Management of Bipolar Disorders in Prison Populations

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1. PURPOSE

The Federal Bureau of Prisons (BOP) Clinical Guidance for the *Management of Bipolar Disorder* provides recommendations for the management of bipolar disorder in federal inmates.

2. INTRODUCTION

Bipolar disorder is a mood disorder that is characterized by episodes of mania, hypomania, and major depression. Bipolar disorder is categorized into ***bipolar I*** disorder and ***bipolar II*** disorder. Patients with bipolar I disorder experience manic episodes, and nearly always experience hypomanic and major depressive episodes. Patients with bipolar II disorder experience at least one hypomanic episode, at least one major depressive episode, and no manic episodes.

Bipolar disorder is commonly misdiagnosed, especially in patients presenting with symptoms of depression. Recognition of bipolar disorder is important, as it is associated with substantial morbidity and mortality if left untreated, and treatment differs from that of unipolar depression. Bipolar disorder should always be considered as part of the differential diagnosis for depression or anxiety. Patients presenting with depressive symptoms may be erroneously treated for major depressive disorder, which likely will not provide the greatest benefit to a patient with bipolar disorder.

OCCURRENCE

The estimated lifetime prevalence of bipolar I disorder among adults is approximately 1%, and for bipolar II disorder, approximately 1.1%.

- The mean ages of onset for bipolar I disorder and bipolar II disorder are 18 and 20 years, respectively.
- The ratio of men to women who develop bipolar I disorder is approximately 1:1, whereas bipolar II disorder is more common in women.
- Bipolar disorder is a recurrent illness, and 90% of patients will have more than one episode in their lifetime, lasting from a few weeks to several months.
- Lifetime suicide attempts for bipolar I disorder and bipolar II disorder are 36.3% and 32.4%, respectively. A large cohort study found that the absolute risk of suicide among men was highest with bipolar disorder, compared to any other psychiatric condition. In women, it was second highest, below schizophrenia.

RISK FACTORS

There are several risk factors for the development of bipolar disorder including a family history of mood disorders, perinatal stress, head trauma, environmental factors (including circadian rhythm disorders), and psychosocial or physical stressors.

Most patients with bipolar disorder can achieve stabilization of their mood episodes and related symptoms with proper, continuous treatment. Since bipolar disorder is a recurrent illness, long-term maintenance treatment is strongly recommended and almost always indicated. Treatment should include a strategy that combines medication and psychosocial treatment to manage the disorder over time.

THIS CLINICAL 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 the case management of comorbid medical and psychiatric conditions.
- The guidance in this document 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.
- The guidance in this document is 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 due to an increased prevalence of drug-drug interactions, medication side effects, lifestyle issues, and assaultive or suicidal behaviors. These potential complexities are not covered in this guidance.

3. SCREENING AND DIAGNOSIS

SCREENING QUESTIONNAIRES

★ ***Screening for bipolar disorder can be difficult. The screening questionnaires discussed below should NOT be used as diagnostic tools.*** *Patients who screen positive on these questionnaires should be interviewed to confirm a positive diagnosis.*

MANIC SYMPTOMS

Screening for manic symptoms can be effectively accomplished by utilizing the Mood Disorder Questionnaire.* This questionnaire can help clinicians in their assessments and can be found online at http://www.sadag.org/images/pdf/mdq.pdf.

* Hirschfeld RM, Williams JB, Spitzer RL, et al. Development and validation of a screening instrument for bipolar spectrum disorder: The Mood Disorder Questionnaire. *Am J Psychiatry*. 2000;157:1873.

Patients are considered to screen "positive" for manic symptoms if their answers on the Mood Disorder Questionnaire are as follows:

- **Section 1: "YES" to at least 7 of the 13 items, *AND***
- **Section 2: "YES," *AND***
- **Section 3: "MODERATE PROBLEM" *OR* "SEVERE PROBLEM"**

DEPRESSIVE SYMPTOMS

Screening for depressive symptoms can be effectively accomplished by utilizing the questionnaire in ***TABLE 1*** below. Positive findings for two or more core diagnostic symptoms are particularly sensitive for screening for depression.

TABLE 1. SCREENING QUESTIONS FOR DEPRESSION

DIAGNOSTIC SYMPTOMS	QUESTIONS*	
1. Sleep disturbance	"Do you have trouble falling asleep? Are you sleeping too much or waking up too early?"	Y/N
2. Low self-esteem	"Do you feel that you are a bad person, or that you have failed or have let people down?"	Y/N
3. Decreased appetite	"Have you lost your appetite or found that you are not interested in eating?"	Y/N
4. Anhedonia *(inability to experience pleasure)*	"Does it seem that you have lost interest in most things, or that you no longer take pleasure in activities that you normally find pleasurable?"	Y/N
* *Patients with positive responses to any two of the four screening questions, or who otherwise confirm other significant diagnostic criteria for depression during the screening process, should be further evaluated.*		

DSM-5 DIAGNOSTIC CRITERIA FOR MANIC EPISODE

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) is now copyrighted. Readers are referred to the actual DSM-5 text for specific diagnostic criteria.

DSM-5 DIAGNOSTIC CRITERIA FOR HYPOMANIC EPISODE

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) is now copyrighted. Readers are referred to the actual DSM-5 text for specific diagnostic criteria.

DSM-5 DIAGNOSTIC CRITERIA FOR BIPOLAR MAJOR DEPRESSION

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) is now copyrighted. Readers are referred to the actual DSM-5 text for specific diagnostic criteria.

PHYSICAL EXAMINATION AND LABORATORY ASSESSMENT

A complete physical examination is recommended to confirm a bipolar diagnosis and to rule out any underlying comorbidities, such as hypothyroidism.

The following baseline laboratory studies are recommended for all patients:

- Complete blood count and differential
- Comprehensive chemistry panel
- TSH to rule out hypothyroidism
- Urine toxicology to screen for substances of abuse

Additional laboratory testing is patient-specific and based on potential comorbid medical conditions, as well as any other concerns.

4. ASSESSMENT

INITIAL ASSESSMENT

An initial clinical status assessment is recommended for all patients diagnosed with bipolar disorder to **(1)** develop a specialized, patient-specific treatment plan, while **(2)** continuing optimal care for the patient's other medical and psychiatric conditions. See **TABLE 2** below.

TABLE 2. INITIAL CLINICAL STATUS ASSESSMENT

AREAS TO BE ASSESSED	ISSUES
Medical comorbidities	Comorbid medical problems can contribute to mood dysregulation.
Psychiatric comorbidities	Assess for and treat all psychiatric comorbid conditions.
Psychosocial stressors	Current stressors can contribute to mood problems and adherence to treatment.
Current medications	Assess the frequency and dosages of the patient's prescription and over-the-counter medications.
Past medications	Check for historical responses/failures to mood stabilizers and antipsychotic medications. Note reasons for discontinuation and side effects experienced.
Medication compliance	Evaluate current and past medication compliance.
Suicide risk	Evaluate risk factors for suicide, including (but not limited to) family history, previous attempts, and co-occurring substance use.
Substance abuse	Substance abuse can contribute to or precipitate a relapse, and can be a reason for the patient's lack of response to medication
Adapted from: *VA/DoD Clinical Practice Guideline for Management of Bipolar Disorder in Adults* (see References).	

FOLLOW-UP ASSESSMENTS

Follow-up assessments of bipolar patients should include a reassessing for most of the areas listed in ***TABLE 3***. In patients who reach full remission, assessment of symptoms should be continued periodically to monitor for relapse or recurrence.

TABLE 3. FOLLOW-UP ASSESSMENT

AREAS TO BE ASSESSED	
• Development of/changes in depressive symptoms • Development of/changes in symptoms of mania/hypomania • Neurovegetative symptoms • Psychotic symptoms • Suicidal ideation or homicidal ideation	• Substance use • Adverse effects/monitoring of medications • Adherence • Medical stability (such as blood pressure) • Significant changes in psychosocial circumstances
Adapted from: *VA/DoD Clinical Practice Guideline for Management of Bipolar Disorder in Adults* (see References).	

STANDARDIZED RATING SCALES

A standardized rating scale should be used to obtain necessary information about symptom severity and effect on daily functioning. Clinician preference determines which scale is used, as none of the scales have demonstrated superiority over another. The same scale used to assess severity should also be used to monitor the patient's response to treatment. Standardized rating scales for evaluating mania and depression are listed in ***TABLE 4*** and ***TABLE 5*** below.

TABLE 4. STANDARDIZED RATING SCALES FOR THE EVALUATION OF MANIA

SCALE NAME	PURPOSE	CLINICIAN-RATED OR SELF-RATED?	VALUES & INTERPRETATION
Young Mania Rating Scale (YMRS)	To assess severity of abnormality.	Clinician-rated	11 Items, with a maximum score of 60: ≥ 25 = severe mania 19–24 = probable mania 12–18 = hypomania < 11 = euthymia
Manic-State Rating Scale (MSRS)	To assess severity of manic symptoms. Useful for patients who are difficult to interview.	Clinician-rated	26 items, each with: 0–5 frequency score 1–5 intensity score
Internal State Scale (ISS)	To assess both manic and depressed states.	Self-rated	15 items, each on a 10-point scale: 0 = not at all, rarely 9 = very much so, most of the time

TABLE 5. STANDARDIZED RATING SCALES FOR THE EVALUATION OF DEPRESSION

SCALE NAME	PURPOSE	CLINICIAN-RATED OR SELF-RATED?	VALUES & INTERPRETATION
Hamilton Rating Scale for Depression (HAM-D)	To assess severity of depression.	Clinician-rated	Standard scale has 17 items: 0–7 = normal 8–13 = mild depression 14–18 = moderate depression 19–22 = severe depression ≥ 23 = very severe depression Multiple versions of the scale exist, with number of items varying from 7–29.
Montgomery-Asberg Depression Rating Scale (MADRS)	For diagnosis and to assess changes in symptoms.	Clinician-rated	10 items, with total scores as follows: 0–6 = symptoms absent 7–19 = mild depression 20–34 = moderate depression 35–60 = severe depression
Inventory of Depressive Symptomatology (IDS)	To assess severity of depression.	Clinician-rated	30 items, with total scores as follows: ≤ 12 = normal 13–22 = mildly ill 23–30 = moderately ill 31–38 = moderately-to-severely ill
Zung Self-Rating Depression Scale	Screening tool and to assess symptoms.	Self-rated	20 items, with total scores as follows: < 50 = normal 50–59 = mild depression 60–69 = moderate-to-severe depression ≥ 70 = severe depression

Table 5 continues below.

SCALE NAME	PURPOSE	CLINICIAN-RATED OR SELF-RATED?	VALUES & INTERPRETATION
Table 5 continued from previous page.			
Beck Depression Inventory (BDI)	For diagnosis and to assess behavioral manifestations of depression.	Self-rated	21 items, with total scores as follows: 0–9 = minimal 10–16 = mild 17–29 = moderate 30–63 = severe
Quick Inventory of Depressive Symptomatology – Self Report (QIDS-SR)	To assess severity of depression.	Self-rated	16-item version of the IDS (above): 0–5 = normal 6–10 = mild 11–15 = moderate 16–20 = severe ≥ 21 = very severe
Patient Health Questionnaire 9 (PHQ9)	For diagnosis and to assess response to treatment.	Self-rated	9 items: ◆ Drop ≥ 5 points from baseline = adequate response to treatment ◆ Drop 2–4 points from baseline = probably inadequate response to treatment ◆ Drop or 1 point, no change, or increase = inadequate response to treatment

RISK ASSESSMENT FOR SUICIDE OR VIOLENCE TOWARDS OTHERS

The mortality rate of bipolar patients is two to three times higher than in the general population. Suicide attempts occur in up to 50% of patients with bipolar disorder. Therefore, it is important to assess each patient's risk of suicide. To evaluate suicide risk, the clinician should specifically ask the patient the questions listed in ***TABLE 6***.

TABLE 6. SCREENING QUESTIONS FOR ASSESSING RISK OF SUICIDE

1	**"Do you ever feel so bad that you wish you were dead?"** Regardless of the answer, ask the next question:
2	**"Do you ever think of hurting yourself or taking your own life?"** If the answer is yes, follow-up by asking:
3	**"Do you currently have a plan?"** If the answer is yes, then ask:
4	**"What is your plan?"**
➔	***If suicidal ideation is present, as indicated by a "yes" answer to one or more of these questions, please contact Psychology Services immediately and keep the patient under constant visual surveillance.***

A complete risk assessment includes covering all factors listed in ***TABLE 7*** below. These factors should be reviewed and documented for all patients with bipolar disorder until their symptoms have completely abated, as some of these patients are more likely to act on suicidal thoughts during the early phase of recovery than during the acute phase of the disease.

TABLE 7. RISK FACTORS FOR SUICIDE OR VIOLENCE TOWARDS OTHERS

The presence of the following factors may indicate an increased risk of suicide or violence towards others. These factors should be reviewed for all patients with bipolar disorder, and symptoms monitored until they have COMPLETELY ABATED.

• Past history of acts of harm towards self or others
• Presence of thoughts of harm towards self or others
• Presence of a plan to harm self or others, including:
  ▸ Lethality of the plan
  ▸ Presence of a means to carry out the plan
  ▸ Presence of intent to carry out the plan
• Family history of suicide or violence
• Presence of psychotic symptoms
• History of substance abuse
• Lack of support systems
• Recent severe stressor or loss
• Presence of comorbid personality disorder or anxiety disorder
• Poor institutional adjustment (including prolonged SHU placement, PC status, and poor cooperation and compliance with treatment)

5. TREATMENT CHALLENGES

Treating bipolar patients with comorbid 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 affect 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 an under-utilized intervention for non-adherence 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.
  - ➔ *See the BOP Program Statement on Psychiatric Services, as well as Appendix 1, Informed Consent, for information on obtaining and documenting informed consent.*

6. TREATMENT REGIMENS

Treatment of bipolar patients may differ depending on whether the individual is experiencing an ***acute manic episode*** or a ***depressive episode***, or needs ***maintenance treatment***—all of which are discussed below. If appropriate, the medication employed for the acute manic episode is also utilized in maintenance treatment.

ACUTE MANIA, HYPOMANIA, OR MIXED EPISODE

Despite clinical differences between manic and hypomanic episodes, they are treated with the same medications. The treatment goal for both ***acute mania*** and ***hypomania*** is remission. ***Remission*** is defined as resolution of the mood symptoms or improvement to the point that only one or two symptoms of mild intensity persist. If a patient is unable to achieve remission, the goal of treatment becomes response. ***Response*** is defined as stabilization of the patient's safety and substantial improvement in the number, intensity, and frequency of mood symptoms.

- **Pharmacotherapy for mania and mixed episode should start with initiation or optimization of a medication that has been shown to be the most effective in treating manic episodes while minimizing potential risks.** If applicable, agent(s) that have been effective in treating the patient's previous mania or mixed episodes should be utilized. Medications for mania and mixed episodes will often take 5–10 days before they begin to show an effect. Patients who have had an acute manic episode should be treated for at least 6 months after the initial episode is controlled, and patients should be encouraged to continue on life-long course of prophylactic medication.
  - ➔ *See the discussion of Maintenance Therapy later in this Section.*
- **Symptoms of mania should be reassessed every 1–2 weeks for 6 weeks.** A large percentage of patients will not respond to a single medication for mania or mixed episode—even when the

medication is taken regularly at proper dosages, and drug levels are within the therapeutic range. For these patients, the clinician should try different strategies in order to obtain remission. Possible strategies include switching to a different monotherapy agent or combining agents. Medications should be adjusted if there is no response within 2–4 weeks. After any change in dose or medication, the patient should be monitored for positive and adverse effects.

- **Drug classes commonly used to treat patients with acute mania, hypomania, or mixed episode** include mood stabilizers/antimanic agents, second-generation antipsychotics, and first generation antipsychotics. Benzodiazepines can be used for immediate relief of symptoms.
  ➔ *See **TABLE 8** below for recommended treatments.*

SEVERE MANIA

Patients with severe mania will often have psychotic symptoms such as delusions or hallucinations. They are at risk of harming themselves or others and may have greater functional impairment. Patients with severe mania, with or without psychotic features, should be started on a combination of an antipsychotic and another antimanic agent.

➔ *See combination therapies in **TABLE 8** below.*

TABLE 8. ACUTE MANIA, HYPOMANIA, OR MIXED EPISODE TREATMENT RECOMMENDATIONS

RECOMMENDED TREATMENT	MEDICATIONS
First-line monotherapy	Lithium, divalproex, olanzapine, risperidone, quetiapine, aripiprazole, *OR* ziprasidone
First-line adjunctive therapy with lithium or divalproex	Risperidone, olanzapine, aripiprazole, *OR* quetiapine
Second-line monotherapy	Carbamazepine *OR* haloperidol (or other first-generation antipsychotic)
Second-line combination therapy	Lithium + divalproex
Third-line monotherapy	Asenapine, clozapine, tamoxifen[1], *OR* ECT[2]
Third-line combination therapy	Adjunctive tamoxifen[1]
NOT RECOMMENDED	Gabapentin, topiramate, lamotrigine, tiagabine, risperidone + carbamazepine, olanzapine + carbamazepine, adjunctive ziprasidone

ECT = electroconvulsive therapy
[1] Has only been studied as adjunct therapy to lithium
[2] Reserved for manic patients who to not respond to 4–6 medication trials

ACUTE DEPRESSIVE EPISODE

It is important to obtain a careful history when diagnosing patients with ***bipolar major depression***; it is commonly misdiagnosed as ***unipolar depression***, and the two conditions require different treatment. The goals for treatment of bipolar depression depend on the patient's phase:

ACUTE PHASE: Lasts days to weeks; treatment focuses on managing the patient's safety and presenting symptoms.

CONTINUATION PHASE: Lasts weeks to months; treatment focuses on remission and restoration of functioning.

MAINTENANCE PHASE: Lasts months to years; treatment focuses on preventing recurrence of a new mood episode.

Medication for bipolar depression:

- Patients with a bipolar depressive episode should be treated with medications that have demonstrated efficacy while minimizing the risk of inducing a manic, hypomanic, or mixed manic episode. Drug classes commonly used to treat bipolar patients with acute depressive episodes include antidepressants, mood stabilizers/antimanic agents, and second-generation antipsychotics. For patients with bipolar depression with psychotic features, an antipsychotic medication should be initiated.
  ➔ *See **TABLE 9** below for recommended treatments.*
- **Continuation phase:** Medications for depression may take up to 6 weeks to demonstrate initial effectiveness, and up to 8–12 weeks to demonstrate full efficacy.
- **Maintenance phase:** After remission of the depressive episode is achieved, it is appropriate to consider withdrawing antidepressant treatment after 4–6 months. Any discontinuation of medication used to treat bipolar depression should be tapered, and the patient should be monitored for Antidepressant Discontinuation Syndrome and the emergence of depressive symptoms.
  ➔ *See discussion of Antidepressant Discontinuation Syndrome under antidepressants in Section 7.*

TABLE 9. ACUTE DEPRESSIVE EPISODE TREATMENT RECOMMENDATIONS

RECOMMENDED TREATMENT	MEDICATIONS
First-line monotherapy	Lithium, Lamotrigine, *OR* Quetiapine
First-line combination therapy	Olanzapine + SSRI[1], Lithium + Divalproex, *OR* Lithium or Divalproex + SSRI[1]
Second-line monotherapy	Divalproex *OR* Lurasidone
Second-line combination therapy	Adjunctive Modafinil, Lithium or Divalproex + Lamotrigine, *OR* Lithium or Divalproex + Quetiapine or Olanzapine
Third-line monotherapy	Olanzapine, Carbamazepine[2], *OR* ECT
Third-line combination therapy	Lithium + Pramipexole *OR* Quetiapine + Lamotrigine
NOT RECOMMENDED	Gabapentin, Antidepressant monotherapy, Ziprasidone, Aripiprazole, adjunctive Ziprasidone

ECT = electroconvulsive therapy [1] Excluding paroxetine [2] Limited data

MAINTENANCE THERAPY

The goals for maintenance therapy are to:

- Reduce residual symptoms
- Delay and prevent recurrence of new mood episodes
- Reduce the risk of suicide
- Improve psychosocial functioning

More than half of manic patients experience recurrence of a mood episode an average of about eight months after the previous event. Therefore, it is typically necessary for the patient to stay on maintenance treatment to prevent or delay another mood episode. The same regimen that was used successfully to treat the acute episode is typically selected for maintenance treatment. In addition, it is suggested to combine pharmacotherapy with psychotherapy—cognitive behavioral therapy (CBT) or family therapy—to improve adherence.

Patients who have had more than one manic episode should be encouraged to continue on life-long prophylactic treatment. Patients should be assessed for adverse effects and tolerability within two weeks of any changes in treatment strategy.

➔ *See **TABLE 10** below for recommended maintenance treatments.*

If symptoms of mania, hypomania, or depression reoccur, but the patient is not believed to have relapsed:

- Assess compliance and check blood concentrations of medications to assure they are in the therapeutic range (if applicable).
- Assess for other factors that may be causing the symptoms such as medical conditions or substance use.
- Consider adding a psychotherapeutic intervention or augmenting the current regimen with additional medication,
- Consider switching to an alternative maintenance treatment.

TABLE 10. MAINTENANCE TREATMENT RECOMMENDATIONS

RECOMMENDED TREATMENT	MEDICATIONS
First-line monotherapy	Lithium, Lamotrigine[1], Divalproex, *OR* Quetiapine
First-line adjunctive therapy with lithium or divalproex	Quetiapine, Aripiprazole[2], *OR* Ziprasidone[2]
Second-line monotherapy	Olanzapine, Risperidone LAI[2], *OR* Aripiprazole[2]
Second-line combination therapy	Lithium + Divalproex, Lithium + Carbamazepine, Lithium or Divalproex + Olanzapine or Risperidone LAI, *OR* Lithium + Lamotrigine
Third-line monotherapy	Carbamazepine, Asenapine, *OR* Paliperidone ER
Third-line adjunctive therapy	Clozapine, Topiramate[3], *OR* ECT
NOT RECOMMENDED	Antidepressant monotherapy, Gabapentin, , Benzodiazepine monotherapy
LAI = long-acting injection ECT = electroconvulsive therapy	[1] Limited data in preventing mania [2] Primarily for preventing mania [3] Limited data

7. STEPWISE APPROACH IN SELECTING TREATMENT REGIMENS

The following factors should be considered when selecting medications:

- Previous response to medication by the patient or a blood relative
- Side effect profile of the medication
- Potential drug-drug interactions
- Comorbid medical conditions of the patient
- Patient's preference
- Frequency of administration and medication formulation
- Formulary status

In selecting a drug treatment regimen for patients with bipolar disorder, clinicians should take into consideration the patient's other psychiatric and medical conditions. In particular, clinicians should be aware of patients with diabetes or obesity, and consider the risk and benefit of using medications that are weight neutral or less associated with weight gain.

➔ *See **TABLES 11** and **12** below for a stepwise approach to treating manic and depressive episodes in bipolar patients.*

TABLE 11. STEPWISE APPROACH TO MEDICAL TREATMENT OF AN ACUTE MANIC/HYPOMANIC EPISODE

1	Patient is diagnosed with acute mania/hypomania.
2	Initiate first-line treatment.★ If patient presents with severe mania, initiate first-line treatment with combination therapy.★
3	If no response, maximize the dose and assess compliance.
4	If no response, consider switching from lithium to divalproex (or vice versa, if applicable).
5	If no response, consider switching to a second generation antipsychotic, or adding a second generation antipsychotic (if applicable),
6	If no response, initiate second-line treatment.★
7	If no response, initiate third-line treatment.★
8	If no response, consider ECT.
★ *See **TABLE 8** for recommended treatments.*	

TABLE 12. STEPWISE APPROACH TO MEDICAL TREATMENT OF AN ACUTE DEPRESSIVE EPISODE

1	Patient is diagnosed with bipolar major depression.
2	Initiate first-line treatment. ★★
3	If no response, maximize the dose and assess compliance. If utilizing an SSRI, allow adequate time for medication to be effective (at least 4 weeks).
4	If no response, initiate second-line treatment. ★★
5	If no response, initiate third-line treatment. ★★
6	If no response, consider ECT.
★★ *See **TABLE 9** for recommended treatments.*	

8. MEDICATIONS USED IN THE TREATMENT OF BIPOLAR DISORDER

MOOD STABILIZERS

Mood stabilizers approved for bipolar disorder include lithium, and the anticonvulsants valproate/divalproex, carbamazepine, and lamotrigine.

➔ *See Appendix 2 for information on mood stabilizer dosing and monitoring.*

➔ *See Appendix 3 for information on side effects associated with mood stabilizers.*

LITHIUM

Lithium is commonly the first-line drug for treating bipolar disorder, whether for acute treatment or maintenance therapy. Having been in use longer than other medications for bipolar disorder, lithium has generated a rich history of efficacy studies. Lithium has also been shown to decrease the number of suicides in patients with bipolar disorder.

- The plasma concentration at which lithium is known to be the most effective is 0.8–1.2 mEq/L for acute mania, and 0.6–1.2 mEq/L for maintenance. Levels should be drawn 4–5 days after initiation or a dose increase; they should be drawn in the morning, 10–12 hours after the last dose. Thereafter, weekly monitoring is required until the patient is stable, which usually takes 4–5 weeks. Lithium may require 6–10 days before an initial response is seen in a manic episode, while its effect on depression can take up to one month or more.
- Lithium can be taken with or without food; patients should be instructed to take the medication with food if it causes an upset stomach.
- Use caution during pregnancy, and do not use in patients who are breast-feeding.
  - ➔ *See the discussion of treatment during pregnancy in Section 11.*

Lithium serum levels and toxicity can be affected by diet and by other medications. It is important to educate patients on the signs of toxicity and potential drug interactions.

➔ *See Appendix 4a, which lists interactions that decrease or increase lithium levels, or which increase toxicity without affecting levels.*

- Patients must maintain a consistent salt intake. Changes in salt intake can change lithium drug levels in the body. Lithium competes with sodium for reabsorption as they are both positive cations. When sodium levels are low, lithium retention is high, and vice versa. When patients dramatically decrease their salt intake, lithium levels in the body will rise and potentially become toxic. When patients increase their salt intake, lithium levels will decrease and potentially become sub-therapeutic.
- Excessive caffeine intake should be avoided. Caffeine can increase the amount of lithium that is excreted from the body through the kidneys.
- Patients should avoid becoming dehydrated; they should drink plenty of fluids in hot weather or when exercising extensively.

Lithium Black Box Warning

Lithium toxicity is closely related to serum lithium levels and can occur at doses close to therapeutic levels. Facilities for prompt and accurate serum lithium determinations should be identified before initiating therapy.

➔ *See Appendix 4b for more information on signs of lithium toxicity.*

ANTICONVULSANT MOOD STABILIZERS

Anticonvulsants commonly used to treat bipolar disorder include valproate, carbamazepine and lamotrigine. Anticonvulsants require 6–10 days before an initial response is seen.

VALPROATE/DIVALPROEX: The plasma concentration at which valproate/divalproex is known to be most effective is 50–125 mcg/mL. Levels should be drawn 4–5 days after initiation or a dose increase; they should be drawn in the morning 10–12 hours after the last dose.

- Valproate/divalproex can be taken with or without food; patients should be instructed to take the medication with food if it causes an upset stomach.
- This medication can cause liver problems and is therefore contraindicated in patients with liver disease. Signs of liver failure include dark urine, tiredness, decreased appetite, nausea, vomiting, and yellowing of the skin or eyes.
- This medication can cause pancreatitis. Signs of pancreatitis include nausea, vomiting, severe abdominal pain, and decreased appetite.
- Use with caution during pregnancy, and do not use in patients who are breast-feeding.

➔ *See the discussion of treatment during pregnancy in Section 11.*

CARBAMAZEPINE: This medication appears to be most useful in mixed states, but is only FDA-approved for the treatment of bipolar disorder during acute manic or mixed episodes.

- Carbamazepine therapeutic plasma concentrations for treating acute mania have not been well-established, although most clinicians aim for a range of 4–12 mcg/mL. Because carbamazepine is a potent CYP3A4 inducer and induces its own metabolism, serum levels should be rechecked after 14 days of treatment.
- Immediate-release formulation should be taken with food. Food intake increases the rate and extent of carbamazepine absorption, as well as minimizing adverse gastrointestinal events.
- Carbamazepine is contraindicated in patients with a history of bone marrow suppression, acute intermittent porphyria, and in patients prescribed MAOIs, clozapine, or other medications known to cause bone marrow suppression.
- Use carbamazepine with caution in patients with liver disease, heart block, benign prostatic hyperplasia (BPH), and narrow angle glaucoma.
- Do not use carbamazepine in pregnant or breast-feeding patients.

➔ *See the discussion of treatment during pregnancy in Section 11.*

Carbamazepine Black Box Warnings

(1) Serious dermatologic reactions to carbamazepine are more prevalent in patients with the HLA-B*1502 allele. Testing for HLA-B*1502 in genetically susceptible populations, such as Han Chinese, is recommended due to increased risk of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).

(2) Carbamazepine use can be associated with aplastic anemia and agranulocytosis. Signs and symptoms of agranulocytosis include flu-like symptoms, fever, sore throat, and mouth ulcers. Medication should be discontinued when WBC < 2000 or ANC < 500.

LAMOTRIGINE: This medication is most useful in the depressive phase of bipolar disorder.

- Lamotrigine's onset of action is delayed, due to the need for slow dose titration. Because there is no known therapeutic plasma concentration for this medication, lamotrigine should be increased according to titration schedule until significant improvement is seen, side effects become intolerable, or the dose reaches the manufacturer's suggested upper limits (200 mg/day; 400 mg/day if patient is also taking enzyme-inducing drugs).
- Lamotrigine can be taken with or without food; patients should be instructed to take the medication with food if it causes an upset stomach.
- Dose adjustments are necessary if the patient is also taking valproate or carbamazepine.
- The use of oral contraceptives may decrease lamotrigine levels.

Lamotrigine Black Box Warning

Lamotrigine carries a black box warning for serious skin reactions, including SJS and TEN. Benign rashes are also caused by lamotrigine, but it is not possible to predict how serious the rash may become. Therefore, this medication should be discontinued if the patient develops any form of rash, unless it is known that the rash is not drug-related.

ANTIPSYCHOTICS

DOSING AND TAPERING

Antipsychotics are generally regarded as faster-acting than mood stabilizers. Antipsychotics have no known therapeutic plasma concentration and should therefore be increased until significant improvement is seen, side effects become intolerable, or the dose reaches the manufacturer's suggested upper limits.

When discontinuing an antipsychotic, the dose should be tapered down over several weeks to avoid withdrawal symptoms. Withdrawal symptoms—including nausea, vomiting, malaise, and headache—usually begin 2–3 days after abrupt discontinuation.

→ *See Appendix 5 for information on dosing for Second Generation Antipsychotics.*
→ *See Appendix 6 for information on dosing for First Generation Antipsychotics.*

SIDE EFFECTS

Consideration of the side effects of antipsychotics is a critical component when making decisions regarding treatment, both in choosing among medications and in deciding to discontinue them. It is generally accepted that Second Generation Antipsychotics (SGAs), when given in low doses, are less likely than First Generation Antipsychotics (FGAs) to cause significant extrapyramidal side effects (EPS) or tardive dyskinesia (TD). However, many SGAs have their own troublesome side effects that make them less acceptable than FGAs for some patients. Choice of an antipsychotic should be guided by considering the clinical characteristics of the patient and the efficacy and side effect profile of the medication.

→ *See Appendix 7 for information on selected adverse effects of antipsychotic medications.*

Antipsychotics Black Box Warning

Increased mortality is associated with the use of antipsychotics in elderly patients with dementia-related psychosis, with most of the deaths being cardiovascular (e.g., heart failure) or infectious (e.g., pneumonia) in nature.

SGAs (Atypical Antipsychotics)

The most significant side effect associated with the SGAs is the development of insulin resistance and type 2 diabetes mellitus (DM). The mechanism of action is still unknown, but is likely due to a combination of factors. Individuals with bipolar disorder 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 experienced significant weight gain. Diabetic ketoacidosis (DKA) has been the presenting sign of DM for some individuals. Patients with an established diagnosis of DM who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control.

➔ *See Appendix8a for more information SGA side effects.*
➔ *See App endix 8b for information on SGA monitoring.*

Neuroleptic malignant syndrome (NMS) 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 9 for more information on NMS.*

Asenapine Concerns: Asenapine is formulated as a sublingual (SL) dosage form. Advise patients to avoid eating or drinking for 10 minutes after administration.

Clozapine Concerns: Clozapine contains a black box warning due to the medication's potential side effects.

Clozapine Black Box Warning
The following conditions are associated with the use of clozapine: orthostatic hypotension, bradycardia, and syncope; seizures; myocarditis and cardiomyopathy; and agranulocytosis.

- Patients treated with clozapine must be registered with the national Risk Evaluation Mitigation Strategy (REMS) program.
- The patient's Absolute Neutrophil Count (ANC) must be drawn at baseline and monitored weekly for 6 months, then every 2 weeks for the following 6 months, and then monthly.

➔ *See the BOP Clinical Guidance on the Pharmacological Management of Schizophrenia for more details on Clozapine side effects and monitoring.*

Olanzapine Concerns: Olanzapine levels can be affected by age, smoking status (smoking increases metabolism), and gender; dosing adjustments may be necessary.

Quetiapine Concerns: Quetiapine's unique properties 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 patients selling their quetiapine (sometimes referred to as "Quell"). While the specific pharmacological/ neurotransmitter action that makes quetiapine a drug of abuse is unknown, it clearly has become one, and generally should not be prescribed in the correctional setting. If prescribed, it should be reserved for those cases refractory to other SGAs, and it should be administered crushed and floated in water to reduce the potential for diversion. Consult the current BOP National Formulary for specific restrictions and criteria.

Ziprasidone Concerns: Ziprasidone is a highly lipophilic compound, which impacts its absorption profile with respect to food. It should be given with food to insure proper absorption.

FGAs (Typical Antipsychotics)

The FGA medications, as a group, share similar side effect profiles. In general, with an increase in antipsychotic potency, there will be a decrease in anticholinergic side effects and an increase in extrapyramidal side effects. All FGAs cause sedation and drowsiness to varying degrees. Chlorpromazine causes the most sedation, and haloperidol causes the least. FGAs should be initiated at a low dose and titrated up in order to improve tolerability. FGAs should be given cautiously in patients with hepatic and renal dysfunction.

→ *See Appendix 10a for more information FGA side effects.*
→ *See Appendix 10b for information on FGA monitoring.*

Thioridazine Concerns: Due to the additional black box warning for thioridazine, it is not a medication of choice in treating bipolar disorder.

Thioridazine Black Box Warning

Thioridazine carries a black boxed warning for proarrhythmic effects. Thioridazine has been shown to prolong the QTc interval in a dose-related manner and has been associated with torsades de pointes-type arrhythmias and sudden death.

Antidepressants

Dosing and Tapering

Antidepressants, most commonly selective serotonin reuptake inhibitors (SSRIs), are commonly used in combination with either a mood stabilizer or an SGA to treat acute bipolar major depression. Of the SSRIs, fluoxetine has the most data supporting its efficacy in bipolar major depression, while paroxetine has the least. SSRIs (excluding paroxetine) and bupropion can be used as first-line treatments in conjunction with a mood stabilizer or an SGA for acute short-term treatment of bipolar depression, with the objective of tapering and discontinuing antidepressants 6–8 weeks after full remission of depression.

- Avoid the use of tricyclic antidepressants (TCAs) and venlafaxine, as they are associated with an increased risk of a switch to a manic state.
- When starting a patient on any antidepressant, monitor closely for signs of switching into mixed or manic/hypomanic states.
- It may take 2–3 weeks of treatment for an initial response to be seen. It is important not to abruptly discontinue an antidepressant, since it can cause ***Antidepressant Discontinuation Syndrome (ADS)***. Symptoms of ADS include dizziness, headache, paresthesia, nausea, diarrhea, insomnia, and irritability. Antidepressants should be tapered off over a 2–4 week period, with the exception of fluoxetine. Due to fluoxetine's very long half-life, it may be discontinued without tapering, with a relatively low risk of side effects.
  - → *If a patient is experiencing symptoms of ADS, increase the antidepressant dose back to where no ADS symptoms were present, and then continue to taper down at a slower rate.*
- Antidepressants should not be used to treat patients with a current mixed episode or a history of rapid cycling.
- Monotherapy with antidepressants is not recommended.

→ *See Appendix 11a for information on dosing specific antidepressants.*

SIDE EFFECTS AND MONITORING

Common side effects of SSRIs include anxiety, insomnia, sedation, headache, nausea, diarrhea, and delayed ejaculation. SSRIs can also cause decreased platelet aggregation and prolonged bleeding times; therefore, it is important to monitor patients for signs of increased bleeding if they are also taking an antiplatelet or anticoagulant medication such as an NSAID.

➔ *See Appendix 11b for more information on the side effects of specific antidepressants.*

ANTIDEPRESSANTS HAVE A BLACK BOX WARNING FOR SUICIDALITY. In short-term studies, antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults, compared with placebo. Therefore, it is important to closely monitor patients started on an antidepressant for worsening suicidality or unusual changes in behavior.

SEROTONIN SYNDROME: Antidepressants also have the potential to cause serotonin syndrome, especially when used in combination with other medications that can increase serotonin levels. Signs and symptoms of serotonin syndrome include mental status changes, autonomic instability, neuromuscular abnormality, and gastrointestinal symptoms. If the patient develops serotonin syndrome, discontinue the offending agent and initiate supportive care with IV fluids for hydration.

➔ *See Appendix 11c for more information on monitoring antidepressant use.*

BENZODIAZEPINES

Benzodiazepines should not be used as monotherapy for the treatment of bipolar disorder, but are useful adjuncts in sedating acutely agitated patients. Clonazepam or lorazepam are recommended.

- The most common side effects associated with benzodiazepines include disinhibition, sedation, and respiratory depression.
- Clonazepam is started at a dose of 1–3 mg per day, taken in two divided doses, and can be titrated up as needed. Lorazepam is started at a dose of 2–4 mg per day, taken in three to four divided doses, and titrated up as needed.

INSTITUTIONAL CONCERNS: Benzodiazepines can have a negative impact on the safety and security of an institution, secondary to diversion. Vulnerable patients on benzodiazepines can be pressured by other patients to divert their medications, placing them at risk for exacerbation of symptoms or acute withdrawal. Also, intoxication on any substance (alcohol, benzodiazepines, or others) can result in loss of normal inhibition, resulting in behaviors that place both patients and staff at risk. Therefore, whenever benzodiazepines are prescribed in a correctional environment, the prescriber needs to carefully assess the risks and benefits for that patient and the institution.

➔ *Consult the BOP National Formulary for current restrictions and criteria related to benzodiazepines.*

9. TREATMENT OF ANTIPSYCHOTIC SIDE EFFECTS

TREATMENT OF SIDE EFFECTS IN GENERAL

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 antipsychotic medication
- Changing the antipsychotic medication
- Adding other medication to treat the side effects

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

The rest of this section focuses on extrapyramidal side effects, which can be treated with medication. Extrapyramidal side effects tend to be proportional to the dopamine-2 receptor blocking activity of the antipsychotic medication.

TREATMENT OF EXTRAPYRAMIDAL SIDE EFFECTS

Extrapyramidal symptoms (EPS) can be ***acute***, ***subacute***, or ***insidious/chronic*** in their onset.

➔ *When monitoring for EPS, the clinician should utilize the Abnormal Involuntary Movement Scale (AIMS) found in Appendix 12.*

ACUTE EPS

Acute EPS include dystonia, pseudoparkinsonism, and akathisia.

➔ *Refer to Appendix 13a for a list of EPS and their treatment, and Appendix 13b for antiparkinsonian agents and their doses. Only dystonia and akathisia are discussed at greater length below.*

DYSTONIA: Dystonia typically develops within a period of hours to days of initiating treatment or escalating dosage, and can be treated with antiparkinsonian agents.

- Dystonia requires immediate treatment with parenteral antiparkinsonian medication, either IV or IM, which should then be followed by ongoing treatment with an 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. The patient can be prescribed the same or similar antipsychotic medication in the future, if he or she is treated prophylactically with an antiparkinsonian medication.
- The antipsychotic 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 with antiemetics such as promethazine or prochlorperazine.

PSEUDOPARKINSONISM: Pseudoparkinsonism is a medication-induced condition that is characterized by parkinsonian-like symptoms.

- 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: 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, pseudoparkinsonism, and Pisa syndrome.

➔ *Akathisia is discussed above under Acute EPS. For information on pseudoparkinsonism and Pisa syndrome, refer to Appendix 13a.*

INSIDIOUS/CHRONIC ONSET EPS

Symptoms of chronic onset EPS include tardive dyskinesia, tardive dystonia, tardive akathisia, Pisa syndrome, and Rabbit syndrome.

➔ *Risk factors for the development of these syndromes are listed in Appendix 13a.*

Generally, the rate of development of tardive dyskinesia 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 tardive dyskinesia. 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. However, for patients with chronic psychotic disorders, discontinuing the antipsychotic may not be an option.

10. NON-MEDICATION INTERVENTIONS FOR BIPOLAR DISORDER

ELECTROCONVULSIVE THERAPY (ECT)

ECT is considered first-line therapy in patients with severe suicidality, severe psychosis, catatonia, and manic delirium. ECT has shown efficacy in treating bipolar major depression, mania, mixed features, rapid cycling, and peripartum patients. ECT is indicated in treating such episodes in patients who have been shown to be resistant to multiple courses of medication therapy (i.e., three to five different medication combination strategies).

ECT is rarely utilized in the BOP correctional setting, but may be the most appropriate treatment in some cases. A course of ECT typically consists of 6–12 treatments given two or three times per week on alternating days. Patients undergoing ECT generally will require treatment with medications before, during, and after a course of ECT treatment. There are no absolute medical contraindications to ECT, and treatment is considered safe since patients treated with ECT generally do not suffer adverse neurocognitive effects. ECT is to be performed in accordance with BOP policy.

PSYCHOSOCIAL INTERVENTIONS

When used as adjuncts to pharmacotherapy, psychosocial interventions such as ***group psychoeducation***, ***cognitive behavioral therapy***, and ***interpersonal and social rhythm therapy*** have demonstrated significant benefits, both in the treatment of acute depressive episodes and in long-term maintenance treatment. These treatments have been shown to decrease relapse rates, mood fluctuations, and the need for medications and hospitalizations, as well as increasing functioning and medication adherence. Typically, these treatments are most effective in euthymic patients during maintenance treatment.

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 appropriately within the context of the correctional setting.

GROUP PSYCHOEDUCATION

Group psychoeducation should focus on increasing illness awareness. It should cover topics such as symptom awareness, medication options and adherence, identifying prodromal signs, avoiding substance abuse, and regulating habits. Treatment should be administered by a therapist. The therapist can be a psychiatrist, psychologist, psychiatric nurse, or social worker. Patients best suited for this setting are typically euthymic, but it is acceptable to include mildly ill and reasonably stable patients.

These groups are closed, and new members are not permitted to join after the group's first meeting. The optimal size of a group is 8–12 patients, but dropout rates of 25% are common, so it is acceptable to recruit 15 patients for the first session. Patients undergo six to twelve 90-minute sessions. The sessions provide patients with tools to help them become more active in their treatment and more self-managing of their illness. Other topics that may be addressed in group psychoeducation include factors and stressors that trigger mood episodes, the course of the illness, avoiding substance abuse, pregnancy and heritability, alternative therapies, stress management, and problem solving.

COGNITIVE BEHAVIORAL THERAPY (CBT)

The benefit of CBT in preventing or delaying a mood episode is controversial. CBT has been found to be the most effective in patients with depression, and appears to be the most useful technique for improving adherence to treatment.

Utilization of CBT should include the following components:

- Education regarding symptoms, course, and treatment of bipolar disorder
- Scheduling of pleasurable events to alleviate inactivity
- Teaching the skill of cognitive re-structuring
- Learning to identify maladaptive thoughts and challenge them on logical grounds
- Learning to replace maladaptive thoughts with balanced or adaptive thinking
- Problem-solving skills
- Learning to detect the earliest signs of recurrence of symptoms and to implement early intervention plans

INTERPERSONAL AND SOCIAL RHYTHM THERAPY (IPSRT)

IPRST has been shown to delay or prevent recurrent mood episodes. It may be considered for patients with bipolar disorder who have achieved remission from an acute manic episode and are maintained on prophylactic medication.

IPRST should contain the following components:

- Patients can complete a questionnaire such as the Social Rhythm Metric questionnaire, which can be found online—a self-report instrument for tracking and quantifying daily and nightly routines, as well as mood ratings.
- Providers need to assist patients in keeping regular routines (bed times, wake times, exercise) and minimizing the impact of events that could disrupt their moods and daily/nightly stability.
- Providers need to maintain an interpersonal focus that concerns the resolution of the patient's current problems and developing strategies for preventing the same problems from recurring in the future.

11. SPECIAL POPULATIONS

PREGNANCY

The decision to institute or continue medication or ECT in a pregnant patient should be based on consideration of the potential risks of the treatment to the fetus and mother, versus the potential risks of untreated bipolar disorder. The patient's primary physician and obstetrician should be part of the decision process.

Psychotherapy is a good option for pregnant patients with bipolar disorder, since it does not expose the patient or the fetus to the side effects of pharmacologic treatment. For pregnant bipolar patients treated with pharmacotherapy, it is recommended to use drugs with fewer known teratogenic effects, adhere to monotherapy, and utilize doses at the low end of the therapeutic range. Many patients may require medication combinations, but it is recommended to first increase the dose of the monotherapy to the maximum tolerated dose before adding a second medication. Abrupt discontinuation of medication should be avoided, and the psychiatric status of the patient should be regularly monitored.

TABLE 13. PREGNANCY CATEGORIES OF BIPOLAR DISORDER MEDICATIONS

DRUG	FDA PREGNANCY CATEGORY*
Lithium	D
Valpraote	D
Carbamazepine	D
Lamotrigine	C
SGAs	C**
FGAs	C

* For an explanation of the FDA Pregnancy Categories, see: http://www.drugs.com/pregnancy-categories.html
** The SGA Clozapine is in Category B.

TREATMENT OF ACUTE MANIA OR HYPOMANIA

FGAs have been widely used during pregnancy, although symptoms of withdrawal and EPS have been observed in newborns. A higher potency FGA is recommended in order to minimize anticholinergic, antihistaminic, and hypotensive effects. Haloperidol contains the least amount of anticholinergic side effects and appears to be the safest FGA to use during pregnancy; it is therefore recommended as the first-line treatment of mania and hypomania in pregnant patients. If a patient does not respond to or tolerate haloperidol, reasonable alternatives include risperidone, quetiapine, or olanzapine. Case reports of gestational diabetes have been reported with the use of SGAs, particularly olanzapine; therefore, metabolic parameters must be monitored in pregnant patients taking a SGA.

TREATMENT OF ACUTE BIPOLAR DEPRESSION

Lamotrigine should be used with caution during pregnancy, but it is considered the first-line treatment for bipolar depression. The pregnancy registry showed no increased risk of teratogenicity. Folate supplementation is encouraged. Lamotrigine clearance is increased during pregnancy, therefore requires careful dose management. For treatment-resistant patients, the

second-line recommendation is the SGA quetiapine, since studies suggest that quetiapine is not associated with teratogenic effects. However, quetiapine does have the potential of causing metabolic complications.

REFRACTORY PATIENTS

ECT and lithium are recommended for refractory patients. ECT may be considered for severe depression in pregnancy. Lithium during the first trimester may cause cardiac defects such as Ebstein's anomaly. Despite this, lithium may be used in refractory patients since the risk is considered to be small. Lithium serum levels may be lowered by pregnancy. The risk and benefits of treatment must be weighed and discussed with the patient, and the patient must be counseled on the risk of teratogenicity.

MEDICATIONS TO AVOID DURING PREGNANCY

Valproate should be avoided during pregnancy, if possible. This is most important during the first trimester due to the risk of neural tube defects. This risk can be decreased by using <1,000 mg/day, in three or more divided doses. Valproate levels should be monitored closely.

Carbamazepine should be avoided during pregnancy if possible, especially in the first trimester, due to spina bifida and neural tube defects. If treatment with carbamazepine becomes necessary, use as monotherapy in divided doses.

ELDERLY

It is estimated that 25% of all bipolar patients are elderly, and this percentage is expected to increase as the general population ages. Elderly patients can present with either early-onset or late-onset bipolar disorder.

- Elderly patients with ***early-onset*** bipolar disorder are those who have had the disorder for many years prior to age 60.
- ***Late-onset*** bipolar disorder develops in the individual after they reach 60 years of age. Late-onset bipolar disorder may be associated with longer episodes, increased debilitation, and increased difficulty in achieving complete remission. New-onset mania in older adults also calls for neuroimaging studies to rule out tumor and stroke.
- Older bipolar patients have been found to experience more rapid cycling, fewer suicide attempts, and less severe manic and psychotic symptoms than younger patients, but no difference in depressive symptomatology.

Prescribing medications in older adults requires careful consideration. Metabolic changes such as decreased absorption, decreased hepatic and renal function, decreased protein binding, and increased volume of distribution can influence pharmacokinetics. These changes are combined with increased risks of medical co-morbidities, increased number of concurrent medications, and increased sensitivity to side effects. Therefore, the likelihood of possible benefits with all medications used to treat bipolar disorder in older adults need to be balanced against potential risks, and polypharmacy should be avoided if possible.

Treatment for geriatric bipolar patients begins with a psychiatric and general medical history, mental status and physical examination, and focused lab and imaging studies to establish symptoms and any comorbid disorders that need treatment—as well as any contraindications to

treatment. For example, if the patient has renal impairment, lithium should be avoided; if the patient has hepatic disease, valproate should be avoided.

➔ *All pharmacological interventions for older adults with bipolar disorder should be combined with cognitive, behavioral, family, and interpersonal and social rhythm therapies in conjunction with psychoeducation and chronic disease management.*

SPECIAL CONSIDERATIONS FOR USING BIPOLAR MEDICATIONS IN THE ELDERLY

- Medication should be started at a low dose and increased in small increments. These patients need to be monitored closely for side effects, and their mental health provider should coordinate care with other clinicians who are managing medical comorbidities.
- Continuation on maintenance treatment is recommended for the geriatric population, since the risk of recurrence remains constant with increased age. As with the younger population, acutely ill older patients who remit with a particular medication regimen should generally be maintained on the same regimen.
- When a medication has failed, the failed medication should be tapered and discontinued over 1–2 weeks, at the same time that the new drug regimen is started and titrated up.
- Antipsychotics have been associated with an increase in mortality rates when used in geriatric patients with dementia.
- The use of anticonvulsants is associated with an increased risk of fracture.

TABLE 14. STEPWISE APPROACH TO MEDICAL TREATMENT FOR GERIATRIC BIPOLAR PATIENTS

	MANIA AND HYPOMANIA
1	Patient is diagnosed with bipolar disorder.
2	Initiate first-line treatment with either quetiapine, lithium, olanzapine, or valproate.
3	If no response within 4 weeks of reaching target dose or if patient does not tolerate the medication, another first-line medication can be tried; if more appropriate, a second-line medication can be utilized.
4	If no response, initiate second-line treatment with: • lithium or valproate *plus* quetiapine or olanzapine ***OR*** • lithium *plus* valproate.
5	If no response, initiate third-line treatment with either aripiprazole, asenpaine, risperidone, or ziprasidone.
6	If no response with 4–8 medication trials, consider ECT.
	BIPOLAR DEPRESSION
1	Patient is diagnosed with bipolar disorder.
2	Initiate first-line treatment with either lurasidone or quetiapine.
3	If no response within 4 weeks of reaching target dose or if patient does not tolerate the medication, another first-line medication can be tried; if more appropriate, a second-line medication can be utilized.
4	If no response, initiate second-line treatment with lamotrigine, olanzapine *plus* fluoxetine, lithium, or valproate.
➔ See *Appendix 14* for drug dosing in elderly patients.	

12. PATIENT EDUCATION

Patient education is crucial to successful treatment. Clinicians should provide counseling regarding the patient's disease state and medication, including the following points, at minimum:

- ★ Importance of medication compliance
- ★ The gradual nature of response to medication
- ★ Importance of continuing medications even when feeling better
- ★ Not stopping medications without checking with the provider
- ★ The risks of relapse and how to identify symptoms
- ★ Importance of contacting the provider immediately if any emerging symptoms are noticed

DEFINITIONS

AKATHISIA, an internal sense of restlessness, is a common, early-onset *EXTRAPYRAMIDAL SIDE EFFECT* 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 thereafter benzodiazepines, are the treatment of choice.

ANTIDEPRESSANT DISCONTINUATION SYNDROME (ADS) is a condition that can occur following the interruption, dose reduction, or discontinuation of antidepressant drugs, including selective serotonin re-uptake inhibitors (SSRIs) or serotonin–norepinephrine reuptake inhibitors (SNRIs). The symptoms can include flu-like symptoms and disturbances in sleep, senses, movement, mood, and thinking. In most cases symptoms are mild, short-lived, and resolve without treatment. More severe cases are often successfully treated by reintroduction of the drug, which usually leads to resolution within one day.

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

DELUSIONS are disturbances of thought processes and are fixed, false beliefs that are very strongly held and immutable, even in the face of evidence to the contrary. Delusions can be simple, containing few elements, or they can be complex, encompassing virtually all of a person's reality. Delusions vary in type, including: delusions of persecution; delusions of grandeur; delusions of influence; delusions of having sinned; delusions of replacement of significant others; delusions with nihilistic, somatic, erotomanic, or jealous characteristics; and delusions about mood, perception, or memory.

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.

DYSTONIA is an idiosyncratic *EXTRAPYRAMIDAL SIDE EFFECT* 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 group. It most often affects the muscles of the eyes, mouth, head, and neck. In such cases, 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**.

ELECTROCONVULSIVE THERAPY (ECT) is a treatment in which seizures are electrically induced in an anesthetized inmate. ECT can be used for major depression, mania, catatonia, or schizophrenia. Initially, ECT is administered in a course of 6–12 treatments, with a frequency of 2 to 3 times a week.

EXTRAPYRAMIDAL SIDE EFFECTS, also sometimes called **EXTRAPYRAMIDAL SYNDROMES**, or **PSEUDOPARKINSONISM**, are a group of motor side effects caused by dopamine-blocking medications, including antipsychotics and antiemetics. **EXTRAPYRAMIDAL SYMPTOMS (EPS)** include *AKATHISIA*, muscle rigidity, tremor, bradykinesia, affective flattening, *PISA SYNDROME*, *RABBIT SYNDROME*, choreoathetotic movements, *DYSTONIA*, and tardive syndromes. Treatments for EPS that should be considered include: antipsychotic medication dose reduction, adding an anticholinergic agent, or switching to a second-generation antipsychotic (if the original antipsychotic agent is proving ineffective).

HALLUCINATIONS are disturbances of perception and occur in the absence of corresponding sensory stimuli. They can include any of the sensory experiences, alone or in combination—auditory, visual, gustatory, olfactory, or tactile. Hallucinations can occur in a number of mental disorders, but they can also occur as a symptom of many other medical/neurological conditions such as drug withdrawal, tumor, toxic disturbances, or inflammatory or infectious processes.

HYPOMANIA is a mood disturbance that is 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" (or irritable) mood. 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, as well as 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 may 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.

NEUROVEGETATIVE SYMPTOMS are a collection of symptoms that include effects on sleep, effects on appetite, loss of enjoyment in interests, feelings of guilt/hopelessness, lack of energy, inability to concentrate, psychomotor retardation/agitation, and suicidality.

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

PSYCHOTIC FEATURES include the symptoms of hallucinations or delusions. Psychotic features *always* indicate the presence of a severe mood disorder or episode.

RABBIT SYNDROME is an early- to mid-onset *EXTRAPYRAMIDAL SIDE EFFECT* 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 of *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 in found in DMS-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 6 months. Formal diagnosis is made by satisfying the criteria set forth in DSM-5.

SEROTONIN SYNDROME is a rare, but potentially fatal, syndrome; it is due to excessive serotonergic activity usually associated with the use of multiple serotonergic agents (such as SSRIs together with MAOIs), but it can also occur with SSRIs alone. The syndrome can include abdominal pain, diarrhea, flushing, sweating, hyperthermia, lethargy, mental status change, tremor, myoclonus, rhabdomyolysis, renal failure, cardiovascular shock, and possibly death.

THERAPEUTIC TRIALS of antipsychotic medication require the use of a therapeutic dose (not always easily established) for a minimum of 6–8 weeks. 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 full therapeutic benefits for many months after discontinuation of treatment. Providers often fail to undertake full therapeutic trials of medication, either 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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ADDITIONAL RESOURCES

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APPENDIX 1. 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 2. MOOD STABILIZER DOSING AND MONITORING

NAME: generic/brand	DOSE RANGE (or blood level, when applicable)	MONITORING
LITHIUM **Levels drawn:** On days 4–5 from initiation; in the morning,10–12 hours post-dose.	**Acute Mania:** Usual dose is 600 mg, three times daily for IR or 900 mg twice daily for SR. May need to start at a lower dose initially for 3-4 days to minimize side effects and improve tolerance. ***Levels:*** 0.8–1.5 mEq/L **Maintenance:** Usual dose is 900 mg/day. Usual range = 900–2400 mg per day in 2–4 divided doses, preferably with meals. ***Levels:*** 0.6–1.2 mEq/L	• Renal function (BUN & SCr) – baseline, at 3 months, at 6 months, then annually. • Serum electrolytes – baseline, then annually. • Serum calcium – baseline, 2–6 weeks after initiation, then every 6–12 months. • Thyroid (T3, T4, TSH) – baseline, at 6 months, then annually. • ECG w/ rhythm strip – baseline if > 40 years old or risk factors for CV disease. • CBC w/ diff – baseline and as clinically indicated. • Weight – baseline, then annually. • Baseline pregnancy test in females. • Serum lithium levels – twice weekly until stable, then repeat every 1–3 months.
VALPROATE/ DEPAKENE® and others **Levels drawn:** On days 4–5 from initiation; in the morning,10–12 hours post-dose.	750 mg/day in divided doses, adjusting dose as rapidly as possible to desired clinical effect. ***ER:*** 25 mg/kg/day once daily adjusted to desired clinical effect. ***Maximum dose:*** 60 mg/kg/day ***Levels:*** 50–120 mcg/mL	• Liver enzymes – baseline and frequently during the first 6 months. • CBC w/ platelets – baseline, then every 6–12 months. • Weight – baseline, then at 6 months. • Serum ammonia – baseline and if symptoms of lethargy or mental status change. • Baseline pregnancy test in females. • Serum valproate levels – until stable, then annually.
CARBAMAZEPINE/ TEGRETOL® **Levels drawn:** On days 2–5 from initiation; in the morning,10–12 hours post-dose.	Initially 200 mg twice daily; increase every 3–4 days by 200 mg. Usual range = 600–1600 mg/day in divided doses. ***Levels:*** 8–12 mcg/mL	• CBC w/ platelet count & differential – baseline, at 6 months. • LFTs – baseline, at 6 months. • ECG – baseline. • Weight – baseline, at 6 months. • Monitor for rashes and skin reactions. • Baseline pregnancy test in females. • Serum carbamazepine levels – repeat every 1–3 months for 6 months, then annually.
LAMOTRIGINE[1]/ LAMICTAL®	***Weeks 1 and 2:*** 25 mg once daily ***Weeks 3 and 4:*** 50 mg once daily ***Week 5:*** 100 mg once daily ***Week 6 and maintenance:*** 200 mg once daily	• Close periodic assessments for dermatologic side effects. • Serum levels not necessary.

[1] Lamotrigine dosing will be different if patient also taking valproic acid, carbamazepine, phenytoin, phenobarbital, primidone, rifampin, or lopinavir/ritonavir.

APPENDIX 3. SIDE EFFECTS OF MOOD STABILIZERS

DRUG	COMMON SIDE EFFECTS	SERIOUS SIDE EFFECTS
LITHIUM	• GI upset • Hand tremor/shakiness • Polyuria/polydipsia • Weight gain • Dermatological effects • Cardiac effects (benign and reversible)	• Nephrogenic diabetes insipidus • Hypothyroidism • Leukocytosis
CARBAMAZEPINE	• GI upset • Dizziness/orthostasis • Somnolence • Anticholinergic side effects • Diplopia	• Agranulocytosis • Aplastic anemia • SJS/TEN • Hepatic failure • Dermatitis/rash • Serum sickness • Pancreatitis • Lupus syndrome
LAMOTRIGINE	• GI upset • Sedation • Headache • Dizziness • Diplopia • Blurred vision • Ataxia	• SJS/TEN • Multi-organ hypersensitivity • Hematologic effects • Aseptic meningitis
VALPROATE	• GI upset • Weight gain • Sedation • Dizziness • Tremor • Alopecia	• Agranulocytosis • SJS/TEN • Aplastic anemia • Hepatic failure • Dermatitis/rash • Serum sickness • Pancreatitis • Polycystic ovary syndrome • Neural tube defects in pregnancy • Hyperammonemia

APPENDIX 4A. LITHIUM DRUG-DRUG INTERACTIONS

INCREASE LITHIUM LEVELS	DECREASE LITHIUM LEVELS	INCREASE TOXICITY WITHOUT AFFECTING LITHIUM LEVELS
• Thiazide diuretics • ACE inhibitors and ARBs • NSAIDS (Sulindac least likely) • Sodium depletion	• Caffeine • Acetazolamide • Theophylline • High dietary sodium intake	• SSRIs • Methyldopa • Phenytoin • Carbamazepine • Calcium Channel Blockers • Antipsychotics (rare)

APPENDIX 4B. LITHIUM TOXICITY

LEVEL OF TOXICITY	SERUM LEVEL	SYMPTOMS	TREATMENT
MILD	1.5–2.0 mEq/L	• Nausea/vomiting, loose stools/diarrhea • Lethargy • Drowsiness • Coarse Hand Tremor • Muscular Weakness	• Discontinue and remove any unabsorbed lithium (lavage). • If mild toxicity, hold lithium for 1 day and reevaluate. • Correct fluid and electrolyte imbalances with IV NaCl 0.9% (body will take in sodium and excrete lithium). • Supportive care. • Intermittent hemodialysis (12 hours on, 12 hours off) if severe toxicity, with a goal to decrease serum lithium level to < 1 mEq/L on a sample drawn 6–8 hours after dialysis completion.
MODERATE	2.0–2.5 mEq/L	• Severe nausea, vomiting, and diarrhea • Confusion • Dysarthria • Nystagmus • Ataxia • Myoclonic Twitches • EKG changes (flat or inverted T waves)	
SEVERE	> 2.5 mEq/L	• Severe nausea, vomiting, and diarrhea • Growly impaired consciousness • Increased deep tendon reflexes • Seizures • Syncopy • Coma	

APPENDIX 5. BIPOLAR DOSING FOR SECOND-GENERATION ANTIPSYCHOTICS (SGAS)

NAME: Generic (Brand)	DOSING
Aripiprazole (Abilify®)	• INITIAL DOSE = 15 mg once daily (if adjunct to lithium or valproate,10–15 mg once daily). • MAXIMUM DOSE = May increase to 30 mg once daily, if clinically indicated.
Asenapine (Saphris®)	• INITIAL DOSE = 10 mg twice daily, sublingual (MAXIMUM DOSE) • Decrease to 5 mg twice daily, if dose not tolerated. • If adjunct to lithium or valproate, start at 5 mg twice daily & increase to 10 mg twice daily.
Clozapine (Clozaril®)	• INITIAL DOSE = 25 mg daily. • Increase as tolerated in increments of 25 mg daily to a MAXIMUM DOSE of 550 mg daily.
Iloperidone* (Fanapt®)	• INITIAL DOSE = 1 mg twice daily. • RECOMMENDED DOSAGE RANGE = 6–12 mg twice daily (MAXIMUM DOSE = 20 mg daily). • Titrate to the RECOMMENDED DOSAGE RANGE with dosage adjustments every 24 hours, not to exceed 2 mg twice daily (4 mg daily).
Lurasidone (Latuda®)	• INITIAL DOSE = 20 mg once daily; slow/scheduled titration not required. • MAXIMUM DOSE = 120 mg daily.
Olanzapine (Zyprexa®)	• INITIAL DOSE = 10–15 mg once daily. • Increase dose by 5 mg daily to a MAINTENANCE DOSE of 5–20 mg daily.
Olanzapine + Fluoxetine (Symbyax®)	• INITIAL DOSE = olanzapine 6 mg and fluoxetine 25 mg once daily in the evening. • Adjust dose based on response and tolerability. • USUAL DOSE = olanzapine 6–12 mg and fluoxetine 25–50 mg daily.
Paliperidone* (Invega®)	• **ORAL:** INITIAL AND USUAL DOSE = 6 mg once daily in the morning; titration not required. • If dose needs to exceed 6 mg, increases of 3 mg daily are recommended, no more frequently than every 5 days, up to a MAXIMUM DOSE of 12 mg daily.
Paliperidone* (Invega Sustenna®)	• **IM:** INITIATION REGIMEN = 234 mg on treatment day 1, followed by 156 mg 1 week later. • One month after the initiation week +/- 7 days, begin a MONTHLY MAINTENANCE DOSE of 78mg–234mg based on response and tolerability.
Quetiapine (Seroquel IR®, Seroquel ER®)	**DEPRESSIVE EPISODES:** • IR AND ER: INITIAL DOSE = 50 mg once daily at bedtime on day 1. • Increase to 100 mg once daily on day 2; continue to increase by 100 mg daily each day until 300 mg once daily is reached on day 4. **MANIA:** • **IR:** INITIAL DOSE = 50 mg twice daily on day 1. Increase by 100 mg daily, given in equal doses administered twice daily • TARGET DOSE: 400MG • MAXIMUM DOSE: 800MG • **ER:** INITIAL DOSE = 300 mg once daily. • Increase to 600 mg once daily on day 2; then adjust to 400– 800 mg once daily on day 3. • **IR or ER:** MAINTENANCE DOSE = 400–800 mg daily.
Risperidone (Risperdal®)**	• **ORAL:** INITIAL DOSE = 2–3 mg once daily. • If needed, adjust dose by 1 mg daily in intervals ≥ 24 hours. • USUAL DOSAGE RANGE = 1–6 mg daily.
Risperidone (Risperdal Consta®)**	• **IM:** 25 mg every 2 weeks, up to 50 mg every 2 weeks. • Do not adjust more frequently than every 4 weeks.
Ziprasidone (Geodon®)	• INITIAL DOSE = 40 mg twice daily. • May increase to 60 or 80 mg, twice daily on day 2. • USUAL DOSAGE RANGE = 40–80 mg twice daily.

* Schizophrenia dosing is given, since standard bipolar dosing is not available.

** Oral risperidone (or another antipsychotic) should be administered with the initial injection of Risperdal Consta. continued for 3 weeks, and then discontinued to maintain adequate therapeutic plasma concentrations.

APPENDIX 6. BIPOLAR DOSING FOR FIRST-GENERATION ANTIPSYCHOTICS (FGAS)

NAME: Generic (Brand)	DOSING
Chlorpromazine (Thorazine®)	• DOSING RANGE = 30–800 mg daily, in 2 to 4 divided doses. • USUAL DOSE = 200–800 mg daily. • Initiate at lower doses and titrate as needed.
Fluphenazine* (Prolixin®)	• INITIAL DOSE = 2.5–10 mg daily, in divided doses at 6- to 8-hour intervals. • MAINTENANCE DOSE = 1–5 mg daily.
Haloperidol* (Haldol®)	• DOSING RANGE = 0.5–5 mg, 2 to 3 times daily. • USUAL MAXIMUM DOSE = 30 mg daily.
Loxapine* (Loxitane®)	• INITIAL DOSE = 10 mg twice daily. • Increase dose to a USUAL MAINTENANCE DOSE of 60–100 mg daily, in divided doses. • MAXIMUM DOSE = 250 mg daily.
Perphenazine* (Trilafon®)	• INITIAL DOSE = 4–8 mg, 3 times a day. • *Reduce dose as soon as possible to a minimum effective dosage*. • MAXIMUM DOSE = 24 mg daily.
Thioridazine* (Mellaril®)	• INITIAL DOSE = 50–100 mg, 3 times daily. • Dosage may be increased at gradual increments to a USUAL DOSE: 300–800 mg daily in 2 to 4 divided doses. • MAXIMUM DOSE = 800 mg daily.
Thiothixene* (Navane®)	• Dosing is dependent on symptoms. • MILD SYMPTOMS = 2 mg, 3 times daily; typically up to 15 mg daily. • MAXIMUM DOSE = 60 mg daily
Trifluoperazine* (Stelazine®)	• INITIAL DOSE = 2–5 mg twice daily. • Titrate dose gradually to 15–20 mg daily in divided doses. • Some patients may require up to 50 mg daily.
* Schizophrenia dosing is given, since standard bipolar dosing is not available.	

APPENDIX 7. SELECTED ADVERSE EFFECTS 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	+++++	+	+++	++	+
Trifluperazine	++++	+	++	+++	+
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

[5] **Diabetes Mellitus:** Relative risk.

APPENDIX 8A. SIDE EFFECTS OF SECOND-GENERATION ANTIPSYCHOTICS (SGAS)

SERIOUS REACTIONS	COMMON REACTIONS
• 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	• 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	
Dementia-Related Psychosis: *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.*	

APPENDIX 8B. MONITORING FOR SECOND-GENERATION ANTIPSYCHOTICS (SGAS)

TEST	INPATIENT[1]	OUTPATIENT[1]
AIMS[2]	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

[1] Assuming no diagnosis of hyperglycemia or diabetes
[2] AIMS = Abnormal Involuntary Movement Scale (see *Appendix 12*)

OTHER MONITORING	BASELINE	MONTHLY[3]	QUARTERLY[4]	ANNUALLY
Family History	X			
Weight & Body Mass Index (BMI)	X	X		
Waist Circumference	X			X
Blood Pressure	X	X		
Fasting Lipids	X			X
Fasting Glucose	X		X	

[3] Or at each visit
[4] May be decreased to every 6 months if consistently normal

ADDITIONAL MONITORING:

- **Quetiapine:** TSH, free T4, and thyroid clinical assessment at baseline and follow-up.
- **Ziprasidone:** ECG as clinically indicated; monitor potassium and magnesium levels in patients at risk for electrolyte disturbances, and periodically monitor if taking diuretics.
- **Paliperidone:** Renal function annually.
- **Asenapine:** Prolactin at baseline.
- **Clozapine:** ECG as clinically indicated; signs and symptoms of myocarditis and cardiomyopathy; WBC and ANC at baseline and at least weekly for the first 6 months, if WBC ≥ 2500/mm^3 and ANC ≥2000/mm^3, then test every other week for the next 6 months; if still acceptable, monitor every 4 weeks.
- **Iloperidone:** Potassium and magnesium measurements in patients at risk for electrolyte disturbances, and periodically monitor if taking diuretics.

APPENDIX 9. NEUROLEPTIC MALIGNANT SYNDROME

Neuroleptic malignant syndrome (NMS) is an idiosyncratic extrapyramidal 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, 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 change 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 reinstituted until the patient has been medically stable for two weeks. When reinstituted, 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 CPK
- 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 DIAGNOSIS:

- 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 benzodiazepines)
- Malignant hyperthermia
- Heat stroke

APPENDIX 10A. SIDE EFFECTS OF FIRST-GENERATION ANTIPSYCHOTICS (FGAS)

ANTICHOLINERGIC/ ANTIHISTAMINIC EFFECTS	RELATED TO DOPAMINE BLOCKAGE	OTHER POTENTIAL SIDE EFFECTS
• 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	• 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	• 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		
Dementia-Related Psychosis: *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.*		

APPENDIX 10B. MONITORING FOR FIRST-GENERATION ANTIPSYCHOTICS (FGAS)

TEST	INPATIENT[1]	OUTPATIENT[1]
AIMS[2]	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

[1] Assuming no diagnosis of hyperglycemia or diabetes
[2] AIMS = Abnormal Involuntary Movement Scale (see *Appendix 12*)

APPENDIX 11A. ANTIDEPRESSANT DOSING

CLASS	MEDICATION Generic (Brand Name)	START DOSE (MG DAILY)	USUAL DOSE* (MG DAILY)
Selective Serotonin Reuptake Inhibitor (SSRI)	Citalopram (Celexa®)	20	20–40
	Escitalopram (Lexapro®)	10	10–20
	Fluoxetine (Prozac®)	20	20–80
	Fluvoxamine	50	50–200
	Paroxetine (Paxil®)	20	20–50
	Sertraline (Zoloft®)	25–50	75–200
Tricyclic Antidepressant (TCA)	Amitriptyline (Elavil®)	25–50	100–300**
	Desipramine (Norpramin®)		
	Doxepin (Silenor®)		
	Imipramine (Tofranil®)	75	50–150**
	Nortriptyline (Pamelor®)	25	50–150**
Selective Serotonin Norepinephrine Reuptake Inhibitor (SNRI)	Duloxetine (Cymbalta®)	40–60	60–120
	Venlafaxine (Effexor®)***	37.5–75	75–225
Atypical Aminoketone Derivative	Bupropion (Wellbutrin®)	IR: 100 BID ER: 150	IR: 100 TID ER: 150–300

* **USUAL DOSE:** Severely depressed patients may require higher doses. Elderly patients may require lower starting and therapeutic doses.

** **USUAL DOSE FOR TCAS:** Blood levels vary as much as a factor of 10 among individuals.

*** **VENLAFAXINE:** BID dosing in non-time release formula

Adapted from: Lexicomp Online® , Lexi-Drugs®

APPENDIX 11B. ANTIDEPRESSANT SIDE EFFECTS

CLASS	SIDE EFFECTS*
Selective Serotonin Reuptake Inhibitor (SSRI)	Headache, nausea, flatulence, somnolence, insomnia, agitation, anxiety, weight loss or anorexia, weight gain, tremor, sexual dysfunction, myoclonus, restless legs, bruxism, akathisia, increased dreaming/nightmares, bradycardia, galactorrhea, paresthesias, mania, GI bleed
Tricyclic Antidepressant (TCA)	*Anticholinergic:* Dry mouth, constipation, urinary retention, blurred vision, dry eyes, sweating, confusion *Antihistaminic:* Weight gain, somnolence, nightmares, confusion *Other:* Cardiac arrhythmia, prolonged conduction time, orthostatic hypotension, seizures, tachycardia, tremor, sexual dysfunction, mania
Selective Serotonin Norepinephrine Reuptake Inhibitor (SNRI)	Headache, agitation, anxiety, insomnia, somnolence, dry mouth, sweating, urinary retention, constipation, increased blood pressure (dose-related), nausea, dizziness, tachycardia, orthostatic hypotension, sexual dysfunction, mania
Bupropion	Increased risk of seizures, insomnia, anxiety, agitation, headache, tremor, myoclonus, tinnitus, palpitations ➔ *Do not use in patients with eating disorders or seizure disorders, or those acutely withdrawing from alcohol, barbiturates, or benzodiazepines.*
***** For a complete list of side effects, consult the *Physicians' Desk Reference, the respective manufacturer's prescribing information, or other appropriate sources.*	

APPENDIX 11C. ANTIDEPRESSANT MONITORING

BASELINE MONITORING	PERIODIC MONITORING (IF INDICATED)
• Thyroid function test • Electrolytes • Renal function • Liver function tests • Pregnancy test • Urine drug screen • ECG (citalopram)	• Electrolytes, if hyponatremia suspected • Liver function tests, if hepatic impairment suspected

APPENDIX 12. ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)*

Patient Identification:		
Evaluation Date: ___/___/____ ☐ Baseline ☐ 6 Months ☐ Annual ☐ Other: _____		
Instructions: Complete *AIMS Examination Procedure* (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 *increase* 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.

APPENDIX 13A. MANAGEMENT OF ANTIPSYCHOTIC-INDUCED SIDE EFFECTS

SIDE EFFECT	RISK FACTORS*	USUAL ONSET	MANAGEMENT**
Akathisia	• None known	Hours to days *(persistent and chronic, once developed)*	Beta blocker, e.g., propranolol *If ineffective at maximum dose, change to another beta-blocker or a benzodiazepine if needed. After resolution of akathisia, try antipsychotic from another class.*
Anticholinergic Side Effects	• Low-potency antipsychotics • Use of antiparkinsonian meds	Hours to days	Palliative treatment
Dystonia	• 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
Metabolic Syndrome	• History of high glucose • Family history of DM • Overweight • Use of SGAs	Days to years	Diabetic management
NMS → *See Appendix 9 for more details.*	• Male gender • Young age • Past history of NMS	Hours to days	Hospitalization → *Do not rechallenge with same antipsychotic after NMS has resolved.*
Pisa Syndrome	• Older age • Brain disease or damage • High-potency antipsychotic	Hours to months or years	Anticholinergic or antihistaminic (higher doses, generally)
Pseudoparkinsonism *(muscle rigidity, bradykinesia, tremor, drooling, flat affect, etc.)*	• Older age • Brain disease or damage • High-potency antipsychotic	Hours to weeks	Anticholinergic or antihistaminic at lowest effective dose
Rabbit Syndrome	• Older age • Brain disease or damage • High-potency antipsychotic	Weeks to months	Anticholinergic or antihistaminic
Tardive Akathisia	• Other tardive syndromes	Months to years, or upon withdrawal of antipsychotic	Consider change to SGA or clozapine
Tardive Dyskinesia	• 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)*	• 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

* Serious side effects may occur in patients with no known risk factors.

** 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.

APPENDIX 13B. ANTIPARKINSONIAN AGENTS

MEDICATION*	USUAL DOSE RANGE	INDICATION
Amantadine (presynaptic dopaminergic agent)	100–200 mg in once or twice daily dosing (tolerance may develop)	Stiffness, rigidity, bradykinesia
Ativan, clonazepam (benzodiazepines)	1–4 mg in BID dosing	Akathisia
Benztropine (anticholinergic and antihistaminic)	1–6 mg daily (at higher doses, give in twice daily dosing)	Stiffness, rigidity, bradykinesia, tremor drooling, dystonia
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
Trihexyphenidyl (anticholinergic)	5–20 mg daily (at higher doses, give in twice daily dosing)	Stiffness, rigidity, bradykinesia, tremor

* 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.

APPENDIX 14. DRUG DOSING IN ELDERLY PATIENTS

DRUG	INDICATION**	DOSING
Aripiprazole	Mania & Hypomania (2)	• Start with 2.5-5 mg once daily. • Target dose = 10 mg twice daily. • Maximum dose = 30 mg/day.
Asenapine	Mania & Hypomania (2)	• Start with 5 mg twice daily. • Target dose = 10 mg twice daily. • Maximum dose = 20 mg/day.
Fluoxetine	Depression (2)	• Start with 10 mg/day. • Increase dose every 4 weeks by the same amount. • Target dose = 20 mg/day.
Lamotrigine	Depression (2)	• Start with 25 mg/day for 2 weeks; then, increase to 25 mg twice daily for the next 2 weeks. • The dose can then be increased by 25–50 mg/day, one week at a time. • Target dose = 100–200 mg in 2 divided doses.
Lithium*	Mania & Hypomania (1)	• Start with 150 mg once or twice daily. • Increase dose every 1 to 5 days as tolerated. • Target doses are determined by a 12-hour serum trough level drawn 5 to 7 days after each dose increase. • Doses > 900–1200 mg/day are rarely required.
	Depression (2)	• Same dosing as with mania.
Lurasidone	Depression (1)	• Start with 20 mg in the evening. • May increase dose every 2 to 7 days by increments of 20 mg/day. • Target dose = 20–120 mg/day.
Olanzapine	Mania & Hypomania (1)	• Start with 2.5–5 mg once daily. • Increase dose every 2 to 5 days by increments equal to the starting dose. • Target dose = 5–15 mg/day. • Maximum dose = 20 mg/day.
	Depression (2)	• Same dosing as with mania.
Quetiapine	Mania & Hypomania (1)	• Start with 12.5–25 mg once daily or 25–50 mg in 2 divided doses. • Increase dose every 2 to 5 days by increments equal to the starting dose. • Target dose = 100–300 mg in 2 divided doses. • Maximum dose = 800 mg/day.
	Depression (1)	• Same starting dose, dosing increase, and target dose as with mania. • Maximum dose = 600 mg/day.
Risperidone	Mania & Hypomania (2)	• Start with 0.1–1 mg once daily or in 2 divided doses. • Target dose = 1–4 mg once daily or in 2 divided doses. • Maximum dose = 6 mg/day.
Valproate*	Mania & Hypomania (1)	• Start with 125–250 mg/day. • Increase dose every 1 to 5 days by the same amount. • Target doses are determined by a 12-hour serum trough level of both total and free valproate, drawn 2 to 5 days after each dose increase. • Doses > 500–1500 mg/day are rarely required.
	Depression (2)	• Same dosing as with mania.
Ziprasidone	Mania & Hypomania (2)	• Start with 20 mg once daily or 40 mg in 2 divided doses. • Target dose = 80–120 mg in 2 divided doses. • Maximum dose = 160 mg/day.

* The half- life of lithium and valproate increases as patients get older. Therefore, older patients generally require smaller doses of these medications to reach and maintain a steady serum level.

** (1) = first-line medication; (2) = second-line medication