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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 (FGA); second generation antipsychotics (SGA), sometimes referred to as "atypical antipsychotics."

Examples of first generation antipsychotics include haloperidol, fluphenazine and chlorpromazine. Examples of second generation antipsychotics include risperidone, olanzapine and clozapine. There are numerous other antipsychotics in both sub-groups.

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

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 medication trials, family history, side effect profile and other factors.

CONCURRENT USE OF TWO OR MORE ANTIPSYCHOTIC MEDICATIONS: 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 the use of risperidone long-acting injection due to multiple reports of needle and syringe assembly failure. BHS does not recommend olanzapine extended release injection due to risk of post-injection delirium/sedation syndrome.

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 2 below). Patients must adhere with scheduled blood testing to continue clozapine. In addition, all individuals receiving clozapine therapy must be enrolled in the new clozapine Risk Evaluation and Mitigation Strategy (REMS) program as of October 12, 2015 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 docusate sodium, or Senna as prophylaxis.

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 side effect of clozapine. These are dose-related. 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.

Hypersalivation 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. If severe, some clients benefit from taking atropine eye drops sublingually.

ROLE OF ANTICHOLINERGIC MEDICATIONS: Medications with anticholinergic properties have historically been utilized to counter extrapyramidal symptoms induced by antipsychotic medications. Examples of antipsychotic-induced extrapyramidal side effects include acute dystonic reactions, pseudo-Parkinsonism and akathisia.

Commonly prescribed anticholinergic medications include benztropine, trihexphenidyl, and diphenhydramine. These agents may have a role in the acute treatment of some antipsychotic-induced extrapyramidal side effects. 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 $5\text{-}HT_{2A}$ 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 an increased risk of developing tardive syndrome.

Approach for managing antipsychotic-induced extrapyramidal side effects:

- Use anticholinergic medications for the acute management of antipsychotic-induced extrapyramidal side effects 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 extrapyramidal or other troublesome side effects occur.
- Avoid anticholinergic medications in individuals taking clozapine.
- Attempt gradual taper of anticholinergic medications in all individuals after antipsychotic-induced extrapyramidal side effects are 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 WITH CHRONIC EXPOSURE TO ANTIPSYCHOTIC MEDICATIONS: 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. Although treatment for tardive syndrome remains limited, there is some evidence for a variety of medication interventions.

Clinicians should advise clients about the risks of developing tardive syndrome. The Abnormal Involuntary Movement Scale (AIMS) may be a useful monitoring tool.

METABOLIC RISKS ASSOCIATED WITH ANTIPSYCHOTIC MEDICATION USE:
Research has shown that "atypical" or second-generation antipsychotic medications 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)
- Weight gain

An individual is considered positive for Metabolic Syndrome if three or more of the following measurements meet or exceed the risk criteria: waist circumference, blood pressure (BP), HDL cholesterol, Triglycerides, Fasting Glucose or HbG A1C. *Please note: a risk factor (for example, hypertension or elevated fasting glucose) is considered positive in individuals receiving specific treatment for that condition, even if the measurement is in the normal range.*

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:

- Increased Glucose: Consider referral to primary care and change in SGA
- Increased Weight/BMI: Consider referral to primary care and change in SGA
- Increased Lipids: Consider change in SGA; increase frequency of monitoring
- Positive Family History: More frequent monitoring
- Positive 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 3 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.

REFERENCES AND FURTHER READING

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APPENDIX 1: LONG-ACTING INJECTABLE ANTIPSYCHOTICS

HALOPERIDOL DECANOATE

What is the starting dose?
10-20 times the daily oral dose

What is the target dose?
10-15 times the daily oral dose

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

What is the dosing interval?
Injections should be given every 4 weeks

Should there be an 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

How is the Medication Supplied, Stored and Handled?

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

What is the starting dose?
12.5mg- 25mg

What is the target dose?
12.5mg- 50mg

What is the maximum dose?
100mg per dose

What is the dosing interval?
Injections should be given every 2-4 weeks

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

What is the conversion between oral dose to injectable dose?

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

How is the Medication Supplied, Stored and Handled?

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)

Why is a loading dose necessary?
A loading dose provides rapid plasma drug levels, allowing for immediate discontinuation of oral dosing.

What is the recommended loading dose?
Recommended loading method: 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. 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.

Subsequent maintenance doses should be given every 4 weeks and may be administered +/- 7 days of its due date.

How do I convert a patient 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

How do I convert a patient 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.

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

What if my patient misses their second loading dose?

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

Do I have to re-load a patient if a maintenance dose is missed?

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

How is the Medication Supplied, Stored and Handled?

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)

What is it?
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.

What is the 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**) 3**9mg dose was not studied

How Should I Handle 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	1 month after 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).

How is the Medication Supplied, Stored and Handled?

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)

What is the starting dose?
25mg every 2 weeks (12.5mg every 2 weeks for hepatic or renal impairment)

What is the target dose?
25mg- 50mg every 2 weeks

What is the maximum dose?
50mg every 2 weeks

What is the dosing interval?
Injections should be given every 2 weeks

Should there be an overlap with oral medication?
Yes, there should be an overlap with oral medications for 3-4 weeks after the first injection

What is the 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

How is the Medication Supplied, Stored and Handled?

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

ARIPIPRAZOLE EXTENDED RELEASE INJECTION (ABILIFY MAINTENA)

How is it dosed?
The starting, target and maximum dose is 400mg

What is the dosing interval?
Injections should be given every 4 weeks

Should there be an overlap with oral medication?
Yes, there should be an overlap with oral medications for 14 days after the first injection

Are there any 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**

How do I manage missed doses? Give the injection as soon as possible and follow the recommendations below regarding whether a PO overlap is required.

Dose Number	Length of Time Since Last Injection	
	No PO Overlap Required	Overlap with 14 Days PO Aripiprazole
Second or Third	< 5 weeks	> 5 weeks
Fourth or Subsequent Doses	< 6 weeks	> 6 weeks

How is the medication supplied, stored and handled?

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)

How do I convert a patient taking 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.

Should there be an overlap with oral medication?
Yes, there should be an overlap with oral medications for 21 days after the first injection

Are there any dosage adjustments for drug interactions? Yes if the 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

How do I manage a missed injection of aripipirazole lauroxil? Give the injection as soon as possible and follow the recommendations below regarding the whether a PO overlap is required and for what duration. The supplemental PO aripiprazole dose should be the same as when the patient started aripiprazole lauroxil.

Last Aripipirazole Lauroxil Dose	Length of Time Since Last Injection		
	No PO Overlap Required	Overlap with 7 Days PO Aripiprazole	Overlap with 21 Days of PO 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

How is the Medication Supplied, Stored and Handled?

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	29 – 35 days	4 days with PO overlap 16 weeks with no PO overlap

APPENDIX 2: CLOZAPINE MONITORING AND MANAGEMENT*

ANC level	Treatment Recommendation	ANC Monitoring
Normal Range for a New Patient - General Population (ANC> 1500/µL) **BEN Population** -BEN Population (ANC> 1000/ µL) -Obtain at least two baseline ANC levels before initiating treatment	-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
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 3: 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