This care process model (CPM) was developed by Intermountain Healthcare’s Behavioral Health Clinical Program as part of a care management system for bipolar disorder. The CPM recommends screening, diagnosis, and treatment processes to improve care and outcomes for patients with bipolar disorder. Related tools — including evaluation forms, reference tools, and patient education handouts — support implementation of these recommended processes.

Why Focus ON BIPOLAR DISORDER?

- **High prevalence.** A 2005 report on National Comorbidity Survey Replication (NCS-R) data estimated that bipolar disorder affects about 5.7 million American adults, or about 2.6% of the population 18 years and older (1-year prevalence). The same study noted a lifetime prevalence of 3.9%, suggesting the chronic nature of this illness.

- **Inadequate detection.** Estimates from surveys of people who screen positive for bipolar disorder note that clinicians misidentify their condition more than half of the time. Patients may visit several clinicians before being correctly diagnosed. Many suffer for a decade or more before being diagnosed and appropriately treated. Misidentification leads to increased hospitalization and emergency room visits and higher healthcare costs.

- **Inappropriate use of antidepressants.** When providers mistake bipolar depression for unipolar depression, they are likely to treat using only antidepressants. In patients with bipolar disorder, using antidepressants alone (unopposed by mood-stabilizing medications) can induce mania, mixed states, and more severe rapid cycling varieties of this disorder. Medications with mood-stabilizing properties should be used to treat this illness.

- **Poor treatment adherence.** Patients with bipolar disorder typically have low adherence to treatment; reported non-adherence for long-term prophylactic pharmacotherapy is about 40%. Psychosocial interventions can significantly improve adherence.

- **Risk of death.** Bipolar disorder can be a debilitating disease with a high risk of death by suicide (19%). People with this disorder rate their illness as “severe” 83% of the time — much higher than they rate the severity of other mental illnesses (22%) — and have trouble functioning in many areas of life. Treatment can significantly reduce suicide rates, even in those who are more severely ill.

- **Lost productivity.** According to a recent study funded by the National Institute of Mental Health (NIMH), bipolar disorder costs the U.S. workplace $14.1 billion annually; this is nearly half as much as lost-productivity costs due to unipolar depression, although unipolar depression is more than six times as prevalent. Over the past 20 years, the World Health Organization (WHO) has consistently rated bipolar disorder among the top 10 leading causes of disability in the world.
DIMENSIONS OF IMPAIRMENT

- **Moods.** Extreme mood episodes are the hallmark of this disorder.
- **Thoughts.** Several studies detail cognitive impairment in bipolar disorder—in particular, problems with memory and executive function, attention and verbal skills.
- **Actions.** Impulsivity and excessive risk-taking are common, especially during episodes of mania. People can find themselves acting in ways that aren’t characteristic for them and don’t represent their personal values. Excessive spending, sudden travel, uncharacteristic substance abuse and sexual promiscuity are common expressions of bipolar impulsivity.

MAJOR TYPES OF BIPOLAR DISORDER

**Bipolar I Disorder:**
Diagnosis requires at least one lifetime manic or mixed episode (causing significant impairment); most people with bipolar I have also had one or more episodes of major depression.

**Bipolar II Disorder:**
Diagnosis requires at least one lifetime episode of hypomania (causing less significant impairment) and at least one episode of major depression.

**Cyclothymia:**
Diagnosis requires at least 2 years (only 1 year in children and adolescents) of clinically significant distress/impairment in key areas of functioning (at work, at school, at home, with friends, etc.). This period is characterized by numerous periods where the person experiences hypomanic and depressive symptoms that fail to meet the full criteria of either hypomania or major depression.

UNDERSTANDING BIPOLAR DISORDER

Bipolar disorder, previously called manic-depressive disorder, is a chronic biological disease, not a character defect or moral failing. People with this illness experience changes in their mood and ability to think and to function. At other times they can be completely without signs or symptoms of their illness. Depression is the most common mood in bipolar disorder but people also experience hallmark periods of euphoria and irritability. It is not unusual for these mood states to overlap and profoundly disrupt a person’s work, school, home, and social life. The risk of suicide for this illness is very high but does decrease with treatment.

**Genetic basis**

The exact cause of bipolar disorder is not known. Recent studies have identified that a patient’s genetic predisposition to the disorder may derive from those genes that are involved in hormone regulation, calcium channels, secondary messenger systems, and glutamate signaling. The risk of bipolar disorder increases if a parent or sibling suffers from the disorder. First-degree biological relatives of someone with bipolar I disorder have a 4 – 24% chance of developing bipolar I disorder, a 1 – 5% chance of developing bipolar II disorder, and a 4 – 24% chance of having unipolar depression. When one identical twin has bipolar disorder, the other twin is 7 – 8 times more likely to have it than a fraternal twin.

**Bipolar depression versus unipolar depression**

Depressive symptoms are the most common in bipolar disorder. They can appear identical to those of a person with unipolar depression. More than 10% of patients with depression will go on to experience a mania or hypomania episode in the next decade. Unlike unipolar depression, which is more common in women than men, bipolar I disorder is equally common in men and women. Unlike unipolar depression, bipolar I disorder includes an onset before the age of 25, a parent or sibling with bipolar disorder, a history of psychotic depression, postpartum depression, multiple recurrent depressive episodes, or a history of mania or hypomania induced by antidepressants. Further, bipolar depression is often associated with “atypical” symptoms including hypersomnia and hyperphagia. Depression frequently occurs with partial or complete mania symptoms such as racing thoughts, irritability, impulsivity, and psychosis.

**Predictors of progression from unipolar to bipolar I or II depression:** Among patients who have major depression and go on to develop bipolar disorder, a more acute, severe, and psychotic episode predicts bipolar I disorder (about 4% of depressives followed long-term) and mood lability or temperamental instability predicts bipolar II disorder (about 9% of depressives followed long-term).

**Bipolar spectrum**

Bipolar disorder and unipolar depression seem to exist at two ends of a spectrum. In the middle of the spectrum are patients with major depression and some symptoms associated with bipolar disorder (e.g., racing thoughts). These patients have more risk factors of bipolar disorder (e.g., early age of depression onset and family history) than those suffering unipolar depression without those symptoms. If these patients do not respond to standard depression treatment, clinicians should consider medications with mood stabilizing properties.

Family history studies support this view of the bipolar spectrum. Patients with bipolar I disorder may have offspring with bipolar I, bipolar II, or unipolar depression, whereas patients with bipolar II disorder tend to have offspring with bipolar II or unipolar depression.
Variety in symptom expression

The average age of onset of bipolar disorder is in the teen years to early 20s. The first episode can be either a depressive or manic episode. Transitioning from a manic/hypomanic episode to a depressive episode or from a depressive episode to a manic/hypomanic is considered one “cycle” of bipolar disorder. The episodes in each cycle can vary from mild to severe in intensity. They can be interspersed by long periods of euthymic mood or be followed immediately by another mood cycle. Disability in functioning is usually related to how frequently people cycle and how severe their symptoms are during their cycle.

• **Proportion of time spent in various mood states.** People with bipolar disorder suffer reoccurring mood symptoms throughout their life. One study tracked patients’ moods weekly for over a decade for the two major types of the illness (bipolar I disorder and bipolar II disorder). In this study, most of the time symptomatic was spent depressed and a minority of time was spent either manic or hypomanic. These results are shown below:

![Diagram showing the proportion of time spent in various mood states for Bipolar I and Bipolar II disorders.]

- **Severity of symptoms.** Over the long-term course, the majority of symptoms are subsyndromal or not severe enough to diagnose as major depression or as overt mania. Nevertheless, subsyndromal depressive symptoms can be significantly disabling. Hypomanic episodes are often rated by patients as causing no disability (and some feel it to be a state of superior functioning). Severe manic symptoms are as disabling as severe depressive symptoms.

- **Combinations of symptoms.** It is common to have symptoms of mania/hypomania and depression at the same time. An estimated 40% of manic episodes and more than half of all hypomanic episodes are associated with significant depressive symptoms. Some people with bipolar disorder experience mixed states — episodes in which they have symptoms that meet criteria for both mania and depression nearly every day for a 1-week period or longer. Mixed episodes are common and can be very severe. They are also associated with less frequent remissions, poorer response to mood stabilizers, increased suicidal ideation/behavior, and more comorbidities (including substance abuse). Use of antidepressants is also associated with increased incidence of mixed episodes.

- **Frequency of episodes.** Cycling varies from an average of 1 cycle every 3 years to the severe variation called rapid cycling. Rapid cycling is when people cycle between mood episodes four or more times a year. This variety can be either bipolar I or bipolar II. The typical patient is bipolar II and female. In this variant, there appears to be a continuous distribution from limited mood cycling to the extreme of intra-day (ultraradian) cycling. This form of the illness may be less sensitive to the effects of lithium carbonate. Factors associated with rapid cycling include the following:
  - Female gender and early life trauma (more strongly associated with cycling between mood states more than once a month)
  - Antidepressant use
  - Genetic susceptibility (higher prevalence of the double short allele of the serotonin transporter protein)
  - Clinical or subclinical hypothyroidism

The variables noted above should be considered when diagnosing bipolar disorder — and when treating it. Medication(s) can alter the expression of the disorder.

**WHAT IS MANIA?**

Mania is defined as a mental state characterized by rapid thoughts, irritable/euphoric mood, increased activity, talkativeness, and/or impaired judgment. Manic or hypomanic patients exhibit these types of symptoms:

- **Activity or stimulation:** Symptoms are similar to those experienced when one takes excessive doses of stimulant medications, such as euphoria and irritability. Actions and feelings are also stimulated: a manic patient may need less sleep, have increased speed of thoughts, speak faster or with pressure, have increased focus on activities, and be overtly agitated. Increased activity can range from doing a routine task excessively, such as doing housework all night long, to becoming involved in uncharacteristic activities, such as planning multiple risky business ventures.

- **Intensity:** Mania symptoms are experienced with heightened intensity. They may be intensely pleasurable or intensely dysphoric.

- **Impaired judgment and thinking:** Behavior and actions are often impulsive and pleasure-seeking. When manic, patients can participate in uncharacteristic overspending, promiscuity, substance abuse, or other impulsive behavior. Judgment may be affected by perceptual disturbances such as auditory hallucinations, thought problems such as paranoia, flight of ideas (ideas that change so rapidly that they are confusing), or false beliefs (e.g., that one is more powerful, famous, or successful than in reality). Over half of patients who have bipolar disorder experience psychotic symptoms at some time during their illness.
ALGORITHM NOTES

(a) PHQ-2 Scoring
The PHQ-2 consists of the first two questions in the PHQ-9 (see page 5) used as a first step in screening patients for depression. Scoring for each question is indicated below:

**TABLE 1. PHQ-2 Scoring**

<table>
<thead>
<tr>
<th>Item</th>
<th>Score Range*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Little interest or pleasure in doing things</td>
<td>0 – 3</td>
</tr>
<tr>
<td>Feeling down, depressed or hopeless</td>
<td>0 – 3</td>
</tr>
<tr>
<td>Total Score (Positive = ≥ 3)</td>
<td>0 – 6</td>
</tr>
</tbody>
</table>

*Score based on the following: 0 = Not at all; 1 = Several Days; 2 = > Half the Days; 3 = Nearly Every Day

(b) PHQ-9 Scoring
The PHQ-9 (see page 5) uses both a symptom score and a severity score. Scoring guidance for each type is indicated below:

**TABLE 2. PHQ-9 Scoring**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Scoring Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom Score</td>
<td>≥ 5 = Administer MDQ (see page xx)</td>
</tr>
<tr>
<td></td>
<td>&lt; 5 = Usual care; see Depression CPM</td>
</tr>
<tr>
<td>Severity Score</td>
<td>≥ 9 = Administer MDQ (see page xx)</td>
</tr>
<tr>
<td></td>
<td>&lt; 9 = Usual care; see Depression CPM</td>
</tr>
<tr>
<td>Suicidal Ideation</td>
<td>If &quot;yes&quot; to question #9, assess suicide risk.</td>
</tr>
</tbody>
</table>

(c) MDQ Scoring
Score the MDQ according to the criteria below and guidance in the Scoring and Evaluating, Adult MHI Forms CPM.

For a positive screen, all three of the following criteria must be met:
- Question 1: 7 / 13 positive (yes) responses
- Question 2: Positive (yes) response
- Question 4: "moderate" or "serious" response

**ALGORITHM 1: DIAGNOSIS**

1. **ADMINISTER and SCORE** the first two questions of the Patient Health Questionnaire (PHQ-2) (a)
   - Positive? (Positive? yes)
     - PROVIDE usual care
   - Positive? (Positive? no)
     - ADMINISTER and SCORE the Patient Health Questionnaire (PHQ-9) to identify and diagnose major depression (see page 5) (b)
       - Positive? (Positive? yes)
         - PROVIDE usual care
       - Positive? (Positive? no)
         - ASSESS suicide risk and DETERMINE associated treatment (see page 5 and Suicide Prevention CPM)

2. **ADMINISTER and SCORE** (c) the Mood Disorder Questionnaire (MDQ) (see page 6 (c)
   - Positive? (Positive? no)
     - PROVIDE usual care
   - Positive? (Positive? yes)
     - TREAT per Depression CPM
   - Positive? (Positive? no)
     - INTERVIEW patient to confirm specific DSM-5 diagnostic criteria.
     - USE SADFIGS mnemonic to aid diagnosis (see page 7).
     - RATE severity of illness with CGI Scale (see page 22).

3. ASSESS for comorbidities (see page 8)
   - Mental health specialist
   - Primary care provider

   - TREAT per algorithm on page 10

   - REFER to a mental health specialist if patient has unmanageable conditions or behaviors such as significant comorbidities, psychotic tendencies, suicidal ideation/behavior, violence, or treatment failures.
   - START treatment (using a medication with mood-stabilizing properties per algorithm on page 11) while awaiting mental health referral or consultation.
   - DO NOT USE UNOPPOSED ANTIDEPRESSANTS.
Discussion: The need for consistent screening and diagnosis

Patients with bipolar disorder may see multiple healthcare providers for as many as 10 years or more before they receive the correct diagnosis. This is due in part to these factors:

- People with bipolar disorder seek treatment more often when depressed, and thus they are often treated for unipolar depression.
- Bipolar disorder is often comorbid with substance abuse and anxiety disorders, which can mask and complicate symptoms. Thus, assessing for comorbidities is a critical part of the screening process (see pages 9 – 10).
- There is often no consistent process for screening and diagnosis in various care settings.

Primary care providers (PCPs) are generally the first care providers who see a patient with bipolar disorder. Unfortunately, since patients often present with symptoms of depression, bipolar disorder is often misdiagnosed as unipolar depression and treated inappropriately with an unopposed antidepressant, which can make the illness worse. Unopposed antidepressants may induce mania and mixed bipolar states, mood instability, and rapid cycling.

Patients eventually diagnosed with bipolar disorder often experience multiple failed antidepressant trials or the onset or worsening of agitation and anxiety while on antidepressants. To improve early identification and treatment of bipolar disorder, this CPM recommends a consistent process for screening and diagnosis in all treatment settings. This includes use of validated screening tools such as the Patient Health Questionnaire (PHQ-9) for depression and suicidal ideation and behavior (content appears at right) and the Mood Disorder Questionnaire (MDQ) for mania (content appears on page 6).

To download the PHQ-9 at: https://m.intermountain.net/forms/Pages/Details.aspx?isForm=true&ncid=521377846&title=MHI PHQ-9 Patient Health Questionnaire
Suicide assessment

As shown in the algorithm on the previous page, an assessment of suicide risk should be done for every patient who responds positively to question 9 on the PHQ-9 or who has experienced suicidal ideation (thoughts of engaging in suicidal behavior). Although suicide is a low-probability event, bipolar disorder is one of the most common psychiatric disorders associated with suicide. Patients with bipolar disorder have a high rate of lifetime suicide completion (about 19%).

Intermountain uses the Columbia-Suicide Severity Rating Scale (C-SSRS) to standardize assessment of suicidal ideation and behavior, determine levels of risk, and make clinical decisions about care. The Suicide Prevention CPM details the C-SSRS versions used and suggested treatment approaches in each care setting. The table below (from page 3 of the Suicide Prevention CPM) provides an overview of risk level (based on a positive response to each C-SSRS Quick Screen question and recommended actions to take in each setting based on patient responses. See the Suicide Prevention CPM for detailed steps for asking these questions.

### TABLE 3: Patient safety measures and response protocols based on Quick Screen responses

<table>
<thead>
<tr>
<th>C-SSRS Quick Screen questions (in the last month)</th>
<th>Action if patient response “Yes”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question</td>
<td>&quot;Yes&quot; indicates</td>
</tr>
<tr>
<td>1. Have you wished you were dead or wished you could go to sleep and not wake up?</td>
<td>Wish to be dead</td>
</tr>
<tr>
<td>2. Have you actually had any thoughts of killing yourself?</td>
<td>Nonspecific thoughts</td>
</tr>
<tr>
<td>3. Have you been thinking about how you might kill yourself?</td>
<td>Thoughts with method (without specific plan or intent to act)</td>
</tr>
<tr>
<td>4. Have you had these thoughts and had some intention of acting on them?</td>
<td>Intent (without plan)</td>
</tr>
<tr>
<td>5. Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?</td>
<td>Intent with plan</td>
</tr>
<tr>
<td>6. Have you ever done anything, started to do anything, or prepared to do anything to end your life?</td>
<td>Behavior</td>
</tr>
</tbody>
</table>

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Mood Disorder Questionnaire (MDQ)
The Mood Disorder Questionnaire (MDQ) is a tool that screens specifically for bipolar disorder. It is NOT a diagnostic instrument. Used alone in a population with low rates of bipolar disorder (e.g., in primary care settings), it will produce significant false positive results. Therefore, screening an enriched population, such as those who meet diagnostic criteria for depression and/or have failed an antidepressant trial, or those for whom the clinician intuits bipolar disorder, is likely to correctly identify the most patients. (Note that patients who have a negative result using the MDQ are unlikely to have bipolar disorder.) Content of the MDQ form appears below; see the notes at right for tips on using and interpreting the tool.

What next?
When a patient screens positive for bipolar disorder using the MDQ:

- Interview the patient to determine if the patient has had at least one lifetime episode of depression and one lifetime episode of mania or hypomania.
- Use DSM-5 diagnostic criteria to determine and confirm a diagnosis (see page 8).

### WHEN TO SCREEN

- **In primary care settings:** Primary care providers should screen all new patients for depression with the PHQ; patients who screen positive for depression should be further screened with the MDQ.

- **In mental health provider settings:** Mental health specialists should screen all new patients with the MDQ.

### INTERPRETING RESULTS

For a positive screening, questions 1 and 2 must both be positive:

- **For question 1,** a positive result is 7 or more of the 13 sub-questions answered “yes.”
- **For question 2,** a positive result is “yes.”

**Question 3** measures potential for medication-induced symptoms.

**Question 4** measures impairment. A response of “moderate” or serious” suggests bipolar I disorder, whereas a response of “minor” or “no problem” suggests bipolar II disorder. (See the following page for more detail on distinguishing these 2 bipolar variants.)

### IMPROVING SENSITIVITY

Adding the following 2 sub-questions to question 1 of the MDQ can improve the sensitivity of the MDQ screening by as much as 10% (as suggested by 2007 Intermountain Healthcare data):

- Have any close family members (parents, siblings, children) ever been diagnosed with bipolar disorder or manic depression?
- Did you have mood problems before the age of 25?

When these two questions are added to the 13 items in section 1, patients who answer “yes” to ≤6 of the 15 questions are very unlikely to have bipolar disorder.
A MNEMONIC TO AID DIAGNOSIS:

**S A D F I G S**

For confirmation of a lifetime episode of mania or hypomania — and a bipolar disorder diagnosis — a patient’s symptoms must meet these criteria:

- A consistently elevated, irritable, or expansive mood lasting at least 1 week (or any duration if hospitalization is required) for mania and at least 4 days for hypomania.
- If elevated mood, at least three of the following SADFIGS symptoms. If irritable mood, at least four of the following SADFIGS symptoms:

<table>
<thead>
<tr>
<th>S</th>
<th>Sleep, less need</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Agitation or increased focused activity</td>
</tr>
<tr>
<td>D</td>
<td>Distractibility</td>
</tr>
<tr>
<td>F</td>
<td>Flight of ideas or racing thoughts</td>
</tr>
<tr>
<td>I</td>
<td>Impulsivity</td>
</tr>
<tr>
<td>G</td>
<td>Grandiosity</td>
</tr>
<tr>
<td>S</td>
<td>Speech, rapid or pressured</td>
</tr>
</tbody>
</table>

---

**Diagnostic criteria**

The table below provides an overview of key diagnostic criteria for bipolar 1 disorder, bipolar II disorder, and cyclothymic disorder — the most prevalent bipolar disorder diagnoses.

**TABLE 4: Overview of Major Bipolar Diagnoses**

<table>
<thead>
<tr>
<th>Bipolar I</th>
<th>Episode Type(s) (Required)¹</th>
<th>Context¹</th>
<th>Duration²</th>
<th>Severity²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Manic</td>
<td>Lifetime</td>
<td>1 week; almost daily; &gt;50% of each day</td>
<td>Impacts all key areas of functioning, includes psychotic features, or necessitates hospitalization</td>
</tr>
<tr>
<td>Bipolar II (ICD-10: F31.81)</td>
<td>Hypomanic AND major depressive</td>
<td>Lifetime</td>
<td>4 days; almost daily; &gt;50% of each day</td>
<td>Functioning is not seen as usual for patient by others in key areas; no psychotic features; no hospitalization needed</td>
</tr>
<tr>
<td>Cyclothymia (ICD-10: F31.4)</td>
<td>Symptoms related to hypomanic AND major depressive BUT not meeting full criteria for either episode as defined by DSM-5</td>
<td>Lifetime or past 2 years?</td>
<td>Past 2 years (1 year if child or adolescent); 50% of overall time; symptom free &lt; 2 months within time frame</td>
<td>Impacts key areas of functioning and causes considerable distress</td>
</tr>
</tbody>
</table>

1. For information related to other bipolar diagnoses (substance/medication-induced bipolar and related disorders, bipolar and related disorders due to another medical condition, and other specified bipolar and related disorders), see *Diagnostic and Statistical Manual of Mental Disorders — Fifth Edition*.4²³
2. **Context**: time frame in which symptomatic episode must have occurred (e.g., lifetime, past 2 years, etc.)
3. **Duration**: specific number of days that symptoms occurred; symptoms last for a specified time and frequency during those days
4. **Severity**: symptoms are severe enough to cause patients considerable distress and impact their daily functioning in key areas of their lives

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**ICD-10 CODING FOR BIPOLAR I**

Diagnostic coding for bipolar I is typically based on current or most recent episode and severity. General ranges appear in this box. For more detailed coding instructions, refer to [ICD10data.com](http://ICD10data.com).

- **F31.0** Bipolar disorder, current episode hypomanic
- **F31.1** Bipolar disorder, current episode manic without psychotic features (specify severity)
- **F31.2** Bipolar disorder, current episode manic severe with psychotic features
- **F31.3** Bipolar disorder, current episode depressed mild or moderate severity (specify severity)
- **F31.4** Bipolar disorder, current episode depressed, severe without psychotic features
- **F31.5** Bipolar disorder, current episode depressed, severe with psychotic features
- **F31.6** Bipolar disorder, current episode mixed (specify severity and presence of psychotic features)
- **F31.7** Bipolar disorder, currently in remission (specify full or partial remission and type of most recent episode)
- **F31.8** Other bipolar disorders (F31.81 Bipolar II disorders; F31.89 other bipolar disorder)
- **F31.9** Bipolar disorder, unspecified

**NOTE:** ICD-10 codes do not correspond exactly to DSM-5 codes and explanations. Intermountain-employed providers can access an online version of the DSM through the eResources page on [IntermountainPhysician.org](http://IntermountainPhysician.org) or [Intermountain.net](http://Intermountain.net).
Comorbidities

Those with bipolar disorder typically suffer from at least one comorbid medical or psychiatric disorder (some studies indicate a large number of patients having at least three chronic medical conditions) as well as having higher lifestyle risk factors that occur at a younger age. These comorbidities can confuse and confound diagnosis and treatment and also make the disorder more severe and difficult to treat. Comorbidities are associated with increased emergency room visits and more hospitalizations. The most common mental health comorbidities are described below; medical comorbidities are discussed on page 10.

Mental Health Comorbidities

The most common comorbid mental health conditions are anxiety disorders and substance use disorder. When co-occurring major psychiatric illnesses and/or significant suicidal ideation/behaviors or homicidity are present, clinical guidelines emphasize the importance of referring these patients to specialty care (see also suicide assessment information on page 6).

Anxiety disorders. Anxiety disorders are the most common mental health comorbidities in patients with bipolar disorder — nearly 75% of patients have comorbid bipolar disorder and some type of anxiety disorder. Common features of anxiety include panic attacks, fears, and worries. Somatic symptoms include poor concentration, agitation, muscle tension, headache, and perspiration. It may be difficult to differentiate agitation caused by mania from anxiety caused by a comorbid anxiety disorder. Anxiety symptoms may be difficult to separate from symptoms of agitation while a patient is experiencing mania.

What to do: Treat the bipolar disorder first; treatment may take care of anxiety symptoms.

Substance use disorder. Substance use disorder is the second most common comorbid diagnosis in bipolar disorder. More than half of patients with bipolar disorder will have a substance use diagnosis in their lifetime. Substance use disorder includes alcoholism, tobacco use, prescription drug abuse, and ‘street drug’ abuse. Alcoholism is the most common of the substance use comorbidities. The incidence of alcoholism in those with bipolar disorder is 3 times higher for men and 7 times higher for women.

What to do: Use the NIDA Quick Screen (download the full-size version of this tool here: Intermountain-Modified National Institute on Drug Abuse (NIDA) Quick Screen) to screen for substance use disorder. If identified, aggressively treat the substance use disorder concurrently with bipolar disorder based on the Substance Use Disorder CPM. Successful treatment of bipolar disorder is unlikely with ongoing substance-use problems. Avoid lithium as a primary mood stabilizer in these patients, and use habit-forming sedatives with caution.

Intermountain-Modified National Institute on Drug Abuse (NIDA) Quick Screen

<table>
<thead>
<tr>
<th>In the past year, how often have you used the following?</th>
<th>Never</th>
<th>Once or twice</th>
<th>Monthly</th>
<th>Weekly</th>
<th>Daily or Almost daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For men, ≥5 standard drinks* a day</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>For women, ≥4 standard drinks* a day</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Tobacco products (including e-cigarettes)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Prescription medications for non-medical reasons</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Prescription medications in amounts greater than prescribed, for reasons other than prescribed, or that weren’t prescribed to you</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Illegal drugs (illicit, street drugs)</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
</tbody>
</table>

*Definition of a "standard drink:"
- Beer or cooler (5% alcohol): 12 ounces
- Malt liquor (7% alcohol): 8–9 ounces
- Table wine (12% alcohol): 5 ounces
- 80-proof spirits (hard liquor) (40% alcohol): 1.5 ounces

Other Comorbidities/ Differential Diagnoses

- Attention deficit hyperactivity disorder
- Disruptive mood dysregulation disorder
- Eating disorders
- Intermittent explosive disorder
- Major depressive disorder
- Personality disorders including borderline personality disorder

For complete differential diagnosis information on these disorders, see the Diagnostic and Statistical Manual of Mental Disorders — Fifth Edition.
Medical comorbidities

Medical problems can not only cause mood episodes but can exacerbate the course of bipolar disorder and complicate treatment in terms of greater illness severity, reduced recovery, and increased or premature mortality. These comorbidities often accentuate psychological stressors related to employment and disability reimbursement and increase healthcare utilization.\(^\text{VA}\)

Major medical comorbidities in patients with bipolar disorder include cardiovascular disease, autoimmune diseases, cancer, and metabolic disorders. Of these, metabolic disorders (especially diabetes and obesity) offer significant challenges, in part due to the weight-gain side effects of many medications used to treat bipolar disorder. In addition, there are significant challenges of care associated with comorbid diabetes, including:\(^\text{VA}\)

- Almost double the overall health care costs for bipolar patients who have diabetes
- Greater impairment in both physical and mental health
- Lower quality of life
- Less satisfaction with health

According to recent research, there is a bi-directional relationship between comorbid metabolic disorders and bipolar disorder because those with bipolar disorder tend to take in more calories with a higher glycemic load and are significantly more sedentary than the general population.\(^\text{MAN}\) In addition, a 2012 population-based study of 800,000 people indicated that those with untreated type 2 diabetes had a significantly increased risk of developing bipolar disorder and that treating diabetes may prevent bipolar onset.\(^\text{MAN}\)

Other medical comorbidities can include thyroid dysfunction, migraines, and cardiovascular disease. Considerations include:

- **Thyroid dysfunction.** Hypothyroidism is associated with rapid cycling and difficult-to-treat depression, and hyperthyroidism can produce agitation and anxiety that can make the identification of mania more difficult.

- **Other medical comorbidities** lead to additional disability and mortality for bipolar patients. Note that compared to people without bipolar disorder,\(^\text{CAS, ELM, MAH, SCHI, WEE}\)
  - Incidence of migraines is 5 times higher.
  - Incidence of cardiovascular disease is 1.9 times higher.

**What to do:** Assessment for bipolar disorder must include assessment for the medical the conditions above. Patients should be treated concurrently — and extra monitoring may be necessary. Many medications used to treat this illness can aggravate cardiovascular risk factors (cardiovascular disease is the leading cause of death in patients with bipolar disorder).
TREATMENT FOR ADULTS

Patients with bipolar disorder have better outcomes with aggressive, multimodal treatment that includes appropriate medication, patient/family education, psychotherapy, and (when available) care management. The target for treatment is FULL REMISSION. Patients who achieve remission will have lower rates of relapse. To assess progress toward this goal, providers should have a consistent method — such as the CGI scores described on page 18 — to assess response to treatment. Note that because of limited quality studies comparing treatment outcomes, the guidelines presented in this CPM are reasonably broad and focus primarily on bipolar I disorder. There is little quality evidence to support specific treatments for bipolar II disorder, and no published research for bipolar not otherwise specified (NOS). The algorithm below and the discussion and tables that follow present a recommended approach to treatment based on the best available evidence, along with expert opinion from clinical practice.

ALGORITHM 2: TREATMENT

Patient diagnosed with bipolar I or bipolar II

START monotherapy with a medication with mood stabilizing properties*

START with a mood stabilizer with “A” quality data for treatment of the appropriate pole.

See the medication tables on pages 13 – 16 for details.

• PROVIDE patient/family education (see pages 27 – 28)
• REFER for psychotherapy
• CONSIDER care management

FOLLOW UP in 1 – 2 weeks as indicated by acuity and severity

Adequate response? no

ADD a second mood stabilizer.

(Somewhat or much improved CGI global improvement score 1 – 3)

FOLLOW UP in 4 weeks until remission. At every follow-up visit:

• EVALUATE adherence
• ASSESS clinical response and side effects at current dose
• USE outcome measures to assess progress (see page 22)
• ASSESS educational needs
• ASSESS therapeutic alliance (see page 21)
• ASSESS for substance abuse (see page 9)

Improved?

• RAISE dose of mood stabilizer as tolerated.
• ADD a second mood stabilizer focused on specific symptoms

Much improved

CGI score 1 – 2

CONTINUE at present dosage(s).

• FOLLOW UP every 4 weeks until remission (CGI severity score 1 – 2).
• When in remission, FOLLOW UP at least every 6 months to monitor symptoms, lab values, and functional outcomes.

TARGET: FULL REMISSION

(CG1 severity score 1 – 2)

Somewhat improved

CGI score 3

RAISE dose as tolerated; if at maximum dose, change to a different primary mood stabilizer.

OR

ADD a second mood stabilizer focused on specific symptoms

CONSIDER consultation/referral to a mental health specialist

No improvement or worsening

CGI score 4 – 7
THE 3 Ms OF MEDICATION MANAGEMENT FOR BIPOLAR DISORDER

Mood stabilizers
In general, people with bipolar disorder should be treated with mood stabilizers for extended periods of time (years). Other medications are added when necessary, typically for shorter periods, to treat episodes of mania or depression that break through despite the mood stabilizer. 

NOTE: if antidepressants are prescribed, mood-stabilizers must be continued as well. 

Multiple medications
Studies indicate that most patients will need more than one medication to achieve remission. Expert consensus guidelines suggest adding a second medication after 1–2 weeks of inadequate response to one medication or for moderate-to-severe symptoms. Combining lithium or divalproex sodium with an atypical antipsychotic can be effective. However, mixing atypical antipsychotics has no clinical research to support its efficacy and may increase the impact of shared side effects.

Monitoring
Because using multiple medications increases side effects, complicates treatment, and worsens patient compliance, monitor patients carefully for these problems. See the treatment algorithm on page 10 and the medication table at right for specific considerations. In addition, monitoring is especially warranted for patients taking antidepressants due to the risk of manic switch. 

ADJUNCT MEDICATIONS
Benzodiazepines such as alprazolam, clonazepam, and lorazepam are often useful for treating insomnia, anxiety, and agitation. Anticholinergics and beta-blockers are used for patients at risk for or currently experiencing medication-induced extrapyramidal symptoms (EPS) such as pseudo-Parkinsons, akathisia and acute dystonia. Thyroid supplements may be necessary for some patients on lithium carbonate since it can interfere with thyroid functioning.

Medications
Because bipolar disorder is a recurrent and chronic illness, long-term pharmacotherapy is almost always indicated. Optimizing medication for people with bipolar may require some trial-and-error to balance medication effectiveness with the associated side-effect burden. Overall, this process should be driven by the best scientific evidence possible — starting with FDA approved treatments or treatments that have shown positive effects in large controlled trials. Medication recommendations (detailed on pages 13–18) are based on the strength of evidence derived from review of literature, product package inserts, and experience from clinical practice.

Mood stabilizers
Medications with mood-stabilizing properties are the mainstay of treatment for bipolar disorder. Mood stabilization happens when a medication effectively treats at least one pole of bipolar disorder without worsening the opposite pole. Medications with mood-stabilizing properties are a heterogeneous group that can be categorized by drug class and by whether they best treat mania, depressive symptoms, or both. The group includes the following:

- **Anticonvulsants**, including carbamazepine, divalproex, lamotrigine, and oxcarbazepine
- **Lithium carbonate**
- **Atypical antipsychotics**, including aripiprazole, asenapine, lurasidone, olanzapine, quetiapine, risperidone, and ziprasidone

Providers should choose a mood-stabilizing medication based on whether the patient presents with depression, mania, or a mixed state — and on the severity of symptoms. Because of significant side effects, careful monitoring is important for patients taking mood stabilizers. Tables 6A and 6B on page 16 detail recommended monitoring for each medication/class. Preference should be given to a mood stabilizer intended for maintenance; some medications are better at preventing mania and some are better at preventing depressive relapse (see information on use in table 5 on pages 13–15).

Antidepressants
Although bipolar disorder is mostly a depressive illness, evidence indicates that antidepressant monotherapy is no more effective than mood stabilizers at treating bipolar depression — and lacks maintenance properties. In fact, unopposed antidepressants may actually induce or worsen mania, promote rapid cycling between poles, and destabilize the course of bipolar treatment. Despite this, antidepressants remain the most widely prescribed medications for the treatment of bipolar depression. Antidepressants should not be used without mood-stabilizing medications to minimize a patient’s risk of switching to mania or rapid cycling, which further increases the risk of future switches.

Bipolar II disorder (characterized by at least 1 depressive and 1 hypomanic episode over the course of a lifetime) lacks clear treatment guidelines; however, interventions are critical for these patients for treatment and prevention, especially due to suicide risk. Internationally, patients with bipolar II experience similarly high rates of suicidal ideation (50.6%) and attempted suicide (20.8%) as those with bipolar I disorder. A review of recent, evidence-based treatment strategies for bipolar II depression and bipolar depression with mixed features strongly recommends treatment with quetiapine for acute therapy and lithium for maintenance therapy.
## TABLE 5. Medications used to treat bipolar disorder

<table>
<thead>
<tr>
<th>Class</th>
<th>Medication (common brands)</th>
<th>Use (strength of evidence)</th>
<th>Dosage guidelines</th>
<th>Tier/ Cost</th>
<th>Side effects and other comments (see page 16 for monitoring guidelines)</th>
</tr>
</thead>
</table>
| Anticonvulsants | **carbamazepine** (Carbatrol, Tegretol) | Mania (A), but due to significant side effects, use only after trying all other meds with (A) strength evidence | Initiate: at 200 mg/twice daily; then increase by 200 mg/day at weekly intervals | 1 $** – $$$ | • Strong inducer of CYP1A2, CYP2B6, CYP2C19, CYP2CB, CYP2C9, and CYP3A4.  
• Auto-inducer: Monitor and adjust serum levels due to liver induction.  
• Common side effects include dizziness, headache, nausea, moderate weight gain, sedation and ataxia.  
• Agranulocytosis, aplastic anemia, thrombocytopenia, hepatic failure and toxic dermal eruptions can rarely occur.  
• Prior to therapy, screen with HLA-B*1502 genotype. |
| | | Bipolar depression (C) Maintenance (B) FDA-approved | Target: serum level 4 – 12 mcg/mL | | |
| | **valproate (or divalproex sodium)** (Depakote, Depakote ER) | Mania and maintenance (A) Bipolar depression (B) (Better at preventing manic episodes than depressive episodes) FDA-approved (for treatment of mania) | Initiate: at 25 mg/kg/day in divided doses  
Titrates: rapidly to desired clinical effect | 1 $** – $$$ | • Common side effects include nausea, diarrhea, thrombocytopenia and moderate weight gain.  
• Dose range presented is for valproate (divalproex). May be given as an extended release formula once daily instead; add 8 – 20% to total daily dose (usual 250 – 500 mg).  
• Agranulocytosis, aplastic anemia, hyperammonemia, hepatic failure and toxic dermal eruptions can rarely occur. |
| | | | Range: 750 – 3,000 mg/day  
Target: serum level 50 – 125 mcg/mL (mid to upper range generally required) | | |
| Anticonvulsants | **lamotrigine** (Lamictal) | Bipolar depression, maintenance (A) Mania (D): no acute efficacy for mania FDA-approved | Initiate: at 25 mg once daily  
Titrates: per set schedule:  
• 25 mg once daily x 2 wks  
• 50 mg once daily x 2 wks  
• 100 mg once daily x 1 wk  
• 200 mg once daily thereafter  
• Further titrations <100 mg per day at weekly intervals | 1 $ – $$ | • Do not titrate more rapidly than recommended dosing schedule due to increased risk of potentially fatal rash.  
• If taking with divalproex, halve titration doses; if taking with carbamazepine, double titration doses (but no more than 100 mg/day increase).  
• Dose adjustment is needed if concomitant enzyme-inducing antiepileptic medication or valproic acid is discontinued.  
• May provoke toxic dermal eruptions (Stevens-Johnson Syndrome, toxic epidermal necrolysis), but markedly reduced risk when titrated as directed; patient should seek medical attention immediately if a rash appears.  
• Common side effects include nausea and rash; if continuing therapy despite rash, reduce dose and titrate more slowly once rash resolves.  
• Estrogen-containing oral contraceptives may decrease lamotrigine levels by 50%. |
| | | | | | |
| | **oxcarbazepine** (Trileptal) | Mania, bipolar depression, and maintenance (C) Not FDA-approved | Initiate: at 300 mg twice daily; increase by 600 mg/day at weekly intervals  
Range: 600 – 2400 mg/day divided  
Usual Target: 1,200 mg/day | 1 $$ | • Strong inducer of CYP3A4.  
• Common side effects include dizziness, headache, nausea and sedation.  
• Agranulocytosis, aplastic anemia, hepatic failure, hyponatremia and toxic dermal eruptions can rarely occur.  
• May reduce effectiveness of contraceptives  
• Prior to therapy, screen for HLA-B*1502 genotype. |

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1 **Strength of evidence key:** (A) = Based on data from large controlled trials; (B) = Based on data from smaller controlled trials; (C) = Based on expert opinion, open-label data, or usual-care experience; (D) = No acute efficacy  
2 Some dosage guidelines are based on usual care experience and may differ from manufacturer’s package data.  
3 Tier 1 = Generic; Tier 2 = Preferred Brand; Tier 3 = Non-Preferred Brand. Cost is based on 30-day actual cost (not copay), and on generic, when available: $=1 – 25; $$=26 – 75; $$$=76 – 150; $$$$>= $1500
### TABLE 5. Medications used to treat bipolar disorder (continued)  

<table>
<thead>
<tr>
<th>Class</th>
<th>Medication (common brands)</th>
<th>Use (strength of evidence)</th>
<th>Dosage guidelines</th>
<th>Tier/ Cost</th>
<th>Side effects and other comments (see Table 6A on page 16 for monitoring guidelines)</th>
</tr>
</thead>
</table>
| Lithium Preparations | lithium carbonate (Eskalith, Eskalith CR, Lithobid) | Mania, maintenance (A) Bipolar depression (B) Decreased efficacy in mixed episodes, rapid cycling, and comorbid substance abuse FDA-approved for treatment of acute mania and maintenance | Initiate: at 300 mg twice daily; increase by ≤ 300 mg/day every 3 – 4 days Range: 600 – 1500 mg/day Acute Mania Target: Serum level 1 – 1.5 mEq/L Maintenance Target: 0.6 – 1.2 mEq/L | 1 $–$$ | • Effective for reducing suicide risk\(^1\)  
• May be given once daily as tolerated; immediate release formulations generally given in doses divided 2–3 times/day  
• Multiple drug interactions (e.g., NSAIDs, ACEIs, diuretics)  
• Moderate weight gain.  
• Common side effects include polydipsia, polyuria, acne, GI discomfort, hand tremor; most are serum-level related  
• No significant sedation or stimulation |
| | lithium citrate | | 8 mEq/5mL solution | | |
| Atypical Antipsychotics | aripiprazole (Abilify) | Mania, maintenance (A) Bipolar depression (C) FDA-approved (for acute treatment of manic and mixed episodes associated with bipolar 1 disorder) | Initiate: at 5 – 15 mg once daily Titrte: as tolerated to 30 mg/day, if clinically indicated Range: 15 – 30 mg/day | 1 $$$ | • Common side effects include restlessness, stimulation, and nausea  
• Minimal risk of extrapyramidal symptoms (EPS) other than akathisia |
| | asenapine (Saphris) | Mania (A) Bipolar depression, maintenance (B) FDA-approved (for treatment of acute mania or mixed episodes associated with bipolar 1 disorder as monotherapy or in combination with lithium or valproate) | Monotherapy — Initiate: at 5 – 10 mg twice daily by mouth Combination therapy — Initiate: at 5 mg twice daily Titrte: to 10 mg twice daily based on clinical response | 3 $$$ | • Sublingual administration only; no eating or drinking for 10 minutes after placing under tongue  
• Common side effects include headache, dizziness and oral hypoesthesia  
• Minimal risk of EPS other than akathisia  
• Minimal sedation and little to no weight gain |
| | lurasidone (Latuda) | Mania, maintenance (C) Bipolar depression (B) FDA-approved (for treatment of depressive episodes associated with bipolar 1 disorder as monotherapy or in combination with lithium or valproate) | Initiate: at 40 mg by mouth once daily (increase as clinically indicated) Range: 20 – 120 mg/day | 3 $$$ | • Medication must be taken with food (at least 350 calories)  
• Common side effects include sedation, EPS, and nausea  
• Little to no weight gain |

\(^1\) Strength of evidence key: (A) = Based on data from large controlled trials; (B) = Based on data from smaller controlled trials; (C) = Based on expert opinion, open-label data, or usual-care experience; (D) = No acute efficacy

\(^2\) Some dosage guidelines are based on usual care experience and may differ from manufacturer’s package data.

\(^3\) Tier 1 = Generic; Tier 2 = Preferred Brand; Tier 3 = Non-Preferred Brand. Cost is based on 30-day actual cost (not copay), and on generic, when available: $= $1–25; $$= $26–75; $$$= $76–150; $$$$= > $1500

\(^4\) Strength of evidence is based on use as an adjunct to lithium or divalproex.
<table>
<thead>
<tr>
<th>Class</th>
<th>Medication (common brands)</th>
<th>Use (strength of evidence(^1))</th>
<th>Dosage guidelines(^2)</th>
<th>Tier/Cost(^3)</th>
<th>Side effects and other comments (see Table 6B on page 16 for monitoring guidelines)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Initiate: at 10 mg at bedtime</td>
<td>1</td>
<td>• Significant sedation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Titrate: by 5 mg increments at daily intervals</td>
<td></td>
<td>• Severe weight gain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Range: 5 – 20 mg at bedtime (may be split twice daily)</td>
<td>$ - $$</td>
<td>• Medium risk of extrapyramidal symptoms (EPS)</td>
</tr>
<tr>
<td></td>
<td>olanzapine (Zyprexa, Zydis)</td>
<td>Mania, maintenance (A)</td>
<td></td>
<td></td>
<td>• Potential for dyslipidemia and hyperinsulinemia, case reports of diabetes risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bipolar depression (B)(^4)</td>
<td></td>
<td></td>
<td>• IM formulation effective for acute agitation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FDA-approved (for treating bipolar 1 disorder as follows):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Acute mania or mixed episodes as monotherapy or in combination with lithium or valproate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Maintenance treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Bipolar depression in combination with fluoxetine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>olanzapine + fluoxetine</td>
<td>Mania, bipolar depression, and maintenance (A)</td>
<td>Initiate: at 50 – 100 mg at bedtime</td>
<td>1</td>
<td>• Significant sedation and moderate weight gain; dry mouth</td>
</tr>
<tr>
<td></td>
<td>(Symbayx)</td>
<td>FDA-approved (for treating bipolar 1 disorder as follows):</td>
<td>Titrate: as clinically indicated</td>
<td></td>
<td>• Lowest EPS risk of the atypical antipsychotics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Acute mania or mixed episodes as monotherapy or in combination with lithium or valproate</td>
<td>Range: 300 – 400 mg/day; up to 800 mg/day may be needed</td>
<td>$ - $$$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Maintenance treatment (in combination with lithium or valproate)</td>
<td>May be given once nightly as tolerated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Acute treatment of depressive episodes (bipolar I and II disorder)</td>
<td>Range: 1 – 6 mg at bedtime; may be split twice daily</td>
<td>$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>quetiapine (Seroquel)</td>
<td>Mania, bipolar depression, and maintenance (A)</td>
<td>Initiate: at 50 – 100 mg at bedtime</td>
<td>1</td>
<td>• Moderate sedation and weight gain; increases prolactin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FDA-approved (for treating bipolar 1 disorder as follows):</td>
<td>Titrate: as clinically indicated</td>
<td></td>
<td>• Minimal risk of EPS below 4 mg daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Acute mania or mixed episodes as monotherapy or in combination with lithium or valproate</td>
<td>Range: 300 – 400 mg/day; up to 800 mg/day may be needed</td>
<td>$ - $$$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Maintenance treatment (in combination with lithium or valproate)</td>
<td>May be given once nightly as tolerated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Acute treatment of depressive episodes (bipolar I and II disorder)</td>
<td>Range: 1 – 6 mg at bedtime; may be split twice daily</td>
<td>$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>risperidone (Risperidal)</td>
<td>Mania (A)</td>
<td>Initiate: at 10 mg at bedtime</td>
<td>1</td>
<td>• Poor absorption without food; for best results take once daily with evening meal (minimum 500 calories)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bipolar depression (C)</td>
<td>Titrate: by 1 mg increments at daily intervals</td>
<td></td>
<td>• Minimal sedation at lower doses; little to no weight gain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintenance (B)</td>
<td>Range: 1 – 2 mg at bedtime</td>
<td>$</td>
<td>• Moderate risk of EPS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FDA-approved (for treatment of acute mania or mixed episodes associated with bipolar 1 disorder as monotherapy or in combination with lithium or valproate)</td>
<td>Range: 1 – 6 mg at bedtime; may be split twice daily</td>
<td></td>
<td>• Significant additional monitoring requirements (see Table 6B on page 16)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Range: 1 – 2 mg at bedtime</td>
<td>Range: 1 – 6 mg at bedtime; may be split twice daily</td>
<td>$$$ - $$$$</td>
<td>• IM formulation effective for acute agitation</td>
</tr>
<tr>
<td></td>
<td>ziprasidone (Geodon)</td>
<td>Mania (A)</td>
<td>Initiate: at 40 mg twice daily with food</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bipolar depression (C)</td>
<td>Titrate: to 60 – 80 mg twice daily with food on day 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maintenance (B)</td>
<td>Range: 40 – 80 mg twice daily with food</td>
<td>$$$ - $$$$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FDA-approved (for treatment of acute manic or mixed episodes associated with bipolar disorder with or without psychosis; for maintenance treatment of bipolar disorder in combination with lithium or valproate)</td>
<td>Range: 40 – 80 mg twice daily with food</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Strength of evidence key: (A) = Based on data from large controlled trials; (B) = Based on data from smaller controlled trials; (C) = Based on expert opinion, open-label data, or usual care experience; (D) = No acute efficacy

\(^2\) Some dosage guidelines are based on usual care experience and may differ from manufacturer’s package data. In patients with repeated compliance issues, consider a long-acting injectable medication.

\(^3\) Tier 1 = Generic; Tier 2 = Preferred Brand; Tier 3 = Non-Preferred Brand. Cost is based on 30-day actual cost (not copay), and on generic, when available: $=$1 – 25; $$=$26 – 75; $$$=$76 – 150; $$$$$= > $1500

\(^4\) Strength of evidence is based on use as an adjunct to lithium or divalproex.

\(^5\) Grade A evidence based on use in combination with fluoxetine
### TABLE 6A. Monitoring Guidelines for Anticonvulsants and Lithium — Monitor (as clinically indicated)

<table>
<thead>
<tr>
<th>Test</th>
<th>Anticonvulsants</th>
<th>Lithium</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>carbamazepine</td>
<td>divalproex</td>
</tr>
<tr>
<td>HLA-B*1502 genotype</td>
<td>screening prior to therapy</td>
<td></td>
</tr>
<tr>
<td>CBC w/differential</td>
<td>every 2 – 4 wks X 2 mos, then every 3 – 6 mos</td>
<td>at baseline; then 1 – 2 wks after any dose change</td>
</tr>
<tr>
<td>Hepatic Function</td>
<td>at baseline; then every 6 – 12 mos</td>
<td>at baseline; then every 6 – 12 mos</td>
</tr>
<tr>
<td>Renal Function</td>
<td>6 – 12 mos</td>
<td>at baseline</td>
</tr>
<tr>
<td>Thyroid Function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test</td>
<td>at baseline</td>
<td>at baseline; then yearly</td>
</tr>
<tr>
<td>Fasting Lipids</td>
<td>at baseline</td>
<td></td>
</tr>
<tr>
<td>Serum Sodium</td>
<td>at baseline</td>
<td></td>
</tr>
<tr>
<td>Serum Medication Level (Trough)</td>
<td>3 – 4 wks after any sustained dose adjustment</td>
<td>1 – 2 wks after any dose change</td>
</tr>
<tr>
<td>Serum Ammonia</td>
<td>when clinically indicated</td>
<td></td>
</tr>
<tr>
<td>ECG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Electrolytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinalysis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 6B. Monitoring Guidelines for Atypical Antipsychotics — Monitor (as clinically indicated)

<table>
<thead>
<tr>
<th>Test</th>
<th>Antipsychotics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aripiprazole, clozapine, olanzapine, quetiapine, risperidone</td>
</tr>
<tr>
<td></td>
<td>ziprasidone (Geodon)</td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
</tr>
<tr>
<td></td>
<td>Clozapine</td>
</tr>
<tr>
<td></td>
<td>Aripiprazole</td>
</tr>
<tr>
<td>Pregnancy Test</td>
<td>at baseline, if indicated (see page 17)</td>
</tr>
<tr>
<td>Fasting Lipids</td>
<td>at baseline; at 12 weeks; then annually</td>
</tr>
<tr>
<td>BMI</td>
<td>initial measurement; then at 4, 8, and 12 weeks; then every visit</td>
</tr>
<tr>
<td>HgA1c/fasting plasma glucose</td>
<td>at baseline; at 12 weeks; then annually</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>at baseline; at 12 weeks; then annually</td>
</tr>
<tr>
<td>Extrapyramidal symptoms (EPS)</td>
<td>baseline; then at each visit</td>
</tr>
</tbody>
</table>

1. In patients of Asian descent, **DO NOT USE** if the HLA-B*1501 allele is present.
2. For unexplained lethargy, vomiting, or mental status changes.
3. For ziprasidone (Geodon), also do baseline ECG if known heart disease, personal history of syncope, family history of early sudden death or congenital long QT syndrome. Also monitor ECGs as clinically indicated for symptoms of prolonged QT interval (e.g., syncope).
<table>
<thead>
<tr>
<th>Circumstance</th>
<th>Medication Considerations</th>
</tr>
</thead>
</table>
| Acute illness                | • Lithium has been proven effective for reducing the risk of suicide in patients with acute illness.  
  • Titrate medication dosage rapidly (except for lamotrigine — never rapidly titrate lamotrigine).  
  • Use respective adjunctive medications at beginning of treatment.  
  • Start co-therapy with two primary mood stabilizers from separate classes at beginning of treatment.                                                                                                     |
| Akathisia                    | • Consider a cautious antipsychotic dose reduction.  
  • Use lorazepam 0.5 mg twice daily (B); titrate as needed to manage symptom severity.  
  • Use propranolol 10 mg twice daily (C); gradually increase to 20 mg three times daily.  Avoid in patients with asthma; watch for bradycardia and hypotension.  
  • Use benztropine 1 mg twice daily (C); increase to 2 mg twice daily as needed and tolerated.                                                                 |
| Anxiety, agitation, and/or insomnia | • Augment with a sedating atypical antipsychotic medication (see page 13), adjunctive sleeping pill, or sedative (benzodiazepine such as clonazepam, lorazepam, alprazolam) 0.5 – 6 mg, in divided doses (A).  
  • Suppression of manic symptoms, anxiety, or agitation with sedatives is a short-term solution. Avoid or use cautiously in patients with a history of substance abuse. |
| Bipolar II disorder          | • The hypomanic state of bipolar type II is often experienced as a functional and non-pathologic state.  Aggressive treatment of this state may lead to patient non-compliance. The consequences of not treating hypomania are unknown.  
  • Due to the possibility of lower manic conversion rates, antidepressant use may be less risky with this population compared to the bipolar type I population. However, antidepressants should be avoided in patients who are rapid cycling. |
| Elderly patient              | • Consider half doses of medication. Older patients are more susceptible to lithium toxicity and suffer more side effects from medication.  
  • Monitor for increased suicide risk, more accidents, and self-neglect.  
  • Atypical antipsychotic medications may increase the risk of death in patients with dementia.                                                                                                           |
| Female of child-bearing years | • Use anticonvulsant mood stabilizers with caution — many are generally regarded as teratogens.  
  • For patients that plan to become pregnant, consider lamotrigine as first-line therapy (C).  
  • Failing lamotrigine, consider quetiapine or risperidone as second-line therapies (C). Lurasidone may also be considered as second-line therapy.  
  • For treatment refractory patients, lithium is considered a reasonable option. While it is generally considered teratogenic (increased risk for cardiac defects), the absolute risk is low.  
  • Evaluate sexual activity, menstrual status, and birth control use at every visit for child-bearing age females on divalproex sodium, lithium, or carbamazepine. |
| Insomnia                     | • May be chronic in patients with bipolar disorder. Lack of adequate sleep may be both a sign of and a precipitant to relapse.  
  • Use adjunct sleeping medications. Benzodiazepine and related sedatives are helpful as sleep aids as well as for treatment (with mood stabilizer) of residual agitation and anxiety, though habit-forming sedatives should be avoided in patients with history of substance abuse.  
  • Educate patient on proper sleep hygiene: No evening caffeine or tobacco; no daytime napping; avoid reading and TV in bed; go to bed when sleepy; get out of bed if unable to fall asleep in less than 30 minutes. |
<p>| Pregnancy                    | Risk of relapse is high for those who discontinue mood stabilizers; near-term pregnant women are vulnerable to relapse.                                                                                                       |</p>
<table>
<thead>
<tr>
<th>Circumstance</th>
<th>Medication Considerations</th>
</tr>
</thead>
</table>
| **Rapid cycling** (four or more mood cycles per year) | **For patients with bipolar depression:**  
  • Quetiapine is the preferred first-line therapy (C).  
  • Consider lamotrigine, lithium, and fluoxetine plus olanzapine second-line agents, in order of preference (C).  
  • Failing the above, treatment refractory patients should be referred to a psychiatrist and potentially considered for electroconvulsive therapy (ECT), rather than additional pharmacotherapy trials (C).  

**For patients with manic, hypomanic or mixed episodes:**  
  • Consider risperidone, aripiprazole, or olanzapine monotherapy as first-line therapy (B).  
  • Second-line agents include lithium, valproate, quetiapine, haloperidol or carbamazepine, in order of preference (C).  
  • Failing the above, treatment refractory patients should be considered for combination therapy with either lithium or valproate and a first-line atypical antipsychotic. Alternately, in cases of severe mania, consider combination therapy a first-line option (C).  
  • For severe mania unresponsive to a single trial of combination pharmacotherapy, consider addition medication trials over electroconvulsive therapy (ECT). However, for severe mania unresponsive to 4 – 6 trials of combination pharmacotherapy, consider referral to a psychiatrist for electroconvulsive therapy (ECT) rather than additional pharmacotherapy trials (C).  

**For all patients:**  
  • Optimize thyroid function.  
  • Augment with psychotherapy.                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| **Side effects intolerable prior to efficacy**    | • Consider lower dose.  
  • Change medications.  
  • Treat with low dose of two primary mood stabilizers.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| **Switch to opposite pole or mixed symptoms**    | • Add mood stabilizer with efficacy for appropriate pole.  
  • **If depressed,** raise lithium level to more than 0.8 mEq/L, add lamotrigine, quetiapine, OR add an antidepressant. Avoid TCAs, venlafaxine, and duloxetine.  
  • **If manic or mixed,** discontinue antidepressant (if that caused switch) or add a primary mood stabilizer for mania/mixed mania.  
  • Patients who have a history of manic conversion on antidepressants are at high risk of future conversion with antidepressants.                                                                                                                                                                                                                                                                                              |
| **Substance use disorder**                       | • Avoid lithium as a primary mood stabilizer in these patients.  
  • Give appropriate referral and treatment for substance use issues.  
  • Use habit-forming sedatives with caution                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| **Thyroid dysfunction**                          | • Thyroid supplements may be necessary for some patients on lithium, since lithium carbonate can interfere with thyroid functioning. Consider treating subclinical hypothyroidism in patients who have resistant depression or rapid cycling.                                                                                                                                                                                                                                                                                                      |
| **Weight gain ≥5% of initial weight or weight gain prevention** | • Modify treatment plan to include exercise and calorie restriction.  
  • Follow weight, serum lipids, and fasting glucose.  
  • Consider medication change — atypical antipsychotics may be associated with more weight gain than other mood stabilizing agents.  
  • Consider adjunctive use of metformin (B) or topiramate (B). Three small controlled studies showed diminished or reversed weight gain with metformin in patients who were taking atypical antipsychotics. One large trial showed an average three-year weight loss of 2.5% with metformin therapy, which was maintained over a 10-year observation period. A meta-analysis of six trials showed an average 6-month weight loss of 6.5% with topiramate therapy.                                                                                                                                 |
| **Worsening mania**                              | • Assess medication adherence.  
  • Raise dose of existing mood-stabilizing medications AND/OR add second mood stabilizer for mania.  
  • Discontinue antidepressant if it is considered a precipitant.                                                                                                                                                                                                                                                                                                                                                                                                                                         |

Strength of evidence key: (A) = Based on data from large controlled trials; (B) = Based on data from smaller controlled trials; (C) = Based on expert opinion, open-label data, or usual-care experience; (D) = No acute efficacy
Psychosocial therapy

Patients with bipolar disorder suffer a variety of psychosocial consequences — stigmatization; interpersonal issues in marriage, family, childbearing, and parenting; academic, occupational, legal, and social problems — related to acute episodes (typically resulting from reckless and/or inappropriate behaviors or being withdrawn or violent). The resultant stress of past episodes often sets these patients up for ongoing vulnerability to future episodes. In addition, patients struggle to adhere to a long-term pharmacological treatment regimen with frequently unpleasant side effects. As a result, recent research-based clinical guidelines recommend that psychosocial therapy be an essential part of a bipolar disorder treatment plan, especially for maintenance treatment to:

- Reduce stress
- Increase patient functioning between episodes
- Decrease likelihood and severity of future episodes

Treatment strategies vary in terms of format (individual, group, or family unit), duration of treatment, patient cohort (in remission, recovering from an acute episode, or both). As part of a treatment plan, therefore, psychosocial treatment strategies should be individualized over time for each patient in terms of form, intensity, and focus.

Evidence-based adjunctive psychosocial treatments for bipolar disorder include:

- **Individual cognitive-behavioral therapy (CBT)** — Likely the most extensively researched modality as adjunctive therapy, CBT research reflects varying protocols and outcomes in comparison to other psychosocial treatments. CBT is recommended for those in remission from acute mania who have experienced fewer than 12 previous acute episodes. With this treatment approach, patients learn about their symptoms, course of illness, and treatments as well as techniques for cognitive restructuring and problem-solving strategies for adapting activity levels to mood, detecting early signs of relapse, and implementing prevention strategies. Providers may want to consider booster sessions after 18 months to maintain treatment benefits.

- **Individual and/or group psychoeducation** — This treatment approach focuses on helping patients become active partners in their treatment by learning:
  - The nature and course of the illness
  - Benefits/risks of treatment options
  - How to recognize early signs and stressors that may signal relapse
  - How sleep regulation and substance misuse impact likelihood of relapse

Psychoeducation can involve the patient’s family members/caregivers if the patient agrees and providers should consider structured group psychoeducation, which has been validated in two randomized trials as effective for reducing the duration of patients’ manic episodes, lowering mania scores, and significantly improving patients’ social functioning and quality of life. In addition, brief group psychoeducation has been found to be as effective as longer-term individual CBT at a significantly reduced cost (an 85% savings).

- **Interpersonal and Social Rhythm Therapy (IPSRT)** — This treatment approach addresses resolving patient-specific problems and focuses on stabilizing sleep/wake rhythms as well as patterns of social routines and stimulation. IPSRT uses a self-report tool, the Social Rhythm Metric, to track routines and mood. Designed for use with patients in remission, the treatment homes in on individualized problem resolutions and strategies for preventing problem recurrence. Some research indicates that IPSRT may be associated with longer time between episodes, better occupational functioning for those undergoing acute treatment, and even improved depression scores when used as monotherapy for those with bipolar II disorder.

**ADJUNCTIVE PSYCHOSOCIAL THERAPY GOALS**

**Help patients better:**
- Understand and accept the nature of their chronic illness and treatments
- Adhere to medication regimens
- Recognize early warning signs of and stressors that trigger relapse
- Regulate their emotions and improve functioning
- Communicate and solve problems within family relationships
- Regulate sleep/wake cycles and other daily routines
- Avoid substance misuse

**Help family members/caregivers:**
- Increase illness management and their own self-care skills
- Decrease their own depressive symptoms
- Decrease their health-risk behavior
THE ROLE OF FUNCTIONAL REMEDIATION

Those with bipolar disorder struggle with both social and occupational functioning — challenges that represent both clinical concerns as well as social and economic burdens. Functional remediation programs address struggles patients face with attention, memory, and executive functioning in their daily routines. Elements of IPSRT (see page 19) also focus on functional remediation by addressing stabilization of daily routines and sleep/wake cycles.

Adjunctive psychosocial interventions focused on functional remediation have been associated with significant improvements in occupational and interpersonal functioning among patients with both bipolar I and II disorder. In a 2-year study of patients with bipolar I disorder, IPSRT combined with medical management rapidly improved occupational functioning as compared to other psychosocial approaches (especially among women), and these gains were maintained for two years following the study. A multicenter, randomized controlled trial of 239 euthymic patients with bipolar disorder compared functional remediation with psychoeducation and treatment as usual over 21 weeks. Results indicated significant improvements in both occupational and interpersonal functioning.

- **Family Focused Therapy (FFT)** — Targeting couples and families of patients stabilizing from acute episodes, this treatment approach includes both the patient and the family members and offers an initial assessment followed by education about:
  - The illness, medication adherence, early warning signs of relapse, and relapse prevention strategies
  - Communication and problem-solving skills to improve family relationships

While patients whose families experience more conflict and intensity of relationships may benefit the most, research indicates that overall, patients involved in FFT as an adjunct to pharmacotherapy may experience a 35 – 40% reduction in recurrence rates over 2 years as compared to those undergoing brief psychoeducation and pharmacotherapy. In addition, FFT can help caregivers increase illness management skills as well as their own self-care, which is associated with decreased depressive symptoms and health-risk behavior among caregivers as well as decreased depressive symptoms in patients.

**Electroconvulsive therapy (ECT)**

With ECT, patients undergo a generalized cerebral seizure via administration of low-level electrical current to the scalp while under general anesthesia and muscle relaxation. Treatment usually requires 6 – 12 sessions over a 2- to 4-week period.

Although considered a standard treatment for unipolar depression, ECT has also been proven effective for acute mania, bipolar depression, mixed affective states, and especially for treatment-resistant bipolar disorder. Other typical indications for the use of ECT include multiple treatment failures, pregnancy, prior positive ECT response, and patient preference. Studies also indicate that ECT may be effective as a first-line treatment to achieve rapid clinical response in urgent cases where patients present with severe suicidal ideation and behaviors, severe psychosis, malignant catatonia, or with dangerous, depression-related refusal of fluid and food.

There are no absolute medical contraindications for using ECT; however, relative risk may differ depending on a patient’s clinical situation. Because of potential side effects, such as confusion and short-term memory loss (as well as side effects associated with anesthesia), ECT has typically been considered with treatment-resistant bipolar disorder patients. However, recent research indicates that these patients do not generally suffer adverse neurocognitive consequences and in fact, ECT may also be associated with a favorable long-term influence on some cognitive functions.

**Care management**

With routine phone or clinic contact, care managers can educate patients regarding their care, set expectations, assist with social emergencies, and direct patients to return to the clinic sooner rather than later. Care managers offer both knowledge and a supportive relationship to patients — both of which are necessary for success. Patients who receive this type of care for depression have much better results than those who don’t. Working inside and outside the clinic, a care manager can assist with the following:

- Treatment adherence (medications and/or psychotherapy)
- Patient education, self-management, and reinforcement of ongoing physician, patient, and family contact
- Communication and coordination between mental health and primary care
- Support with requests for consultation
- Improving timely contact with patients and monitoring their response
FOLLOW UP AND MAINTENANCE

Since bipolar disorder is a chronic and reoccurring illness, it usually requires regular follow-up, lifetime maintenance pharmacotherapy, and ongoing, objective outcomes assessment. Sustained remission lowers relapse risk.

Follow-up schedule

Multimodal treatment of this complex disorder demands regular, lifelong follow-up. Objectives of follow-up include:

- Adjusting medications and addressing side effects
- Monitoring lab values (e.g., lithium serum levels) as indicated
- Managing comorbidities
- Continuing/coordinating therapy and education for patients and families
- Measuring outcomes

See below for a recommended follow-up schedule:

**TABLE 8. Recommended follow-up schedule**

<table>
<thead>
<tr>
<th>When</th>
<th>Why</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 to 2 weeks</strong> after diagnosis and initial medication therapy</td>
<td>• Assess initial response to treatment, assess outcome.</td>
</tr>
</tbody>
</table>
| **Every 4 weeks** after diagnosis and initial medication therapy until patient is much improved (CGI global improvement score 1 – 2). | • Achieve target doses.  
• Assess functional outcome (see page 18).  
• Monitor side effects and adherence.  
• Assess educational needs.  
• Assess therapeutic alliance (see sidebar).  
• Assess for substance abuse (see page 8). Even limited alcohol use can destabilize the course of bipolar disorder. |
| **At least every 6 months** | • Monitor symptoms, lab values, and functional outcomes. |
| PRN | • Respond to worsening of symptoms or side effects, reinforce compliance. |

Remission and maintenance

Bipolar disorder is a recurrent illness. The goal of treatment is full, continuous remission of symptoms. Nearly 3 in 4 patients will relapse within 5 years, and many patients who do not have formal relapse will still exhibit significant residual symptoms. More than 90% of patients who experience one manic episode requiring hospitalization will have a second episode. Patients hospitalized for mania are more likely to have a mania relapse than a depressive relapse. Even with lifetime maintenance therapy, patients may experience only partial remission of symptoms. Due to the recurrent nature of bipolar disorder—and high probability of relapse—lifetime maintenance regimens of medication are recommended following the successful treatment of an acute episode. Although few studies involving patients with bipolar II disorder have been conducted, consideration of maintenance treatment for this form of the illness is also strongly warranted. One long-term follow-up study showed that patients with bipolar II disorder have chronic depressive symptoms more than half of the time.

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Outcomes assessment tools

Traditionally, symptomatic outcome measures — such as the Young Mania Rating Scale or the Hamilton Depression Rating Scale — have been used in bipolar disorder. These measures focus specifically on the core disease symptoms and are useful in research. However, bipolar disorder is a highly comorbid condition; over half of patients also suffer anxiety disorder and substance abuse disorders throughout their lifetime. Medication side effects can also add a significant burden. For these and other reasons, basic symptom measures do not adequately track these issues and often miss significant functional impairment important to both patients and clinicians.

To address shortcomings in traditional outcomes measurement, this CPM recommends two essential types of clinical measures:

- The clinician-rated Clinical Global Impressions (CGI) Scale for treatment response
- The patient-rated Intermountain Disability Scale for functional response

In addition to these clinical measures, having selected patients use a daily mood chart (see page 23) to track function impairment is also useful.

The Clinical Global Impressions (CGI) Scale

Requiring only 5 minutes or less to complete, the Clinical Global Impressions (CGI) Scale is a simple, valid measure of treatment response. In its simplest form, the clinician rates a patient’s severity of illness and response to treatment. This scale tracks well with symptom scales, and clinicians often closely agree with each other when scoring the same patient.

To use the CGI Scale, rate the severity of illness at the initial visit and at all subsequent visits. Based on your experience with this disorder, use the 1 – 7 scale below. Severely ill patients routinely suffer comorbid illness; incorporate this factor into the rating.

<table>
<thead>
<tr>
<th>Severity scale 1 – 7:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>normal, not ill</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>borderline ill</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>mildly ill</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>moderately ill</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>markedly ill</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>severely ill</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>extremely ill</td>
</tr>
</tbody>
</table>

The Intermountain Disability Scale

Intermountain’s functional disability rating scale (on the next page) can be downloaded at: https://intermountainhealthcare.org/ext/Dcmnt?ncid=526842760

Instruct the patient to rate their level of disability by asking, “In the past 2 weeks, how much have your mental health symptoms interfered in the following areas of life?”

Patients should rate each of the three domains (family life and home responsibilities, work or school, and social or leisure activities), providing a total functional disability score from 0 – 30.
Rate Impairment Daily

Instruct the patient to use this chart every day to rate impairment caused by symptoms, medications, stress, sleep, and other variables.

Daily Mood Charting

Daily mood charting provides a way for patients to rate impairment caused by depressive or manic systems in relation to daily medications, interpersonal stress, sleep, and other variables. Use of a mood chart is widely recommended for patients with rapid cycling, particularly those who have mood cycling within a single month. Recording a mood along with any medications taken, medication changes, or other events can provide evidence for which interventions are helpful or destabilizing.
TOOLS USED FOR SCREENING AND DIAGNOSIS

Although there is disagreement within the specialty of child psychiatry regarding bipolar diagnoses, there are reasonable guidelines and tools for diagnosing childhood and adolescent bipolar disorder. However, it is critical that the care provider use the symptom expression information at right and not rely solely on screening instruments. Validated tools include:

- **The MDQ-A (Mood Disorder Questionnaire-Adolescent).**
  This screening instrument has been validated in adolescents, with the parent report version having the greatest sensitivity and specificity.

- **The Young Mania Rating Scale.**
  This scale was developed to rate acute mania severity but also functions as a screening instrument when rated by a parent. The P-YMRS is the parent-rated version of this scale.

- **FIND guidelines.**
  Childhood bipolar disorder may present with symptoms that are frequent, brief, and intense with outbursts and behavioral dysregulation fundamentally different from the adult presentation of the illness. The FIND guidelines below include duration and intensity criteria, and are recommended by many researchers to ascertain the presence or absence of manic symptoms.

### FIND GUIDELINES FOR PEDIATRIC PATIENTS

These guidelines can help clinicians ascertain the presence or absence of manic symptoms:

- **Frequency.** Symptoms occur most days of the week.
- **Intensity.** Symptoms are severe enough to cause extreme disturbance in 1 domain or moderate disturbance in 2 or more domains (school, home, friends, etc.).
- **Number.** Symptoms occur 3 or 4 times per day.
- **Duration.** Symptoms occur 4 or more hours a day total (not necessarily contiguous hours).

### BIPOLAR DISORDER IN CHILDREN AND ADOLESCENTS

Many emotional and behavioral illnesses of childhood have symptoms that converge and confuse the identification and appropriate treatment of bipolar disorder in children and adolescents. Presentation of symptoms often differs from that in adults, and children tend to have higher rates of chronicity, mixed states, and rapid cycling.

A reliable diagnosis of bipolar disorder in the pediatric population depends on symptoms:

- **Occurring in concert** rather than sequentially
- **Being considered in the context of age and comorbidity**

The diagnosis of cyclothymic disorder in children and adolescents is one year of both hypomanic and depressive episodes without ever meeting criteria for mania, depression, or hypomania, while the requirement for adults is 2 years.

### Symptom expression

Symptom expression of bipolar disorder in children and adolescents differs from that of adults and is influenced by developmental changes, temperament, and reaction to environmental stress. Distinct periods of depression and mania are less likely in younger populations, and these patients may present with chronic symptoms of irritability, along with difficulties regulating moods, emotions, and behavior. Younger children may also have periods of agitation, irritability, and oppositionality as generic symptoms of any severe mental illness.

Mania in adolescents presents many diagnostic challenges based on historical reporting. Both adolescents and their parents may either minimize symptoms of mania (to downplay the seriousness of the situation) or exaggerate these symptoms (hoping that a bipolar disorder diagnosis will explain the difficulties the patient is experiencing). Symptoms that typically present include:

- **Grandiosity:** Determine the child’s ability to distinguish between pretending and reality to establish if grandiose symptoms are due to bipolar disorder.
- **Euphoria/Irritability:** Review these moods in the context of special events, the behavior of other children, and exposure to steroids or substance abuse. Irritability that results in major “meltdowns” lasting hours for trivial reasons should be separated from less severe irritable moods.
- **Decreased need for sleep:** A child with bipolar disorder may need 2 hours less sleep per night (adjusted for age without daytime fatigue). Children with limited sleep due to mania are often active during the night whereas depressed children may lie in bed and brood.
- **Pressured speech:** Speech is louder, faster, and more difficult to interrupt than a child with ADHD who talks a lot.
- **Mood lability:** For adolescents, mood lability may be the way mania presents. In fact, it is not unusual for patients to experience mixed manic and depressive features of a mood disorder, a more common symptom picture than the persistent euphoria found in adults.
• **Racing thoughts:** These thoughts should be severe enough to interfere with daily activities. Parents can help distinguish what behaviors are different than baseline.

• **Distractibility:** Compare distractibility to baseline symptoms when mood is euthymic. Symptoms in children with comorbid ADHD should have distractibility worse than baseline distractibility.

• **Increase in goal-directed activity/agitation:** Mania may be associated with periods of copious drawing, writing, or play activities. This should be above and beyond normal and associated with other diagnostic symptoms.

• **Excessive Involvement in Pleasurable or Risky Activities:** Hypersexual behaviors may be present in children with or without a history of childhood abuse. This behavior may be exhibited in an anxious and compulsive manner. Hypersexuality in children due to mania can appear as erotic and pleasure-seeking behaviors that might be appropriate between consenting adults in private but grossly inappropriate in a child. Sexual and/or seductive advances towards a parent would not be unusual.

• **Psychosis:** It is important to differentiate hallucinations or delusions from common childhood perceptual disturbances such as hearing one’s name called or other distortions when falling asleep. Symptoms of psychosis frequently occur in adolescents experience bipolar disorder.

### Differential diagnosis and comorbidity

One of the biggest challenges is differentiating children and adolescents with mania from those with attention deficit hyperactivity disorder (ADHD). These patients should also be screened for other problems such as learning problems, substance use, and conduct disorders — and those problems should be treated concurrently.

There are high rates of comorbid disruptive, impulse-control, and conduct disorders that accompany the bipolar diagnosis. Additionally, in disruptive mood dysregulation disorder (a depressive disorder), children present with irritability as the chief complaint. Temper outbursts occur on average more than 3 times per week, but the moods in between the outbursts are “persistently irritable” unlike with bipolar disorder where there is often some cycling nature.

### Treatment guidelines

Treatment of bipolar disorder in young patients generally reflects that of adult patients — and should include patient/family education, psychotherapy, and pharmacotherapy. Young patients experiencing bipolar symptoms can benefit from psychosocial interventions (see pages 19–20). In addition, patients may require specialized educational programming, day treatment, and vocational training.

The literature on the use of ECT (see page 20) in pediatric bipolar patients is extremely limited, and the treatment should only be considered for adolescent patients suffering from bipolar I disorder with severe symptoms of mania or depression that are unresponsive to multiple medication therapies.

### THE IMPORTANCE OF REFERRAL

Bipolar disorder is relatively rare in children and complicated to diagnose. In terms of mania, “Bipolar ‘mood episodes’ include unusual mood changes along with unusual sleep habits, activity levels, thoughts, or behavior. In a child, these mood and activity changes must be very different from their usual behavior and from the behavior of other children.” Highly irritable children are more likely to have ADHD or an anxiety or depressive disorder.

Red flag symptoms for diagnosing mania in this patient population include:

• **Rage outbursts or verbal or physical aggression** — The patient may be easily frustrated or provoked.

• **Episodes of requiring little sleep** — The patient gets less sleep frequently without suffering any loss of energy.

• **Spontaneous mood shifts** — The patient may be giddy, then depressed, then angry without any apparent trigger for the mood shifts.

• **Grandiosity** — The patient may exhibit a grossly inflated belief in himself beyond typical boastfulness.

• **Agitation or mania when taking an antidepressant** — The patient may have had symptoms of being unusually edgy, happy when taking an antidepressant.

Given the uncertainty and potential complications in diagnosing and treating bipolar disorder in this population, consultation with or referral to a child mental health specialist is recommended before initiating treatment.
FDA-APPROVED MEDICATIONS

The following medications are approved for treating bipolar disorder in children and adolescents as indicated:

- **lithium carbonate** (Eskalith, Eskalith CR, Lithobid) — Approved for ages >12 years as monotherapy for acute mania and maintenance
- **aripiprazole** (Abilify) — Approved for ages >10 years (as monotherapy or in combination with lithium or valproate (or divalproex) for acute mania
- **asenipine** (Saphris) — Approved for ages >10 years as monotherapy for acute mania/mixed episodes
- **olanzapine** (Zyprexa, Zydis) — Approved for ages >13 years as monotherapy for acute mania/mixed mania and maintenance
- **olanzapine** (Zyprexa, Zydis) in combination with **fluoxetine** (Prozac) — Approved for ages 10–17 for treatment of bipolar depression
- **quetiapine** (Seroquel) — Approved for ages >10 years as adjunct and monotherapy for acute mania
- **risperidone** (Risperidol) — approved for ages >10 years (as monotherapy for acute mania/mixed episodes

CARE MANAGEMENT

The follow-up and maintenance care of children and adolescents as well as outcomes assessment tools used follow the same processes as detailed for adults on pages xx through xx. Note that, for a younger child, a parent or other caregiver would be completing the forms.

Medications

The choice of the medications used to treat pediatric bipolar disorder should be based on evidence of efficacy, the phase of illness (manic versus depressive symptoms), the drug’s side-effect profile, the patient’s history of medication response, and patient and family preferences.

Prescribing guidelines emphasize a stepwise nature of medication management as well as rationale for combining medications. At each step in pharmacotherapy, the physician is balancing the benefits and risks of either staying with a current regimen (if the patient appears to be stable or improving) or changing medications or doses to optimize treatment. This process should be very patient-specific, with the following key issues guiding decision making at each step:

- Making only one medication change at a time
- Addressing the most problematic symptom or cluster of symptoms first
- Reducing the number of medications that will eventually be needed
- Making management of adverse effects a priority when warranted
- Targeting symptoms that appear to trigger other symptoms
- Preferring medications that work quickly

Both the range of symptoms present with bipolar disorder and the symptoms that occur as a result of comorbidities often make medication management particularly challenging for children and adolescents. Combining medications is often appropriate when:

- Using an augmentation agent to address only partial response when symptoms either improve but not to a degree that lessens significant distress or when symptoms fail to improve at all
- Targeting a specific symptom that causes significant distress such as insomnia
- Cross-tapering medication that is not working as expected with another medication
- Treating symptoms of comorbid disorders such as those with ADHD or anxiety disorder

Use the dosage guidelines in the medication table (page 27) for treating children and adolescents. For each medication, refer to the adult medication tables on pages 13 through 15 for tier/cost and side effect information that pertain to all populations. Dosages must be modified for age, and response to treatment must be carefully monitored. Side effects — particularly weight gain — may be exaggerated in children, and children are more prone to medication toxicity.

Maintenance and medication monitoring

Patients are likely to require maintenance therapy to prevent symptom relapse with a recommended trial of 12 to 24 months after an acute manic episode. Decisions to continue treatment must be weighed along with risks of medication side effects.

Recommended medication monitoring for children and adolescents is the same as for adults (see Tables 6A and 6B on page 16).
### Table 9. Medications for treating children and adolescents<sup>ELB, LEC2, LEX, STA1, STA2</sup>

<table>
<thead>
<tr>
<th>Class</th>
<th>Medication (common brands)</th>
<th>Strength of Evidence&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Dosage guidelines&lt;sup&gt;2&lt;/sup&gt;/Notes (see pages 13 – 16 for specific medication side effects and monitoring guidelines)</th>
</tr>
</thead>
</table>
| Anticonvulsants            | divalproex sodium (Depakote, Depakote ER) Not FDA approved for this population            | Mania, bipolar depression, and maintenance (C) | Children:  
  - Initiate at 125 mg 2 – 3 times daily  
  - Increase gradually until side effects limit dose or therapeutic plasma levels are reached  
  - Range: 1000 – 1250 mg/day  
  - Target: Serum level 50 – 125 mcg/mL (mid to upper range generally required)  

  Adolescents:  
  - Initiate at 250 mg 2 – 3 times daily  
  - Increase gradually until side effects limit dose or therapeutic plasma levels are reached  
  - Range: 1000 – 2500 mg/day  

| Metallic salt, antimanic   | lithium carbonate (Eskalith, Eskalith CR, Lithobid)                                      | Mania, bipolar depression (C) maintenance (B) | Ages 6 – 12 years:  
  - Initiate at 15 mg/kg/day in 3 – 4 divided doses  
  - Adjust dose weekly based on serum concentrations  
  - Range: 15 – 60 mg/kg/day (do not exceed adult dosage)  

  Ages ≥ 12 years:  
  - Initiate at 300 mg twice daily  
  - Increase by ≤ 300 mg per day every 3 – 4 days  
  - Range: 600 – 1800 mg/day  
  - Target: Serum level 0.8 – 1.2 mEq/L |
|----------------------------|--------------------------------------------------------------------------------------------|-----------------------------------|------------------------------------------------------------------------------------------------------------------|
| Atypical Antipsychotics    | aripiprazole (Abilify)                                                                     | Mania, maintenance (B), bipolar depression (C) | Ages ≥ 10 years:  
  - Initiate at 2 mg once daily x 2 days  
  - Increase to 5 mg PO once daily x 2 days, then may increase in 5 mg increments  
  - Range: 10 – 30 mg/day |
|                           | asenapine (Saphris)                                                                        | Mania, maintenance (B), bipolar depression (C) | Ages ≥ 10 years (Note): Sublingual administration only; no eating/drinking for 10 minutes after placing under tongue:  
  - Initiate at 2.5 mg twice daily  
  - Increase to 5 mg twice daily after 3 days, then to 10 mg twice daily in another 3 days based on tolerability |
|                           | olanzapine<sup>3</sup> (Zyprexa, Zydus)                                                   | Mania, maintenance (B), bipolar depression (B)<sup>4</sup> | Ages 6 – 12 years:  
  - Initiate at 2.5 mg at bedtime  
  - Increase in 2.5 – 5 mg increments  
  - Range: 10 – 20 mg/day  

  Ages 6 – 10 years:  
  - Initiate at 5 mg  
  - Increase as clinically indicated  

  Ages ≥ 12 years:  
  - Initiate at 2.5 – 5 mg at bedtime Increase in 2.5 – 5 mg increments weekly  
  - Range: 10 – 20 mg/day  

  Ages 10 – 17 years:  
  - Initiate at 10 mg  
  - Increase as clinically indicated |
|                           | combined with fluoxetine<sup>5</sup> (Prozac, Symbax)                                      | Bipolar depression: ages 10 – 17 (C), ages 6 – 10 (D) | Ages ≥ 10 years (Note): May be given once nightly if tolerated):  
  - Initiate at 25 mg twice daily  
  - Increase to 50 mg twice daily on day 2, then 100 mg twice daily on day 3, 150 mg twice daily on day 4, and 200 mg twice daily on day 5.  
  - Range: 400 – 600 mg/day in divided doses |
|                           | quetiapine (Seroquel)                                                                      | Mania, maintenance (B), bipolar depression (C) | Ages ≥ 10 years (Note):  
  - Initiate at 0.5 mg at bedtime  
  - Titrate by 0.5 – 1 mg increments at daily intervals, as tolerated  
  - Range: 0.5 – 2.5 mg at bedtime (may be split twice daily)  

  Ages ≥ 10 years:  
  - Initiate at 20 mg once daily with food  
  - Titrate as tolerated  
  - Range: 60 – 80 mg/day divided twice daily (weight ≤ 45 kg) or 120 – 160 mg/day divided twice daily (weight > 45 kg) |
|                           | risperidone (Risperidal)                                                                  | Mania, maintenance (B), bipolar depression (C) | Ages ≥ 10 years:  
  - Initiate at 0.5 mg at bedtime  
  - Titrate by 0.5 – 1 mg increments at daily intervals, as tolerated  
  - Range: 0.5 – 2.5 mg at bedtime (may be split twice daily)  

  Ages ≥ 10 years:  
  - Initiate at 20 mg once daily with food  
  - Titrate as tolerated  
  - Range: 60 – 80 mg/day divided twice daily (weight ≤ 45 kg) or 120 – 160 mg/day divided twice daily (weight > 45 kg) |
|                           | ziprasidone (Geodon)                                                                       | Mania (B), bipolar depression, maintenance (C) | Ages ≥ 10 years:  
  - Initiate at 0.5 mg at bedtime  
  - Titrate by 0.5 – 1 mg increments at daily intervals, as tolerated  
  - Range: 0.5 – 2.5 mg at bedtime (may be split twice daily)  

  Ages ≥ 10 years:  
  - Initiate at 20 mg once daily with food  
  - Titrate as tolerated  
  - Range: 60 – 80 mg/day divided twice daily (weight ≤ 45 kg) or 120 – 160 mg/day divided twice daily (weight > 45 kg) |

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<sup>1</sup> Strength of evidence key: (A) = Based on data from large controlled trials; (B) = Based on data from smaller controlled trials; (C) = Based on expert opinion, open-label data, or usual-care experience; (D) = No acute efficacy. NOTE: See FDA-approved medication information for this population in the sidebar on page 26.

<sup>2</sup> Some dosage guidelines are based on usual care experience and may differ from manufacturer’s package data.

<sup>3</sup> Zyprexa is ONLY FDA-approved for treatment of acute bipolar depression for ages 10 – 17 in combination with fluoxetine and for treatment of acute manic or mixed episodes for ages 13 – 17.

<sup>4</sup> Strength of evidence is based on use as an adjunct to lithium or divalproex.

<sup>5</sup> While an FDA advisory panel has advised that ziprasidone is effective in patients 10 – 17 years of age for the treatment of mixed and manic episodes of bipolar disorder, they were unable to conclude that it was safe due to the large number of subjects lost to follow-up and ambiguity within QTc prolongation data.
USING TEACH-BACK STRATEGIES

What is Teach-back? — Teach-back is a way to confirm that patients understand what we tell them using open-ended questions that invite the patient and family to “teach-back” the information to us. It’s not a test of the patient’s knowledge — it’s a test of how well we explained something.

Why is it important? — Not understanding medical information is a common reason for readmissions. Teach-back is a proven tool for improving patient understanding.

Who can use it? — Everyone who explains anything to a patient or family.

When can I use it? — Use early in the care process and at each decision point or transition, especially when families or caregivers are present. Make sure caregivers participate in the Teach-back process to ensure they understand key information.

What are the Steps?

1. Explain or demonstrate a concept, using simple lay language.
   Tips: Avoid covering too much at one time — explain no more than 2 or 3 concepts at a time. Slow down and take pauses. If you’re giving the patient printed information, mark or highlight key areas of the handout or booklet as you explain.

2. Ask the patient/caregiver to repeat the information in their own words or demonstrate the process.
   Tips: Own the responsibility (“I want to see whether I explained this well”). Ask the patient to tell you how he or she would explain the information to a spouse or family member. Avoid yes/no questions.

3. Identify and correct misunderstandings.
   Tips: Show empathy and caring as you correct. Avoid making the patient feel they’ve failed a “test.” Don’t repeat the entire explanation or demonstration again unless it’s necessary — just focus on areas that need clarification.

4. Ask the patient/caregiver to explain or demonstrate again, to show improved understanding.
   Tips: Own the process again. “Let’s see if I cleared that up.” Avoid yes/no questions (such as “do you understand now?”).

5. Continue this loop until you’re convinced the patient/caregiver understands the concept.
   Tips: Be patient — this process is worth the time it takes. Continue to be gracious in the process — patients can worry about judgment or wasting your time.

Patient and family education can lead to better compliance and treatment outcomes. Review the available patient education materials (see page 29) and resources for using teach-back strategies (see the information at left and the Teach-back Flashcard).

In addition to basic information about the symptoms, neurobiologic basis, and treatment of the disease, patient education should include the following topics:

• **Warning symptoms and prodromal symptoms.** Symptoms may arise weeks or months prior to a full-blown episode. Often, these symptoms are the same before each episode for an individual patient and are likely to include changes in sleep, activity level, and impulsivity. Help patients recognize these symptoms and act to prevent relapse. Patients who develop strategies to handle prodromal symptoms are less likely to relapse.

• **The effects of substance use and abuse.** Alcohol and illegal drug use can lead to more frequent relapse, poor response to lithium, and a more severe course of illness. Even limited use of alcohol or marijuana can destabilize this illness. Educate patients who use or abuse substances on how and where to get help.

• **The importance of treatment adherence.** Treatment adherence is improved by a better understanding of this illness, its course, and likelihood of relapse. During times of normal mood or hypomania, patients may not perceive themselves as being sick or needing treatment. Encourage patients to stick to the medication schedule even when they are feeling well. Medication side effects may also lead to poor treatment adherence. Teach patients to recognize and report side effects so medications can be adjusted.

• **The role of stress.** Patients who understand the link between stress and symptom recurrence and then learn strategies for coping with stressful events may be able to reduce the impact stress has on the onset of mania and depression. Research indicates that many patients with bipolar disorder suffer from recurring symptoms after stressful life events that affect one’s ability to attain goals. Additionally, there is an association between recurrent episode onset and patients who have experienced childhood physical, sexual, or emotional abuse.

• **The connection between sleep and episode severity.** It is important to help patients understand that the amount of sleep they get and the regularity of their sleep patterns translates to less severe symptoms of both mania and depression. Results from a study of concurrent and prospective associations from the National Institute of Mental Health Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) trial indicated an association between shorter total sleep time and increased mania severity as well as an association between greater sleep variability and increased mania and depression severity over 12 months.
RESOURCES AND REFERENCES

Intermountain patient resources
Clinicians can order Intermountain patient education booklets and fact sheets for distribution to their patients from Intermountain’s Online Library and Print Store, printstore.org. Call 801-442-3186 for ordering information.

Choose from an array of booklets, trackers, and forms to help, including:

- Bipolar Disorder Information for Patients and families
- PHQ-9
- MDQ
- Daily Mood Tracking Chart

Provider resources
To find this CPM, clinicians can go to intermountain.net/clinical/Pages/All-Care-Process-Models-(CPMs).aspx, and select “Behavioral Health” from the topic list on the screen (as indicated below).
References


MANAGEMENT OF BIPOLAR DISORDER


This CPM presents a model of best care based on the best available scientific evidence at the time of publication. It is not a prescription for every physician or every patient, nor does it replace clinical judgment. All statements, protocols, and recommendations herein are viewed as transitory and iterative. Although physicians are encouraged to follow the CPM to help focus on and measure quality, deviations are a means for discovering improvements in patient care and expanding the knowledge base. Send feedback to Mark Foote, MD, Intermountain Healthcare, Medical Director Behavioral Health (Mark.Foote@imail.org) or Carolyn Tometich, APRN, Intermountain Healthcare, Behavioral Health Operations Director (Carolyn.Tometich@imail.org).