

PHARMACOLOGICAL MANAGEMENT OF SCHIZOPHRENIA

**Federal Bureau of Prisons
Clinical Guidance**

OCTOBER 2015 (REVISED)

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WHAT'S NEW IN THIS DOCUMENT?

This revised BOP Clinical Guidance on the Pharmacological Management of Schizophrenia contains the following revisions to the October 2015 BOP Clinical Practice Guidelines (CPG):

- The *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* is now copyrighted.
 - ▶ The Appendix containing a summary of DSM-5 criteria for schizophrenia has therefore been deleted. The Abnormal Involuntary Movement Scale (AIMS) is now [Appendix 15](#).
 - ▶ Readers are referred to the actual DSM-5 text for specific diagnostic criteria.
- The October 2015 CPG underwent a pharmaceutical review in October 2016. As a result, changes were made to [Appendix 6, Antipsychotic Dosing Charts](#), as follows:
 - ▶ The starting dose for haloperidol D is now 25–100 mg IM every 2 weeks.
 - ▶ In addition, a note has been added to advise establishing tolerance to oral fluphenazine or oral haloperidol prior to changing to an IM decanoate injection.

The October 2015 guidelines contained the following revisions to the 2010 BOP Clinical Practice Guidelines for the Medical Management of Schizophrenia:

- The title was changed to *Pharmacological Management of Schizophrenia* since the guidelines address only the pharmacologic intervention for inmates with schizophrenia. While pharmacologic management is among the well-established treatments for schizophrenia, other modes—as outlined in the *Program Statement 5310.13 (Treatment and Care of the Inmate with Mental Illness)*—must also be addressed in treating schizophrenia. The total treatment approach involves medical and psychology personnel working together.
- Changes were made to [Section 5, Antipsychotic Medication](#):
 - ▶ The term *third-generation antipsychotics (TGAs)* is no longer in use. Aripiprazole is now considered a second-generation antipsychotic (SGA).
 - ▶ In addition to the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, results of several other studies comparing the efficacy of different antipsychotics are noted. Overall, in terms of relative efficacy, SGAs have no predictable advantage over first-generation antipsychotics (FGAs), and both classes of drugs seem to be similarly efficacious. See [Studies of the Relative Effectiveness of Antipsychotics](#) in [Section 5](#).
- Changes were made to [Section 6, Adjunctive Medications](#).
 - ▶ The section on selecting an antidepressant was expanded to include selective serotonin reuptake inhibitors (SSRIs) more broadly.
- Changes were made to the following Appendices:
 - ▶ [Appendix 1, Antipsychotic Treatment Algorithm](#) was revised. The current algorithm is adapted from one developed by the Veterans Affairs Pharmacy Benefits Management Services in June 2012. This algorithm applies only to schizophrenia and schizoaffective disorders, and is not applicable to other conditions where an antipsychotic is indicated, such as monotherapy or adjunctive therapy for bipolar disorder (manic, mixed, or depressed) or unipolar depressed with or without psychosis. Second-generation psychotic indications for these disorders are also continuously evolving.
 - ▶ [Appendix 3, Antipsychotic Medications](#) was updated to list only FGAs and SGAs, and now includes several new SGAs. The statement concerning formulary status was expanded.
 - ▶ [Appendix 4a, Side Effects of First-Generation Antipsychotics](#) was updated. It now contains a “black box” warning that antipsychotics are not approved for dementia-related psychosis.
 - ▶ [Appendix 4b, Side Effects of Second-Generation Antipsychotics](#) was updated so that it no longer refers to TGAs.

- ▶ [Appendix 5, Relative Side Effect Incidence of Antipsychotic Medications](#) was updated so that it no longer refers to TGAs.
- ▶ [Appendix 6, Antipsychotic Dosing Charts](#) was updated to include only FGAs and SGAs, and now includes several new SGAs.
- ▶ [Appendix 7](#) was replaced by [Appendix 7a, Monitoring for the Side Effects of Antipsychotic Medications](#) (for FGAs and SGAs) and a new [Appendix 7b, Metabolic Monitoring Guidelines for SGAs](#) was added.
- ▶ The previous [Appendix 13, Rating Scales for Positive and Negative Symptoms](#), was deleted.
- The following Appendices were added:
 - ▶ [Appendix 13, Quick Reference Guide: Treatment for Schizophrenic Spectrum Disorders and Mood Disorder with Psychosis](#) provides brief step-by-step treatment guidance for several disorders.
 - ▶ [Appendix 14, FDA-Indicated Medications](#) lists FDA-indicated medications for mania or mixed episodes of bipolar disorder, as well as maintenance medications for bipolar disorder.

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1. PURPOSE

The purpose of the Federal Bureau of Prisons (BOP) Clinical Guidance for *Pharmacological Management of Schizophrenia* is to provide recommendations for treatment of inmates in federal facilities who are diagnosed with chronic psychotic disorders—primarily the schizophrenic disorders.

2. OVERVIEW

THE FOCUS OF THIS GUIDANCE

The primary focus of this guidance is medication management for psychotic disorders, including antipsychotic medication and adjunctive medication for common, comorbid psychiatric syndromes. In addition, this guidance reviews monitoring and treatment of the common side effects of antipsychotic medication.

Psychotic symptoms may be present in many psychiatric conditions, including schizophrenia, schizoaffective disorder, mood disorders, and personality disorders. However, the presence of psychotic symptoms does not, in and of itself, lead to a diagnosis of a psychotic disorder.

→ *For the purpose of this guidance, the term **psychotic disorders** refers to illnesses that are chronic and severe, and manifest primarily as disturbances in thought processes.*

This guidance is best utilized for prescribing antipsychotic medications for patients in the following diagnostic categories:

- **Schizophrenic disorders**
- **Schizoaffective disorders** (usually in conjunction with appropriate treatment of the mood symptoms)
- **Mood disorders with psychotic features** (in conjunction with appropriate treatment of the mood symptoms)

MIXED SYMPTOMATOLOGY: Mental disorders—such as schizoaffective disorders or mood disorders with psychotic features—have a mix of psychotic and mood symptoms, where the relative prominence of psychotic symptomatology varies from individual to individual within a given diagnostic category, or even in the same individual during the course of the illness. When individuals suffer from mixed symptomatology (for example, a patient with schizophrenia who develops a major depressive disorder), it is usually necessary to use a combination of medications aimed at treating both the psychotic symptoms and the mood symptoms. In such cases, refer to relevant guidelines (e.g., BOP Clinical Practice Guidelines for *Management of Major Depressive Disorder*) or evidence-based guidelines published by nationally recognized entities.

MEDICATIONS: Antipsychotic medications are the mainstay of treatment for patients with psychotic disorders. Adjunctive medications that are commonly used include: mood stabilizers, antianxiety agents, antidepressants, and medications aimed at controlling side effects such as anticholinergics, antihistaminics, and beta blockers.

THIS GUIDANCE: WHAT IS NOT COVERED

- It is beyond the scope of this guidance to discuss additional interventions that are often required to address deficits in social, occupational, academic, and relational functioning in patients with chronic mental illness.
- Also not included here is the complex array of issues associated with case management of comorbid medical and psychiatric conditions.
- In addition, this guidance is not intended to be used for individuals suffering from acute psychotic symptoms such as those seen in delirium, substance withdrawal, or intoxication; nor should they be used for the circumscribed psychotic symptoms seen in individuals with personality disorders. This guidance is also not meant to be used for individuals with a primary diagnosis of a dementia with concurrent psychotic symptoms or behavioral dyscontrol.
- Further, individuals with chronic mental illnesses are at high risk for suffering psychiatric and medical comorbid conditions that require special attention to risk management issues, including drug-drug interactions, medication side effects, lifestyle issues, and assaultive or suicidal behaviors. These potential complexities are not covered in this guidance.

3. EVALUATION

The BOP *Psychiatric Services Program Statement* (available on Sallyport) should be followed when evaluating patients for initiation of treatment with antipsychotic medication, or for continuation of antipsychotic treatment started prior to the patient's arrival at a BOP facility. All patients presenting with significant psychotic symptoms require a complete history and physical, as well as basic laboratory studies (summarized in **TABLE 1**).

TABLE 1. LABORATORY STUDIES FOR EVALUATING PSYCHOTIC SYMPTOMS

<ul style="list-style-type: none">• CBC with differential• Fasting chemistry panel with lipid profile• Urinalysis• TSH• HIV• EKG• RPR or FTA/ABS• B-12 and folate• Blood levels of relevant medications, e.g., digoxin, antidepressants, mood stabilizers, antipsychotic (if clinically indicated), anti-seizure medications, etc.
<p>Note: Other studies may be warranted depending on the patient (e.g., EEG in inmates with a history of seizures or recent head trauma; MRI or CT of the head in inmates with neurological findings).</p>

EVALUATION OF PSYCHOTIC SYMPTOMS

The evaluation of psychotic symptoms requires assessment of positive and negative symptoms, the level of impairment, and risk management issues. Patients with psychotic disorders often have comorbid psychiatric and medical conditions that require treatment. Psychotic symptoms can generally be divided into positive, negative, and cognitive symptoms, as discussed below.

POSITIVE AND NEGATIVE SYMPTOMS

➔ See lists of symptoms in **TABLE 2** below.

POSITIVE SYMPTOMS tend to be bizarre, dramatic, and unsettling to both the observer and the patient; these symptoms are the most accessible to assessment and the most responsive to antipsychotic medications.

NEGATIVE SYMPTOMS are more difficult to diagnose and far less responsive to medications. They often are very disabling and a source of significant distress to family members and care providers.

- Negative symptoms are almost exclusively assessed through observation of the patient’s daily activities and functioning. This may require gathering collateral data from a range of sources: correctional officers and other institutional staff, family members (with the appropriate signed releases of information), the pre-sentence investigation report, etc.
- Negative symptoms are remarkably similar to—and sometimes indistinguishable from—symptoms of depression and antipsychotic medication side effects. Thus, early and continued evaluation and documentation of these symptoms is crucial in planning effective treatment interventions.

TABLE 2. POSITIVE AND NEGATIVE PSYCHOTIC SYMPTOMS

Positive Symptoms	Negative Symptoms
<ul style="list-style-type: none"> • Hallucinations • Delusions • Disorganized behavior • Disturbed language 	<ul style="list-style-type: none"> • Affective flattening • Anhedonia • Alogia • Asociality • Avolition

COGNITIVE IMPAIRMENTS

Cognitive impairments appear to be an integral part of chronic psychotic disorders, especially schizophrenia. These impairments include problems with attention, memory, and executive function (i.e., abstraction, problem-solving, insight, and cognitive flexibility). Cognitive impairments have been found in individuals prior to their developing psychotic symptoms, as well as in first-degree relatives of individuals with schizophrenia. It is unclear if any pharmacological treatment has a significant impact on these symptoms. Cognitive rehabilitation/remediation training has been shown to have some positive impact.

The cognitive symptoms are the most disabling and misunderstood of all the symptom complexes associated with psychotic disorders. Lack of insight into one’s own symptoms appears to be the result of cognitive impairments, and not psychological defenses such as denial. Difficulties in achieving treatment compliance are often related to a patient’s lack of insight regarding his or her own symptoms.

EVALUATION OF MOOD SYMPTOMS

Mood symptoms are commonly present in individuals with psychotic symptoms and usually require treatment aimed specifically at their alleviation. Symptoms that may occur with a mood disorder are summarized in **TABLE 3**.

TABLE 3. SYMPTOMS THAT MAY OCCUR WITH MOOD DISORDERS

- Sleep disturbance (increased or decreased)
- Appetite disturbance (increased or decreased)
- Disturbance in energy level (agitation, hyperactivity, or low energy)
- Poor concentration or distractibility
- Change in rate of thought processing (increased or decreased)
- Change in quantity and/or rate of speech (increased or decreased)
- Disturbance in self-image (low self-esteem or grandiosity)
- Disturbance in mood (depressed, euphoric, irritable, or mixed)
- Excessive guilt or shame
- Loss of interest or enjoyment, or excessive pleasure-seeking with excessive risk-taking behaviors
- Decrease or increase in goal-directed activities
- Morbid preoccupation or suicidal ideation
- Thoughts of harm toward others

For patients with psychotic disorders, aggressive treatment of mood symptoms is crucial.

Symptoms that are present for prolonged periods (days, weeks, or longer) may be consistent with mania, hypomania, depression, or a mixed state.

- Antipsychotic medications will generally provide only partial relief to individuals with schizoaffective disorder, bipolar disorder, and major depressive disorder with psychotic features.
- Up to 50% of individuals with schizophrenia will suffer from a major depressive episode.
- Ten to 15% of individuals with chronic psychotic disorders or mood disorders commit suicide.

Anxiety symptoms may or may not require specific treatment beyond treatment of the primary psychotic disorder.

- Treatment of anxiety early in the course of the psychotic disorder may reduce patient suffering and promote compliance.
- Ongoing treatment of anxiety symptoms is not always necessary once the antipsychotic medication has significantly reduced or eliminated the positive symptoms.
- As with other mood symptoms, symptoms of anxiety are often indistinguishable from certain side effects of antipsychotic medication, including agitation and akathisia.

CONSIDERATIONS IN EVALUATING PATIENTS

There are many aspects of assessing psychotic symptoms. Evaluating clinicians should:

- Assess or diagnose medical conditions presenting with psychotic symptoms.
- Gather collateral data supporting or refuting the diagnosis of a psychotic disorder.
- Explore the quality and quantity of positive symptoms.
- Understand the impact of cognitive impairments on functioning and treatment compliance.
- Explore the patient's understanding of his or her symptoms and methods of coping with them.
- Recognize and integrate negative symptoms into the diagnosis and treatment plan.
- Assess for mood disturbance.
- Thoroughly explore risk management issues (especially harmful behaviors toward self or others).
- Review the pre-sentencing report or psychological assessment for otherwise inaccessible information.

4. TREATMENT ISSUES AND CHALLENGES

TREATMENT CHALLENGES

Treating patients with psychotic disorders presents unique challenges to the clinician. Common issues and challenges related to treatment include the following:

- **Establishing and maintaining a reasonable level of rapport with the patient:**
Maintaining excellent interpersonal boundaries, behaving honestly and predictably (and thus being perceived as trustworthy), being available during times of crisis, and establishing cooperative relationships with other staff members who interact regularly with the patient will all facilitate the development of a productive doctor-patient relationship.
- **Responding to patients with impaired reality testing:**
To varying degrees, this impairment will impact the entire treatment process, from evaluation to transition and discharge planning. Some patients may experience significant dysphoria secondary to their symptoms, recognizing that their suffering stems at least in part from an illness, and may actively seek help in managing their symptoms through medication and counseling. Other patients may *not* recognize their experiences as internally generated; instead, they interpret the cause to be something or someone in their environment. Most patients will fall somewhere between these two extremes, with varying levels of understanding and willingness to pursue treatment. Often a patient's openness to medication will fluctuate during the course of his or her illness.
- **Maintaining a conscious awareness of the patient's cognitive impairments:**
The patient's cognitive limitations can be severe and usually include difficulties with processing and retrieving information, as well as other impairments in executive and memory functions. These limitations further complicate the communication process between provider and patient.

- **Caring for patients who fail to comply with treatment:**
Noncompliance with medication regimens is extremely common and poses a major challenge to adequately controlling symptoms. Long-acting injectable formulations (decanoate formulation and others) are a well-studied and under-utilized intervention for nonadherence in this population.
- **Caring for patients who refuse treatment in spite of severe symptomatology:**
It is a common misperception that when a patient refuses treatment, the treatment cannot be provided—even in an emergency. This is not the case. See the *BOP Program Statement on Psychiatric Services* for more information on treating inmates with antipsychotic medication in emergency situations.
- **Obtaining informed consent and ensuring patient education:**
All patients receiving medications for psychiatric conditions (other than in emergencies or under court order) must give informed consent. Patients who voluntarily agree to being treated with antipsychotic medication will require initial and ongoing education about the risks and benefits of treatment.
 - ➔ The reader is referred to the *BOP Program Statement on Psychiatric Services* and [Appendix 2. Informed Consent](#) in this document for information on obtaining and documenting informed consent.

CONSIDERATIONS IN TREATING PATIENTS

Below is a list of important considerations in the clinical care of patients with psychotic disorders:

- Many patients undertake sub-therapeutic (dosing and/or time-frame) trials of medications.
- Antipsychotic medications are slower to take clinical effect than the onset of side effects.
- Patients are often noncompliant with their antipsychotic regimen.
- Many patients are on medications that could be consolidated into once-a-day scheduling, when possible.
- Side effects need to be watched for and treated as soon as possible to ensure compliance.
- Mood symptoms should be clinically assessed during each visit.
- Medications should be reviewed often with the patient—to simplify the regimen and possibly utilize depot formulations when available.
- The patient, as well as other staff (health services, psychology, and correctional), should be engaged in the treatment process to encourage the best chance of success for this patient.

5. ANTIPSYCHOTIC MEDICATION

OVERVIEW

CLASSIFICATIONS OF ANTIPSYCHOTIC MEDICATION

Antipsychotic medications include several classes of pharmacologically dissimilar medications. Our current understanding of the therapeutic action of these medications is that they affect various neurotransmitters in the brain—primarily the dopamine receptors, although they also have influence on the receptors for serotonin, histamine, norepinephrine, and others. Their benefits and side effects result from their impact on these receptors in the brain and the periphery.

The current classification system of antipsychotic medication lumps together dissimilar drugs, based primarily on their relative propensity to produce motor side effects and/or the medication’s relative “newness” to the market. These classifications are outlined in **TABLE 4**.

TABLE 4. CLASSIFICATIONS OF ANTIPSYCHOTIC MEDICATION AND ALTERNATE TERMINOLOGY

Classification	Abbreviation*	Alternate Names
First-generation antipsychotics	FGAs	Typical or conventional antipsychotic, neuroleptic
Second-generation antipsychotics	SGAs	Atypical or novel antipsychotic
* In this document, the above medications are referred to by the abbreviations FGA and SGA.		

➔ See [Appendix 3](#) for a list of antipsychotic medications by generic name, brand name, and class.

SIDE EFFECTS OF ANTIPSYCHOTICS

Side effects form a critical aspect of treatment with antipsychotics because they frequently affect choice of medication, as well as decisions to discontinue them. It is generally accepted that SGAs are less likely than FGAs to cause significant extrapyramidal symptoms (EPS), although the risk is still present. It is also clear that SGAs are less likely to cause tardive dyskinesia (TD) than FGAs. There is some evidence to support that at least one SGA, clozapine, may actually improve TD. However, SGAs have their own troublesome side effects that make them less acceptable than FGAs for some patients, particularly sedation and cardio-metabolic side effects.

STUDIES OF THE RELATIVE EFFECTIVENESS OF ANTIPSYCHOTICS

Many patients require multiple trials of different medications prior to obtaining maximal benefit. Unfortunately, there is little to guide a clinician in choosing the medication most likely to provide benefit in a treatment-naïve patient. The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study was the first randomized, controlled study evaluating the effectiveness of antipsychotic treatment for schizophrenia in the community.

➔ For in-depth information on the CATIE study design and results, consult: <http://www.nimh.nih.gov/funding/clinical-research/practical/catie/index.shtml>.

CATIE Phase 1: The CATIE study compared the effectiveness of newer SGAs (available since the 1990s) with an older FGA (first available in the 1950s). Of note is that the newer (atypical) SGAs cost roughly ten times as much as the older (typical) FGAs. During Phase 1 of the CATIE study (published in 2005), patients with schizophrenia were randomized to one of five medications. They were then followed for up to 18 months. At the time of the study, aripiprazole (Abilify) was not available.

The primary outcomes related to the five antipsychotics evaluated in CATIE Phase 1 were:

- All five medications—perphenazine (FGA) and risperidone, ziprasidone, olanzapine, and quetiapine (SGAs)—were comparably effective.
- All were associated with very high rates of discontinuation (60–80%), due to either intolerable side effects or failure to adequately control symptoms.

One SGA, olanzapine, performed slightly better than the other drugs, but also was associated with significant weight gain as a side effect. Perphenazine (the FGA) was found to be equally effective and as well-tolerated as the three other SGAs (risperidone, quetiapine, and ziprasidone), which performed similarly to one another. Extrapyramidal side effects, which are usually associated with the older FGA medications, occurred no more frequently with perphenazine than with the newer drugs. The advantages of olanzapine over perphenazine, in symptom reduction and duration of treatment, were modest and must be weighed against the increased side effects of olanzapine.

➔ ***Thus, a significant finding of the CATIE Phase 1 study was that the newer SGAs had no substantial advantage over the older FGA medication that was used.***

CATIE PHASE 2: Clozapine is the only antipsychotic medication known to be more effective than other antipsychotics in controlling positive symptoms. Phase 2 of the CATIE Study evaluated clozapine against other SGAs for patients whose symptoms were inadequately controlled in Phase 1. CATIE Phase 2 confirmed that clozapine is indeed far more effective than other antipsychotics. However, clozapine has serious side effects, including life-threatening agranulocytosis and myocarditis.

➔ ***Due to these safety concerns, clozapine is generally only utilized after multiple unsuccessful trials with other antipsychotic drugs and requires strict adherence to national monitoring guidelines.***

CUTLASS: Another landmark trial comparing efficacy of antipsychotics was the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUTLASS). This was a government-funded (United Kingdom), randomized controlled trial, in which 277 patients were randomized to either an FGA or an SGA (other than clozapine). After one year of follow-up, the study found no significant differences in Quality of Life Scale scores between patients receiving an FGA versus an SGA. The authors concluded that there is no disadvantage across one year in terms of quality of life, symptoms, or associated costs of care in using FGAs rather than SGAs. The specific SGAs included in the study were amisulpride, olanzapine, quetiapine, and risperidone.

META-ANALYSIS: A meta-analysis of 150 studies comparing the efficacy of different antipsychotics concluded that the overall efficacy of aripiprazole, quetiapine, and ziprasidone were equal to FGAs. Clozapine, olanzapine, and risperidone were found to have greater efficacy than FGAs.

The numbers needed to treat (NNT) were 7 for clozapine, 11 for olanzapine, and 15 for risperidone. The risk of relapse was found to be less for risperidone (RR=0.67, 95% CI 0.63–0.87; NNT 11) and olanzapine (RR=0.67, 0.49–0.92; 17) than for FGAs. The risk of relapse with aripiprazole and clozapine was equal to FGAs. (See [References](#) section: Leucht, et al., 2009.)

COMPARISON OF ARIPIPRAZOLE AND PERPHENAZINE: Lastly, a study comparing aripiprazole and perphenazine in 300 patients with treatment-resistant schizophrenia showed that after six weeks of treatment, both agents were associated with similar effectiveness in improving symptoms and increasing quality of life. Patients treated with perphenazine reported a higher incidence of EPS-related adverse events and a higher rate of elevated prolactin levels than those treated with aripiprazole. (See [References](#) section: Kane, et al., 2007.)

IN SUMMARY: In terms of relative efficacy, SGAs have no predictable advantage over FGAs, and both classes of drugs seem to be similarly efficacious.

DRUG SELECTION

FIRST-LINE TREATMENT: There is insufficient evidence to determine recommendations for specific first-line agents. Choice of an antipsychotic should be guided by considering the clinical characteristics of the patient and the side effect profile of the medication. In general, FGAs and risperidone are considered first-line treatment in the BOP.

→ See [Appendix 1](#) for an antipsychotic treatment algorithm, developed by the Veterans Affairs Pharmacy Benefits Management Services in June 2012, and modified for use in the BOP.

Successful treatment early in the course of psychotic disorders may improve prognosis, and treatment compliance is essential for successful treatment. Some studies show that treatment with clozapine improves patient functioning, and that such improvement may continue even after the medication is changed to another SGA or an FGA. Clozapine has been shown in some studies to be more useful when used earlier for patients who have a history of recurrent suicidality, violence, or comorbid substance abuse.

ACUTE AND EMERGENCY TREATMENT: In acute and emergency treatment, there is no evidence to support the use of an SGA over an FGA—all antipsychotics are considered equally efficacious for the treatment of acute psychosis and agitation in schizophrenia. FGAs, especially haloperidol, have proven effective and have an excellent safety profile in the treatment of acute psychoses. The concern over the development of TD is not relevant in these cases, and the possible development of dystonia can be addressed through the use of adjunctive medications such as benztropine (Cogentin). There is currently no evidence to support or refute that FGAs may be more likely than SGAs to cause neuroleptic malignant syndrome (NMS).

PATIENT-RELATED FACTORS IN SELECTING MEDICATIONS: One factor to consider in prescribing antipsychotic medication is the patient's history of noncompliance, which may be an indication for the use of a long-acting, injectable antipsychotic. Another factor is patient choice. Many patients with psychotic illnesses have strong preferences for (or aversions to) certain medications. In cases where the patient's preference is less appropriate than the prescriber's recommendation (e.g., when a patient with severe TD prefers an FGA to an SGA), every attempt should be made to help the patient come to an agreement with the prescriber. This may require significant patient

education. Once the patient has consented to the change, and stability in the patient's symptoms has been achieved, it may be necessary to gradually cross-taper the patient-preferred medication with the recommended medication. Clearly, the benefit of the patient's compliance with treatment should be weighed against the potential side effects that could result from continued treatment with the patient-preferred medication.

→ *Many patients with symptoms of schizophrenia will undoubtedly go through a time when they do not want to take their medications. This is normal, and clinicians should be prepared to monitor for this. As these are life-long illnesses, it is strongly encouraged that patients remain on their medications even when symptoms are in remission. If patients are having a difficult time remembering to take their medications, there are a number of long-acting medications available in injectable form in both the first-generation and second-generation antipsychotics.*

MULTIPLE TREATMENT TRIALS AND CROSS-TAPER: For patients requiring multiple trials of medications, it is generally advisable to **cross-titrate** the two medications slowly over a period of several days to a few weeks.

Example: *Start the new antipsychotic at 25% of the usual dose and decrease the current antipsychotic by 25%. Then, increase the dose of the one and decrease the dose of the other by 25%, respectively, every 7 days.*

In cases where intolerable side effects are the reason for changing medications, cross-titration may not be feasible. In either situation, it is important for the clinician and the patient to recognize that the side effects and benefits from the new medication may not be clearly seen for several weeks, while the effects of the previous medication may diminish slowly.

DRUG-DRUG INTERACTIONS: Drug-drug interactions are important to consider in selecting an antipsychotic medication. The prescriber is advised to consult with the pharmacist in cases where potential drug-drug interactions could occur.

FIRST-GENERATION ANTIPSYCHOTICS (FGAs)

The FGAs have been available for more than 50 years and, until clozapine (an SGA) was introduced, were the only options for the treatment of psychotic disorders. They remain an important option for patients with acute symptomatology requiring rapid relief. In addition, the relative antipsychotic potency of these medications has been fairly well delineated, making conversion from one FGA to another FGA relatively easy.

→ *FGAs can be effective as first-line treatment for schizophrenia and (along with risperidone) are the BOP-preferred antipsychotics of choice, unless there is compelling clinical evidence for starting with another agent.*

SIDE EFFECTS OF FGAs

The FGA medications share similar side effect profiles, varying quantitatively more than qualitatively. In general, the more potent the antipsychotic, the less the anticholinergic side effects and the greater the extrapyramidal side effects.

- **Chlorpromazine (Thorazine)**, a very low-potency FGA, has fallen out of general use. It has a higher risk than other FGAs for potentially dangerous cardiac side effects. .
- **Pimozide** is well-known to increase the risk of torsade de pointes, due to prolongation of the QT interval.

→ See [Appendix 4a](#) for an overview of FGA side effects.

FACTORS THAT INFLUENCE THE USE OF FGAs

As when prescribing any medication, the prescriber should be familiar with the specific medication and its indications, contraindications, precautions, pharmacokinetics, and drug interactions. Indications for the use of FGAs in individuals with psychotic disorders are summarized in **TABLE 5**.

TABLE 5. INDICATIONS FOR USE OF FGAs

- Patient preference
- Acute symptoms requiring rapid effect
- History of excellent response in a highly symptomatic patient
- Need for a long-acting injectable medication

DOSING FOR FGAs

- **Low-potency FGAs** should generally be avoided, even in patients with a history of response to these agents. The potential side effects of low-potency FGAs generally outweigh any benefits.
- **High-potency FGAs** such as haloperidol or fluphenazine are recommended for acute treatment.
- **For maintenance treatment with FGAs**, high- to medium-potency medications are preferable to low-potency agents. The use of medium-potency FGAs such as perphenazine or trifluoperazine often has the added benefit of reducing or eliminating the need for anticholinergic medication and its associated side effects.

→ See [Appendix 6](#) for guidance on FGA dosage.

SECOND-GENERATION ANTIPSYCHOTICS (SGAs)

There are now eleven SGAs: aripiprazole, asenapine, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. Although all these agents are grouped together, they are different enough from one another to be in distinct chemical classes. Due to these differences, it is more difficult to generalize about SGA side effect profiles, potential drug-drug interactions, and activities at the level of neurotransmitters.

Although FGAs are recommended for initiation of schizophrenia treatment, there will be circumstances when an SGA is the preferred agent due to the side effect profile of FGAs (e.g., wanting to avoid an FGA in a patient with a pre-existing movement disorder). Historically, SGAs are thought to have a more beneficial effect than FGAs on negative symptoms, although this has not been proven in clinical trials

SIDE EFFECTS OF SGAs

EXTRAPYRAMIDAL SYMPTOMS (EPS): All of the SGAs, at currently recommended doses, are less likely than the FGAs to cause EPS. However, risperidone is well known to cause EPS in susceptible individuals, as well as in most of the individuals taking doses higher than 6 mg per day. At the higher dosage levels, risperidone appears to have a side effect profile much more like an FGA than the other SGAs have. The incidence of TD is not clearly known for the SGAs, but it has occurred with risperidone in otherwise antipsychotic-naïve patients. Clozapine appears to have

some benefit in the treatment of movement disorders in patients with psychotic disorders or other neurological disorders such as Huntington's chorea.

→ See [Appendix 4b](#) for an overview of SGA side effects. See [Appendix 5](#) to compare the relative incidence of side effects.

DIABETES MELLITUS (DM): The most significant side effect associated with the SGAs is the development of insulin resistance and type 2 DM. The mechanism of action is still unknown and is likely due to a combination of factors. Individuals with bipolar disorder or schizophrenia already have an increased incidence of type 2 DM, independent of treatment factors. Significant weight gain is associated with some of the SGAs, particularly olanzapine and clozapine. However, DM has developed in individuals on SGAs who have not had significant weight gain. Diabetic ketoacidosis (DKA) has been the presenting sign of DM in some individuals.

→ For recommendations on monitoring patients taking an SGA, see [Appendix 7a](#) and [Appendix 7b](#).

NEUROLEPTIC MALIGNANT SYNDROME (NMS): Neuroleptic malignant syndrome is a potential side effect of all antipsychotic medications, including the SGAs. Prescribers should remain vigilant for the development of symptoms consistent with NMS.

→ See [Appendix 8](#) for more information on NMS.

CLOZAPINE SIDE EFFECTS: Of all the available antipsychotic medications, clozapine (Clozaril) is considered the gold standard for the treatment of schizophrenia. **However, clozapine carries a black box warning for the risk of agranulocytosis.** The white blood cell and absolute neutrophil count should be obtained at baseline, then weekly for 6 months, then bimonthly for an additional six months, and then monthly thereafter. Prior to initiation of treatment with clozapine, patients must be registered with the Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program (www.clozapinerems.com). The REMS program is an FDA-mandated single, shared patient registry that replaces the clozapine patient registries previously provided by individual manufacturers.

→ See [Appendix 9](#) for more complete information on clozapine: Side effects, contraindications, dosing, and monitoring for die effects, including agranulocytosis,

Other side effects: Both quality and quantity of other side effects vary from agent to agent. It is the prescriber's responsibility to be familiar with potential risks associated with particular medications, as well as potential drug-drug interactions.

→ See [Appendix 10](#) for a more complete overview of managing side effects.

CONCERNS ABOUT QUETIAPINE IN THE CORRECTIONAL SETTING: Quetiapine has some unique properties that make it a relatively undesirable agent for use in the correctional population. Cases of abuse (oral, intranasal, and intravenous) have been documented in the literature, and multiple BOP institutions have reported incidents of inmates selling their quetiapine (sometimes referred to as "Quell"). While it is unclear as to the exact pharmacological/neurotransmitter action that makes this a drug of abuse, it clearly has become one and generally should not be prescribed routinely or first-line in the correctional setting. If prescribed, it should be reserved for cases refractory to other SGAs, and should be administered crushed or in liquid formulation to reduce diversion. Consult the current *BOP National Formulary* for specific restrictions and criteria. An extended-release formulation of quetiapine is now available that is less abusable and better tolerated than the immediate-release version.

CONCERNS ABOUT ZIPRASIDONE IN THE CORRECTIONAL SETTING: Ziprasidone is another SGA with some unique qualities that may make it difficult to use in a correctional setting. Ziprasidone needs to be combined with food to be effective. It is a highly lipophilic compound, and this property impacts its absorption profile with respect to food. Ziprasidone should be given at meal time to help its efficacy. Ziprasidone was the first antipsychotic possibly associated with prolonged QT interval. This continues to be a controversy in the literature. Nonetheless, it is good clinical practice to obtain a baseline ECG when considering the risks of this medication as compared to the cardiometabolic risks of olanzapine and quetiapine.

ANTIPSYCHOTIC COMBINATION THERAPY

For the purposes of this guidance, the term **combination therapy** (as opposed to **polypharmacy**) refers to the use of two or more antipsychotic medications in a patient who has failed monotherapy on multiple agents. The term polypharmacy is generally used in a pejorative manner, implying a less than thoughtful approach to medication management. Polypharmacy, or the use of multiple antipsychotic medications without previous therapeutic trials of single agents, is generally poor practice; it can unnecessarily contribute to excessive costs, increased side effects, increased risk of drug-drug interactions, and reduction of patient compliance.

While there are no studies available that provide definitive guidance on the use of combination therapy, knowledge about the pharmacology of antipsychotic agents can offer the provider some theoretical basis for decision making. The following recommendations are made based on these theoretical issues:

- **Combinations of antipsychotics with similar side effect profiles should be avoided.** For example, an antipsychotic with significant anticholinergic effects should not be combined with another highly anticholinergic antipsychotic (e.g., combining chlorpromazine with olanzapine). Likewise, an antipsychotic known to cause significant weight gain and/or increased risk of DM should not be added to another antipsychotic with similar risks (e.g., adding olanzapine to clozapine).
 - **Combinations of antipsychotics with similar potency at the same dopamine sites should be avoided.** For example, risperidone and haloperidol are both potent D-2 blockers. Such a combination probably does not offer a therapeutic advantage over therapeutic doses of either agent alone, and is likely to increase the EPS side effect burden.
 - **Combinations of antipsychotics utilized in the acute phase or when cross-titrating from one antipsychotic agent to another should not be continued indefinitely.** Combination therapy should be reintroduced if and when multiple therapeutic trials of different single agents have proven ineffective.
 - **The second antipsychotic should be pharmacologically complementary to the first antipsychotic, both in its side effect profile and in its therapeutic action.** For example, adding a high-potency FGA with high D-2 antagonism to an SGA with low D-2 antagonism (e.g., adding haloperidol to quetiapine or olanzapine) may offer significant benefits for some especially refractory cases or during the acute phase of stabilization.
- ***It is important to emphasize that there is no evidence that treatment with multiple antipsychotic agents offers any benefit over treatment with a single antipsychotic agent. The use of combination antipsychotic treatment must be carefully weighed against the risk of increased side effects, higher cost of treatment, and increased complexity of treatment regimen.***

6. ADJUNCTIVE MEDICATIONS

Adjunctive medications generally come from one of the following categories of medications, each of which are discussed below in this section:

- **ANTIDEPRESSANTS**
- **ANTI-ANXIETY AGENTS**
- **MOOD STABILIZERS**

→ See [Section 7](#) for information on medications for treating the side effects of antipsychotics.

ANTIDEPRESSANTS

Depression is a common mood disturbance seen in individuals with chronic psychotic disorders of all types. It may be integral to the psychotic disorder—as in some kinds of schizoaffective disorder—or it may present as a separate, co-occurring disorder. Approximately 10% of the individuals with schizophrenia die from suicide. Depression may occur in individuals even when their psychotic symptoms are well-controlled. Therefore, it is essential to treat the depression with antidepressant medications or electroconvulsive therapy (ECT).

There is little evidence to support the use of antidepressants as adjunctive treatments for individuals who have psychotic disorders, but do not have a depressive element or co-occurring depression. However, many of the symptoms of depression—apathy, blunted affect, anhedonia, loss of energy and motivation, and psychomotor retardation—can be impossible to distinguish from the negative symptoms of schizophrenia or the side effects of antipsychotic medication. Therefore, when individuals with psychotic disorders display symptoms of depression, the examiner should carefully consider a therapeutic trial of an antidepressant medication to attempt to alleviate a possible mood disorder.

SELECTING AN ANTIDEPRESSANT

The first-line agents recommended for the treatment of depression are the selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine. These medications have proven efficacy in depression and are generally well-tolerated. Fluoxetine, in particular, has the unique benefit of an extremely long half-life—if found to be ineffective, it can be abruptly discontinued with minimal risk of withdrawal syndrome.

- **If a patient fails a trial of one SSRI**, a trial with a different SSRI is recommended, as lack of response to one agent in this class does not determine lack of effect to all agents in the same class.
- **The potential for drug-drug interactions** should be discussed with the pharmacist.
- **Tricyclic antidepressants** should generally be avoided in individuals on antipsychotic medications because of the increased burden of side effects associated with these medications.
- **Bupropion** is an effective antidepressant, and most likely the only one that does not appear to increase the risk of mania in susceptible patients. Therefore, it may be an especially good choice for an individual with schizoaffective disorder, bipolar type. However, caution is warranted in that bupropion appears to be associated with abuse within the correctional environment (often crushed and snorted), causing amphetamine-like effects. Another cause

for caution is that the seizure threshold is lowered with bupropion, as it is with some antipsychotics.

- For further information, see the BOP Clinical Practice Guidelines for the Treatment of Major Depressive Disorder.

ANTIANXIETY AGENTS

For the purpose of this guidance, antianxiety agents are divided into two categories: **benzodiazepines** and **non-benzodiazepine anxiolytics**.

BENZODIAZEPINES

Benzodiazepines are generally the treatment of choice for acute management of anxiety and agitation in psychotic disorders. However, benzodiazepines are not appropriate in all situations (see the discussion of [non-benzodiazepine anxiolytics](#) below).

PROBLEMATIC IN THE CORRECTIONAL ENVIRONMENT: Benzodiazepines can have a negative impact on the safety and security of an institution, secondary to diversion and “black market” activities. In addition, vulnerable inmates on benzodiazepines can be pressured by other inmates to distribute their medications, placing them at risk for exacerbation of symptoms or an acute withdrawal syndrome. Also, intoxication on any substance (alcohol, benzodiazepines, or others) can result in loss of normal inhibition, resulting in behaviors that place both inmates and staff at risk.

- **Therefore, whenever benzodiazepines are prescribed in a correctional environment, the prescriber needs to carefully assess the risks and benefits for the patient and the institution.** Consult the BOP National Formulary for current restrictions and criteria related to benzodiazepines.

CONTRAINDICATED FOR LONG-TERM USE: Benzodiazepines are not generally recommended for long-term use for anxiety disorders, due to the inevitable development of physiological dependence (in as few as two to three weeks), and the potential risk for psychological dependence. In addition, benzodiazepines are well-known to impair cognitive function, even after long-term use when sedation is no longer significant. Finally, abrupt discontinuation of benzodiazepines, which can unintentionally occur with intra- or inter-system transfers or after release from custody, can result in a life-threatening withdrawal syndrome.

Short-acting benzodiazepines such as alprazolam should not be prescribed, due to the development of rebound symptoms between doses. Rebound symptoms are similar—and sometimes identical—to the anxiety symptoms for which the medication is prescribed, making recognition of the phenomenon and appropriate interventions more difficult.

INDICATED FOR TREATMENT OF CERTAIN PSYCHOTIC SYNDROMES: Benzodiazepines can be the treatment of choice in certain psychotic syndromes, particularly those presenting with catatonia. High-dose lorazepam, 8–12 mg per day, is generally recommended. Clonazepam in similar doses has also been effective in some cases. ECT is also an effective treatment for catatonia.

Individuals with psychotic disorders other than catatonia, whose symptoms include agitation, sleeplessness, restlessness, or significant emotional distress, may respond well to short-term treatment with benzodiazepines. Lorazepam (1–2 mg by mouth or injection, IV or IM, every 2–4 hours) or clonazepam (1–2 mg by mouth every 4–12 hours) are generally effective in reducing

agitation and helping a patient rest. Benzodiazepines may be more effective in restoring an appropriate sleep-wake cycle in individuals with schizoaffective disorder, bipolar type.

MANAGING PHYSIOLOGICAL DEPENDENCE ON BENZODIAZEPINES: Within as few as three weeks of regular use, physiological dependence to benzodiazepines can develop. The BOP Clinical Practice Guidelines for *Detoxification of Chemically Dependent Inmates* should be followed for any inmates being tapered off of benzodiazepines.

→ **Discontinuation of benzodiazepines after three weeks or more should occur only under close clinical supervision.**

If catatonia is present, tapering of the benzodiazepine may result in worsening of the inmate's condition. If this occurs, the dose of medication previously found effective should be reinstated and continued for at least several months prior to attempting a very slow taper. Some patients with catatonia may require long-term benzodiazepine treatment.

SELECTING A BENZODIAZEPINE:

- **Lorazepam** is a good choice for patients with liver disease, as it does not require oxidation and does not have active metabolites that accumulate. However, it generally should be given no less than twice a day for short-term treatment; it often must be given three to four times per day for the desired effect.
- **Clonazepam** requires oxidation by the liver and generally should not be used in individuals with severe liver disease. It also has a very long half-life and may accumulate over several days, requiring a dosage adjustment to prevent over-sedation or intoxication. However, once a stable dose has been established (usually after four days), it can be given once or twice daily, making it more convenient for nonmedical institutions with limited pill lines.
- **Lorazepam** and **clonazepam** can be given in crushed or liquid forms, which helps reduce the risk for noncompliance and/or diversion. Consult the *BOP National Formulary* for current restrictions.
- **Chlordiazepoxide** and **diazepam** should not be utilized in the short-term or long-term treatment of psychotic disorders. They have multiple active metabolites, making accumulation and over-medication a much more likely outcome. In addition, neither medication should be given intramuscularly, due to their unpredictable absorption.

ROLE OF BENZODIAZEPINES IN TREATING SIDE EFFECTS OF ANTIPSYCHOTIC DRUGS: Benzodiazepines can also be used in treating the side effects of antipsychotics, particularly akathisia. Akathisia, one of the most troubling side effects from the patient's perspective, generally does not respond to antiparkinsonian agents. Ordinarily, beta blockers are the first-line treatment for this distressing side effect, particularly in the correctional environment. However, in the event that beta blockers are not effective, benzodiazepines may be necessary to control the akathisia if a dose reduction or change in antipsychotic medication is not feasible or effective.

POTENTIAL SIDE EFFECTS OF BENZODIAZEPINES: Benzodiazepines have a wide therapeutic window and are generally quite safe, particularly when not combined with other sedating medications. Potential side effects from benzodiazepines are summarized in **TABLE 6**.

TABLE 6. SIDE EFFECTS OF BENZODIAZEPINES

♦ Somnolence/sedation	♦ Respiratory depression
♦ Cognitive impairment (especially with long-term use)	♦ Behavioral disinhibition
♦ Intoxication	♦ Incoordination and increased risk for falls
♦ Anterograde amnesia	♦ Dizziness
♦ Hypotension	♦ Hypersalivation (with clonazepam)
	♦ Dysarthria

NONBENZODIAZEPINE ANXIOLYTICS

TREATING ANXIETY WHEN BENZODIAZEPINES SHOULD NOT BE USED: While benzodiazepines are the treatment of choice for acute management of anxiety and agitation in psychotic disorders, there are some situations in which benzodiazepines may be inappropriate for inmates with chronic psychotic disorders:

- When the patient has a comorbid anxiety disorder requiring long-term treatment.
- When the patient has a history of substance abuse.
- When there are underlying syndromes contributing to the anxiety (e.g., obsessive-compulsive disorder, panic disorder, social phobia, post-traumatic stress disorder [PTSD], or generalized anxiety disorder).

In situations where benzodiazepines are inappropriate, treating the chronic psychosis with an SGA may adequately reduce the anxiety symptoms so that they do not interfere with daily functioning. In other cases, cognitive behavioral methods may alleviate symptoms of anxiety.

When adequate treatment of the psychosis does not sufficiently alleviate anxiety symptoms that are interfering with the patient's functioning, treatment should be undertaken specifically for the anxiety disorder itself. Treatment of anxiety disorders in individuals with chronic psychotic illnesses is not inherently different from treatment of patients who do not have a psychotic disorder.

→ *The reader is referred to the National Clearing House for the most recent relevant treatment guidelines or the classic psychiatric textbooks, most recent version.*

DRUG-DRUG INTERACTIONS: When treating anxiety disorders in individuals with psychotic disorders, special attention should be given to potential drug-drug interactions. SSRIs are the pharmacological treatment of choice for several anxiety disorders, including panic disorder, obsessive-compulsive disorder, and social phobia. Because SSRIs often have significant interactions with other medications, it is crucial that the prescriber consult with the pharmacist regarding drug-drug interactions.

SELECTING NONBENZODIAZEPINE DRUGS FOR TREATING ANXIETY:

- **FLUOXETINE** is recommended as the SSRI of first choice.
- **SERTRALINE** is the second-line choice.
- **TRICYCLIC ANTIDEPRESSANTS** should generally be avoided in individuals on antipsychotic medications; these antidepressants are associated with an increased burden of side effects and have a limited efficacy in anxiety disorders, other than panic disorder.

- **BUPROPION** has not been shown to be effective in anxiety disorders; in fact, one of its more common side effects is anxiety. Moreover, because it can lower the seizure threshold (as do some of the antipsychotics), especially in higher doses, it should not be prescribed for the treatment of anxiety disorders.
- **BUSPIRONE** is the only nonbenzodiazepine medication developed and approved specifically for the treatment of anxiety. It has significant serotonergic activity and, at high doses (>90 mg per day), may have activity similar to SSRIs. Its indications include generalized anxiety disorder and anxiety disorder, not otherwise specified. It has been used as an adjunct to SSRIs and clomipramine for the treatment of obsessive-compulsive disorder. However, because of its slow onset of action (several weeks), acceptance by patients and prescribers has never been widespread. It is used more extensively in treating the agitation and anxiety associated with developmental disabilities and dementing conditions. Usual doses are 10–20 mg, three times daily, with smaller doses for elderly patients. Side effects are minimal—headache, dizziness, and nausea—especially when slowly titrated to therapeutic doses. On rare occasions, worsening of EPS and/or psychoses has been reported, especially with higher doses (presumably due to dopaminergic activity).
- **OTHER ANTIDEPRESSANT AGENTS** such as mirtazapine, venlafaxine, and trazodone may be appropriate in some patients with anxiety. Venlafaxine should generally be reserved for those patients refractory to the SSRIs, mirtazapine, and trazodone.
- **BETA BLOCKERS** are sometimes used in treating the peripheral manifestations of anxiety (e.g., tremor) in individuals who might benefit from acute treatment for performance anxiety. However, beta blockers are not generally indicated for the treatment of other anxiety disorders. They can be beneficial in the treatment of some side effects associated with antipsychotic medication, particularly akathisia.
 - ➔ For more information on treating the side effects of antipsychotics, see [Section 7](#).
- **PRAZOSIN** can be used as *adjunct treatment* for symptoms of PTSD, particularly nightmares and sleep disturbances.
 - ➔ Prazosin is generally not effective in globally treating the symptoms of PTSD or other anxiety disorders, and should not be used as monotherapy for the treatment of anxiety.

MOOD STABILIZERS

MOOD STABILIZERS AS ADJUNCTIVE MEDICATION: In some cases, an individual with a chronic psychotic disorder may have had several therapeutic trials of antipsychotic medication, including clozapine, without an adequate response. In these cases, it may be prudent to undertake a trial of a mood stabilizer as an adjunctive medication. While there are no controlled studies on use of mood stabilizers as adjunctive medication, anecdotal reports suggest that they can be useful. The possibility of achieving some improvement in an individual with a chronic psychotic disorder makes such a trial potentially worthwhile. This may be most appropriate in individuals with a history of head injuries or other central nervous system dysfunction where mood stabilizers, especially the antiepileptic medications, have shown some positive effect.

ROLE OF MOOD STABILIZERS IN TREATING PSYCHOTIC DISORDERS: Mood stabilizers have not been conclusively shown to be effective in the treatment of psychotic disorders when an underlying mood disorder or seizure disorder is not present. (There are some studies that suggest that these

medications may be helpful for reducing aggressive or suicidal behavior). Patients with psychotic symptoms commonly have mood disorders as part of their psychotic illness or comorbid with it. It is sometimes difficult to differentiate between an individual with schizophrenia in an agitated psychotic state and an individual with a manic psychosis. Fortunately, many of the SGAs have been shown to be very effective as single agents in the treatment of mania, rendering the need for such differentiation less crucial in some cases.

With the exception of lithium and lamotrigine, mood stabilizers have not been effective in the treatment of depression. Neither lithium nor lamotrigine should be utilized as the primary treatment of depression in the absence of a bipolar condition.

Mood stabilizers are generally reserved for use in individuals with mania, hypomania, or rapid cycling. Such mood disturbances can be seen in bipolar disorder (type I and type II), as well as in schizoaffective disorder (bipolar type). **TABLE 7** lists medications commonly prescribed for mood stabilization.

TABLE 7. MOOD STABILIZING MEDICATIONS

• Lithium	• Oxcarbazepine
• Valproate	• Topiramate
• Lamotrigine	• Levetiracetam
• Carbamazepine	• Clonazepam

INFORMATION ABOUT SPECIFIC DRUGS: The medications utilized for mood stabilization are unique chemically and pharmacologically. Therefore, no general guidance can be provided regarding dosing, side effects, or drug-drug interactions. [Appendix 12](#) offers a brief summary of specific recommendations for each of the more common mood stabilizers, including dosing ranges, titration schedules, potential side effects, and monitoring needs.

➔ *For complete information on mood stabilizers, the reader is referred to the pharmacist and other sources of information on the pharmacology of these medications.*

SPECIFIC COMMENTS ON LITHIUM: Lithium has a narrow therapeutic window; long-term use can cause nephrogenic diabetes insipidus. However, there are reasons to consider this drug. Therapeutic blood levels are well-established, it is generally well-tolerated, and there is some evidence to suggest that it can reduce suicidal behaviors in some individuals. It may have a minor positive impact on depression, as well. As noted above, common side effects of lithium are summarized in [Appendix 12](#). Signs of toxicity include ataxia, nausea and vomiting, severe tremor, and mental status changes. Be aware of interacting medications that can increase or decrease lithium blood levels with commencement or discontinuation of therapy (e.g., hydrochlorothiazide).

7. MEDICATIONS TO TREAT ANTIPSYCHOTIC SIDE EFFECTS

In addition to patient education and support, effective treatment for the side effects of antipsychotics may include any or all of the following:

- Reducing the dose of the medication
- Changing the medication
- Adding medication to treat the side effects

This section focuses on side effects that can be treated with medication. Side effects amenable to such treatment are extrapyramidal in origin and tend to be proportional to the D-2 blocking activity of the antipsychotic medication.

Side effects related to the anticholinergic or antihistaminic activity are generally approached from a symptomatic/palliative approach, as these symptoms tend to occur early and last throughout treatment. For example, constipation can be treated with stool softeners, increased fluids and fiber, and laxatives. Dry mouth is treated with measures such as increased attention to oral hygiene and use of sugarless candy.

EXTRAPYRAMIDAL SYMPTOMS (EPS)

Extrapyramidal side effects can be *acute*, *subacute*, or *insidious/chronic* in their onset.

ACUTE EPS

Symptoms of acute EPS include dystonia, pseudoparkinsonism, and akathisia. The reader is referred to [Appendix 10](#) for a list of EPS and their treatment. Only dystonia and akathisia are discussed at greater length below.

- **DYSTONIA** typically develops within a period of hours to days of initiation of treatment or escalation of dosage. It requires immediate treatment with parenteral medication, either IV or IM, which should then be followed by ongoing treatment with oral antiparkinsonian medication such as benztropine, trihexyphenidyl, or diphenhydramine. Patients find dystonic reactions frightening and painful. If the throat and tongue muscles are involved, dystonic reactions can be dangerous. Such reactions are often referred to by the patient as an “allergic reaction.” This is inaccurate, and it incorrectly implies that the patient cannot receive the same medication in the future. Rather, the patient should be treated prophylactically with antiparkinsonian medication if he or she is prescribed the same or similar antipsychotic medication in the future. Medications most likely to cause dystonic reactions are high-potency FGAs. However, dystonia is an idiosyncratic reaction and has occurred with low doses of low-potency antipsychotics and antiemetics such as promethazine or prochlorperazine.

ANTIPARKINSONIAN AGENTS are associated with side effects related to their anticholinergic and antihistaminic actions. Thus, the smallest effective dose should be prescribed for the shortest possible period of time. Some patients on antipsychotic medications do not require treatment with antiparkinsonian agents. Other patients eventually accommodate the antipsychotic medication, requiring smaller doses of the antiparkinsonian agent or tolerating discontinuation of it altogether.

- **AKATHISIA** is under-recognized and under-treated. Some authors have attributed an increased suicide rate to the presence of akathisia. While this has not been conclusively shown, akathisia is a significant source of distress for patients and can have a negative impact on daily functioning and on sleep. Unlike other extrapyramidal side effects, akathisia does not respond well to antiparkinsonian agents. The treatments of choice are beta blockers or benzodiazepines. Beta blockers are generally well-tolerated and can be slowly titrated to an effective dose (e.g., up to 120 mg or more per day of propranolol, in divided doses). Blood pressure, particularly orthostatic changes, should be monitored during the titration phase and periodically thereafter. Benzodiazepines, such as clonazepam or lorazepam, can be utilized if beta blockers are ineffective.

SUBACUTE EPS

Symptoms of subacute EPS include akathisia (discussed above under [Acute EPS](#)), as well as pseudoparkinsonism and Pisa syndrome (both discussed in [Appendix 10](#)).

INSIDIOUS/CHRONIC ONSET EPS

Symptoms of chronic onset EPS include tardive dyskinesia (TD), tardive dystonia, tardive akathisia, Pisa syndrome, and Rabbit syndrome. Risk factors for the development of these syndromes are listed in [Appendix 10](#). Generally, the rate of development of TD in patients treated with FGAs is 4% per year.

No treatments have been shown to be consistently effective in the tardive syndromes. Part of the difficulty in determining the effectiveness of any intervention is the natural history of TD. In some cases, continuing the antipsychotic medication results in remission of the tardive syndrome. In others, discontinuing the antipsychotic medication may cause the initial manifestation or worsening of the tardive syndrome, followed by gradual resolution. For patients with chronic psychotic disorders, discontinuing the antipsychotic may not be an option. In some cases, clozapine may cause remission of tardive dyskinesia or tardive dystonia.

8. NONMEDICATION TREATMENT INTERVENTIONS

Although medications are essential in the treatment of psychotic disorders, they alone are not sufficient. Nonmedication treatment interventions include electroconvulsive therapy, psychosocial interventions, and cognitive rehabilitation.

ELECTROCONVULSIVE THERAPY (ECT) has been shown to be an effective treatment for catatonic disorders and mood disorders. It is also effective in the treatment of refractory psychotic disorders. ECT is rarely utilized in the BOP correctional setting, but in some cases it may be the most appropriate treatment. (Consult the *Program Statement on Psychiatric Services* for more information on BOP policy regarding ECT.) Patients undergoing ECT for psychotic disorders generally will require treatment with medications before, during, and after a course of ECT treatment. Infrequently, some individuals may require maintenance ECT to remain in remission.

PSYCHOSOCIAL INTERVENTIONS are essential in the management of individuals with chronic illnesses, especially psychiatric conditions. In the correctional setting, accommodations may need to be made in the patient's living conditions, work and education settings, and other institutional activities in order to reduce stress and improve outcomes. Individuals with chronic psychotic conditions often have significant impairments in cognition, perception, social interactions, hygiene, and other aspects of functioning. In addition, some individuals with chronic psychiatric illnesses are more vulnerable to exploitation by other inmates. Correctional and health care staff need to be aware of these potential vulnerabilities and address them as appropriately as possible within the realities of the correctional setting.

Other important psychosocial interventions include psychoeducation and psychotherapy. Psychotherapy interventions may include crisis intervention, supportive therapy, group therapy, and cognitive-behavioral therapy.

COGNITIVE REHABILITATION/REMEDICATION has been shown to reduce relapse and hospitalization in individuals with schizophrenia when they are released and living in the community. Cognitive rehabilitation services are currently limited to Medical Referral Centers (MRCs) and Step-Down Unit programs.

DEFINITIONS

AFFECTIVE FLATTENING is the severe reduction or loss of normal external expressions of internal emotional experiences. Flat or blunted affect may be seen in [MOOD DISORDERS](#), psychotic disorders, some personality disorders, and some neurological conditions such as Parkinson’s disease. It may also be the side effect of antipsychotic medication. Flat or blunted affect in a patient can make it difficult to discern his or her internal emotional state (or mood).

AKATHISIA is an internal sense of restlessness and is a common, early-onset [EXTRAPYRAMIDAL SYMPTOM](#) of dopamine-blocking medications. Outward manifestations may include motor agitation, pacing, shifting of weight in a rhythmic manner, rocking, or other purposeless movements. Internally, the person may experience anxiety, agitation, and dysphoria. Akathisia is under-recognized and under-treated. Patients do not accommodate this side effect with continued exposure to the medication, and anticholinergic medications are generally ineffective in managing the symptoms. Beta blockers and benzodiazepines are the treatment of choice.

ALOGIA is a specific language disturbance in which the quantity of language or ability to initiate language is severely disturbed. Individuals with [SCHIZOPHRENIA](#) may have a relative decrease in the quantity of speech production and may not initiate conversation. Some individuals with schizophrenia may produce a normal number of words, but the speech itself may be relatively lacking in actual content. Alogia can also be seen in other conditions that cause brain dysfunction, such as dementia or mental retardation.

AMOTIVATION is a lack of motivation or initiative (much like [AVOLITION](#)). This symptom, like other negative symptoms of [SCHIZOPHRENIA](#), impairs the individual’s ability to take part in both simple and complex activities of daily living—preparing or attending meals, maintaining hygiene, attending a pill line, getting or keeping a job, and actively engaging in the treatment process.

ANHEDONIA is a lack of interest in pleasurable activities, and it is sometimes described as a lack of enjoyment in usual activities. A symptom of [SCHIZOPHRENIA](#), anhedonia is also frequently seen in [MOOD DISORDERS](#). Anhedonia contributes to the individual’s inability to participate in relationships with others, or even to engage in leisure and other activities that add depth and meaning to a person’s life.

AVOLITION is a lack of will or initiative. In [SCHIZOPHRENIA](#), this symptom results in the individual appearing unable or unwilling to initiate goal-directed activities. Individuals with this symptom may spend most of their time in idle behaviors such as sleeping or watching television. They can appear apathetic. Of particular importance in the therapeutic setting, avolition impairs the patient’s ability to seek assistance when experiencing an inability to function, e.g., self-care.

COMORBID condition is another disease or disorder that co-occurs with a disease or disorder. Generally, comorbid conditions have a significant impact on the manifestation and/or treatment of the primary condition.

DEPRESSION is a mood disturbance in which the primary manifestation is a decrease in mood, energy, interest, and cognitive functioning. Depression is seen in a number of psychiatric and medical conditions.

DISORGANIZED BEHAVIOR is an external sign of cognitive impairment in executive functioning, including planning and executing goal-oriented behaviors. Examples of disorganized behavior may include repetitive and irrational behaviors (such as repeatedly flushing a toilet for hours), poor or bizarre hygiene or grooming, posturing, hyperactivity or hypoactivity, or other unusual behaviors.

DISTURBED LANGUAGE is the outward manifestation of brain dysfunction. In psychotic individuals, the language can be disturbed in form, syntax, prosody, or any number of characteristics. The ability to physically form words is intact in psychotic disorders, but the processing and/or expression of language is abnormal. Perseveration is a common, though often subtle, finding in individuals with genuine psychosis.

DYSTONIA is an idiosyncratic [EXTRAPYRAMIDAL SYMPTOM](#) of antipsychotic medication, which occurs in the acute phase of treatment. It is more common in young males than in other populations and is more common with the use of high-potency medications. It is characterized by slow, sustained muscle contractions and can involve any muscle groups. It most often affects the muscles of the eyes, mouth, head, and neck. When it involves these muscles, it is sometimes called an oculogyric crisis. If it involves the musculature of the tongue and throat, it can cause potentially fatal dysphagia. Dystonic reactions are usually very painful, though acutely psychotic patients may not even notice the reaction. Regardless of the patient's reaction or insight, it should be treated as a medical emergency with parenteral anticholinergic medication. When dystonia develops late in the course of treatment and persists, it is called **TARDIVE DYSTONIA**.

EXTRAPYRAMIDAL SYMPTOMS (EPS), also sometimes called **EXTRAPYRAMIDAL SYNDROMES** or **PSEUDOPARKINSONISM**, are a group of motor side effects caused by dopamine-blocking medications, including antipsychotics and antiemetics. EPS include [AKATHISIA](#), muscle rigidity, tremor, bradykinesia, [AFFECTIVE FLATTENING](#), [PISA SYNDROME](#), [RABBIT SYNDROME](#), choreoathetotic movements, [DYSTONIA](#), and [TARDIVE DYSKINESIA](#). Antipsychotic medication dose reduction, adding an anticholinergic agent or switching to a second-generation antipsychotic (if the originally prescribed agent is proving ineffective), should be considered.

HALLUCINATIONS are disturbances in perceptions in one of the five senses—sight, sound, touch, smell, and taste—that occur in the absence of any external stimulus. Hallucinations may occur in any one sensory realm or in multiple senses. Hallucinations occur in many different psychiatric and medical conditions and are not pathognomonic for any particular condition.

HYPOMANIA is a mood disturbance similar qualitatively to [MANIA](#), but less intense. Judgement and impulse control may be disturbed, but to a lesser degree than in mania. Individuals with hypomania have an increase in goal-directed activities, energy, and being in a “good” mood (or irritable). Hypomania is seen in bipolar disorders and schizoaffective disorder, bipolar type.

MANIA is a mood syndrome characterized by hyperactivity, decreased need for sleep, and increased rate of speech and thoughts, in addition to disturbances in the thought process, poor judgement, and poor impulse control. The mood disturbance may include euphoria and/or irritability. Psychiatric conditions with manic states include bipolar disorder, type I, and schizoaffective disorder, bipolar type. Mania can also be seen in medical conditions such as Cushing's disease and in substance abuse syndromes, including intoxication and withdrawal.

MOOD DISORDERS are those psychiatric conditions that manifest as their primary symptoms a disturbance in mood, with associated vegetative signs and symptoms. They include bipolar disorders and depressive disorders. *The Diagnostic and Statistical Manual of Mental Disorders (DSM-5)* lists the criteria necessary to diagnose these conditions.

NEUROLEPTIC MALIGNANT SYNDROME (NMS) is a potentially fatal condition that can occur in any patient taking antipsychotic medication, including the SGAs. The diagnosis remains somewhat controversial, as it shares some characteristics with malignant catatonia. The constellation of symptoms vary qualitatively and quantitatively from patient to patient, as well as over time within the same patient. Prescribers should remain vigilant for the development of symptoms consistent with NMS. See [Appendix 8](#) for more complete information.

OBSESSIVE-COMPULSIVE DISORDER (OCD) is an anxiety disorder characterized by a disturbance in thoughts and behaviors. The thoughts (*obsessions*) are experienced as uncontrollable, repetitive ruminations that usually provoke anxiety. To cope with the anxiety, the individual then engages in repetitive behaviors (*compulsions*) that are also experienced as involuntary or uncontrollable. Although obsessions and compulsions are generally thought of as being ego-dystonic, they can become ego-syntonic and cause more distress to family and friends than to the individual afflicted with them. OCD can be seen as a primary disorder, a [COMORBID](#) disorder, or a complex of symptoms associated with other conditions. OCD can be seen in medical and psychiatric conditions.

PISA SYNDROME is a late-onset (tardive), persistent [EXTRAPYRAMIDAL SYMPTOM](#) caused by dopamine-blocking medications. The patient has a flexion of the trunk to one side, causing a leaning posture.

RABBIT SYNDROME is an early- to mid-onset [EXTRAPYRAMIDAL SYMPTOM](#) caused by dopamine- blocking medications. It is a tremor involving the musculature of the lips.

SCHIZOAFFECTIVE DISORDERS are a group of psychiatric disorders characterized by the presence of a mood syndrome, concurrent with a psychotic disorder that itself meets the diagnostic criteria for [SCHIZOPHRENIA](#). In addition, at some point during the active phase of the disorder, there must be a two-week period in which the criteria for schizophrenia are met, but without a concurrent mood disorder. Mood syndromes seen in schizoaffective disorder include [MANIA](#), [DEPRESSION](#), or mixed (mania and depression together). Patients with schizoaffective disorders seem to appear along a spectrum in their presentations, impairments, and responses to treatment, from very closely resembling schizophrenia, to more closely resembling a mood disorder with psychosis (bipolar disorder or major depression with psychotic features). Formal diagnostic criteria are found in *The Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*.

SCHIZOPHRENIA is a group of neurodevelopmental disorders or syndromes characterized by disturbances in perceptions, cognitive functions, emotions/mood, motor activity, and behavior. Such disturbances range from moderate to severe and may fluctuate over an individual's lifetime. By definition, the disorder must last at least six months. Formal diagnosis is made by satisfying the criteria set forth in *The Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. The criteria have been simplified to include [HALLUCINATIONS](#), *disorganized language*, [DISORGANIZED BEHAVIOR](#), and negative symptoms, the two most prominent being [AFFECTIVE FLATTENING](#) and [AVOLITION](#).

TARDIVE DYSKINESIAS (TDs) are involuntary movements of the tongue, lips, face, trunk, and extremities that occur in patients treated with long-term dopaminergic antagonist medications. Although they are associated with the use of neuroleptics, TDs apparently existed before the development of these agents. People with schizophrenia and other neuropsychiatric disorders are especially vulnerable to the development of TDs after exposure to conventional neuroleptics, anticholinergics, toxins, substances of abuse, and other agents.

THERAPEUTIC TRIALS of antipsychotic medication require the use of a therapeutic dose (not always easily established) for a minimum of six to eight weeks after ending treatment. Antipsychotic medication has a slow onset of action; it is hypothesized that it changes the sensitivity of the neuroreceptors, as well as the quantity of neurotransmitters available to the neuroreceptor. Some antipsychotics, such as clozapine, have been shown to continue to exert additional therapeutic benefits for many months after initiation of treatment. Providers often fail to undertake full therapeutic trials of medication, because they may not be aware of the slow onset of action or because they fail to apply objective measurements of patient progress.

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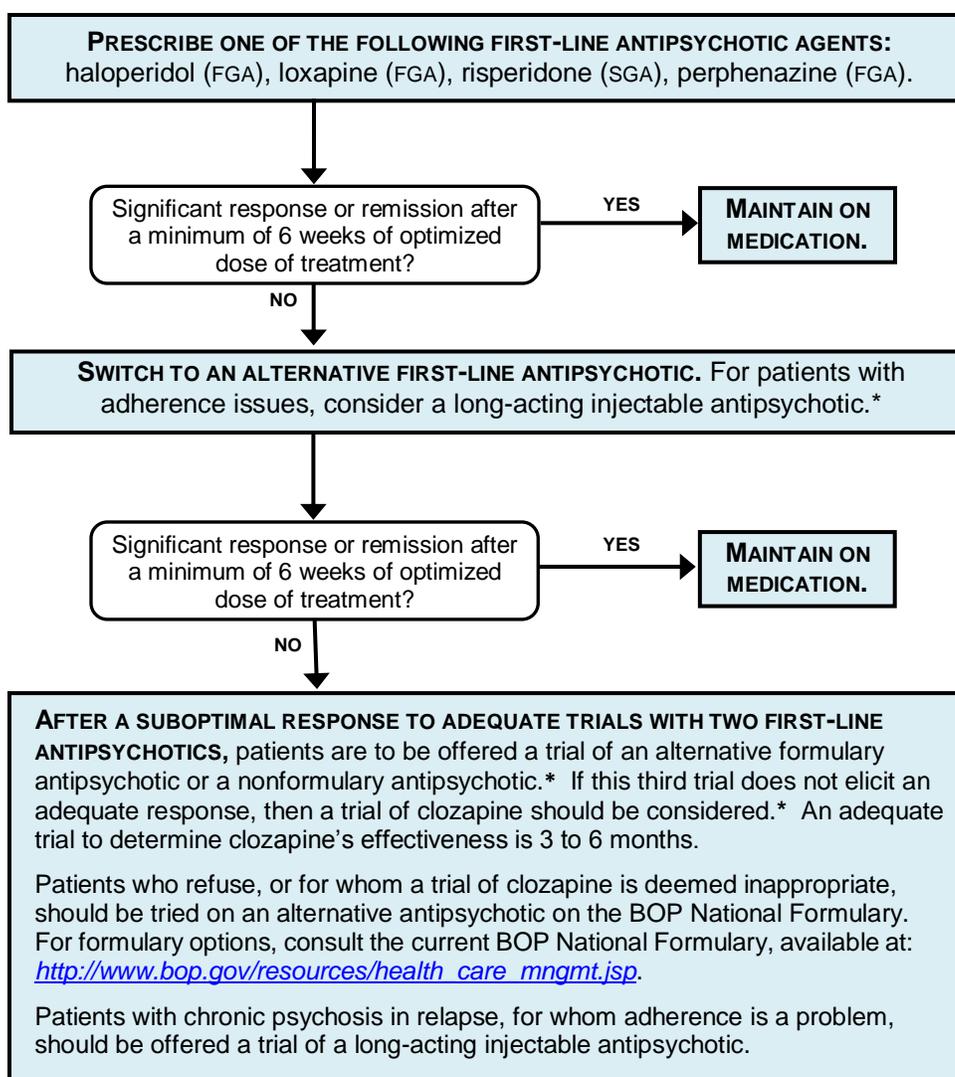
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APPENDIX 1. ANTIPSYCHOTIC TREATMENT ALGORITHM

The following algorithm is adapted from the June 2012 *Recommendations for Antipsychotic Selection in Schizophrenia and Schizoaffective Disorders* of the Veterans Affairs (VA) Pharmacy Benefits Management Services, Medical Advisory Panel, and *Veterans Integrated Service Networks (VISN) Pharmacist Executives* (available at: <http://www.pbm.va.gov/clinicalguidance/clinicalrecommendations.asp>).

Selection of therapy for individual patients is ultimately based on the physician's assessment of clinical circumstances and patient needs. At the same time, prudent policy requires appropriate management of resources. These recommendations are not intended to interfere with clinical judgment. Rather, they are intended to assist practitioners in providing care that is cost-effective, consistent, and high quality. *The following recommendations are subject to change as new evidence becomes available.*

- ➔ **This algorithm applies only to schizophrenia and schizoaffective disorders and is not applicable to other conditions where an antipsychotic is indicated, e.g., bipolar disorder or treatment augmentation for major depressive disorder.**



* For more information, see the next two pages of this appendix.

(Appendix 1. Antipsychotic Treatment Algorithm, page 1 of 3)

DESCRIPTION OF ANTIPSYCHOTIC TREATMENT ALGORITHM

The algorithm is based on numerous clinical trials (see [Further Reading](#) section below) comparing both FGAs and SGAs in the treatment of schizophrenia or schizoaffective disorder. To summarize, there is no strong evidence to support any particular class of antipsychotic agents as offering a superior benefit with regard to either efficacy or safety. Each antipsychotic agent's unique safety profile must be considered when selecting treatment (see [Appendix 4a](#) and [Appendix 4b](#) for side effects of FGAs and SGAs).

- *The algorithm in this Appendix outlines guidance on the antipsychotic agents to be considered as first-line so as to avoid agents associated with more significant safety issues, and to ensure prudent use of BOP resources.*

ANTIPSYCHOTIC AGENTS TO BE USED FOR SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER:

- **Formulary first-line agents:** haloperidol (available as a long-acting injectable), loxapine, risperidone (available as a long-acting injectable), and perphenazine.
 - **Alternative formulary agents:** fluphenazine (available as a long-acting injectable), olanzapine, ziprasidone, trifluoperazine
 - **Formulary-restricted agents:** clozapine (requires initiation at a Medical Referral Center)
 - **Non-formulary agents:** aripiprazole, asenapine, chlorpromazine, iloperidone, lurasidone, quetiapine, paliperidone, pimozide, thioridazine, thiothixene
- *Formulary status of medications is subject to change. For the most up-to-date formulary options, consult the current BOP National Formulary at: http://www.bop.gov/resources/health_care_mngmt.jsp. Ultimately, the local P & T Committee may determine what drugs on the National Formulary will be available locally. Consultation with the facility pharmacist should be part of researching the most up-to-date options for a particular inmate. All orders for non-formulary agents require a prior authorization request.*

FOR NEW STARTS OF ANTIPSYCHOTIC TREATMENT FOR SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER:

- Follow [Antipsychotic Treatment Algorithm](#) on the first page of this appendix.

FOR PATIENTS CONTINUING CARE FROM ANOTHER FACILITY:

- Follow current BOP formulary guidelines and institution policies for continuation of care.

(Appendix 1. Antipsychotic Treatment Algorithm, page 2 of 3)

FURTHER READING:

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APPENDIX 2. INFORMED CONSENT

Policy for obtaining informed consent is contained in Program Statement 6340.04, Psychiatric Services. Following is an excerpt from the Program Statement:

Psychiatric Medication: Except in an emergency, informed consent will be obtained and documented prior to administering medication for psychiatric symptoms or conditions (refer to the *Program Statement on Pharmacy Services*). Ordinarily, the prescribing physician will be responsible for obtaining the informed consent. Patient education for obtaining informed consent includes the following information:

- Symptoms of the illness
- Potential benefits of treatment
- Potential risks and side-effects (especially serious ones)
- Appropriate use of the medication
- When to notify staff of problems
- Consequences of noncompliance
- Alternative treatments, including no treatment, and associated risks

The inmate's competency to give informed consent will be assessed and documented on the corresponding "Consent to Use (name of medication)" form. An informed consent form will be obtained in *any* of the following situations:

- A psychiatric medication is prescribed for which an informed consent has not previously been obtained.
- An inmate has previously given informed consent, but has been off the medication for at least a year.
- Clinical judgment deems that a new informed consent is appropriate because of a significant change in the inmate's clinical status.
- An inmate on psychiatric medication is newly committed to the Bureau and does not have informed consent documented on any of the standard forms noted above.

APPENDIX 3. ANTIPSYCHOTIC MEDICATIONS

Generic Name*	Common Brand Name
First-Generation Antipsychotics (FGAs)	
Chlorpromazine	Thorazine
Fluphenazine	Prolixin
Haloperidol	Haldol
Loxapine	Loxitane
Molindone	Moban
Perphenazine	Trilafon
Pimozide	Orap
Thioridazine	Mellaril
Thiothixene	Navane
Trifluoperazine	Stelazine
Second-Generation Antipsychotics (SGAs)	
Aripiprazole	Abilify
Asenapine	Saphris
Cariprazine	Vraylar
Clozapine	Clozaril
lloperidone	Fanapt
Lurasidone	Latuda
Olanzapine	Zyprexa
Paliperidone	Invega
Quetiapine	Seroquel
Risperidone	Risperdal
Ziprasidone	Geodon

* Formulary status of medications is subject to change. For the most up-to-date formulary options, consult the current BOP National Formulary, available at: http://www.bop.gov/resources/health_care_mngmt.jsp. Ultimately, the local P & T Committee may determine what drugs on the National Formulary will be available locally. Consultation with the facility pharmacist should be part of researching the most up-to-date options for a particular inmate.

APPENDIX 4A. SIDE EFFECTS OF FIRST-GENERATION ANTIPSYCHOTICS (FGAs)

Anticholinergic/ Antihistaminic Effects	Related to Dopamine Blockage	Other Potential Side Effects
<ul style="list-style-type: none"> • Blurred vision • Constipation • Urinary retention • Sexual dysfunction • Retrograde ejaculation • Postural hypotension • Tachycardia • Cardiac dysrhythmias • Somnolence • Slowed thinking • Poor concentration • Confusion • Dry mouth • Decreased sweating • Weight gain • Increased appetite • Nausea • Restlessness • Worsening or precipitation of narrow angle glaucoma 	<ul style="list-style-type: none"> • Muscle rigidity • Flattened affect • Bradykinesia • Tremor • Dystonia • Increased prolactin resulting in amenorrhea, sexual dysfunction, galactorrhea, and/or gynecomastia • Akathisia • Rabbit syndrome • Dysphagia • Tardive dyskinesia • Neuroleptic malignant syndrome 	<ul style="list-style-type: none"> • Decreased seizure threshold • Sun sensitivity • Decreased ability to regulate body temperature, predisposing to hyperthermia • SIADH, polydipsia/polyuria (may occur without antipsychotic treatment also) • Lenticular and/or retinal pigmentation • Priapism • Elevated liver function tests • Insulin resistance/hyperglycemia • Agranulocytosis • Thrombocytopenia • Prolonged QT interval
Black Box Warning		
<p><i>Dementia-Related Psychosis:</i> Antipsychotics are not approved for dementia-related psychosis. There is an increased mortality risk in elderly dementia patients on conventional or atypical antipsychotics. Most deaths are due to cardiovascular or infectious events. The extent to which increased mortality can be attributed to antipsychotic medication vs. particular patient characteristic(s) is not clear.</p>		

APPENDIX 4B. SIDE EFFECTS OF SECOND-GENERATION ANTIPSYCHOTICS (SGAs)

Serious Reactions	Common Reactions
<ul style="list-style-type: none"> • Neuroleptic malignant syndrome (NMS) • Extrapyramidal symptoms, severe (EPS) • Tardive dyskinesia (TD) • Dystonia • QT prolongation • Torsades de pointes • Seizures • Syncope • Priapism • HTN, severe • Hyperglycemia, severe • Diabetes mellitus • Serotonin syndrome • Allergic reactions • Leukopenia • Neutropenia • Agranulocytosis 	<ul style="list-style-type: none"> • Somnolence • Headache • Nausea • Constipation • Dyspepsia • Dizziness • Respiratory disorders • Extrapyramidal symptoms (EPS) • Asthenia • Diarrhea • Weight gain • Rash • Urticaria • Dry mouth • Visual disturbances • Hypersalivation • Tachycardia • Hypotension, orthostatic • Menstrual irregularities • Hyperprolactinemia
Black Box Warning	
<p><i>Dementia-Related Psychosis:</i> Antipsychotics are not approved for dementia-related psychosis. There is an increased mortality risk in elderly dementia patients for conventional or atypical antipsychotics. Most deaths are due to cardiovascular or infectious events. The extent to which increased mortality can be attributed to antipsychotic medication vs. particular patient characteristic(s) is not clear.</p>	

APPENDIX 5. RELATIVE SIDE EFFECT INCIDENCE OF ANTIPSYCHOTIC MEDICATIONS

Medication	Extra-pyramidal (EPS) ¹	Anti-cholinergic ²	Anti-histaminic ³	anti α -1 ⁴	Diabetes Risk ⁵
First-Generation Antipsychotics (FGAs)					
Chlorpromazine	+++	+++	+++	++++	+
Fluphenazine	+++++	+	+++	+++	+
Haloperidol	+++++	+	+	+++	+
Loxapine	++++	++	+++	+++	+
Molindone	++++	—	+	+	+
Perphenazine	++++	+	++++	+++	+
Pimozide*	+++++	+	+	+++	+
Thioridazine	+++	++++	++++	++++	+
Thiothixene	+++++	+	+++	++	+
Trifluoperazine	++++	+	++	+++	+
Second-Generation Antipsychotics (SGAs)					
Ariprazole	++	+	+	+	+
Asenapine	++	+	+	+	+/-
Cariprazine	+++	+	+	+/-	+/-
Clozapine	+	+++	++++	++++	+++
Iloperidone	++	+	++	+++	+/-
Lurasidone	++	+	+	+++	+/-
Olanzapine	+++	++++	++++	+++	+++
Paliperidone	+++++	++	+++	++++	++
Quetiapine	+	++++	++++	++++	+++
Risperidone	+++++	++	+++	++++	++
Ziprasidone*	++++	+++	+++	+++	+/-
* Pimozide and ziprasidone may prolong the QT interval. They should not be used with other medications known to prolong the QT interval.					

¹ **Extrapyramidal side effects:** Proportional to dopamine blockade. Can include blockade of D-1, D-2, D-3, and D-4 receptors, although D-2 blockade seems most important in the development of most EPS. D-2 blockade is generally directly proportional to antipsychotic activity in FGAs (this relationship does not appear to hold for SGAs). Side effects from dopamine blockade include muscle rigidity, flattened affect, bradykinesia, tremor, dystonia, prolactinemia, akathisia, Rabbit syndrome, Pisa syndrome, tardive dyskinesia, and neuroleptic malignant syndrome.

² **Anticholinergic side effects:** Help attenuate EPS side effects. Side effects include dry mouth, blurred vision, urinary retention and incontinence, constipation, sinus tachycardia, QRS changes, cognitive slowing, and sedation.

³ **Antihistaminic side effects:** Include sedation, hypotension, weight gain, and dry mouth.

⁴ **Anti α -1 side effects:** Include postural hypotension, tachycardia, dizziness, potentiation of other alpha-1 blockers, urinary incontinence, hypersalivation, and sedation.

⁵ **Diabetes Mellitus:** Relative risk.

APPENDIX 6. ANTIPSYCHOTIC DOSING CHARTS

First-Generation Antipsychotics (FGAs)					
Drug	Starting Dose	Dose Range	Usual Maximum Dose		
Chlorpromazine	50–100 mg/day	300–1000 mg/day	1000 mg/day		
Fluphenazine	5 mg/day	5–20 mg/day	20 mg/day		
Fluphenazine D****	12.5–25 mg IM every 2–3 weeks	6.25–50 mg IM every 2–4 weeks	100 mg IM over 4 weeks		
Haloperidol	2–5 mg/day	2–20 mg/day	20 mg/day		
Haloperidol D****	25–100 mg IM every 2 weeks	50–200 mg IM every 2–4 weeks	300 mg IM over 3–4 weeks		
Loxapine	20 mg/day	50–150 mg/day	150 mg/day		
Molindone	20 mg/day	50–150 mg/day	150 mg/day		
Perphenazine	4–8 mg/day	16–64 mg/day	64 mg/day		
Pimozide	2 mg/day	2–10 mg/day	20 mg/day		
Thioridazine	50–100 mg TID	150–800 mg/day	800 mg/day		
Thiothixene	5–10 mg/day	15–50 mg/day	50 mg/day		
Trifluoperazine	2 mg/day	5–40 mg/day	40 mg/day		
Second-Generation Antipsychotics (SGAs)					
Drug	Starting Dose	Titration	Dose Range	Max. Dose	Schedule
Aripiprazole	10–15 mg/day	Every 2 weeks	10–30 mg/day	30 mg/day	HS or AM
Asenapine	5 mg bid	N/A	N/A	10 mg/day	HS or AM
Cariprazine	1.5 mg/day	1.5 mg/day	1.5–6 mg/day 1.5–3 mg/day with coadministration of CYP3A4 inhibitor	6 mg/day	HS or AM
Clozapine	12.5 mg (half of a 25 mg tablet) Starting on DAY 3, dose is increased every 3 days. (See Titration column.)	DAY 2: 25 mg HS DAY 3: 25 mg BID DAY 6: 25 mg AM, 50 mg HS DAY 9: 50 mg BID DAY 12: 75 mg BID DAY 15: 100 mg BID DAY 18: 125 mg BID DAY 21: 150 mg BID DAY 24: 100 mg AM, 200 mg HS	300–900 mg/day Serum level for doses > 600 mg/day.	900 mg/day	BID Eventual maintenance dose schedule: BID (1/3 in AM, 2/3 in PM).
Iloperidone	1 mg bid	2 mg/day	12–24 mg/day	24 mg/day	HS or AM
Lurasidone	40 mg/day	N/A	40–160 mg/day	160 mg/day	HS or AM
Olanzapine	5–10 mg/day	5 mg/week	10–20 mg/day	40 mg/day*	HS

(Appendix 6, Antipsychotic Dosing Charts, page 1 of 2)

Second-Generation Antipsychotics (SGAs) (continued)					
Drug	Starting Dose	Titration	Dose Range	Max. Dose	Schedule
Paliperidone	6 mg/day	every 5 days	6–12 mg/day	12 mg/day	HS or AM
Paliperidone LAI	234 mg IM once	Day 8: 156 mg	39– 234 mg IM per month	234mg IM per month	HS or AM
Quetiapine	25 mg bid	50 mg/day	300–800 mg/day	800 mg/day	BID
Risperidone	1–2 mg/day	1 mg /2–3 days	2–6 mg/day	16 mg/day **	HS or AM
Risperidone LAI	25 mg IM every 2 weeks	25 mg every 4 weeks	25–50 mg every 2 weeks	50 mg every 2 weeks	HS or AM
Ziprasidone***	40–80 mg/day	20–40 mg every 2–3 days	80–160 mg/day	160 mg/day	BID
<p>* Some data indicate that olanzapine doses > 20 mg may benefit patients who only partially respond to an adequate trial of olanzapine 20 mg.</p> <p>** The risk of EPS is significantly increased by using > 6 mg of risperidone daily.</p> <p>*** Ziprasidone should be taken with food in order to increase absorption.</p> <p>**** Establish tolerance to oral fluphenazine /haloperidol prior to changing to IM decanoate injection.</p>					
(Appendix 6, Antipsychotic Dosing Charts, page 2 of 2)					

APPENDIX 7A. MONITORING FOR SIDE EFFECTS OF ANTIPSYCHOTIC MEDICATIONS

Test	Inpatient*	Outpatient*
First-Generation Antipsychotics (FGAs)		
AIMS**	At admission, then quarterly	At first visit, then every 6 months
Fingerstick/Fasting Blood Glucose	At admission, then annually	At first visit, then annually
Lipids	At admission, then annually	At first visit, then annually
Weight	At admission, then monthly	At first visit, then every 6 months
Second-Generation Antipsychotics (SGAs)		
AIMS**	At admission, then quarterly	At first visit, then every 6 months
Fingerstick/Fasting Blood Glucose	At admission, then quarterly	At first visit, then quarterly
HgA1C	At admission, then every 6 months	At first visit, then every 6 months
Lipids	At admission, then annually	At first visit, then annually
Weight	At admission, then monthly	At first visit, then every 6 months
<p>* Assuming no diagnosis of hyperglycemia or diabetes ** AIMS = Abnormal Involuntary Movement Scale (see Appendix 15)</p>		

APPENDIX 7B. METABOLIC MONITORING GUIDELINES FOR SGAS

	Baseline	Monthly*	Quarterly**	Annually
Family History	X			
Weight and Body Mass Index (BMI)	X	X		
Waist Circumference	X			X
Blood Pressure	X	X		
Fasting Lipids	X			X
Fasting Glucose	X		X	

* Or at each visit

** May be decreased to every 6 months if consistently normal

APPENDIX 8. NEUROLEPTIC MALIGNANT SYNDROME

Neuroleptic malignant syndrome (NMS) is an idiosyncratic reaction to antipsychotic medication. The diagnosis remains somewhat controversial, as it shares some characteristics with malignant catatonia. NMS has no pathognomonic sign or symptom upon which to base the diagnosis; rather, it is a constellation of symptoms associated in time with the use of antipsychotic medication. The symptoms vary qualitatively and quantitatively from patient to patient, as well as over time within the same patient.

NMS is a potentially fatal condition that can occur in any patient taking antipsychotic medication. While the typical risk factors of NMS are summarized below, the clinician must remain alert to the possible presence of NMS in *any* patient with recent exposure to antipsychotic medication who develops mental status changes or other signs and symptoms consistent with NMS.

- Treatment of the patient should not be undertaken in the outpatient setting. The patient should be referred to the local hospital for treatment and stabilization.
- Antipsychotic medication should not be reinstated until the patient has been medically stable for two weeks. When reinstated, the new medication—from a different class of antipsychotics than the potentially offending agent—should be initiated at low dose. The patient should be followed closely, and the titration should occur very slowly.
- Due to the possible overlap with malignant catatonia, lorazepam or clonazepam may be utilized as needed to control agitation or insomnia during the early phase of stabilization of the psychosis.

POTENTIAL SYMPTOMS OF NMS:

- Autonomic instability, including variability in blood pressure, pulse, temperature, and diaphoresis
- Elevated CPKs
- Fever
- Mental status changes
- Muscle rigidity
- Renal failure
- Rhabdomyolysis

RISK FACTORS FOR THE DEVELOPMENT OF NMS:

- Initiation or increased dose of an antipsychotic medication
- Dehydration
- Young, male patient
- High ambient temperature/humidity

DIFFERENTIAL DIAGNOSES:

- Anticholinergic rebound (with abrupt discontinuation of anticholinergic medication)
- Serotonin syndrome (in the presence of serotonergic agents, including some antiemetics)
- Malignant catatonia (best treated with high dose of benzodiazepines)
- Malignant hyperthermia
- Heat stroke

APPENDIX 9. CLOZAPINE: SIDE EFFECTS AND MONITORING

→ More information is available at www.clozaril.com.

SIDE EFFECTS

- **Dose-Related Side Effects**
 - ▶ Sedation
 - ▶ Weight gain
 - ▶ Hypersalivation
 - ▶ Tachycardia
 - ▶ Hypotension
 - ▶ Fever
 - ▶ Seizures—especially in patients with seizure disorders, on medications that reduce the seizure threshold, or on doses exceeding 300 mg per day
- **Idiosyncratic Side Effects**
 - ▶ Agranulocytosis—**black box warning**

TREATMENT

- **Initiation of Treatment**

Prior to being treated with clozapine, patients must be registered with the Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program (at www.clozapinerems.com). The REMS program is an FDA-mandated single, shared patient registry that replaces the clozapine patient registries previously provided by individual manufacturers.
- **Absolute Contraindications**
 - ▶ WBC < 3500/mm³
 - ▶ History of myeloproliferative disorder
 - ▶ History of clozapine-induced granulocytopenia
 - ▶ On other medication known to have risk of granulocytopenia, such as carbamazepine
 - ▶ Immunosuppression
- **Relative Contraindications**
 - ▶ Seizure disorder
 - ▶ Outpatient status: Normally, clozapine may only be initiated at an MRC with a psychiatric inpatient unit. Consult the BOP National Formulary for current restrictions on use.
- **Dosing Schedule**
 - ▶ Initiate at 25 mg per day.
 - ▶ Increase gradually, no faster than 25–50 mg per day or 100 mg twice weekly.
 - ▶ Therapeutic trial should be at maximal tolerated dose for minimum of four months.

(Appendix 9. Clozapine: Side Effects and Monitoring, page 1 of 2)

MONITORING FOR SIDE EFFECTS OF CLOZAPINE

- Monitor orthostatic blood pressure and pulse during titration phase or whenever symptomatic.
- Consider plasma levels if patient is not responding at 400 mg per day, or is showing excessive side effects at any dose.
- Follow tests for weight, lipids, and glucose, as indicated in [Appendix 7a](#), *Monitoring for Side Effects of Antipsychotic Medications*.

MONITORING WHITE BLOOD CELL COUNT (WBC)

- Check WBC prior to initiation of treatment.
- Check WBC weekly for first six months of treatment, then every two weeks.
- Check WBC if patient shows any signs of infection (fever, sore throat, lethargy, etc.).
- Check WBC weekly for four weeks after termination of treatment.

White Blood Cell Count (WBC) and Interventions	
WBC and/or ANC*	Action
WBC < 2000/mm ³ and/or ANC < 1000/mm ³	<ul style="list-style-type: none"> ♦ STOP clozapine. ♦ Check WBC and differential, daily. ♦ Check VS q 8 hours. ♦ Consider Neupogen treatment. ♦ Consider protective isolation. ♦ DO NOT rechallenge with clozapine.
WBC = 2000–3000/mm ³ and/or ANC = 1000–1500/mm ³	<ul style="list-style-type: none"> ♦ STOP clozapine. ♦ Check WBC and differential, daily. ♦ Check VS q 8 hours. ♦ Consider Neupogen treatment if WBC or ANC continues to decline, or if signs of infection occur. ♦ Clozapine may be resumed if Neupogen was not necessary (WBC > 3000/mm³ and ANC > 1500/mm³). WBC should then be checked twice weekly until WBC > 3500/mm³.
* ANC = absolute neutrophil count	

(Appendix 9. Clozapine: Side Effects and Monitoring, page 2 of 2)

APPENDIX 10. MANAGEMENT OF ANTIPSYCHOTIC-INDUCED SIDE EFFECTS

Side Effect	Risk Factors*	Usual Onset	Management**
Dystonia	<ul style="list-style-type: none"> Male gender Young age High-potency antipsychotic 	Hours to days	STAT: Diphenhydramine, 50 mg IM OR Benztropine, 2 mg IM AND: Place on oral anticholinergic
Akathisia	<ul style="list-style-type: none"> None known 	Hours to days <i>(persistent and chronic, once developed)</i>	Beta blocker, e.g., propranolol <i>If ineffective at maximum dose, change to another antipsychotic or clonazepam.</i> <i>(See also Appendix 11.)</i>
Pseudoparkinsonism (muscle rigidity, bradykinesia, tremor, drooling, flat affect, etc.)	<ul style="list-style-type: none"> Older age Brain disease or damage High-potency antipsychotic 	Hours to weeks	Anticholinergic or antihistaminic at lowest effective dose. <i>(See also Appendix 11.)</i>
Pisa Syndrome	<ul style="list-style-type: none"> Older age Brain disease or damage High-potency antipsychotic 	Hours to months or years	Anticholinergic or antihistaminic (higher doses, generally)
Rabbit Syndrome	<ul style="list-style-type: none"> Older age Brain disease or damage High-potency antipsychotic 	Weeks to months	Anticholinergic or antihistaminic
Tardive Dyskinesia	<ul style="list-style-type: none"> Older age Female gender Previous EPS Brain disease or damage Affective disorder Chronic use of antiparkinsonian meds 	Months to years, or upon withdrawal of antipsychotic	Consider change to SGA or clozapine
Tardive Dystonia (or other chronic side effects)	<ul style="list-style-type: none"> Young age Male gender Brain disease or damage Other tardive syndromes 	Months to years, or upon withdrawal of antipsychotic	Consider change to SGA or clozapine
Tardive Akathisia	<ul style="list-style-type: none"> Other tardive syndromes 	Months to years, or upon withdrawal of antipsychotic	Consider change to SGA or clozapine
NMS (See Appendix 8 for more details.)	<ul style="list-style-type: none"> Male gender Young age Past Hx NMS 	Hours to days	Hospitalization Do not rechallenge with same antipsychotic after NMS has resolved.

(Appendix 10. Management of Antipsychotic-Induced Side Effects, page 1 of 2)

Side Effect	Risk Factors*	Usual Onset	Management**
Anticholinergic Side Effects	<ul style="list-style-type: none"> ♦ Low-potency antipsychotics ♦ Use of antiparkinsonian meds 	Hours to days	Palliative treatment
Metabolic Syndrome	<ul style="list-style-type: none"> ♦ Hx of high glucose ♦ FHx DM ♦ Overweight ♦ Use of SGAs 	Days to years	Diabetic management
<p>* Serious side effects may occur in patients with no known risk factors.</p> <p>** The most appropriate management of any side effects may include changing the antipsychotic medication or reducing the dose. The risks of reducing the dose or changing an otherwise effective medication should be carefully weighed against the severity of the side effects and risks associated with them (including the risk of noncompliance), as well as the patient's preferences regarding possible interventions.</p>			
<p><i>(Appendix 10. Management of Antipsychotic-Induced Side Effects, page 2 of 2)</i></p>			

APPENDIX 11. ANTIPARKINSONIAN AGENTS

Medication*	Usual Dose Range	Indication
Benzotropine (anticholinergic and antihistaminic)	1–6 mg daily (at higher doses, give in twice daily dosing)	Stiffness, rigidity, bradykinesia, tremor drooling, dystonia
Trihexyphenidyl (anticholinergic)	5–20 mg daily (at higher doses, give in twice daily dosing)	Stiffness, rigidity, bradykinesia, tremor
Amantadine (presynaptic dopaminergic agent)	100–200 mg in once or twice daily dosing (tolerance may develop)	Stiffness, rigidity, bradykinesia
Diphenhydramine (antihistamine)	25–50 mg BID to QID	Stiffness, rigidity, bradykinesia, tremor drooling, dystonia
Propranolol** (beta-blocker)	20–120 mg daily in TID to QID dosing	Akathisia, tremor
Ativan, clonazepam (benzodiazepines)	1–4 mg in BID dosing	Akathisia
<p>* Side effects of these medications are related to class of agent. ** Metoprolol 200–300 mg, nadolol 40–80 mg, pindolol 5 mg, or betaxolol 5–20 mg also have efficacy in akathisia.</p>		

APPENDIX 12. MOOD STABILIZERS

Name (generic/brand)	Dose Range (or blood level, when applicable)	Side Effects*	Monitoring**
Carbamazepine/ Tegretol and others	<ul style="list-style-type: none"> ♦ Start at 150 mg per day and titrate slowly ♦ 300–1600 mg/day (blood levels 4–12 micrograms/ml, therapeutic for seizure disorders) ♦ May be given once or twice daily 	<ul style="list-style-type: none"> ♦ Many drug interactions ♦ ↑ LFTs, hepatitis ♦ ↓ WBC ♦ ↓ Platelets ♦ Rash, S-J syndrome ♦ Sedation ♦ Lethargy ♦ Nausea ♦ Dizziness ♦ Headache ♦ Insomnia ♦ Agitation ♦ Cognitive changes ♦ Tremor ♦ Ataxia ♦ Paresthesias ♦ Vasculitis ♦ Hyponatremia ♦ Hypersensitivity reaction 	<ul style="list-style-type: none"> ♦ EKG prior to initiation in pts.>45 or with risk factors ♦ CBC with diff at initiation & q 2 weeks during titration, then q 6 months (or if sign of infection) ♦ Electrolytes at initiation & then q 6 months ♦ LFTs at initiation & q 2 weeks during titration, then q 6 months ♦ Blood level, only necessary if no response or to monitor compliance
Oxcarbazepine/ Trileptal	<ul style="list-style-type: none"> ♦ Start at 300 mg BID & titrate slowly. Max dose is 1200 mg/day. 	<ul style="list-style-type: none"> ♦ Generally better tolerated than carbamazepine, but same side effects ♦ ↑ Risk of falls 	<ul style="list-style-type: none"> ♦ Same as carbamazepine, except no need to measure blood levels
Valproate/ Depakene and others	<ul style="list-style-type: none"> ♦ Start 250 mg BID and titrate to therapeutic blood level of 50–115 micrograms/ml ♦ Usual dose range is 750–3000 mg/day ♦ May be given once daily 	<ul style="list-style-type: none"> ♦ Some drug interactions ♦ Weight gain ♦ ↑ LFTs, hepatitis ♦ ↓ WBC ♦ ↓ Platelets ♦ Rash, S-J syndrome ♦ Sedation ♦ Lethargy ♦ Nausea ♦ HA ♦ Cognitive changes ♦ Tremor ♦ Ataxia ♦ Vasculitis 	<ul style="list-style-type: none"> ♦ CBC with diff at initiation & q 2 weeks during titration, then q 6 months (or if sign of infection) ♦ LFTs at initiation & q 2 weeks during titration, then q 6 months ♦ Blood level, weekly during titration, then q 6 months

(Appendix 12. Mood Stabilizer, page 1 of 2)

Name (generic/brand)	Dose Range (or blood level, when applicable)	Side Effects*	Monitoring**
Lamotrigine/ Lamictal	<ul style="list-style-type: none"> ♦ Start 25 mg/day & titrate by no more than 25 mg per week ♦ Target dose is 100–500 mg/day in once daily dose 	<ul style="list-style-type: none"> ♦ Rash, S-J reaction ♦ Significant drug interaction with Valproate ♦ Sedation ♦ Lethargy ♦ Nausea ♦ HA ♦ Cognitive changes ♦ Tremor ♦ Aataxia ♦ WBC ♦ ↓ Platelets ♦ ↑ LFTs, hepatitis—in pts. on Valproate 	None necessary
Topiramate/ Topamax	<ul style="list-style-type: none"> ♦ Start 50 mg per day & titrate VERY slowly ♦ Target dose is 100–200 mg/day 	<ul style="list-style-type: none"> ♦ Nephrolithiasis ♦ Nausea ♦ Weight loss ♦ Cognitive changes ♦ Dizziness ♦ Headache ♦ Minimal drug interactions 	None necessary
Lithium	<ul style="list-style-type: none"> ♦ Start 150–300 mg per day & titrate for 1–2 weeks to therapeutic blood level of 0.5–1.2 mmol/L 	<ul style="list-style-type: none"> ♦ Nephrogenic diabetes insipidus ♦ Nausea ♦ Loose stools ♦ Weight gain ♦ Tremor ♦ Cognitive changes ♦ Sedation ♦ Acne/folliculitis 	<p><i>Prior to initiation:</i></p> <ul style="list-style-type: none"> ♦ CBC & diff ♦ EKG >40 or risk factors ♦ Chem group ♦ sTSH <p><i>Monitoring:</i></p> <ul style="list-style-type: none"> ♦ Li level weekly until stable, then q 3 months ♦ sTSH annually ♦ CBC, diff, Chem group annually ♦ Monitor for drug interactions affecting blood levels
<p>* For complete list of side effects, consult PDR or other source of information on medications. ** More frequent monitoring of certain parameters may be appropriate in some cases, e. g., more frequent measurement of LFTs in patients with hepatitis C infection.</p>			
<p><i>(Appendix 12. Mood Stabilizer, page 2 of 2)</i></p>			

APPENDIX 13. QUICK REFERENCE GUIDE: TREATMENT FOR SCHIZOPHRENIC SPECTRUM DISORDERS AND MOOD DISORDER WITH PSYCHOSIS

Established diagnosis of schizophrenia or schizophrenic spectrum (brief psychotic disorder, schizophreniform):

1. Start on antipsychotic medication per treatment algorithm (see [Appendix 1](#)).
2. If the patient has co-occurring depression, he/she may be given an anti-depressant. SSRIs or SNRIs are first-line treatment, or current antidepressant dose could be increased, as tolerated.
3. If the patient has co-occurring anxiety, treat with an anxiolytic such as an SSRI or SNRI, or treat with buspirone, which is only indicated for generalized anxiety disorder and theoretically is not given for depression. Alternatively, increase the dose of the patient's current anxiolytic medication.

Schizoaffective disorder:

1. For psychotic symptoms, start the patient on antipsychotic medication per treatment algorithm (see [Appendix 1](#)).
2. You may start an antidepressant if the patient has symptoms of major depression, using an SSRI/SNRI as first-line treatment. *Use antidepressants with caution*, due to the risk of inducing manic episodes in patients with schizoaffective disorder, bipolar type.
3. If the patient has symptoms of mania, start the patient on mood stabilizers.
4. The patient's psychotic symptoms will require ongoing antipsychotic use.

Bipolar disorder with psychosis (usually in manic or mixed phase):

1. Start the patient on antipsychotic medication per treatment algorithm (see [Appendix 1](#)). See [Appendix 14](#) for FDA-indicated medications for mania or mixed episode.
2. Once the patient's acute psychosis stabilizes with an antipsychotic medication, continue the medication for maintenance. You may also switch to a mood stabilizer for maintenance if applicable (for example, if the patient is on an antipsychotic, but prefers to be on a mood stabilizer). See [Appendix 14](#) for FDA-indicated medications for bipolar disorder maintenance.

Major depressive disorder with psychotic features:

1. Start the patient on antipsychotic medication per treatment algorithm (see [Appendix 1](#)).
2. If the patient is not already taking an antidepressant, start him/her on an antidepressant, preferably an SSRI/SNRI. If the patient is already taking an antidepressant, you may adjust or increase its dose as tolerated.
3. Once psychosis resolves, you may gradually discontinue the antipsychotic medication.
4. The antidepressant should be continued as a first-line medication for major depression. Psychotic outbreak is usually prevented when depression is in remission.

(Appendix 13, Quick Reference Guide, page 1 of 2)

Emergent psychotic agitation:

1. Give the patient a short-acting PO/IM FGA (e.g., haloperidal 5 mg):
 - a. With or without PO/IM benzodiazepine (e.g., lorazepam 2 mg)
 - b. With or without PO/IM benztropine (e.g., benztropine 1 mg)
2. In BOP, no court order needed if an antipsychotic is used for an emergency dose. For continued use, the patient would need to sign an Informed Consent form, or a court order would need to be obtained.

Treatment of side effects from antipsychotic medications

→ See [Appendix 10](#) and [Appendix 11](#) for more specific information.

1. **Extrapyramidal Symptoms (EPS):** Give anticholinergic medication, or decrease dose of the antipsychotic.
2. **Akathisia:** Give beta-blocker (preferred), decrease dose of antipsychotic, or give benzodiazepine.
3. **Neuroleptic Malignant Syndrome (NMS):** This is an emergent condition requiring inpatient hospitalization (see [Appendix 8](#) for more information).
4. **Tardive Dyskinesia:**

Symptoms may include involuntary movements of the extremities (less common) or orofacial dyskinesia such as:

- ▶ Rhythmic movements of the lips (puckering, smacking), tongue (undulations, rolling motions, protrusions, “fly catching” movements), or face (involuntary blinking, grimacing)
- ▶ Tongue fasciculations and periorbital movements

Treatment: The patient’s medication may be changed to an SGA—in some cases, to Clozapine (but only in an MRC).

(Appendix 13, Quick Reference Guide, page 2 of 2)

APPENDIX 14. FDA-INDICATED MEDICATIONS

FDA-Indicated Medications for Mania or Mixed Episodes of Bipolar Disorder
Mood Stabilizers
<ul style="list-style-type: none">• Carbamazepine ER• Lithium (for mania only, not mixed)• Valproic acid
SGAs
<ul style="list-style-type: none">• Aripiprazole (BOP non-formulary)• Asenapine (BOP non-formulary)• Cariprazine (BOP non-formulary)• Olanzapine• Quetiapine (BOP non-formulary)• Risperidone• Ziprasidone
FDA-Indicated Maintenance Medications for Bipolar Disorder
<ul style="list-style-type: none">• Aripiprazole• Lamotrigine• Lithium• Olanzapine• Quetiapine (BOP non-formulary)• Risperidone

APPENDIX 15. ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)*

Patient Identification:		
Evaluation Date: ___/___/___ <input type="checkbox"/> Baseline <input type="checkbox"/> 6 Months <input type="checkbox"/> Annual <input type="checkbox"/> Other: _____		
Instructions: Complete <i>AIMS Examination Procedure</i> (next page) before making ratings. For movement ratings, rate highest severity observed.		
Rating Codes: 1 = None, 2 = Minimal, may be extreme normal, 3 = Mild, 4 = Moderate, 5 = Severe		Ratings* (circle one)
Facial & Oral Movements	1. Muscles of Facial Expression: e.g., movement of forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing.	1 2 3 4 5
	2. Lips and Perioral Area: e.g., puckering, pouting, and smacking.	1 2 3 4 5
	3. Jaw: e.g., biting, clenching, chewing, mouth opening, lateral movement.	1 2 3 4 5
	4. Tongue: Rate only the <i>increase</i> in movement both in and out of mouth, NOT the inability to sustain movement.	1 2 3 4 5
Extremity Movements	5. Upper (arms, wrists, hands, fingers): Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous), athetoid movements (i.e., slow, irregular, complex, serpentine). Do NOT include tremor (i.e., repetitive, regular, rhythmic).	1 2 3 4 5
	6. Lower (legs, knees, ankles, toes): e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot.	1 2 3 4 5
Trunk Movements	7. Neck, shoulders, hips: e.g., rocking, twisting, squirming, pelvic gyrations.	1 2 3 4 5
Global Judgments	8. Severity of abnormal movements	1 2 3 4 5
	9. Incapacitation due to abnormal movements	1 2 3 4 5
	10. Patient's awareness of abnormal movements: Rate only the patient's report.	1 = No awareness 2 = Awareness, no distress 3 = Aware, mild distress 4 = Aware, moderate distress 5 = Aware, severe distress
Dental Status	11. Current problems with teeth and/or dentures?	1 = Yes 2 = No
	12. Does patient wear dentures?	1 = Yes 2 = No
* A positive examination is a score of 2 in two or more movements, or a score of 3 or 4 in a single movement.		
Rater's Signature:		Doctor's Signature/Date:

AIMS Examination Procedure*

1. Ask the patient to remove shoes and socks.
2. Ask the patient whether there is anything in his/her mouth (e.g., gum, etc.) and, if so, to remove the item.
3. Ask the patient about the current condition of his/her teeth. Ask the patient if he/she wears dentures. Ask whether the patient's teeth or dentures bother him/her now.
4. Ask the patient whether he/she notices any movements in the mouth, face, hands, or feet. If yes, ask the patient to describe the movements. Ask to what extent the movements currently bother him/her or interfere with his/her activities.
5. Have the patient sit in a chair with hands on knees, legs slightly apart, and feet flat on the floor. Look at the patient's entire body for movements while in this position.
6. Ask the patient to sit with hands hanging unsupported — if male, between the legs; if female and wearing a dress, hanging over the knees. Observe the hands and other body areas.
7. Ask the patient to open the mouth. Observe the tongue at rest within the mouth. Do this twice.
8. Ask the patient to protrude the tongue. Observe abnormalities of tongue movement. Do this twice.
9. Ask the patient to tap the thumb with each finger on that hand, as rapidly as possible for 10–15 seconds. Do this separately with each hand. Observe facial and leg movements.
10. Flex and extend the patient's arms, one arm at a time. Note any rigidity.
11. Ask the patient to stand up. Observe in profile. Observe all body areas again, including the hips.
12. Ask the patient to extend both arms at the same time — outstretched in front, with palms down. Observe trunk, legs, and mouth.
13. Have the patient walk a few paces, turn, and walk back to the chair. Observe hands and gait. Do this twice.

* **Scale and examination procedure are adapted from:**

Rush JA Jr. *Handbook of Psychiatric Measures*. American Psychiatric Association; 2000:166–168.