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Safer Prescribing of Antipsychotic Medications Guideline

SCOPE: This Safer Prescribing of Antipsychotic Medications Guideline is intended to offer antipsychotic prescribing guidance for providers, clients and the interested general public to increase the effectiveness and safety of antipsychotic use. It is not intended to be comprehensive in scope. These recommendations are not a substitute for clinical judgment, and decisions about care must carefully consider and incorporate the clinical characteristics and circumstances of each individual patient.

INTRODUCTION: Antipsychotic medications are prescribed for multiple conditions in mental health. They have a critical role in the treatment of most psychotic disorders, particularly schizophrenia and schizoaffective disorder. They have a role in the treatment of mood disorders, including bipolar disorder. These medications may also be used to treat other mental conditions. See References and Further Reading: Antipsychotic Prescribing Guidelines section at the end of this document for suggested treatment algorithms for the use of these medications.

As a class, antipsychotic medications are often divided into two sub-groups: first-generation antipsychotics (FGAs, “typical antipsychotics”) and second-generation antipsychotics (SGAs “atypical antipsychotics”). FGAs exert their therapeutic effect by blocking dopamine D2 receptors in the brain. Their binding affinity to other receptors (ex: histamine, alpha-1) generally lead to adverse effects. SGAs also bind to dopamine receptors, but often have additional therapeutic effects on other receptor systems including serotonin receptors.

Antipsychotic medications are available in oral, sublingual, transdermal patch, immediate release intramuscular injection and long-acting intramuscular injection forms.

ANTIPSYCHOTIC SELECTION AND DOSING: The selection of a specific antipsychotic medication, form of administration, dose and duration of treatment is a complex decision-making process involving multiple factors. These often include individualized treatment goal(s), client choice, history of past antipsychotic trials, family history, side effect profile and other factors. See Tables 1 and 2 below for information on available oral dosage ranges for antipsychotics. Note that fewer companies are manufacturing first generation antipsychotics and that shortages of these medications may arise. Information on long acting injections are available in Appendix 1. See Appendix 6 for information about the use of SGAs in bipolar disorder.

TABLE 1: FIRST GENERATION ANTIPSYCHOTICS

Medication	Daily Dosage Range	Chlorpromazine equivalents	Comments
Low Potency			
Chlorpromazine*	50-800mg	100mg	Sedation, anticholinergic, hypotension
Thioridazine	50-800mg	100mg	
Medium Potency			
Loxapine	20-250mg	10mg	Moderate sedation, moderate extrapyramidal symptoms
Perphenazine	8-64mg	8mg	
High Potency			
Fluphenazine*	2.5-20mg	2mg	Less sedation, extrapyramidal symptoms
Haloperidol*	2.5-20mg	2mg	
Pimozide	0.5-4mg	Unavailable	
Thiothixene	5-60mg	4mg	
Trifluoperazine	2-20mg	2mg	

*Short acting intramuscular injection available for inpatient/emergent use

TABLE 2: SECOND GENERATION ANTIPSYCHOTICS

Medication	Daily Dosage Range	Comments
Aripiprazole	2.5-30mg	Akathisia; fewer metabolic effects Tablet with digital sensor & Bluetooth® monitoring available (Abilify MyCite)
Asenapine	Tablets: 5-20mg Patch: 3.8-7.6mg	Tablets BID dosing; patch once daily dosing Fewer metabolic effects
Brexpiprazole	0.5-4mg	Akathisia; increased triglycerides
Cariprazine	1.5-6mg	Nausea; insomnia; extrapyramidal symptoms
Clozapine	50-900mg	Constipation; sedation; most metabolic side effects; sialorrhea; myocarditis; requires ANC monitoring
Iloperidone	4-24mg	BID dosing; Increased prolactin; weight gain; dizziness
Lumateperone	42mg	Sedation, headache, nausea
Lurasidone	20-160mg	Take with food; akathisia; fewer metabolic side effects
Olanzapine*	5-30mg	Metabolic side effects; sedation
Olanzapine-samidorphan	5mg-10mg to 20 mg-10 mg	Samidorphan is an opioid receptor antagonist that may mitigate weight gain/metabolic abnormalities; CI in those using opioids or going through acute opioid withdrawal. Requires minimum of 7-day opioid-free period after use of short-acting opioids and 14 days after last use of long-acting opioids
Paliperidone	3-12mg	Metabolite of risperidone; increased prolactin; extrapyramidal side effects
Pimavanserin	34 mg	Indicated for parkinson disease psychosis
Quetiapine	200-800mg	Sedation; orthostatic hypotension
Risperidone	0.5-6mg	Increased prolactin; extrapyramidal side effects
Ziprasidone*	20-160mg	Take with food; BID dosing; less metabolic effects

*Short acting intramuscular injection available for inpatient/emergent use

SIDE EFFECT MONITORING AND MANAGEMENT: Below are some of the most common side effects of antipsychotics and methods for management. This list is not exhaustive of all possible side effects. For specific drug recommendations and dosing, see Appendix 3: Side effect management medications by indication.

METABOLIC EFFECTS: Research has shown that SGAs increase the risk of metabolic syndrome, a group of conditions associated with heart disease and diabetes. These conditions include: hypertension (high blood pressure), dyslipidemia (elevated cholesterol and triglycerides), elevated blood glucose (high blood sugar), and weight gain.

An individual is considered positive for metabolic syndrome if three or more measurements meet or exceed the risk criteria (See Appendix 5 for categorical cut-points). Note that a risk factor is considered positive in individuals receiving specific treatment for that condition, even if the measurement is in the normal range. The measurements include: waist circumference, blood pressure, HDL cholesterol, triglycerides, fasting glucose or HbG A1C.

The 2004 Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes recommends the following interventions for abnormal values and/or positive family or medical history:

TABLE 3: RECOMMENDED INTERVENTIONS FOR POSITIVE METABOLIC FINDINGS

Findings	Recommended Intervention
Increased weight/BMI or glucose	Consider referral to primary care and change in SGA
Increased lipids	Consider change in SGA; increase frequency of monitoring
Positive family or medical history	More frequent monitoring

Prescribers should monitor for metabolic abnormalities and work closely with clients and their primary care providers whenever indicated. When a clients metabolic monitoring is abnormal and thought to be secondary to antipsychotic, providers should discuss results with client while also educating how the antipsychotic medication could be contributing. Providers could consider medication management of side effects (see Appendix 3) or switching to an agent with less metabolic side effects if clinically appropriate. There should be attempts made to send abnormal results to client's primary care provider if unable to manage metabolic abnormalities. See Appendix 5 for recommended metabolic monitoring schedule for children, adolescents and adults as well as information about measurement cut-points. To provide patients at risk for metabolic syndrome education about healthy living, see the Antipsychotic Metabolic Monitoring Patient handout on the BHS public website.

Specialty mental health prescribers can not only screen for metabolic abnormalities, but also initiate preliminary treatment for common cardiometabolic disorders (hyperglycemia, hypertension, dyslipidemia). For training on how to initiate treatment for these metabolic side effects, there is a free training on SMI advisor (https://smiadviser.org/) that is currently being updated: Primary Care for Psychiatrists: Addressing Health Disparities Among People With Serious Mental Illness. Guidelines that could be helpful for management metabolic disorders include but are not limited to: 2024 Standards of Care in Diabetes (American Diabetes Association), 2017 American College of Cardiology (ACC) and American Heart Association (AHA) Hypertension Guidelines, and 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease.

EXTRAPYRAMIDAL SYMPTOMS (EPS): All antipsychotics may cause EPS which includes dystonia, akathisia and pseudoparkinsonism. Medications with anticholinergic properties have historically been utilized to counter EPS induced by antipsychotic medications. Commonly prescribed anticholinergic medications include benztropine, trihexyphenidyl, and diphenhydramine. These agents may have a role in the acute treatment of some antipsychotic-induced EPS. However, there is no evidence that

anticholinergic medications are effective for the treatment of akathisia. There is evidence to support the use of propranolol and 5-HT_{2A} receptor antagonists (ex: cyproheptadine, low dose mirtazapine) for the treatment of acute akathisia.

Chronic and prophylactic use of anticholinergic agents is to be avoided. These medications can lead to troublesome side effects like urinary retention, blurred vision, dry mouth, delirium and others. Growing evidence suggests that anticholinergic medications can contribute to cognitive deficits. Additionally, concomitant use of anticholinergic medications with antipsychotic medications is associated with developing tardive syndrome.

Approach for managing antipsychotic-induced EPS:

- Use anticholinergic medications for the acute management of antipsychotic-induced EPS other than akathisia. They are not effective for treating akathisia.
- Avoid chronic or prophylactic use of anticholinergic medications.
- Consider antipsychotic dose reduction or change of antipsychotic medication if antipsychotic-induced EPS or other troublesome side effects occur.
- Avoid systemic anticholinergic medications in individuals taking clozapine. For sialorrhea (drooling), see section below on management
- Attempt gradual taper of anticholinergic medications in all individuals after antipsychotic-induced EPS has been effectively treated for three months.

Clinical treatment teams should periodically review cases of chronic and/or prophylactic anticholinergic use and work together with individual clients to reduce their usage.

TARDIVE SYNDROME: Tardive syndrome includes tardive dyskinesia, tardive dystonia, tardive akathisia, tardive stereotypy, tardive tourettism, tardive myoclonus, tardive tremor and tardive Parkinsonism. These delayed and persistent abnormal movements are thought to be caused by chronic (generally 3 months or more) exposure to dopamine-blocking agents, including antipsychotic medications. FGA, SGA and even clozapine exposure can lead to tardive syndrome. Prevention remains the most effective way to manage this class of side effect. The syndrome may be alleviated by antipsychotic discontinuation, dose reduction, or switching to another antipsychotic medication with less potent dopamine blockade. In patients who need to stay on the current antipsychotic regimen, a vesicular monoamine transporter 2 (VMAT2) inhibitor can be added. VMAT 2 inhibitors have demonstrated efficacy at reducing AIMS and are FDA approved for the treatment of tardive dyskinesia.

Clinicians should advise clients about the risks of developing tardive syndrome. The Abnormal Involuntary Movement Scale (AIMS) may be a useful monitoring tool. (Example: https://www.medicalhomeportal.org/link/6544)

SIALORRHEA: Sialorrhea (excessive salvation or drooling) is a common side effect of the antipsychotic clozapine. Sialorrhea can be treated with anticholinergic medications. Topical agents should be used rather than systemic agents as systemic anticholinergics will increase the risk of constipation.

CONSTIPATION: Antipsychotics with anticholinergic properties can lead to constipation from decreased peristalsis. Constipation can be managed by switching to an antipsychotic with less anticholinergic properties or adding a laxative.

QTc PROLONGATION: Changes in electrical activity that controls cardiac conduction can lead to an abnormally long QTc interval on electrocardiogram (ECG). A prolonged QTc interval may result in a rare, but potentially fatal, ventricular arrhythmia known as Torsades de Pointes (TdP). QTc is considered prolonged for males when >450ms and >470ms for females.

Several antipsychotics are classified as having substantial evidence that they prolong the QTc interval and are associated with TdP when used as directed. Antipsychotics with known risk for TdP include: chlorpromazine, haloperidol, pimozide and thioridazine. The website www.crediblemeds.org (access is free but registration may be required) is a useful source for obtaining updated information on the QTc prolonging risk of antipsychotics.

When possible, QTc-prolonging drugs should be avoided in those with risk factors for TdP (see Table 4 below) or used in the smallest effective dose with close ECG monitoring and patient vigilance for symptoms of TdP. Patients should be educated to go to the emergency room for any symptoms of lightheadedness, dizziness or fainting. Of note, there is no clear-cut consensus on the degree of drug-induced QTc prolongation that should require drug discontinuation.

TABLE 4: RISK FACTORS FOR PROLONGED QTC INTERVAL AND TDP*

Female gender	Underlying cardiac conditions (including congenital long QTc syndrome and bradycardia)
Age >65 years	Heart disease
Electrolyte abnormalities (including hypokalemia, hypomagnesemia and hypocalcemia)	Some endocrine diseases
Renal failure	Some auto-immune diseases
Liver failure	Treatment with multiple QTc prolonging drugs

*For complete list of potential risk factors, see www.crediblemeds.org

When prescribing medications known to prolong QTc interval, and particularly if these are prescribed to patients with risk factors for TdP, a baseline ECG should be obtained whenever possible, and a careful risk-benefit assessment should be performed, including the feasibility of prescribing alternatives with less potential to prolong QTc. To obtain an ECG, clients can be referred to their primary care providers. If treatment with a drug at high risk to cause QTc prolongation or a combination of drugs that increase QTc interval is continued, routine monitoring of ECG and electrolytes is appropriate. However, no clear-cut guidelines as to frequency of this monitoring are defined.

USE OF CLOZAPINE: Clozapine is considered to be the most effective antipsychotic with the best supporting evidence. It has an estimated 50-60% response rate at 6-12 months. Clozapine is specifically indicated for the treatment of refractory schizophrenia. It should be considered in the following:

- After failure of adequate trials of two or more antipsychotics
- To reduce suicidal behavior in patients with schizophrenia or schizoaffective disorder
- For individuals struggling with tardive syndrome
- In individuals taking two or more antipsychotics concurrently

Before initiating clozapine, absolute neutrophil count (ANC) must be obtained (ANC must be $\geq$1,500/mm^3 in order to initiate treatment). To continue treatment, ANC must be monitored regularly (see Appendix 5 for monitoring schedule). Patients must adhere with scheduled blood testing to continue clozapine. In addition, all individuals receiving clozapine therapy must be enrolled in the clozapine Risk Evaluation and Mitigation Strategy (REMS) program and must meet all the program requirements.

Clozapine is often under-utilized due to its potential side effects; the most serious being blood dyscrasias. In addition, there are several, more common side effects that clinicians should educate clients about and help them to manage should they occur.

Constipation is a frequent side effect in individuals taking clozapine. Common strategies to address this include avoidance of concomitant anticholinergic agents, adequate hydration, and addition of a bowel regimen. See Appendix 3: Side effect management medications by indication for more information about the prevention and treatment of constipation.

Clozapine has to be titrated slowly to avoid oversedation and severe orthostatic hypotension (postural low blood pressure) due to alpha blockade. If a patient has missed doses for 72 hours or greater, it is recommended that clozapine be slowly re-titrated.

Seizures are a potential dose-related side effect of clozapine. To minimize seizure risk, avoid concomitant use of other medications that lower the seizure threshold, avoid rapid dosage elevation and minimize clozapine dosage above 600 mg/day. If doses of 600-900mg/day are required, the risk of seizures can be reduced by adding divalproex.

Sialorrhea (excessive salivation/drooling) is a common side effect among individuals taking clozapine. Patients may be advised to chew sugar-free gum during the day to prompt more frequent swallowing. See Appendix 3: Side effect management medications by indication for more information about the treatment of sialorrhea.

PEDIATRICS: Antipsychotics may be used for the treatment of schizophrenia and bipolar disorder in children and adolescents. Haloperidol, pimozide, and aripiprazole are also approved for the treatment of Tourette's among specific age groups. Additionally, the atypical antipsychotics aripiprazole and risperidone have FDA approved indications for the treatment of irritability and aggression associated with autism spectrum disorder. The use of antipsychotics for other indications, such as disruptive behaviors, is not recommended due to a lack of evidence. In the absence of substantial evidence for effectiveness, alternative medications or psychosocial interventions should be considered for off-label indications. When antipsychotics are used in the pediatric population, it is recommended to begin with low doses, to escalate doses slowly and to use the minimum effective dose in order to minimize side effects. Maximum doses should not exceed those recommended for adults. There is little data to support the use an antipsychotics in pre-school aged children (<5 years).

Adverse effects, especially metabolic complications, may occur with more frequency and severity in children and adolescents. See Appendix 3: Metabolic monitoring, for specific recommendations on monitoring metabolic parameters in this population.

OLDER ADULTS: The use of antipsychotics in older adults follow the same general guidelines established for younger adults. They are FDA-approved in the treatment of schizophrenia, bipolar disorder, and major depressive disorder. SGAs are preferred over FGAs in older adults because they are less likely to cause extrapyramidal and other neurological symptoms. Since older adults are more susceptible to experiencing medication-related side-effects, special care and attention should be taken when prescribing antipsychotics. Lower dosages and slower titrations are recommended, especially in the presence of medical comorbidities, cognitive deficits, and polypharmacy.

Antipsychotics are used to treat behavioral and psychological symptoms of dementia (BPSD) such as agitation, psychosis, and socially-inappropriate behaviors. Although SGAs have the strongest evidence for BPSD, benefits are modest and therefore their use should be reserved for when non-pharmacological interventions such as DICE (see Table 5 below) are unsuccessful or if there is concern about imminent harm to the patient or others. Black-box warnings added to all antipsychotics regarding the increased risk of death in elderly dementia patients should prompt their judicious use and continuous evaluation to find the lowest effective dose for the shortest duration. Prescribers can refer to the American Geriatrics Society Beers criteria which lists potentially inappropriate medication use in older adults.

TABLE 5: DICE BEHAVIORAL INTERVENTIONS

Describe the behavioral symptom, including when and under what conditions it occurs
Investigate the possible underlying causes of the behavior: • Patient: pain, sensory changes, medication side-effects, infection • Caregiver: communication style, mismatch of expectations with level of dementia • Environment: clutter, noise, lighting

Create a treatment plan to address the underlying causes • Treat the patient's physical problems • Provide caregiver education and support • Create meaningful activities for the patient • Create a safe and comfortable environment
Evaluate the impact of interventions and devise a new strategy as needed

PREGNANCY: Prescribers should be aware of and discuss potential for adverse effects to the newborn related to antipsychotic exposure during pregnancy. Alternatives to antipsychotics may be appropriate in some situations, however, some women, specifically those with psychotic disorders, may require an antipsychotic to maintain stability during pregnancy. Women taking antipsychotics should not stop them if they become pregnant without speaking to their healthcare provider. Abrupt discontinuation of antipsychotics can significantly increase the risk of illness relapse.

FDA requires that the labels for all antipsychotic medications include warnings on the potential risk for abnormal muscle movements (extrapyramidal symptoms) and withdrawal symptoms in newborns exposed to antipsychotics during the 3rd trimester of pregnancy. The symptoms include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty in feeding. Some symptoms subside within hours or days and do not require specific treatment, but some newborns may require longer hospital stays.

Recent studies analyzed whether the use of antipsychotics during pregnancy increases the risk of gestational diabetes. The results suggested an association between women who take antipsychotics and a higher risk of gestational diabetes. It is not completely clear if the increased risk was caused by medication exposure or to other factors such as maternal psychopathology or lifestyle factors. The increased risk seems to be strongest for the use of olanzapine and quetiapine during pregnancy.

Most studies of typical and atypical antipsychotics in pregnancy have not found them to be associated with an increased risk of major congenital malformations, obstetric complications or neonatal complications. However, a recent review did conclude that risperidone and paliperidone may be associated with a very minor increased risk of congential malformations. Newer atypical agents (asenapine, lurasidone, iloperidone, brexpiprazole, cariprazine, lumateperone, pimavanserin, and samidorphan component of olanzapine-samidorphan) have virtually no or limited published human data on their use in pregnancy. Regarding the use of typical antipsychotics, high potency agents (i.e. haloperidol, fluphenazine) are recommended over low potency agents (chlorpromazine) during pregnancy. See Table 6 below for information about the use of certain antipsychotics during pregnancy.

Regarding the use of long-acting injectables in pregnant patients, it is best to avoid those that have n-methyl-pyrrolidine (NMP) as this excipient has been shown to harm developing fetus in animal studies. There is paucity of data studying the reproductive effects of NMP with human use. Risperidone extended release (Perseris) is the only long-acting injectable antipsychotic that contains NMP.

The use of antipsychotics during pregnancy remains an area that is understudied. Pregnant women who take antipsychotics may consider enrolling in a national pregnancy registry to help gather more information in the area. Information is available at: https://womensmentalhealth.org/research/pregnancyregistry/atypicalantipsychotic/.

LACTATION: A careful decision should be made whether to discontinue nursing or discontinue antipsychotic treatment. The health benefits of breastfeeding should be considered, along with the mother's clinical need for treatment and any potential adverse effects on the breastfed infant from the antipsychotic. Infants should be monitored closely if decision is made to continue antipsychotic and breastfeeding.

See Table 6 below for information about the use of certain antipsychotics during breastfeeding. It is unknown if the following antipsychotics are excreted into breastmilk: asenapine, brexpiprazole, cariprazine, fluphenazine, iloperidone, loxapine, pimavanserin, pimozide, thioridazine, and thiothixene. There is no human data on the use of samidorphan component of olanzapine-samidorphan however metabolites were present in animal breast milk.

TABLE 6: ANTIPSYCHOTICS IN PREGNANCY AND LACTATION

Medication	Pregnancy	Lactation
Aripiprazole	Human data suggests low risk	Drug and metabolite present in breast milk; lactation failure has been observed
Chlorpromazine	Human experience has not shown increase in malformations	Drugs and metabolites present in breast milk; lethargy observed in breastfed infant
Clozapine	Limited data; given indicated for refractory illness, maternal benefits outweigh risks of unknown embryo-fetal risk May increase the risk of gestational diabetes	Breastfeeding is not recommended
Haloperidol	Most safety data for FGAs; human data does not suggest increased risk of congenital anomalies High potency typical antipsychotics preferred over low potency	Drug present in breast milk; breastfeeding is not recommended
Olanzapine	Not expected to increase risk of congenital anomalies May increase the risk of gestational diabetes	Drug present in low levels in breast milk; few adverse effects in infant; **preferred antipsychotic during breastfeeding**
Paliperidone	Unknown; limited data	No data for paliperidone but active metabolite risperidone present in breast milk in low levels
Perphenazine	Unknown; limited data	Drug present in low levels in breast milk
Quetiapine	Most reproductive safety data for SGAs; Human experience has not shown increase in congenital anomalies; low placental transfer	Drug present in breast milk; peak milk concentration occurs 1 hour after oral maternal dose; **2nd line antipsychotic in breastfeeding**
Risperidone	Moderate amount of data, some conflicting data however most data showing no risk of malformations	Drug and metabolite present in breast milk; peak milk concentration occurs 2-4 hours after oral maternal dose; **2nd line antipsychotic in breastfeeding**; recommended that women using IM injection not breastfeed during or for 12 weeks after last injection
Trifluoperazine	Unknown; limited data	Drug present in breast milk; no infant adverse events reported
Ziprasidone	Unknown; limited data	Drug present in low levels in breast milk
Lurasidone	Unknown; limited data	Data from one infant-mother pair found low levels in milk and no adverse effects on infant reported; however until more data available alternate drug may be preferred
Lumateperone	Unknown; limited data	Low levels of drug present in breast milk

RENAL AND HEPATIC IMPAIRMENT: See Table 7 below for information on the use of antipsychotics in renal and hepatic impairment. Note that older medications were not specifically studied in these populations. Practice caution if using antipsychotics in renal or hepatic impairment.

TABLE 7: RENAL AND HEPATIC IMPAIRMENT

Medication	Hepatic Impairment	Renal Impairment
Aripiprazole	No dose adjustments	No dose adjustments
Asenapine	Contraindicated for Child-Pugh class C. No dose adjustment for Child-Pugh class A or B.	No dose adjustments
Brexpiprazole	Child-Pugh class B or C: max dose of 3mg for schizophrenia and 2mg for major depression	CrCl <60ml/min: max dose of 3mg for schizophrenia and 2mg for major depression
Cariprazine	Child-Pugh class C: use not recommended	CrCl<30ml/min: use not recommended
Chlorpromazine	No dose adjustments.	No dose adjustments. Use caution. Not dialyzable.
Clozapine	Dose reductions may be necessary with significant impairment	Dose reductions may be necessary with significant impairment
Fluphenazine	Use is contraindicated.	No dose adjustments. Use with caution.
Haloperidol	No dose adjustments.	No dose adjustments.
Iloperidone	Use not recommended for severe impairment; use caution with moderate impairment	No dose adjustment
Loxapine	No dose adjustments	No dose adjustments.
Lumateperone	Child-Pugh class B or C: avoid use	No dose adjustments
Lurasidone	Child-Pugh class B: max dose 80mg/day; Child-Pugh class C: max dose 40mg/day	CrCl<50 ml/min: max dose of 80mg/day
Olanzapine	No dose adjustment.	No dose adjustment; not removed by hemodialysis
Olanzapine-samidorphan	Use with caution as exposure is increased with moderate hepatic impairment	Severe impairment (eGFR 15 to 29 ml/min/1.73m^2): no dose adjustments but should be used with caution given increased exposure in patients with severe renal impairment End-stage renal disease (eGFR < 15 ml/min/1.73m^2): use not recommended (has not been studied)
Paliperidone	No dose adjustment for Child-Pugh class A or B. Not studied in Child-Pugh class C.	CrCl 50-79ml/min: max dose 6mg/day CrCl 10-49ml/min: max dose 3mg/day CrCl<10ml/min: Use not recommended
Perphenazine	Contraindicated in patients with liver damage.	No dose adjustments.
Pimavanserin	No dose adjustments.	CrCl<30: No dose adjustments. Use with caution
Pimozide	No dose adjustments. Use with caution.	No dose adjustments. Use with caution.
Quetiapine	Lower starting dose.	No dose adjustment
Risperidone	Child-Pugh class C: Initial dose of 0.5mg BID; titrate slowly in	CrCl<30ml/min: Initial dose of 0.5mg BID; titrate slowly in increments of no more than 0.5mg BID

	increments of no more than 0.5mg BID	
Thioridazine	No dose adjustments. Use with caution.	No dose adjustments.
Thiothixene	No dose adjustments.	No dose adjustments.
Trifluoperazine	Use is contraindicated.	No dose adjustments.
Ziprasidone	No dose adjustment; use with caution	No dose adjustment; not removed by hemodialysis

DRUG INTERACTIONS: Antipsychotics are highly metabolized in the liver by the cytochrome P450 system. This introduces the potential for drug interactions. See Tables 8 and 9 below for details on which CYP enzymes metabolize the antipsychotics.

TABLE 8: FGA CYTOCHROME P450 METABOLISM

Antipsychotic	CYP1A2	CYP2C19	CYP2D6	CYP3A4
Chlorpromazine	✓		✓	✓
Fluphenazine			✓	
Haloperidol	✓		✓	✓
Loxapine	✓		✓	✓
Perphenazine			✓	
Pimozide	✓			✓
Thioridazine		✓	✓	
Thiothixene	✓			
Trifluoperazine	✓			

TABLE 9: SGA CYTOCHROME P450 METABOLISM (major substrates only)

Antipsychotic	CYP1A2	CYP2C19	CYP2D6	CYP3A4
Aripiprazole			✓	✓
Asenapine	✓		✓	
Clozapine	✓			✓
Iloperidone			✓	✓
Lumateperone				✓
Lurasidone				✓
Olanzapine	✓			
Olanzapine-samidorphan	✓ (olanzapine)			✓ (samidorphan)
Paliperidone				
Pimavanserin				✓
Quetiapine				✓
Risperidone			✓	✓
Ziprasidone	✓			✓
Brexpiprazole			✓	✓
Cariprazine				✓

CONCURRENT USE OF TWO OR MORE ANTIPSYCHOTIC MEDICATIONS: In general, BHS does not recommend the concurrent use of two or more antipsychotics. Only one antipsychotic medication should be used at any one time, except during brief transitions from one to another or in exceptional circumstances. The reason for concurrent dosing should be well documented in the clinical record. This should be revisited approximately semi-annually and attempts to eliminate concurrent dosing should be made and documented regularly. Clinical treatment teams should periodically review these

cases and work with individual clients to reduce concurrent use of two or more antipsychotic medications. Clients should be counselled about the risks of concurrent antipsychotic use and these discussions should be documented in the medical record.

USE OF LONG-ACTING INJECTABLE ANTIPSYCHOTIC MEDICATIONS: Long-acting injectable antipsychotic medications should be offered under these circumstances:

- Appropriate individuals upon client request
- When there is a history of poor adherence to oral antipsychotic medications
- To avoid certain side effects that may be increased after oral administration
- For those individuals unable to take oral medications
- To simplify complex medication regimens.

See Appendix 1 for prescribing information about long-acting injectable antipsychotic medications. BHS does not recommend olanzapine extended release injection due to risk of post-injection delirium/sedation syndrome.

APPENDIX 1: LONG-ACTING INJECTABLE ANTIPSYCHOTICS

ARIPIPRAZOLE EXTENDED RELEASE INJECTION (ABILIFY MAINTENA)

Dose: The starting, target and maximum dose is 400mg

Dosing interval: Injections should be given every 4 weeks

Overlap with oral medication: There should be an overlap with oral medications for 14 days after the first injection

Dosage adjustments:

Circumstance	Adjustment
Adverse events occur	Lower monthly dosage to 300mg
Strong CYP2D6 ***or*** CYP3A4 inhibitors >14 days	*200mg-300mg per month
Strong CYP2D6 ***and*** CYP3A4 inhibitors >14 days	*160mg-200mg per month
CYP 3A4 Inducers	Avoid use

*160mg and 200mg dose adjustments are obtained only by using the 300mg or 400mg strength single-use vials

Medication supply, storage and handling:

Supplied	Reconstitution	Refrigeration	Administration	Needle Size
Pre-filled dual chamber syringe OR Single-use vials kits: 300mg 400mg	Required for both formulations. Pre-filled dual chamber: reconstituted in syringe. Single-use Vials: reconstituted in vial then drawn up in syringe	None for either formulation	Pre-filled dual chamber: Shake vertically for 20 seconds. Use within 30 minutes of reconstitution. Single-use vials: Shake for 30 seconds. If not using immediately, keep in vial and shake 60 seconds again prior to administration	Deltoid : Non-obese: 23 G, 1” Obese: 22 G, 1.5” Gluteal : Non-obese: 22 G, 1.5” Obese: 21 G, 2”

Pharmacokinetics:

Half-life (single-dose)	Half-life (multiple doses)	Time to maximum concentration
Not published	30-47 days	Deltoid: 4 days Gluteal: 5-7 days

ARIPIPRAZOLE LAUROXIL EXTENDED RELEASE INJECTION (ARISTADA)

Conversion from oral aripiprazole to aripiprazole lauroxil:

Oral Aripiprazole Dose	Aripiprazole Lauroxil Dose	Dosing Frequency*	Site of IM Injection
10mg per day	441mg	Every 4 weeks	Deltoid or Gluteal
15mg per day	662mg **OR** 882mg **OR** 1064mg	Every 4 weeks Every 6 weeks Every 8 weeks	Gluteal
≥20mg per day	882mg	Every 4 weeks	Gluteal

*If an early dose is required, it may be given no earlier than 14 days since the last injection.

Overlap with oral medication: There should be an overlap with oral medications for 21 days after the first injection. Alternatively, patients can be loaded using ARISTADA INITIO- see next page.

Dose adjustments for drug interactions: Adjust dose of aripiprazole lauroxil if interacting medication is taken >14 days:

Circumstance	Aripiprazole lauroxil dose adjustment
Strong CYP3A4 inhibitor	Reduce dose to next lower strength*. No adjustment needed for 441mg dose
Strong CYP2D6 inhibitor	Reduce dose to next lower strength*. No adjustment needed for 441mg dose
Strong CYP2D6 ***plus*** CYP3A4 Inhibitor	Avoid use for 662mg and 882mg dose. No adjustment needed for 441mg dose
CYP 3A4 Inducers	No adjustment for 662mg and 882mg dose. Increase 441mg dose to 662mg

*For 882mg every 6 weeks and the 1064mg administered every 8 weeks, the next lower strength is 441mg every 4 weeks

Medication supply, storage and handling:

Supplied	Reconstitution	Refrigeration	Administration	Needle Size
As prefilled syringe kits: 441mg 662mg 882mg 1064mg	None	None, store at room temperature	Tap injection 10 times then shake 30 seconds	Deltoid (441mg only): Non-obese: 21 G, 1” Obese: 20 G, 1.5” Gluteal: Non-obese: 20 G, 1.5” Obese: 20 G, 2”

Pharmacokinetics

Half-Life (single-dose)	Half-Life (multiple doses)	Time to Maximum Concentration
Not Published	54-57 days	4 days with oral overlap 16 weeks with no oral overlap

ARIPIPRAZOLE LAUROXIL INJECTION (ARISTADA INITIO)

This is a one-time injection used to initiate treatment with aripiprazole lauroxil long acting injection (ARISTADA). It may also be used to re-initiate treatment with ARISTADA following a missed dose.

Dose: When initiating treatment, a single dose of 675mg should be given along with one 30mg dose of oral aripiprazole and the first ARISTADA injection (441mg, 662mg, 882mg or 1064mg). The first ARISTADA dose may be administered on the same day as ARISTADA INITIO or up to 10 days thereafter. Avoid injecting both ARISTADA INITIO and ARISTADA concomitantly into the same deltoid or gluteal muscle

Dose adjustments for drug interactions: This product is only available at a single-dose pre-filled syringe, so dose adjustments are not possible. Avoid use in patients who are known CYP2D6 poor metabolizers, are taking strong CYP3A4 inducers/inhibitors or are taking strong CYP2D6 inhibitors.

Medication supply, storage and handling:

Supplied	Reconstitution	Refrigeration	Administration	Needle Size
As 675mg prefilled syringe kit	None	None, store at room temperature	Tap injection 10 times then shake vigorously 30 seconds	Deltoid: Non-obese: 21 G, 1” Obese: 20 G, 1.5” Gluteal: Non-obese: 20 G, 1.5” Obese: 20G, 2”

Pharmacokinetics

Half-Life (single-dose)	Time to Maximum Concentration
15-18 days	4 days with 30mg oral aripiprazole 27 days without oral overlap

ARIPIPRAZOLE EXTENDED-RELEASE INJECTION (ABILIFY ASIMTUFII)

Dose: The starting, target and maximum dose is 960 mg

Dosing interval: Injections should be given every 2 months

Overlap with oral medication: There should be an overlap with oral medications (either 10-20 mg of aripiprazole or other oral antipsychotic if on different agent before) for 14 days after the first injection, unless transitioning from Abilify Maintena.

Transitioning from Abilify Maintena: Administer Abilify Asimtufii in place of Abilify Maintena only after the second or later injection of Maintena. No PO overlap required.

Dosage adjustments:

Circumstance	Adjustment
Known CYP2D6 poor metabolizer	Lower dosage to 720 mg every 2 months
Strong CYP2D6 ***or*** CYP3A4 inhibitors >14 days	720 mg every 2 months
Strong CYP2D6 ***and*** CYP3A4 inhibitors >14 days	Avoid use
CYP 3A4 Inducers	Avoid use
Known CYP2D6 poor metabolizer taking CYP3A4 inhibitors	Avoid use

Medication supply, storage and handling:

Supplied	Reconstitution	Refrigeration	Administration	Needle Size
Pre-filled syringe: -720 mg/2.4mL -960 mg/3.2 mL	None	None, store at room temperature	Tap syringe on hand at least 10 times and then shake vigorously for at least 10 seconds until medication uniform.	Gluteal administration only: Non-obese: 22 G, 1.5” Obese: 21 G, 2”

Pharmacokinetics:

Half-life (single-dose)	Half-life (multiple doses)	Time to maximum concentration
Not published	Not published	1-49 days

FLUPHENAZINE DECANOATE

Starting dose: 12.5mg- 25mg

Target dose: 12.5mg- 50mg

Maximum dose: 100mg per dose

Dosing interval: Injections should be given every 2-4 weeks

Overlap with oral medication: Yes, there should be an overlap with oral medications for 1-2 weeks after the first injection

Conversion between oral dose to injectable dose:

Daily oral dose	Equivalent injectable dose
10mg/day	12.5mg every 3 weeks

Medication supply, storage and handling:

Supplied	Reconstitution	Refrigeration	Needle Size
Multi-dose vials: 25mg/ml	None	None	Gluteal or deltoid: 21 G

*Protect from light

Pharmacokinetics:

Half-life (single-dose)	Half-life (multiple doses)	Time to maximum concentration
6-9 days	2 weeks	24 hours

HALOPERIDOL DECANOATE

Starting dose: 10-20 times the daily oral dose. The maximum dosage for the first injection is 100mg (test dose due to the risk of developing an allergic reaction to the sesame seed oil vehicle); give the remaining dose in 3-7 days

Target dose: 10-15 times the daily oral dose

Maximum dose: 450mg/month.

Dosing interval: Injections should be given every 4 weeks

Overlap with oral medication: If using a dose that is 10-15 times the oral daily dose, overlap with oral medication for 7 days. An increased duration of oral supplementation may be required depending on clinical picture (i.e., extend oral supplementation for 7 days with 50% dose reduction).

If the dose is 20 times the oral daily dose, no overlap with oral medication is necessary.*

Dosing Tips:

Patient Characteristics	First injection	Maintenance injection (after 1st month)
Stabilized on <10mg/day, elderly, debilitated	10-15 times daily oral dose	10-15 times daily oral dose
Stabilized on >10mg/day, high risk of relapse	20 times daily oral dose*	10-15 times daily oral dose

*Per package insert. However, MUIC Consensus recommends against 20 times daily oral dose due to increased risk of EPS.

Medication supply, storage and handling:**

Supplied	Reconstitution	Refrigeration	Needle Size
Single-dose and multi-dose vials: 50mg/ml 100mg/ml	None	None	Gluteal or deltoid: 21 G

**Protect from light

Pharmacokinetics:

Half-Life (single-dose)	Half-Life (multiple doses)	Time to Maximum Concentration
16 days	3 weeks	6 days

PALIPERIDONE PALMITATE (INVEGA SUSTENNA)

Rationale for loading dose: A loading dose provides rapid plasma drug levels, allowing for immediate discontinuation of oral dosing.

Recommended loading dose: Administer 234 mg on day 1, then 156 mg on day 8, both administered in a deltoid muscle. No oral overlap needed. The second dose (day 8 dose) may be administered +/- 4 days of its due date. Subsequent maintenance doses should be given every 4 weeks and may be administered +/- 7 days of its due date. See summary below:

Dose type	Dose schedule	Dose amount
First loading dose	Day 1 of Treatment	234 MG
Second loading dose	Day 8 of treatment (+/- four days)	156 MG
Maintenance dose	Day 36 of treatment (Five weeks after first injection)	39 – 234 MG*

* Usual maintenance dose is 117 mg monthly; Max dose is 234 mg monthly.

Conversion from oral risperidone or oral paliperidone to paliperidone long-acting injection (SUSTENNA): Administer 2 injection loading doses to ALL patients regardless of oral dose. Discontinue oral dosing after first injection. Select recommended maintenance dose based on conversion chart:

Oral risperidone	Oral paliperidone	Paliperidone palmitate (SUSTENNA)
1mg daily	3 mg daily (either 39mg or 78mg dose may be used)	39mg monthly
2mg daily		78 mg monthly
3mg daily	6 mg daily	117 mg monthly
4mg daily	9 mg daily	156 mg monthly
6mg daily	12 mg daily	234 mg monthly

Conversion from risperidone long-acting injection to paliperidone long-acting injection (SUSTENNA): No wash-out period required before switching treatment. The initial loading dose regimen is also not required. Paliperidone palmitate long-acting injectable (SUSTENNA) can be initiated at the next scheduled dosing in place of risperidone long-acting injectable. See below:

Drug	Risperidone long-acting injection	Paliperidone palmitate (SUSTENNA)
Frequency	Every two weeks	Every month
Dose	12.5 mg	39 mg
	25 mg	78 mg
	37.5 mg	117 mg
	50 mg	156 mg

Medication supply, storage and handling:

Supplied	Reconstitution	Refrigeration	Administration instructions	Needle size
As kits in the following dosages: 39mg 78mg 117mg 156mg 234mg	None	None	Shake vigorously for 10 seconds prior to injection	Deltoid: <200 lbs: 23 G, 1” ≥200 lbs: 22 G, 1.5”
				Gluteal: 22 G, 1.5”

Pharmacokinetics:

Half-life (single-dose)	Half-life (multiple doses)	Time to maximum concentration
25-29 days	Not Published	13-17 days

Please call CBHS Pharmacy (628-754-9110) for special dosing in elderly patients, CrCl <80mL/min, or any other questions.

PALIPERIDONE PALMITATE (INVEGA TRINZA)

Paliperidone palmitate (TRINZA) is a long acting injectable form of paliperidone palmitate that is given every 3 months. It should be used only after a patient has been adequately treated with a stable dose of Paliperidone palmitate (SUSTENNA) for at least 4 months.

Recommended loading dose: Paliperidone palmitate (TRINZA) should only be used in patients who have been on an established, stable dose of paliperidone palmitate (SUSTENNA) for at least 4 months. Initiate the initial dose of Paliperidone palmitate (TRINZA) when the next dose of paliperidone palmitate (SUSTENNA) is due, using the equivalent dose below:

Paliperidone palmitate (SUSTENNA)	Paliperidone palmitate (TRINZA)
78mg	273mg
117mg	410mg
156mg	546mg
234mg	819mg

*Conversion from the Paliperidone palmitate (SUSTENNA) 39mg dose was not studied

Converting from paliperidone palmitate (TRINZA) injection to PO paliperidone ER

	Weeks since last Invega Trinza Dose		
	3 months to 18 weeks	> 18 weeks to 24 weeks	> 24 weeks
Last Invega Trinza dose	**Dose of PO paliperidone ER tablets**		
273mg	3mg	3mg	3mg
410mg	3mg	3mg	6mg
546mg	3mg	6mg	9mg
819mg	6mg	9mg	12mg

Dosing Window: May administer ±2 weeks from scheduled 3-month dose

Medication supply, storage and handling:

Supplied	Reconstitution	Refrigeration	Administration Instructions	Needle Size
As kits in the following dosages: 273mg 410mg 546mg 819mg	None	None	Shake vigorously with the syringe pointing up for at least 15 seconds within 5 minutes prior to administration	Deltoid: <90 kg: 22 G, 1” ≥90 kg: 22 G, 1.5” Gluteal: 22 G, 1.5”

Pharmacokinetics:

Half-life (single-dose)	Half-life (multiple doses)	Time to maximum concentration
Deltoid: 84-95 days Gluteal: 118-139 days	Not Published	30-33 days

Please call CBHS Pharmacy (628-754-9110) for special dosing in elderly patients, CrCl <80mL/min, or any other questions.

PALIPERIDONE PALMITATE (INVEGA HAFYERA)

Paliperidone palmitate (HAFYERA) is a long-acting injectable form of paliperidone palmitate that is given every 6 months. It should be used only after a patient has been adequately treated with a stable dose of paliperidone palmitate (SUSTENNA) for at least 4 months OR after at least one three-month cycle of paliperidone palmitate (TRINZA).

Recommended loading dose: Paliperidone palmitate (HAFYERA) should only be used in patients who have been on an established, stable dose of paliperidone palmitate (SUSTENNA) for at least 4 months* or at least one three-month cycle of paliperidone palmitate (TRINZA)**. Initiate the initial dose of Paliperidone palmitate (HAFYERA) when the next dose of paliperidone palmitate (SUSTENNA or TRINZA) is due, using the equivalent dose below:

SUSTENNA	TRINZA	HAFYERA
156mg	546mg	1092 mg
234mg	819mg	1560 mg

*The two injection cycles immediately preceding the switch should be the same dosage strength before starting HAFYERA. HAFYERA may be administered up to 1 week before or 1 week after next scheduled SUSTENNA.
**HAFYERA can be administered up to 2 weeks before or 2 weeks after next scheduled Trinza dose

Renal impairment: Use is not recommended in patients with CrCl 80-90 ml/min

Dosing Window: May administer 2 weeks before or 3 weeks after scheduled 6-month dose

Medication supply, storage and handling:

Supplied	Reconstitution	Refrigeration	Administration Instructions	Needle Size
As kits in the following dosages: 1092mg 1560mg	None	None	Shake vigorously with the syringe pointing up for at least 15 seconds, then rest briefly and shake again for another 15 seconds within 5 minutes prior to administration. If more than 5 minutes pass before injection, shake vigorously for at least 30 seconds.	Gluteal only: 20 G, 1.5”

Pharmacokinetics:

Half-life (single-dose)	Half-life (multiple doses)	Time to maximum concentration
1092 mg: 148 days 1560 mg: 159 days	Not Published	29-32 days

RISPERIDONE LONG-ACTING INJECTION (RISPERDAL CONSTA)

Starting dose: 25mg every 2 weeks (12.5mg every 2 weeks for hepatic or renal impairment)

Target dose: 25mg- 50mg every 2 weeks

Maximum dose: 50mg every 2 weeks

Dosing interval: Injections should be given every 2 weeks

Overlap with oral medication: There should be an overlap with oral medications for 3-4 weeks after the first injection

Conversion between oral dose to injectable dose:

Daily oral dose	Equivalent injectable dose
2mg	25mg every 2 weeks
4mg	37.5mg every 2 weeks
6mg	50mg every 2 weeks

Dose adjustments for drug interactions:

Scenario	Recommendation
Initiation of strong CYP2D6 inhibitors	**If already on Risperdal Consta:** **-25 mg every 2 weeks**: continue this dose unless clinical judgement necessitates lowering dose to 12.5 mg every 2 weeks or interrupting treatment **-50 mg every 2 weeks**: may place on lower dose between 2-4 weeks before the planned start of inhibitor **New start Risperdal Consta while already taking inhibitor:** Can consider starting 12.5 mg every 2 weeks
Discontinuation of strong CYP2D6 inhibitor	Effects of discontinuation of strong CYP2D6 inhibitors on the PK of risperidone and 9-hydroxyrisperidone has not been studied
Initiation of strong CYP3A4 inducer	-Closely monitor patient during the first 4-8 weeks of initiation -Consider increasing to the next highest dose or addition of PO risperidone
Discontinuation of strong CYP3A4 inducer	-Re-evaluate dose or any PO supplemental risperidone and if necessary, decrease to adjust for expected increase in plasma concentrations -May place patient on lower dose between 2-4 weeks before the planned discontinuation of strong inducer -If patients are on 25 mg monthly, should continue current dose unless clinical judgement necessitates lowering dose to 12.5 mg every 2 weeks or interrupting treatment

Medication supply, storage and handling:

Supplied	Reconstitution	Refrigeration	Needle Size
As kits in the following dosages: 12.5mg 25mg 37.5mg 50mg	Required. Allow the medication to come to room temperature for at least 30 minutes prior to mixing. Injections are stable for 6 hours at room temperature after reconstitution.	Yes. Kits are stable at room temperature (not to exceed 77°F) for 7 days	Deltoid: 21 G, 1” Gluteal: 20 G, 2”

Pharmacokinetics:

Half-life (single-dose)	Half-life (multiple doses)	Time to maximum concentration
3-6 days	4-6 days	4-5 weeks

RISPERIDONE EXTENDED-RELEASE INJECTABLE (RYKINDO)

Starting dose: 25mg every 2 weeks (12.5mg every 2 weeks for hepatic or renal impairment)

Target dose: 25mg- 50mg every 2 weeks

Maximum dose: 50mg every 2 weeks

Dosing interval: Injections should be given every 2 weeks

Overlap with oral medication: There should be an overlap with PO risperidone for 7 days after first injection unless transitioning from Risperdal Consta

Transitioning from Risperdal Consta: The dose of Rykindo will be the same as that of Risperdal Consta. Administer Rykindo after 4 weeks (no later than 5 weeks) from last Risperdal Consta injection. No PO supplementation needed.

Dose adjustments for drug interactions:

Scenario	Recommendation
Initiation of strong CYP2D6 inhibitors	**If already on Rykindo:** **-25 mg every 2 weeks**: continue this dose unless clinical judgement necessitates lowering dose to 12.5 mg every 2 weeks or interrupting treatment **-50 mg every 2 weeks**: may place on lower dose between 2-4 weeks before the planned start of inhibitor **New start Rykindo while already taking inhibitor:** Can consider starting 12.5 mg every 2 weeks
Discontinuation of strong CYP2D6 inhibitor	Effects of discontinuation of strong CYP2D6 inhibitors on the PK of risperidone and 9-hydroxyrisperidone has not been studied
Initiation of strong CYP3A4 inducer	-Closely monitor patient during the first 4-8 weeks of initiation -Consider increasing to the next highest dose or addition of PO risperidone
Discontinuation of strong CYP3A4 inducer	-Re-evaluate dose or any PO supplemental risperidone and if necessary, decrease to adjust for expective increase in plasma concentrations -May place patient on lower dose between 2-4 weeks before the planned discontinuation of strong inducer -If patients are on 25 mg monthly, should continue current dose unless clinical judgement necessitates lowering dose to 12.5 mg every 2 weeks or interrupting treatment

Medication supply, storage and handling:

Supplied	Reconstitution	Refrigeration	Needle Size
As kits in the following dosages: 12.5mg 25mg 37.5mg 50mg	Required. Allow the medication to come to room temperature for at least 30 minutes prior to mixing.	Yes. Kits are stable at room temperature (not to exceed 77°F) for 7 days	Gluteal injection only: 20 G, 2”

Pharmacokinetics:

Half-life (single-dose)	Half-life (multiple doses)	Time to maximum concentration
3-6 days	Not published	14-17 days

RISPERIDONE EXTENDED-RELEASE INJECTION (PERSERIS)

Starting dose: 90mg once per month

Target dose: 90-120mg once per month

Maximum dose: 120mg once per month

Dosing interval: Injections should be given once per month

Overlap with oral medication: No overlap with oral risperidone is necessary. Establish tolerability with oral risperidone prior to starting the long acting injection

Conversion between oral risperidone dose to injectable dose*:

Daily oral dose	Equivalent injectable dose
3mg	90mg once per month
4mg	120mg once per month

*Patients who are on stable oral risperidone doses lower than 3 mg/day or higher than 4 mg/day may not be candidates for this injection

Medication supply, storage and handling:

Supplied	Reconstitution	Refrigeration	Needle Size
As kits in the following dosages: 90mg 120mg	Required. Allow the medication to come to room temperature for at least 15 minutes prior to mixing.	Yes. Kits are stable at room temperature (not to exceed 77°F) for 7 days	Abdominal subcutaneous: 18 G, 5/8”

Pharmacokinetics:

Half-life (single-dose)	Half-life (multiple doses)	Time to maximum concentration
9-11 days	8-9 days	25 mg: 14 days 50 mg: 17 days Risperidone plasma concentrations approached steady-state after the 1st injection

RISPERIDONE EXTENDED-RELEASE INJECTION (UZEDY)

Starting dose: Switch from oral daily risperidone following table below:

Daily oral dose	UZEDY once monthly dose	UZEDY once every two months dose
2mg	50mg	100mg
3mg	75mg	150mg
4mg	100mg	200mg
5mg	125mg	250mg

Renal and hepatic dosing: Carefully titrate oral risperidone to at least 2 mg once daily and transition to recommended dosage of 50 mg once monthly

Target dose: Based on establish PO risperidone dose

Maximum dose: 125 mg every month or 250 mg every two months

Dosing interval: Every 28 or 56 days

Overlap with oral medication: No overlap with oral risperidone is necessary. Establish tolerability with oral risperidone prior to starting the long-acting injection.

Dose adjustments for drug interactions:

Scenario	Recommendation
Initiation of strong CYP2D6 inhibitor	-May place patients on the lowest dose (50 mg monthly or 100 mg every 2 months) prior to the planned start of strong CYP2D6 inhibitor -If already on lowest doses, recommended to continue current treatment with same doses unless clinical judgement suggests interruption is needed
Discontinuation of strong CYP2D6 inhibitor	Effects of discontinuation of strong CYP2D6 inhibitors on the PK of risperidone and 9-hydroxyrisperidone has not been studied
Initiation of strong CYP3A4 inducer	-Closely monitor patient during the first 4-8 weeks of initiation of strong CYP3A4 inducer -Consider increasing to the next highest dose -If receiving highest doses (125 mg once monthly or 250 mg every 2 months), addition of PO risperidone may be considered
Discontinuation of strong CYP3A4 inducer	-Re-evaluate dose of UZEDY or any PO supplemental risperidone and if necessary, decrease to adjust for expective increase in plasma concentrations -If patients are on 50 mg monthly or 100 mg every 2 months, it is recommended to continue treatment with same doses unless clinical judgement suggests interruption is needed

Medication supply, storage and handling:

Supplied	Reconstitution	Refrigeration	Administration Instructions	Needle Size
As pre-filled syringes in the following dosages: 50mg 75mg 100mg 125mg 150mg 200mg 250mg	Not required	Yes. Kits are stable at room temperature (not to exceed 77°F) for 7 days	Forceful downward flicks required to move bubble to the cap of syringe. Flick with a forceful downward whipping motion of your full arm to move bubble to the cap of syringe, repeat 3 times.	Abdominal or upper arm subcutaneous: 21 G, 5/8”

Pharmacokinetics:

Half-life (single-dose)	Half-life (multiple doses)	Time to maximum concentration
Not published	14-22 days	1st peak: 6-24 hours 2nd peak: 8-14 days Risperidone plasma concentrations approached steady-state within 2 months of initiation

APPENDIX 2: MISSED LAI DOSE MANAGEMENT

<table>
<tr><th>Drug</th><th>Dosing Window Flexibility</th><th>Missed Dose Management</th></tr>
<tr><td>Abilify Maintena (aripiprazole)

Dosing frequency: every 4 weeks</td><td>No earlier than 26 days after last injection</td><td>
If 2nd or 3rd injection missed:
<table>
<tr><td>Timing of Missed Dose From Last Injection</td><td>Guidance</td></tr>
<tr><td>> 4 weeks and < 5 weeks from last injection:</td><td>-Administer missed dose ASAP
-No oral overlap required</td></tr>
<tr><td>> 5 weeks</td><td>-Refer for provider assessment
-Order requires PO overlap of 20mg/day for 14 days after missed maintenance dose administer ASAP.</td></tr>
</table>
If 4th or subsequent dose missed:
<table>
<tr><td>Timing of Missed Dose From Last Injection</td><td>Guidance</td></tr>
<tr><td>> 4 weeks and < 6 weeks</td><td>-Administer missed dose ASAP
-No oral overlap required</td></tr>
<tr><td>> 6 weeks</td><td>-Refer for provider assessment
-Order requires PO overlap of 20 mg/day for 14 days after missed maintenance dose administer ASAP.</td></tr>
</table>
</td></tr>
</table>

<table>
<tr>
<td>Aristada (aripiprazole lauroxil)

Dosing frequency: every 4, 6 or 8 weeks</td>
<td>No earlier than 14 days after last injection</td>
<td>Missed dose overlap can either be managed with oral overlap or Aristada Initio (one time 675 mg aripiprazole lauroxil injection):
<table>
<tr><th>Last dose</th><th colspan="3">Length of time since last injection</th></tr>
<tr><td>441 mg</td><td>≤ 6 wks</td><td>> 6 & ≤ 7 wks</td><td>> 7 wks</td></tr>
<tr><td>662 mg</td><td>≤ 8 wks</td><td>> 8 & ≤ 12 wks</td><td>> 12 wks</td></tr>
<tr><td>882 mg</td><td>≤ 8 wks</td><td>> 8 & ≤ 12 wks</td><td>> 12 wks</td></tr>
<tr><td>1064 mg</td><td>≤ 10 wks</td><td>> 10 & ≤ 12 wks</td><td>> 12 wks</td></tr>
<tr><td>Guidance</td><td>Give dose ASAP. No PO overlap or Initio dose required.</td><td>Refer for provider assessment. Requires 7 -day PO overlap* or 1 dose of Initio after maintenance dose administered ASAP</td><td>Refer for provider assessment. Requires 21-day PO overlap* or 1 dose of Initio with one 30 mg PO aripiprazole dose after maintenance dose administered ASAP</td></tr>
</table>
*Refer to Safer Prescribing of Antipsychotic Medications Guideline for PO dose equivalents</td>
</tr>
<tr>
<td>Abilify Asimtufii (aripiprazole)

Dosing frequency: every 2 months</td>
<td>May administer injection up to 2 weeks before or after the 2-month timepoint</td>
<td>
<table>
<tr><th>Timing of Missed Dose From Last Injection</th><th>Guidance</th></tr>
<tr><td>> 8 weeks and < 14 weeks</td><td>Administer next dose ASAP and then resume 2-month schedule</td></tr>
<tr><td>> 14 weeks</td><td>-Refer for provider assessment
-Order requires PO supplementation of 10-20 mg/day for 14 days after missed maintenance dose administer ASAP.</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>Fluphenazine decanoate

Dosing frequency: every 2 to 4 weeks</td>
<td>None specified in package insert</td>
<td>
<u>If patient is at steady state (4-6 weeks of therapy):</u>
<table>
<tr><th>Time from last injection</th><th>Guidance</th></tr>
<tr><td>< 6 weeks</td><td>Administer next dose ASAP</td></tr>
<tr><td>6 to < 8 weeks</td><td>-Administer next dose ASAP
-Assess if symptoms have returned or worsened and notify provider to consider PO supplementation if symptomatic</td></tr>
<tr><td>≥ 8 weeks since last injection</td><td>-Refer for provider assessment
-Patient should be stabilized on PO fluphenazine and then fluphenazine decanoate should be re-initiated</td></tr>
</table>
<u>If patient is not at steady state (<4 weeks of therapy or only 1 injection given):</u>
<table>
<tr><th>Time from last injection</th><th>Guidance</th></tr>
<tr><td>≥ 1 week to < 8 weeks</td><td>-Administer next dose ASAP
-Assess if symptoms have returned or worsened and notify provider to consider PO supplementation if symptomatic</td></tr>
<tr><td>≥ 8 weeks since last injection</td><td>-Refer for provider assessment
-Patient should be stabilized on PO fluphenazine and then fluphenazine decanoate should be re-initiated</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>Haloperidol decanoate

Dosing frequency: every 4 weeks</td>
<td>None specified in package insert</td>
<td>
<u>If patient is at steady state (4 or more months of therapy):</u>
<table>
<tr><th>Time from last injection</th><th>Guidance</th></tr>
<tr><td>≤ 6 weeks since last injection</td><td>Administer next dose ASAP</td></tr>
<tr><td>6 to 12 weeks</td><td>-Administer next dose ASAP
-Assess if symptoms have returned or worsened. Notify provider to consider PO supplementation while also monitoring for adverse effects around Day 6 after injection</td></tr>
<tr><td>≥ 12 weeks since last injection</td><td>-Refer for provider assessment
-Patient should be stabilized on PO haloperidol and then haloperidol decanoate should be re-initiated</td></tr>
</table>
<u>If patient is NOT at steady state (< 4 months of therapy):</u>
<table>
<tr><th>Time from last injection</th><th>Guidance</th></tr>
<tr><td>> 5 to < 12 weeks</td><td>-Administer next dose ASAP
-Assess if symptoms have returned or worsened. Notify provider to consider PO supplementation if symptomatic while also monitoring for adverse effects around Day 6 after injection</td></tr>
<tr><td>≥ 12 weeks since last injection</td><td>-Refer for provider assessment
-Patient should be stabilized on PO haloperidol and then haloperidol decanoate should be re-initiated</td></tr>
</table>
</td>
</tr>
</table>

<table>
<tr>
<td>Invega Sustenna (paliperidone palmitate)

Dosing frequency: every 4 weeks</td>
<td><u>For 2nd initiation dose</u>: can be administered +/- 4 days from scheduled one-month time point

<u>For maintenance dose:</u>
+/- 1 week from scheduled one-month time point</td>
<td>Missed 2nd Initiation Dose:
<table>
<tr><th>Timing of Missed Dose From 1st Initiation Dose</th><th>Guidance</th></tr>
<tr><td>< 4 weeks</td><td>Refer for provider assessment.
Administer 156 mg IM in the deltoid as the 2nd injection and provider should order:
Invega Sustenna 117 mg IM in either deltoid or gluteal muscle to be administered as a <u>3rd injection five weeks after the 1st injection</u> (regardless of timing of the 2nd injection)
Then resume regular monthly dosing in either deltoid or gluteal muscle</td></tr>
<tr><td>4 to 7 weeks</td><td>Refer for provider assessment.
Administer 156 mg IM in the deltoid as the 2nd injection and provider should order:
Invega Sustenna 156 mg IM in deltoid to be administered as 3rd injection <u>one week later</u>
Then resume monthly dosing in either deltoid or gluteal muscle</td></tr>
<tr><td>> 7 weeks</td><td>Refer for provider assessment.
-Provider should re-start Invega Sustenna with the initial starting dose recommendation*:
Administer 234 mg IM in deltoid on Day 1
Administer 156 mg IM in deltoid on Day 8
Then resume monthly dosing in either deltoid or gluteal muscle
*for those with normal renal function</td></tr>
</table>
</td>
</tr>
</table>

Missed Maintenance Dose:

Timing of Missed Dose From Last Injection	Guidance
< 6 weeks	Administer missed dose ASAP, then resume monthly maintenance 4 weeks later
> 6 weeks to 6 months	**Refer for provider assessment.** -Resume regular monthly dosing ASAP in deltoid and provider should order another injection of the same dose 1 week later to be given in deltoid • *the only exception is if patient stabilized on 234 mg, the first 2 doses should be 156 mg -Resume regular monthly maintenance dose 4 weeks after 2nd injection in either deltoid or gluteal muscle
> 6 months	**Refer for provider assessment.** -Provider should re-start Invega Sustenna with the initial starting dose recommendation*: • Administer 234 mg IM in deltoid on Day 1 • Administer 156 mg IM in deltoid on Day 8 into deltoid • Then resume monthly dosing into deltoid or gluteal muscle *for those with normal renal function

<table>
<tr>
<td>Invega Trinza (paliperidone palmitate)

Dosing frequency: every 3 months</td>
<td>With first Invega Trinza injection (after 4 doses of Sustenna), Trinza can be administered 1 week before or after next monthly dose is due

After this, maintenance Trinza doses can be administered up to 2 weeks before or after the 3-month time point</td>
<td>
<u>> 3.5 to <4 months</u>: Administer missed dose ASAP, then resume maintenance dose 3 months later

<u>4 to 9 months</u>: Refer for provider assessment. Provider should follow re-initiation following listed below:

<table>
<tr><th rowspan="2">Trinza dose</th><th colspan="2">Invega Sustenna: 2 doses, 1 week apart into deltoid muscle</th><th>Invega Trinza (into deltoid or gluteal muscle)</th></tr>
<tr><td>Day 1</td><td>Day 8</td><td>1 month after day 8</td></tr>
<tr><td>273 mg</td><td>78 mg</td><td>78 mg</td><td>273 mg</td></tr>
<tr><td>410 mg</td><td>117 mg</td><td>117 mg</td><td>410 mg</td></tr>
<tr><td>546 mg</td><td>156 mg</td><td>156 mg</td><td>546 mg</td></tr>
<tr><td>819 mg</td><td>156 mg</td><td>156 mg</td><td>819 mg</td></tr>
</table>

<u>>9 months</u>: Refer for provider for assessment. Client should be re-initiated on equivalent monthly Invega Sustenna (see Safer Prescribing of Antipsychotic Medications Guideline for Sustenna equivalents) for at least 4 months, then can resume Trinza
</td>
</tr>
</table>

<table>
<tr>
<td>Invega Hafyera (paliperidone palmitate)

Dosing frequency: every 6 months</td>
<td>If transitioning from Sustenna, Hafyera can be administered up to 1 week before or after the monthly time point of next scheduled Sustenna

If transitioning from Trinza, Hafyera may be administered up to 2 weeks before or after the time point of next scheduled Trinza

2 weeks before or 3 weeks after scheduled 6-month time point</td>
<td>If more than 6 months and 3 weeks but less than 8 months since last dose:
• Refer for provider assessment. Provider should follow re-initiation regimen below:

<table>
<tr><th>Last dose</th><th>Administer Invega Sustenna into deltoid</th><th>Administer Invega Hafyera into gluteal muscle</th></tr>
<tr><td></td><td>Day 1</td><td>1 month after Day 2</td></tr>
<tr><td>1092 mg</td><td>156 mg</td><td>1092 mg</td></tr>
<tr><td>1560 mg</td><td>234 mg</td><td>1560 mg</td></tr>
</table>

If 8 to 11 months since last dose:
• Refer for provider assessment. Provider should follow re-initiation regimen below:

<table>
<tr><th rowspan="2">Last dose</th><th colspan="2">Administer Invega Sustenna into deltoid</th><th>Administer Invega Hafyera into gluteal muscle</th></tr>
<tr><td>Day 1</td><td>Day 8</td><td>1 month after Day 8</td></tr>
<tr><td>1092 mg</td><td>156 mg</td><td>156 mg</td><td>1092 mg</td></tr>
<tr><td>1560 mg</td><td>156 mg</td><td>156 mg</td><td>1560 mg</td></tr>
</table>
If more than 11 months have passed since last dose:
-Refer for provider assessment.
-Treatment should be re-initiated with Invega Sustenna for at least 4 months (see Safer Prescribing of Antipsychotic Medications Guideline for Sustenna equivalents) and then can be switched back to Hafyera</td>
</tr>
<tr>
<td>Persersis (risperidone)

Dosing frequency: every 4 weeks (SQ)</td>
<td>None specified in package insert</td>
<td>Refer for provider assessment.
-Provider should determine if PO supplementation is needed and then dose can be administered ASAP</td>
</tr>
</table>

<table>
<tr>
<td>Risperdal Consta (risperidone)

Dosing frequency: every 2 weeks</td>
<td>None specified in package insert

No sooner than 2 weeks</td>
<td>Guidance depends on if steady state (≥ 2 months) reached, see below:

<table>
<tr><th>Timing of Missed Dose From Last Injection Depending If Steady State Reached</th><th>Guidance</th></tr>
<tr><td>Not at steady state (< 2 months of therapy) and > 2 weeks since last injection</td><td>-Refer for provider assessment.
-Provider should order 21 days of PO supplementation* and then maintenance dose can be administered</td></tr>
<tr><td>At steady state (≥ 2 months) and ≤6 weeks since last injection</td><td>Administer next dose ASAP</td></tr>
<tr><td>At steady state (≥ 2 months) and > 6 weeks since last injection</td><td>-Refer for provider assessment
-Provider should order 21 days of PO supplementation* and then maintenance dose can be administered</td></tr>
</table>

*Refer to Safer Prescribing of Antipsychotic Medications Guideline for PO dose equivalents</td>
</tr>
<tr>
<td>Rykindo (risperidone)

Dosing frequency: every 2 weeks</td>
<td>None specified in package insert

No sooner than 2 weeks</td>
<td>Refer for provider assessment.
-Provider should determine if PO supplementation is needed and then dose can be administered ASAP</td>
</tr>
<tr>
<td>Uzedy (risperidone)

Dosing frequency: every month or every 2 months <u>SQ</u></td>
<td>No sooner than every month or every 2 months</td>
<td>Administer next injection ASAP</td>
</tr>
</table>

Note: Dosing frequency as specified in package insert, does not include non-standard dosing

APPENDIX 3: SIDE EFFECT MANAGEMENT MEDICATIONS BY INDICATION*

Drug	Mechanism	Dosing	Pregnancy**	Lactation**	Hepatic Impairment	Renal Impairment
Dystonia (non-acute) and Pseudoparkinsonism						
Amantadine	Unknown	100mg daily x1 week then 100mg BID. Maximum 300mg/day	Limited human data – animal data suggest risk	Limited human data – potential toxicity	No dose adjustments	-CrCl 30-50 ml/min: max dose 100mg/day -CrCl 15-29 ml/min: max 100mg every other day -CrCl: <15ml/min or hemodialysis: 200mg q7 days
Benztropine	Anticholinergic	0.5 – 4mg daily or BID	Limited human data – probably compatible	No human data – probably compatible	No dose adjustments	No dose adjustments
Diphenhydramine	Anticholinergic	25 – 50mg daily. Maximum 300mg/day	Compatible	Limited human data – probably compatible	No dosage adjustments provided in the manufacturer's labeling. Due to 50% liver metabolism, dose adjustments may be needed	No dosage adjustments provided in the manufacturer's labeling
Trihexyphenidyl	Anticholinergic	1mg daily, increase to 5-15mg/day divided in 3 doses with meals	Limited human data – no relevant animal data	Limited human data – probably compatible	No dosage adjustments provided in the manufacturer's labeling	No dosage adjustments provided in the manufacturer's labeling
Akathisia						
Mirtazapine	$5HT_{2A}$ antagonist	15mg QHS	Limited human data – animal data suggest moderate risk	Limited human data – potential toxicity	No dosage adjustments provided in the manufacturer's labeling; Use with caution	No dosage adjustments provided in the manufacturer's labeling; Use with caution
Propranolol	Centrally acting nonselective beta blocker	20-40mg BID. If needed, titrate up to 120mg/day	Human data suggest risk in 2nd and 3rd trimesters	Limited human data – potential toxicity	No dosage adjustments provided in the manufacturer's labeling	No dosage adjustments provided in the manufacturer's labeling
Tardive Syndrome						
Deutetrabenazine	Reversible VMAT 2 inhibitor	6mg BID, may increase by 6mg/day weekly.	No data	No data	Use is contraindicated	No dosage adjustments provided

Drug	Mechanism	Dosing	Pregnancy**	Lactation**	Hepatic Impairment	Renal Impairment
	resulting in depletion of monoamine stores	Maximum 48mg/day				in the manufacturer's labeling
Valbenazine	Reversible VMAT 2 inhibitor resulting in depletion of monoamine stores	40 daily x1 week then increase to 80mg daily	No data	No data	Child-Pugh class B or C: 40mg once daily; No dose adjustments for Child-Pugh class A	CrCl $\geq$ 30ml/min: no dose adjustment CrCl <30ml/min: use is not recommended
Sialorrhea						
Atropine	Topical anticholinergic	1% ophthalmic drops, 1-2 gtts SL qHS, if needed increase to TID	Sublingual: no data Opthalmic: no human data – probably compatible	Sublingual: no data Ophthalmic: no human data – probably compatible	No dosage adjustments provided in the manufacturer's labeling	No dosage adjustments provided in the manufacturer's labeling
Ipratropium	Topical anticholinergic	0.06% nasal spray, 1-2 puffs orally swish and spit daily, if needed increase to TID	Human data suggest low risk	No human data – probably compatible	No dosage adjustments provided in the manufacturer's labeling	No dosage adjustments provided in the manufacturer's labeling
Constipation						
Bisacodyl	Contact laxative stimulates peristalsis in large intestine and colon	Oral: 5 – 15mg daily Rectal: 10mg rectally once	No human data – probably compatible	Limited human data – probably compatible	No dosage adjustments provided in the manufacturer's labeling	No dosage adjustments provided in the manufacturer's labeling
Docusate	Stool softener	100 – 300mg daily in once a day or divided doses. Maximum dose 300mg/day.	Compatible	Compatible	No dosage adjustments provided in the manufacturer's labeling	No dosage adjustments provided in the manufacturer's labeling
Lactulose	Increases osmotic pressure and acidification to	10 – 20g daily x1-2 days then may increase to 40g daily	No human data – probably compatible	No human data – probably compatible	No dosage adjustments provided in the manufacturer's labeling	No dosage adjustments provided in the manufacturer's labeling

Drug	Mechanism	Dosing	Pregnancy**	Lactation**	Hepatic Impairment	Renal Impairment
	cause water retention in stool					
Polyethylene glycol 3350	Osmotic laxative to cause retention of water in stool	17g daily	Compatible	No human data – probably compatible	No dosage adjustments provided in the manufacturer's labeling	No dosage adjustments provided in the manufacturer's labeling
Senna	Stimulant laxative	17.2mg daily. Maximum 34.4mg BID	Compatible	Compatible	No dosage adjustments provided in the manufacturer's labeling	No dosage adjustments provided in the manufacturer's labeling
Metabolic Sequelae						
Hyperglycemia (HbA1c ≥ 5.7)						
Metformin	Reduces hepatic glucose production	Initial 500 mg PO daily with meals. May increase to 500 mg PO BID with meals after one week.	Human data shows likely compatible, may require dose adjustment given potential for increased clearance during pregnancy*	Human data shows low levels of metformin in breastmilk; one large prospective study found no adverse effects in breastfeed infants. Overall likely compatible, use with caution while nursing newborn and premature infants and those with renal impairment*	Avoid use (per manufacturer's labeling) given hepatic impairment may increase risk of developing lactic acidosis (seek consultation if considering use with hepatic impairment, including cirrhosis)	-eGFR ≥ 60 ml/min: no dosage adjustment, monitor Cr annually -eGFR 46-59 ml/min: no adjustment, monitor Cr every 6 months -eGFR 30-45 ml/min: use is not recommended (see expert guidance for use with close Cr monitoring) -eGFR <30: use is contraindicated
Elevated blood pressure (SBP ≥ 140 or DBP ≥ 90)						
Amlodipine	Calcium channel blocker	Initial 5 mg PO daily. May increase to 10 mg PO daily if BP continues to be elevated above 140/90.	Amlodipine crosses the placenta. Calcium channel blockers may be used to treat hypertension in pregnant	Amlodipine is present in breastmilk at acceptable levels. Adverse events were not observed	Titrate slowly in patients with severe hepatic impairment; consider lower initial dose for hypertension (initial 2.5 mg)	No dosage adjustment necessary

Drug	Mechanism	Dosing	Pregnancy**	Lactation**	Hepatic Impairment	Renal Impairment
			women; however, agents other than amlodipine are more commonly used	in the breastfed infants.		
Dyslipidemia (e.g., LDL ≥190)						
Atorvastatin	HMG-CoA reductase inhibitor	Recommend starting dose of 20 mg daily. Initial dose depends on baseline LDL and risk factors. Moderate-intensity: 10-20 mg PO daily. High intensity: 40-80 mg PO daily.	Contraindicated	Contraindicated	AST and ALT should be less than 3 times the upper limit of normal. Contraindicated in active liver disease or in patients with unexplained persistent elevations of serum transaminases	No dosage adjustment necessary
Weight Management						
Metformin	See above	IR: Start at 500 mg once or twice daily then titrate in increments of 500 mg every 1 to 2 weeks to a target dose of 1g BID XR: Start at 500 mg once daily, titrate in increments of 500 mg every 1 to 2 weeks to a target dose of 2 g once daily	Human data shows likely compatible. Per ACOG, medications for weight management are not recommended during pregnancy due to safety concerns and adverse effects.	See above	See sbove	See above
Topiramate	Acts on calcium and sodium channels, enhances GABA-A activity	Start at 50 mg/day and then titrate in increments of 250-50 mg at weekly intervals based on response and	Human and animal data suggest risk. Crosses the placenta. Manufacturer reports risk of cleft	Limited human data, potential toxicity. Nursing mothers, particularly those on high doses,	No dosage adjustments provided in manufacturer labeling. Topiramate clearance may be reduced in hepatic	CrCl < 70 ml/min: reduce dose to 50% of the indication-specific usual dose

Drug	Mechanism	Dosing	Pregnancy**	Lactation**	Hepatic Impairment	Renal Impairment
		tolerability up to recommended dose of 200 mg in 1-2 divided doses depending on formulation	lip and/or cleft palate and small for gestational age. Per ACOG, medications for weight management are not recommended during pregnancy due to safety concerns and adverse effects.	should monitor infants for signs of toxicity and changes in alertness, behavior, and feeding habits.	impairment, use with caution	
Semaglutide (Wegovy , Ozepmic)	Glucagon-like peptide-1 (GLP-1) receptor agonist	**Wegovy (for weight loss)** Week 1-4: 0.25 SQ once **weekly** Week 5-8: 0.5 mg SQ once weekly Week 9-12: 1 mg once SQ weekly Week 13-16: 1.7 mg SQ once weekly Week 17 and thereafter: 2.4 mg once weekly or 1.7 mg once weekly if unable to tolerate higher dose *Consider discontinuing if at least 5% of baseline **Ozempic (for T2DM)** Week 1-4: 0.25 mg SQ weekly Week 5-9: 0.5 mg SQ weekly	No human data. Animal data suggest risk. Per ACOG, medications for weight management are not recommended during pregnancy due to safety concerns and adverse effects. Alternative agents are recommended for management of T2DM in pregnancy.	No human data. Amount in milk likely to be low and absorption unlikely as it is large peptide molecule. Breastfeeding during therapy with oral semaglutide is not recommended due to the unknown risks associated with potential accumulation of salcaprozate sodium (SNAC) in the infant.	No dosage adjustments provided in the manufacturer's labeling.	No dosage adjustments provided in the manufacturer's labeling. Use caution when initiating or escalating doses in initiating or escalating doses as new onset or worsening of existing renal failure has been reported (most commonly in patients experiencing volume depletion from GI losses)

Drug	Mechanism	Dosing	Pregnancy**	Lactation**	Hepatic Impairment	Renal Impairment
		May increase to 1 mg SQ weekly after being on 0.5 mg weekly dose for 4 weeks. May further increase to maximum dose of 2 mg weekly after 4 weeks of 1 mg weekly dose. **Rybelsus (for T2DM):** 1st month: 3 mg PO daily 2nd month: 7 mg PO daily 3rd month: May increase to 14 mg PO daily if additional glycemic control needed				
Liraglutide (Saxenda, Victoza)	GLP-1 receptor agonist	**Saxenda (for weight loss)** Start with 0.6 mg SQ once **daily** for one week and then increase by 0.6 mg daily at weekly intervals up to a target dose of 3 mg SQ once daily *evaluate change in body weight after	No human data. Animal data suggest risk. Per ACOG, medications for weight management are not recommended during pregnancy due to safety concerns and adverse effects. Alternative agents	No human data. Amount in milk likely to be low and absorption unlikely as it is large peptide molecule. Until more data is available, recommended to use with caution.	No dosage adjustments provided in the manufacturer's labeling, use with caution due to limited	No dosage adjustment necessary. Use with caution in severe impairment, limited data is available in this population

Drug	Mechanism	Dosing	Pregnancy**	Lactation**	Hepatic Impairment	Renal Impairment
		12 weeks at max tolerated dose or 16 weeks after initiation, discontinue if at least 4-5% of baseline bodyweight not achieved **Victoza (for T2DM)** Start with 0.6 mg SQ once daily for one week and then increase to 1.2 mg SQ once daily. May increase to 1.8 mg SQ once daily for further glycemic control	are recommended for management of T2DM in pregnancy.			
Dulaglutide (Trulicity)	GLP-1 receptor agonist	**For T2DM:** 0.75 mg SQ **weekly** and can increase to 1.5 mg SQ once weekly after 4-8 weeks if additional glycemic control needed After that could increase to 3 mg SQ weekly after 4 weeks of 1.5 mg SQ weekly and then to a maximum of 4.5 SQ mg once weekly after at least 4	No human data. Animal data suggest low risk however medications for weight management are not recommended during pregnancy due to safety concerns and adverse effects. Alternative agents are recommended for management of T2DM in pregnancy.	No human data. Amount in milk likely to be low and absorption unlikely as it is large peptide molecule. Until more data is available, recommended to use with caution.	No dosage adjustments provided in the manufacturer's labeling, use with caution.	No dosage adjustments provided in the manufacturer's labeling. Use caution when initiating or escalating doses in initiating or escalating doses as new onset or worsening of existing renal failure has been reported (most commonly in patients experiencing volume depletion from GI losses)

Drug	Mechanism	Dosing	Pregnancy**	Lactation**	Hepatic Impairment	Renal Impairment
		weeks on 3 mg weekly dose				
Exenatide (Bydureon ER and Byetta IR for T2DM)	GLP-1 receptor agonist	**For T2DM:** **ER:** 2 mg SQ once **weekly** **IR:** 5 mcg BID within 60 minutes prior to morning and evening meals (or before the 2 main meals of the day, ≥ 6 hours apart), can titrate to 10 mcg BID after one month if further glycemic control needed	No human data. Animal data suggests moderate risk. Medications for weight management are not recommended during pregnancy due to safety concerns and adverse effects. Alternative agents are recommended for management of T2DM in pregnancy.	No human data. Amount in milk likely to be low and absorption unlikely as it is large peptide molecule. Until more data is available, recommended to use with caution.	No dose adjustments required	**IR** -CrCl 30 to 50 ml/min: use with caution with initiation of therapy or when increasing the dose & monitor for hypovolemia -CrCl < 30 ml/min: use is not recommended -ESRD: use is not recommended ER -eGFR ≥45: use with caution, monitor for hypovolemia -eGFR 30 to < 45: use is not recommended per manufacturer however some data exists that it is safe to use; use with caution and monitor -eGFR < 30 & ESRD: use is not recommended
Tirzepatide (Zepbound, Mounjaro)	GLP-1& GIP receptor agonist	**Zepbound (weight loss) and Mounjaro (T2DM):** 2.5 mg SQ once **weekly** for 4 weeks and then can	No human data. Animal data suggest risk. Per ACOG, medications for weight management are not recommended	No human data. Amount in milk likely to be low and absorption unlikely as it is large peptide molecule. Until more data is	No dose adjustments required	No dose adjustments required

Drug	Mechanism	Dosing	Pregnancy**	Lactation**	Hepatic Impairment	Renal Impairment
		increase to 5 mg SQ once weekly May continue to titrate in 2.5mg/week increments every 4 weeks to a maximum of 15 mg/week *2.5 mg once weekly dose not provide weight loss or glycemic control, intended to reduce GI symptoms	during pregnancy due to safety concerns and adverse effects. Alternative agents are recommended for management of T2DM in pregnancy.	available, recommended to use with caution.		

*This table contains off-label uses of medications
**Data from Briggs Drug in Pregnancy and Lactation and NIH LactMed

Additional notes regarding GLP-1 and GIP receptor agonists: GLP-1 receptor agonists and GLP-1/GIP receptor agonists are indicated for use in weight management in patients with a BMI ≥30 kg/m^2 or patients with a BMI ≥27 kg/m^2 and ≥1 weight-associated comorbidity (eg, cardiovascular disease, dyslipidemia, hypertension, obstructive sleep apnea, type 2 diabetes mellitus). These agents should be used in conjunction with diet and exercise. They are also indicated for the treatment of T2DM and not all are FDA approved for weight management. These are all subcutaneous injectable medications, except for semaglutide which comes as an oral tablet indicated for the treatment of T2DM. They are contraindicated patients with a personal or family history of medullary thyroid carcinoma (rats exposed to clinically relevant exposures developed thyroid c-cell tumors) or in patients with multiple endocrine neoplasia syndrome type 2 (MEN 2). Most common side effects are abdominal pain, constipation, diarrhea, nausea, vomiting and dyspepsia. Rare adverse events include: AKI, diabetic retinopathy (mainly observed in patients with pre-existing DR), gallbladder/biliary tract disease, and pancreatitis (monitor for acute sx), and hypersensitivity reactions (immediate or delayed; exenatide has higher odds of developing compared to newer GLP1s). Tachycardia and hypoglycemia may occur (particularly if on other glucose lowering agents).

While there is robust evidence for the use of these agents for weight management in the general population, there is limited published data on the use of GLP-1 RAs or GLP-1/GIP receptor agonists for the management of anti-psychotic induced weight gain or pre-diabetes secondary to antipsychotics. Tirzepatide has not been studied in this population and there are a few randomized control trials that include exenatide and liraglutide for anti-psychotic induced weight gain. Limited data exists for semaglutide in this population however there are ongoing clinical trials that are studying semaglutide in patients taking antipsychotics: NCT05333003, NCT05193578, NCT04892199, and Clozapine Obesity and Semaglutide Treatment study (COaST). Recommend consulting clinical pharmacist to guide choices given insurance coverage and drug shortage issues at the time of this update.

APPENDIX 4: CLOZAPINE MONITORING AND MANAGEMENT*

ANC level	Treatment Recommendation	ANC Monitoring
Normal Range for a New Patient - General Population (ANC> 1500/µL)	-Initiate treatment -If treatment interrupted: - <30 days, continue monitoring as before - ≥30 days, monitor as new patient -Discontinuation for reasons other than neutropenia	-Weekly from initiation to 6 months -Every 2 weeks from 6 to 12 months -Monthly after 12 months - See Section 2.4 of the full Prescribing Information
BEN Population -BEN Population (ANC> 1000/ µL) -Obtain at least two baseline ANC levels before initiating treatment		
Mild Neutropenia (1000 to 1499/µL)*	**General Population** - Continue treatment	**General Population** -Three times weekly until ANC≥1500/ µL -Once ANC ≥1500/ µL, return to patient's last "Normal Range" ANC monitoring interval**
	BEN Population - Mild neutropenia is normal range for BEN population, continue treatment -Obtain at least two baseline ANC levels before initiating treatment -If treatment interrupted: - <30 days, continue monitoring as before - ≥30 days, monitor as new patient - Discontinuation for reasons other than neutropenia	**BEN Population** -Weekly from initiation to 6 months -Every 2 weeks from 6 to 12 months -Monthly after 12 months - See Section 2.4 of the full Prescribing Information
Moderate Neutropenia (500-999/µL)*	**General Population** - Recommend hematology consultation -Interrupt treatment for suspected clozapine induced neutropenia -Resume treatment once ANC normalizes to ≥1000/µL	**General Population** - Daily until ANC ≥ 1000/µL, then -Three times weekly until ANC≥1500/µL -Once ANC ≥ 1500/µL, check ANC weekly for 4 weeks, then return to patient's last "normal range" ANC monitoring interval**
	BEN Population - Recommend hematology consultation - Continue treatment	**BEN Population** -Three times weekly until ANC≥1000/µL or > patient's known baseline -Once ANC ≥ 1000/µL or patient's known baseline, then check ANC weekly for 4 weeks, then return to

		patient's last "normal range" ANC monitoring interval**
Severe Neutropenia (less than 500/µL)*	**General Population and BEN Population** -Recommend hematology consultation -Interrupt treatment for suspected clozapine induced neutropenia -Do not rechallenge unless prescriber determines benefits outweigh risks	**General Population** -Daily until ANC≥ 1000/µL -Three times weekly until ANC ≥1500/µL -If patient rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥ 1500/µL
		BEN Population -Daily until ANC≥ 500/µL -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/µL or at patient's baseline

* Confirm all initial reports of ANC < 1500/µL (< 1000/µL for BEN patients) with a repeat ANC measurement within 24 hours
** If clinically appropriate

APPENDIX 5: METABOLIC MONITORING

The 2004 Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes and 2020 APA Practice Guidelines for the Treatment of Patients with Schizophrenia recommends baseline and routine monitoring as follows:

	Baseline	4 Weeks	8 Weeks	12 Weeks	Quarterly	Annually
Personal/Family history	√					
Weight/BMI	√	√	√	√	√	
Waist Circumference	√					√
Blood Pressure	√			√		√
Fasting Glucose or HbG A1C	√			√		√
Fasting Lipids	√			√		√

2020 APA Schizophrenia Practice Guidelines recommend annual lipid monitoring.

The 2005 American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement on the Diagnosis and Management of the Metabolic Syndrome defines the diagnosis of metabolic syndrome meeting ≥3 of the following 5 categories:

Category	Categorical Cut-points
Waist Circumference	Men: ≥ 40 in (102 cm) Women: ≥ 35 in (88 cm)
Blood Pressure*	Systolic: ≥130 mm Hg OR Diastolic: ≥85 mm Hg
Fasting Plasma Glucose*	≥100 mg/dL
Triglycerides*	≥150 mg/dL
HDL	Men: <40 mg/dL Women: <50 mg/dL

* Also positive if measurement in normal range and receiving treatment for that indication

APPENDIX 6: USE OF SGAS IN BIPOLAR DISORDER

SGAs are effective for the treatment of acute mania and mixed mood states in bipolar I disorder. They are frequently prescribed in the maintenance phase to prevent the recurrence of mania or hypomania. Fewer SGAs have an FDA indication for treatment of the depressed phase of bipolar disorder. Table 10 provides information on which SGAs are FDA approved for each phase of bipolar I disorder in both adults and children. Refer to the BHS Safer Prescribing of Mood Stabilizer Medication Guideline for more information about the treatment of bipolar disorder.

TABLE 10: SGA FDA APPROVED INDICATIONS IN BIPOLAR I DISORDER

	Mania and Mixed Episodes		**Depressive Episodes**		**Maintenance Therapy**	
Medication	**Adults**	**Children**	**Adults**	**Children**	**Adults**	**Children**
Aripiprazole	✓	✓ [1]			✓	
Asenapine	✓	✓ [1]			✓	
Brexpiprazole						
Cariprazine	✓		✓			
Clozapine						
Iloperidone						
Lumateperone			✓			
Lurasidone			✓	✓ [1]		
Olanzapine	✓	✓ [2]			✓	
Olanzapine/fluoxetine			✓	✓ [1]		
Olanzapine/samidorphan	✓					
Paliperidone						
Pimavanserin						
Quetiapine	✓ [4]	✓ [1 4]	✓		✓ [3]	
Quetiapine ER	✓	✓ [1 4]	✓		✓ [3]	
Risperidone	✓	✓ [1]				
Ziprasidone	✓				✓ [3]	

[1] Children ages 10 to 17 years
[2] Adolescents ages 13 to 17 years
[3] For adjunctive therapy with lithium or valproate
[4] Indicated in mania only

REFERENCES AND FURTHER READING

Antipsychotic Prescribing Guidelines

National Institute for Health and Care Excellence (NICE). (2015). Antipsychotics in people with dementia. Available at: https://www.nice.org.uk/advice/ktt7/resources/antipsychotics-in-people-with-dementia-pdf-1632175200709.

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