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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, immediate release intramuscular injection and long-acting intramuscular injection forms.

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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 5 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
Asenapine	5-20mg	BID 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
Lurasidone	20-160mg	Take with food; akathisia; fewer metabolic side effects
Olanzapine*	5-30mg	Metabolic side effects; sedation
Paliperidone	3-12mg	Metabolite of risperidone; increased prolactin; extrapyramidal side effects
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 2: 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 3 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

Clinicians should monitor for metabolic abnormalities and work closely with clients and their primary care providers whenever indicated. See Appendix 4 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.

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.

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 3 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 2: 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 2: 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. 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. 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.

Starting in June 2018, the FDA eliminated the old classification system for pregnancy and lactation. There are two significant changes. First the labeling has changed from the three categories: pregnancy, labor and delivery and nursing mothers to: pregnancy, lactation, and females and males of reproductive potential. Second, instead of discrete categories (e.g. A, B, C, D, X), the label is required to have information about risk summary and clinical considerations. Thus it is more specific than simply classifying a medication into a particular risk category. The new rules also require the label to include information about a pregnancy registry, if one exists. Newer medications will be characterized in this way whereas older medications might have the old system, and/or the new one.

Clozapine and lurasidone are rated as FDA pregnancy category B (animal studies do not show risk to fetus, no well-controlled studies in pregnant women); the remaining antipsychotics are rated as category C (animal studies show adverse effect to fetus, no well-controlled studies in pregnant women). High

potency FGAs (i.e. haloperidol, fluphenazine) are recommended over low potency FGAs (chlorpromazine) during pregnancy.

In 2011, the FDA updated the labels for all antipsychotic medications to 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.

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, lurasidone, pimozide, thioridazine, thiothixene and ziprasidone.

TABLE 6: ANTIPSYCHOTICS IN LACTATION

Medication	Lactation
Aripiprazole	Drug and metabolite present in breast milk; lactation failure has been observed
Chlorpromazine	Drugs and metabolites present in breast milk; lethargy observed in breastfed infant
Clozapine	Breastfeeding is not recommended
Haloperidol	Drug present in breast milk; breastfeeding is not recommended
Olanzapine	Drug present in low levels in breast milk; few adverse effects in infant; **preferred antipsychotic during breastfeeding**
Paliperidone	Drug present in breast milk
Perphenazine	Drug present in low levels breast milk
Quetiapine	Drug present in breast milk; peak milk concentration occurs 1 hour after oral maternal dose; **2nd line antipsychotic in breastfeeding**
Risperidone	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	Drug present in breast milk; no infant adverse events reported

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.
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
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.
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 increments of no more than 0.5mg BID	CrCl<30ml/min: Initial dose of 0.5mg BID; titrate slowly in 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

Antipsychotic	CYP1A2	CYP2C19	CYP2D6	CYP3A4
Aripiprazole			✓	✓
Asenapine	✓		✓	
Clozapine	✓			✓
Iloperidone			✓	✓
Lurasidone				✓
Olanzapine	✓			
Paliperidone				
Quetiapine				✓
Risperidone			✓	✓
Ziprasidone	✓			✓

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

HALOPERIDOL DECANOATE

Starting dose: 10-20 times the daily oral dose

Target dose: 10-15 times the daily oral dose

Maximum dose: 450mg/month. The maximum dosage for the first injection is 100mg; give the remaining dose in 3-7 days

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. 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

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

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

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)
1-2 mg daily	3 mg daily	78 mg monthly
3-4 mg daily	6 mg daily	117 mg monthly
5-6 mg daily	9 mg daily	156 mg monthly
	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

Missed second loading doses:

Time since first injection	Dosing schedule
<4 weeks	156 mg ASAP, then 117 mg 5 weeks after first injection
4-7 weeks	156 mg ASAP, then 156 mg a week later
>7 weeks	Load patient as a new start

Missed maintenance dose re-loading:

Time since last injection	Dosing schedule
≤ 6 weeks	Resume regular monthly dosing ASAP
> 6 weeks to 6 months*	Resume regular monthly dosing ASAP and another injection of the same dose 1 week later *the only exception is if patient stabilized on 234 mg, the first 2 doses should be 156 mg
>6 months	Load patient as a new start

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 (415-255-3659) 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

Missed doses: If less than 4 months have elapsed since the last injection, the previously administered dose of paliperidone palmitate (TRINZA) should be administered as soon as possible. If 4-9 months have elapsed since the last injection use the re-initiation regimen shown below:

Paliperidone palmitate (TRINZA) dose	Administer paliperidone palmitate (SUSTENNA), two doses one week apart (into deltoid muscle)		Then administer paliperidone palmitate (TRINZA) (into deltoid or gluteal muscle)
	Day 1	Day 8	
273mg	78mg	78mg	273mg
410mg	117mg	117mg	410mg
546mg	156mg	156mg	546mg
819mg	156mg	156mg	819mg

If more than 9 months have elapsed since the last injection, re-initiate treatment with paliperidone palmitate (SUSTENNA).

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

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: **T**here 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
3mg	37.5mg every 2 weeks
4mg	50mg every 2 weeks

Medication supply, storage and handling:

Supplied	Reconstitution	Refrigeration	Needle Size
As kits in the following dosages: 12.5mg 25mg 37.5mg 50mg	Required. 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	Gluteal: 20 G, 2” Deltoid: 21 G, 1”

Pharmacokinetics:

Half-life (single-dose)	Half-life (multiple doses)	Time to maximum concentration
6-9 days	4-6 days	4-5 weeks

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 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	4-6 hours; Risperidone plasma concentrations approached steady-state after the 1st injection

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	*200mg-300mg per month
Strong CYP2D6 ***and*** CYP3A4 inhibitors	*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

Managing missed doses: Give the injection as soon as possible and follow the recommendations below regarding whether an oral overlap is required.

Dose number	Length of time since last injection	
	No oral overlap required	Overlap with 14 Days oral aripiprazole
Second or third	< 5 weeks	> 5 weeks
Fourth or subsequent doses	< 6 weeks	> 6 weeks

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	Every 4 weeks	Gluteal
≥20mg per day	882mg	Every 4-6 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, next lower strength is 441mg every 4 weeks

Manage missed doses: Give the injection as soon as possible and follow the recommendations below regarding aripiprazole oral overlap. Supplemental oral aripiprazole dose should be the same as when the patient started aripiprazole lauroxil. Alternatively, missed doses can be managed with ARISTADA INITIO- see next page.

Last aripipirazole lauroxil dose	Length of time since last injection		
	No oral overlap required	Overlap with 7 days oral aripiprazole	Overlap with 21 days oral aripiprazole
441mg every 4 weeks	≤ 6 weeks	> 6 and ≤ 7 weeks	> 7 weeks
662mg every 4 weeks	≤ 8 weeks	> 8 and ≤ 12 weeks	> 12 weeks
882mg every 4 weeks	≤ 8 weeks	> 8 and ≤ 12 weeks	> 12 weeks
882 every 6 weeks	≤ 8 weeks	> 8 and ≤ 12 weeks	> 12 weeks

Medication supply, storage and handling:

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

Missed doses of ARISTADA: Administer the next dose as soon as possible. Supplemental doses may be recommended, see table below:

Dose of last ARISTADA injection	**Length of time since last injection**		
441mg	≤6 weeks	>6 and ≤7 weeks	>7 weeks
662mg	≤8 weeks	>8 and ≤12 weeks	>12 weeks
882mg	≤8 weeks	>8 and ≤12 weeks	>12 weeks
1064mg	≤10 weeks	>10 and ≤12 weeks	>12 weeks
Dosage and administration for re-initiation of ARISTADA	No supplementation required	Supplement with a single dose of ARISTADA INITIO	Re-initiate with a single dose of ARISTADA INITIO and a single dose of oral aripiprazole 30mg

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: 21 G, 1” or 20 G, 1.5” Gluteal: 20 G, 1.5” or 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

APPENDIX 2: 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 2^{nd} and 3^{rd} trimesters	Limited human data – potential toxicity	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
Tardive Syndrome						
Deutetrabenazine	Reversible VMAT 2 inhibitor resulting in depletion of monoamine stores	6mg BID, may increase by 6mg/day weekly. Maximum 48mg/day	No data	No data	Use is contraindicated	No dosage adjustments provided 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

Drug	Mechanism	Dosing	Pregnancy**	Lactation**	Hepatic Impairment	Renal Impairment
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 cause water retention in stool	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
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

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

APPENDIX 3: 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 4: METABOLIC MONITORING

The 2004 Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes recommends baseline and routine monitoring as follows:

	Baseline	4 Weeks	8 Weeks	12 Weeks	Quarterly	Annually	Every 5 Years
Personal/Family history	√						
Weight/BMI	√	√	√	√	√		
Waist Circumference	√					√	
Blood Pressure	√			√		√	
Fasting Glucose or HbG A1C	√			√		√	
Fasting Lipids	√			√		√*	√

*Fasting Lipids should be measured at baseline, 12 weeks, and annually in children and adolescents. Other monitoring recommendations are the same for children, adolescents and adults.

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 5: 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 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						
Lurasidone			✓	✓ [1]		
Olanzapine	✓	✓ [2]			✓	
Olanzapine/fluoxetine			✓	✓ [1]		
Paliperidone						
Quetipine	✓ [4]	✓ [1 4]	✓			
Risperidone	✓	✓ [1]				
Ziprazidone	✓				✓ [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

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