempts should be made to maximize non-pharmacologic supports (e.g. - sleep hygiene, sobriety, physical activity, etc.) to stabilize symptoms before medications are re-increased. If these efforts are not effective in decreasing symptoms, the medication should be increased to the lowest dose at which symptoms were better managed. After 3 months of re-attaining stability, the taper can be resumed, although a slower taper schedule should be considered. If symptoms consistently recur when medication is decreased to a certain level, consideration should be given to continuing the medication long term at this dose. If the patient is taking multiple medications, tapering should start with just one medication as agreed upon by the provider and the patient. That medication should be tapered off, or tapered as low as possible, before attempting to taper a second medication.

Care should be taken when tapering off long acting injectable medications. As these medications have extremely long clinical half-lives, clinical changes often lag 1-3 months behind dosing changes. As such, the pace of tapering should be slowed down accordingly, and oral supplementation should be used if symptoms recur during the taper, to control symptoms more quickly. Injection dosing can also be increased, but will not produce a clinical effect for 1-3 months. Similarly, some oral antipsychotics have long half-lives, including aripiprazole and brexpiprazole, with clinical changes occurring 2-6 weeks after dosing changes. In addition, some medications, such as clozapine, are associated with rebound psychosis (6), especially when tapered quickly. As such, tapering of such oral medications should be done slowly and with caution.

When proceeding with a medication taper, the patient should have increased contact with his/her treatment providers and trusted individuals in his/her social support network to monitor progress and assess for stability. The odds of a successful taper off antipsychotic medications are improved if the client participates in other treatment modalities or health maintenance activities (therapy, OT, physical activity, social activity, sleep hygiene, healthy diet, sobriety, etc.) while tapering off medications.

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5. American Psychiatric Association. (2010), Practice Guideline for the Treatment of Patients With Schizophrenia, Second Edition, American Psychiatric Publishing
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Treatment by Medication:

- Provide crisis intervention to prevent harm to self or others. Refer to [county](#) crisis providers, BHC or transport to ED if safety cannot be established
- Medications are not always required to treat psychosis or schizophrenia
- Order baseline [labs](#) prior to prescribing medications and consider neuroimaging for new onset psychosis
- Dosages may be higher during the acute phase and then tapered to lower doses during the recovery phase to minimize side effects and optimize treatment
- Consider beginning Clozapine should the patient: present with an established diagnosis of schizophrenia, have a history of prior medication trial failures, there are no physical causes for symptoms identified and extreme aggression and/or suicidality are present. Contact [OPAL](#) for consultation
- For patients with a medication treatment history, consider using the most effective prior medication and dosage
- For patients who are stable on a current medication and it is well tolerated, continue with current medication regimen and consider a long-acting injectable form of the medication if available
- For those patients who present with new onset psychosis or for patients with a treatment history and for whom a first-generation anti-psychotic medication was ineffective, consider beginning a second-generation anti-psychotic (SGA)

- If the first SGA trial proves effective and is tolerated, move towards using the long-acting injectable (LAI) form of the medication. LAI's are currently available for aripiprazole, risperidone and paliperidone. **LAI's improve treatment adherence**
- If, after 4-8 weeks the first SGA trial is not helpful, consider a second SGA trial
- If, after 4-8 weeks the second SGA trial is successful, move towards using the long-acting injectable form of the medication
- If, after 4-8 weeks the second SGA trial is not helpful, refer to a specialist for care. Consider prescribing Clozapine. Consult [OPAL](#) prior to use of Clozapine. Order additional lab work before using Clozapine
- Should a Clozapine trial fail, consult with [OPAL](#) for next steps. Evidence does not support specific interventions post-Clozapine failure.