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Challenges in recognition, clinical management, and treatment of bipolar disorder at the interface of psychiatric medicine and primary care

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PrimE-B

PRIMARY EDUCATION
ON BIPOLAR DISORDER



Challenges in recognition, clinical management, and treatment of bipolar disorder at the interface of psychiatric medicine and primary care

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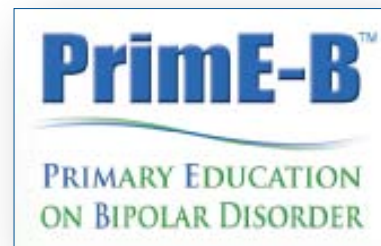
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PART 1

Defining the challenge: Recognizing and treating bipolar disorder wherever patients present

Bipolar disorder often goes unrecognized by primary care providers (PCPs) because patients typically present with what appears to be a major depressive episode and PCPs think it unlikely that they will see bipolar illness.¹⁻³ In psychiatric settings, too, bipolar disorder may be undetected or may be recognized only after a long delay, possibly because of evolving criteria for diagnosing the disorder.^{3, 5-7}

There is increasing recognition that bipolar disorder has a spectrum of symptom expression from subthreshold to meeting full criteria, indicating that bipolar I disorder, at least, may be more common than the 1% prevalence usually cited in population surveys.^{1-3,8,9} Further, there is evidence that mixed episodes are not uncommon in bipolar I and II disorders.^{4,6,10} In considering the whole spectrum of bipolar illnesses (bipolar I disorder, bipolar II disorder, cyclothymic disorder, and bipolar disorder not otherwise specified), some authors have, controversially, suggested that the prevalence rate may be as high as 5% in the population.^{1,3,5}

The burden on clinicians

Psychiatric clinicians and primary care clinicians may be expected to meet a patient presenting with bipolar disorder, take a history, diagnose the patient's condition, prescribe drug treatment for it, and monitor the overall physical health effects of that treatment—all in brief office visits.

Frequently, patients are treated for concurrent psychiatric and general medical conditions. Medication management of psychiatric treatments may have a direct impact on a patient's other medical conditions

—and vice versa. Mental health care professionals and general medical professionals need to consult and collaborate to optimize outcomes for the patient.¹¹⁻¹³

Primary care

As mentioned, patients with bipolar disorder often initially present in a primary care setting with symptoms of depression. They are less likely to report their manic and mixed symptoms, such as little need for sleep, inflated self-esteem, or increase in risky or goal-directed activity.^{9,10,14,15} Diagnosis of bipolar disorder requires the compilation of a detailed history of symptoms, behaviors, treatment responses, and family illness, which presents challenges in the primary care setting.^{1,16}

Mental health care

Significant challenges arise in identifying bipolar presentations that do not involve the “classic” combination of pure manic and pure depressive episodes.^{6,10} Once accurately diagnosed, patients with bipolar disorders require drug treatments that may have an effect on their

physical health. Patients will benefit if mental health care and primary medical care are viewed collaboratively to ensure that psychiatric drug treatment does not cause or exacerbate other medical conditions, and that unwanted drug effects are treated medically.¹⁷

This journal supplement, along with the companion supplement to *The Journal of Family Practice*, is the end result of a meeting of an expert panel of primary and psychiatric care clinicians. These clinicians met to address the issues associated with the diagnosis and management of patients with bipolar disorder in various settings. These supplements are a response to the seminal concerns identified at that meeting and in subsequent communications.

The chapters that follow provide practical advice on recognizing and collaboratively caring for patients with bipolar disorder, as well as a review of available pharmacologic treatments for phases and expressions of the illness. A case presentation examines decision points about assessment and referral of a patient who presents in a primary care setting. We hope that you find this information helpful in treating your patients with bipolar disorder. ■

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PART 2

Challenges in diagnosing bipolar disorder: Identifying mixed episodes

Psychiatric clinicians frequently encounter patients who present with fluctuating and complex mood states, such as depression together with agitation, irritability, and racing thoughts. These patients may appear restless and driven, but they do not exhibit the euphoria and grandiosity characteristic of pure mania. Rather, they may be preoccupied by a dark and distressing view of the world and of themselves. Their symptoms may swing rapidly—perhaps over the course of a few hours—from depression to mania and back. In striving to establish the most appropriate diagnosis and treatment for such patients, the clinician may find only limited guidance in the mood disorders section of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (DSM-IV-TR™).¹

Prevalence of mixed episodes

Bipolar mixed episodes may be far more common than was once believed. A review of the literature by McElroy et al found that rates of mixed symptoms ranged from 5% to 70% in patients who have acute mania (due in large part to variations in the criteria used to define a mixed episode), with a mean prevalence of 31%.² It has also been reported that an average of 40% of patients with bipolar disorder present with a mixed state at some point during their lifetime.³

The prevalence of mixed symptoms is of particular clinical significance since mixed bipolar presentations appear to be associated with poorer short- and long-term outcomes, more protracted episodes, higher rates of recurrence, and greater risk of suicide than pure manic episodes.^{1,2}

FIGURE 1

The continuum view of mood disorders

Unipolarity				Bipolarity	
DSM-IV Major depressive episode	Mixed depressive episode* Meets criteria for an MDE but also has some manic or hypomanic symptoms	DSM-IV mixed episode Meets criteria for both a manic episode and an MDE (except for duration)	Dysphoric mania† Meets criteria for a manic or hypomanic episode but also has some (2 to 3) depressive symptoms	DSM-IV Manic or hypomanic episode	

*Based on descriptions of mixed bipolar states,⁷ depressive mixed states,⁸ agitated depression,⁹ irritable-hostile depression,⁴ unipolar depression with racing thoughts.¹⁰
†Based on operational criteria proposed by McElroy SL, et al. 1992.²

Defining mixed episodes

The DSM-IV-TR describes 4 types of mood episodes: major depressive, manic, hypomanic, and mixed.¹ The diagnostic criteria for a mixed episode are that the conditions for both a manic and a major depressive episode (MDE), except for duration, must be met nearly every day for at least 1 week. However, these criteria do not fully account for cases in which patients display a mix of symptoms that do not qualify as a full mood episode.^{2,4,5} Thus, new efforts are being made to define mixed mood states in a clinically relevant way, one that will encompass the wide range of symptom profiles and patterns that occur.²

Emil Kraepelin originally defined manic-depressive insanity, including a description of multiple mixed mood states, in 1921.⁶ Three of the mixed-state subtypes he described are especially relevant today: (1) depression with flight of ideas, (2) excited or agitated depression, and (3) depressive or anxious mania.^{2,3} Dr. Kraepelin noted that any combination of mood symptoms including both polarities (ie, mania and depression) would constitute a mixed state.^{2,4-6}

Thus, recent researchers have proposed a model in which mood disorders are conceptualized as occurring along a continuum (FIGURE 1).^{2,4,7-10} In this model, presentations that involve episodes of pure mania or pure depression would appear at the extreme ends of the spectrum. Mixed depressive episodes would meet criteria for MDE but have some manic features as well. Dysphoric mania episodes would meet criteria for manic or hypomanic episodes but present some depressive

symptoms as well.³ This question of how mood disorders are conceptualized has implications beyond mere psychiatric nosology, since treating patients with bipolar spectrum disorders as if they had purely unipolar mood disorders can have serious clinical consequences (as discussed in the section “Clinical implications of misdiagnosis”).

Types of mixed episodes

Dysphoric mania

In 1992, McElroy et al proposed operational criteria for dysphoric (mixed) mania or hypomania, (ie, mania or hypomania accompanied by prominent depression) (TABLE 1).² According to these criteria, dysphoric or mixed mania should be diagnosed when a full manic or hypomanic episode is accompanied by 3 or more symptoms of major depression; the presence of 2 depressive symptoms is considered sufficient to justify a probable diagnosis. At the same time, the researchers acknowledged the possibility that mixed affective episodes may represent a heterogeneous condition with numerous etiologies.²

Mixed depressive states

Focusing on the other end of the mood disorder spectrum, a number of researchers have described major depressive episodes characterized by manic or hypomanic symptoms (eg, agitation, racing thoughts, irritability, hostility) that do not meet full criteria for mania or hypomania.^{4,7-11} (The characterization of

these equivocal episodes as “bipolar” is speculative and somewhat controversial, since fear of inducing mania with an antidepressant may lead some clinicians to withhold antidepressant treatment when it would be appropriate.) Besides these symptoms, mixed depressive episodes may also have associated features characteristic of bipolarity, including high rates of comorbid substance use and anxiety disorders, suicidality, psychotic symptoms, postpartum presentations, family histories of bipolar disorder, and drug-induced manic symptoms in response to antidepressant monotherapy.^{1,3,12,13}

Evolving criteria

Although researchers continue to debate exactly what criteria should be used to define a mixed state, the psychiatric field is moving toward a far more inclusive view of the bipolar spectrum of disorders. For example, in a study published in 2000, participants were categorized as having a mixed mood episode if they had either mania or hypomania together with an MDE—even though the DSM-IV criteria do not consider hypomania with a major depressive episode to be diagnostic of a mixed state.^{1,14} The continuing debate notwithstanding, it is important that psychiatrists recognize the variety of mixed mood states that can occur, because primary care providers are especially likely to refer patients with these types of complex presentations for “treatment-resistant” or “treatment-refractory” depression due to adverse consequences from antidepressant monotherapy. Kaye has suggested that psychiatrists consider the issue of cycling as opposed to the issue of polarity when trying to distinguish between unipolar depression and bipolar disorder/bipolar depression (N. Kaye, written communication, June 2007). Preventing the next cycle, as opposed to simply treating the current episode, is necessary to appropriately treat this lifelong disorder.¹⁵

Differential diagnosis of bipolar presentations

Underrecognition of bipolar presentations

Given the potential risks associated with treating bipolar disorder with antidepressant monotherapy (as discussed below), it is essential to determine whether a patient presenting with depression has a unipolar or

TABLE 1

Operational diagnostic criteria for dysphoric mania or hypomania

- I. A full manic or hypomanic syndrome by DSM-III-R criteria
- II. Simultaneous presence of at least 3 associated depressive symptoms from the list below*
 1. Depressed mood
 2. Markedly diminished interest or pleasure in all, or almost all, activities
 3. Substantial weight gain or increase in appetite
 4. Hypersomnia
 5. Psychomotor retardation
 6. Fatigue or loss of energy
 7. Feelings of worthlessness or excessive or inappropriate guilt
 8. Feelings of helplessness or hopelessness
 9. Recurrent thoughts of death, recurrent suicidal ideation, or a specific plan for committing suicide

*Three symptoms indicate a definite diagnosis, 2 symptoms indicate a probable diagnosis, and 1 symptom indicates a possible diagnosis of dysphoric mania or hypomania. Adapted from McElroy SL, et al. *Am J Psychiatry*. 1992;149:1633-1644; reprinted with permission.

a bipolar mood disorder (**TABLE 2**).¹⁵⁻²¹ Since patients with bipolar disorder seek treatment for depression 2 to 3 times more often than for manic symptoms, it is not surprising that as many as 60% of patients with bipolar I disorder are misdiagnosed as having unipolar depression.^{22,23} Patients with bipolar disorder tend to have depressive episodes more frequently and for longer periods of time than they experience mania or hypomania.²⁴ And, as indicated, these patients frequently present with mixed mood states. Because a mixed episode can include elements of depression, and because the manic aspect of the episode may be characterized more by restless energy and irritability than by pure mania, it can be difficult to distinguish a mixed state from a simple depressive episode.²⁵ In both cases, patient history may be the key to a correct diagnosis. But patients with bipolar disorder are often unreliable historians and may not have recognized previous episodes, especially hypomania, as problematic.^{15,20,24}

Even in psychiatric settings, bipolar disorders often go undetected or are recognized only after a long delay. For example, Mantere et al recently screened

TABLE 2

Clinical features that suggest bipolarity

Course of illness	<p>Disruptive behaviors in childhood (attention-deficit disorder, conduct disorder)</p> <p>Early age at onset of major depressive episode (<25 years)</p> <p>Early onset of behavioral or psychiatric problems</p> <p>Seasonal episodes (more common in winter)</p> <p>Postpartum depression</p> <p>Multiple major depressive episodes of short duration (<3 months)</p>
Symptomatic profile	<p>Psychotic symptoms</p> <p>Atypical depressive symptoms (eg, excessive sleepiness, overeating, weight gain, psychomotor retardation)</p> <p>Mixed depressive episodes (presence of hypomanic symptoms during depressive episode)</p> <p>Periods of increased energy or activity with decreased need for sleep that caused problems even if not recognized as illness</p>
Family history	<p>Bipolar disorder in first-degree relative</p> <p>Affective disorder in multiple generations of relatives</p>
Comorbidity	<p>Current substance abuse or history of substance abuse</p> <p>Problems regulating control of impulses</p> <p>Anxiety disorders</p>
Treatment response	<p>Antidepressant-induced mania or hypomania</p> <p>Antidepressant “wear-off”</p> <p>Lack of response to 3 or more adequate antidepressant trials</p>

Kaye NS. *Am Board Fam Prac.* 2005;18:271-281.
 Ghaemi SN, et al. *J Psychiatr Pract.* 2005;7:287-297.
 Swann AC, et al. *Prim Care Companion J Clin Psychiatr.* 2005;7(1):15-21.

a median delay of 7.8 years from first episode to diagnosis. In this study, mixed episodes were detected in 16.7% of patients with bipolar I disorder and depressive mixed states in 25.7% of those with bipolar II disorder.⁸

Clinical implications of misdiagnosis

Unipolar major depressive disorder and bipolar disorder differ substantially in their clinical course and recommended treatment.¹⁵ Treating bipolar depression or mixed states with antidepressant monotherapy may lead to worsening symptoms, increased mood cycling, functional impairment, and even a higher risk of suicide.¹⁵⁻¹⁸ The most recent data show that the use of antidepressants plus mood stabilizers in bipolar depression conveys no additional benefit over mood stabilizers alone.²⁷ Treatment with antidepressants alone can be particularly risky for patients with mixed episodes, amplifying both the mania and the depression.²⁵ Mixed episodes may also be less likely to respond to antimanic agents.^{22,24}

1630 psychiatric patients with the Mood Disorder Questionnaire (MDQ) and identified 191 patients with possible bipolar I and II disorders.^{8,26} Of the 90 patients with bipolar I disorder, a quarter had previously been undiagnosed. Of the 101 patients with bipolar II disorder—which included patients with bipolar disorder not otherwise specified who had hypomania of 2 to 3 days or depressive mixed states, as well as those who met DSM-IV-TR criteria for bipolar II—half had not previously been diagnosed.⁸ Among the patients in the sample who had previously been diagnosed with bipolar disorder, there had been

Assessment for bipolar disorder

An assessment for bipolar disorder should be a routine part of any workup for patients who present with depressive symptoms or report a history of depression.^{15,24} Because it may be difficult to distinguish unipolar from bipolar depression or mixed states on the basis of current clinical features alone, differential diagnosis rests on a disciplined approach to obtaining key history that will place the patient in or out of the bipolar spectrum. One approach is to focus on 5 areas in an orderly manner²⁵:

- **Family history.** One first-degree relative with bipolar disorder or 3 with major psychiatric illness; family

FIGURE**Mood Disorder Questionnaire**

To view this Figure, see the separate PDF, "Mood Disorder Questionnaire."

history of suicide, electroconvulsive therapy, mental breakdowns, or drug or alcohol abuse.

- **Specific sleep abnormalities.** Decreased need for sleep or inability to sleep secondary to racing thoughts.

- **Personal history.** Early age of symptom onset, highly recurrent symptoms, failure to respond to antidepressants, multiple careers or marriages, promiscuity, or substance abuse.

- **Mood instability.** Mania, hypomania, irritability, sudden mood changes, anxiety, panic, obsessive-compulsive disorder, eating disorder.

- **Depression.** Atypical, seasonal, postpartum, sudden onset, highly recurrent, melancholic, mixed features; suicidality.^{17,20}

Screening tools can help clinicians correctly identify bipolar disorder.²⁸ An ideal tool for use in clinical practice should be brief and easy for patients to complete without assistance. The MDQ, a brief self-report form consisting of 13 questions plus items assessing the clustering of symptoms and functional impairment, can be completed by patients in about 5 minutes (FIGURE 2).²⁶ This tool is helpful in screening for current and past symptoms that suggest bipolarity. It has been found to be more sensitive in a psychiatric (73%) than in a general (58%) population, and its specificity has been validated in both psychiatric (90%) and general medical (93%) patients.^{26,28,29} Having a family member complete the MDQ may be helpful in identifying symptoms, especially hypomania, that the patient might not consider a problem.¹⁵ Of course, while screening tools may help raise suspicion for bipolar disorder, they cannot replace the psychiatrist's careful assessment needed to make a clinical diagnosis.

Identifying comorbid psychiatric illnesses

Comorbid anxiety, substance use, and eating and impulse disorders occur at elevated rates in patients with bipolar disorder and may

all be associated with a fundamental dysregulation of mood, behavior, and impulse control.^{1,30,31} For example, the National Comorbidity Survey Replication (NCS-R) found that among patients who had been diagnosed with bipolar I disorder, 86.7% had a co-occurring anxiety disorder at some point in their lives; 71.2% had a co-occurring impulse control disorder; and 60.3% had a substance-use disorder.³⁰ Comorbid substance use disorders are of particular concern because they can produce signs and symptoms that mimic depressed, manic, or mixed states.¹ Although most substance-induced symptoms are short-lived and resolve with sustained abstinence after withdrawal, it is not always clear what role the substance use is playing in the current presentation of mood symptoms.^{3,32} Because comorbidity is the rule rather than the exception in patients with bipolar

disorders—and it is frequently the comorbid problem with which the patient presents—it is important to be aware of these conditions and to consider their ramifications in developing a treatment plan.³¹

Conclusion

Patients with bipolar disorder may have a variety of mixed presentations, including dysphoric mania, mixed depression, or a “classic” DSM-IV-TR–defined mixed episode. Such patients are especially likely to be referred for specialized psychiatric care. In these situations, clear communication among treating clinicians is the key to successful collaborative care and improved outcomes for patients. Strategies for such collaborative care are outlined in Part 3 of this supplement. ■

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PART 3

Clinical management of bipolar disorder: Achieving best outcomes through a collaborative care model

A collaborative care model in which psychiatrists communicate and work closely with primary care providers (PCPs) can lead to improved overall health and wellness for patients with mental illness.¹ When they join forces with PCPs to treat patients with bipolar disorder, psychiatrists address many issues related to referrals, treatment goals, medications, psychosocial interventions, and comorbidities that are unique to the disease (**TABLE 1**).²⁻¹⁸

Promoting positive collaboration with primary care providers

Data from the National Comorbidity Survey (NCS) and the NCS Replication indicate that the number of patients seeking care for mental illness in general medical settings is rising.⁴ Because it is increasingly likely that psychiatrists will be asked to evaluate patients who have already seen a PCP, psychiatrists and PCPs should establish a collaborative relationship.⁵

The following factors affect the overall quality of interactions between psychiatrists and PCPs:

- Accessibility of physicians to discuss the patient
- Adequacy of the background patient information and history provided
- Communication of expectations
- Communication about follow-up care.

Information from the referring primary care provider

To make an accurate diagnosis and prescribe the most appropriate treatment, psychiatrists should obtain a complete patient history

TABLE 1

Key principles in managing bipolar disorder in psychiatric care settings

Diagnosis and assessment	<ul style="list-style-type: none"> • The first and most important task is correctly identifying bipolar disorder (ie, distinguishing unipolar from bipolar presentations).² Although this is relatively straightforward for pure manic episodes, the diagnosis of mixed episodes can be much more difficult given the range of presentations associated with such episodes.³ It may be useful to focus on cycling as well as polarity.
Referral	<ul style="list-style-type: none"> • The best results are often obtained when psychiatrists and PCPs work collaboratively.^{1,4} • In referring a patient to a PCP for medical care, the psychiatrist should provide information on psychiatric and medical history, current medications, and reason for referral. Because many PCPs may not be familiar with side effects of medications used to treat bipolar disorder, it is helpful to inform the physician about any side effects the patient may be experiencing on the current medication regimen. • When a patient is referred from a PCP for assessment of a mood disorder, the psychiatrist should request information about the reason for referral and the patient’s medical and medication history.⁵ Providing PCPs who make frequent referrals with a standard written referral form can help ensure that all pertinent information is recorded.⁵ After the evaluation is completed, the psychiatrist should forward a complete report of the findings and treatment recommendations or plan to the PCP.
Treatment goals	<ul style="list-style-type: none"> • State-of-the-art treatment for patients with bipolar disorder involves focusing on the “whole person,” not just the psychiatric disorder. Goals of treatment are not only to treat acute manic or depressive symptoms but also to reduce relapses and mood cycling, control agitation, and improve functioning^{1,6} <p>Specific goals include:</p> <ul style="list-style-type: none"> • Establishing and maintaining a therapeutic alliance • Monitoring the patient’s psychiatric status • Providing education about bipolar disorder • Promoting treatment adherence • Preventing the next cycle/episode • Encouraging regular patterns of activity and sleep • Anticipating stressors and helping patients develop coping strategies • Identifying early warning signs of new episodes • Minimizing functional impairments⁶
Medication	<ul style="list-style-type: none"> • Patients with bipolar disorder generally need 1 or more medications along with psychotherapy to achieve the best outcomes.¹ • Because the majority of patients treated for bipolar disorder receive at least 2, and often 3, medications, it is important that each drug improve the risk-benefit analysis.^{1,7} • Antidepressants used alone without a mood stabilizer can exacerbate mood symptoms or cause rapid cycling in patients with bipolar disorders.⁸⁻¹¹ • The various agents used to treat bipolar disorder have different side effects that should be considered when making the selection for a specific patient and when monitoring the patient’s health status.^{1,12} • Some agents used to treat bipolar disorder can exacerbate weight gain or metabolic problems or increase the risk of new-onset weight gain or lipid and metabolic abnormalities.¹²
Psychosocial interventions	<ul style="list-style-type: none"> • Psychosocial interventions—including psychotherapy, education, and support groups—are key components in the management of bipolar disorder and can help reduce relapses, shorten hospitalizations, and improve functioning and adherence to medication.^{1, 13, 14}
Psychiatric comorbidity	<ul style="list-style-type: none"> • Patients with bipolar disorder have high rates of comorbid psychiatric disorders, especially anxiety and substance use disorders, that need to be taken into account in treatment planning.^{11,15,16} • In selecting medications for a patient with bipolar disorder, one should, if possible, choose medications likely to also be effective for the comorbid conditions.¹⁶
Medical comorbidity	<ul style="list-style-type: none"> • Patients with bipolar disorder have higher rates of certain medical conditions, especially obesity and diabetes, than individuals in the general population.^{1,17} These conditions need to be treated and considered in selecting psychiatric medications, since some of the agents used to treat bipolar disorder can exacerbate these conditions or increase the risk of new-onset weight gain or lipid and metabolic abnormalities. • Regular monitoring of the physical health of patients with bipolar disorder is essential in promoting the best outcomes.¹⁸

accompanied by information from the family and/or caregivers if possible. The psychiatrist should ask the PCP about the pattern and duration of symptoms, exposure to stressful life events, suicide potential, alcohol and substance use, current and past medical problems or conditions, and personal and family history of psychiatric problems.^{2,19} In addition, the psychiatrist should obtain a detailed treatment history, including medications, dosages and duration, symptom responses, and side effects.

The psychiatrist should also ask whether the patient is to be followed in the psychiatric setting or in the primary care setting. Some of the reasons a patient may be followed in the primary care setting include personal preference, lack of resources, and limited insurance coverage.¹¹ In such situations, it is important that the PCP make it clear that the purpose of the referral is to obtain a care plan and arrange for collaboration with the psychiatrist on an ongoing or as-needed basis.

When collaborating, all parties—psychiatric clinician, PCP, and patient—need to agree on who is managing medication adjustments. This is critical so one clinician does not unintentionally undermine the other's treatment plan if the patient calls with a problem.

Information for the referring primary care provider

It is equally important for the evaluating psychiatrist to provide the PCP with a complete report of the evaluation, diagnosis, prescribed treatment, and plans for future follow-up. A time-saving strategy some psychiatric offices use to facilitate communication is to send the referring PCP a copy of the same comprehensive initial evaluation note that goes into the patient's record. The psychiatrist can also send a copy of ongoing progress notes whenever there is something that needs to be communicated to the PCP, perhaps with the most important points highlighted. The patient signs a release authorizing collaboration between the psychiatric provider and the PCP at the first visit (S. Rosen, written communication, June 2007).

Including family in the assessment

Because patients with bipolar disorder may have limited insight into or may deny their own manic or hypomanic symptoms, it is valuable to include family members in the assessment after obtaining the patient's consent.^{2,20}

This provides an opportunity to assess the family's attitudes about such issues as hospitalization and their ability and willingness to participate in the patient's treatment.

Assessment tools

As noted in Part 2, when making a differential diagnosis for patients with mood disorders, it is important to identify current or past manic, mixed, or hypomanic episodes, as well as any comorbid conditions.²¹ The use of a brief and easy-to-complete self-report tool, such as the Mood Disorder Questionnaire (MDQ),²² can facilitate transfer of information between PCPs and psychiatrists. Psychiatrists may want to provide a copy of the MDQ to PCPs with whom they frequently collaborate. If the PCP has administered the MDQ, it is also helpful to send the results to the psychiatrist before the psychiatrist evaluates the patient.

Assessing comorbid conditions

Comorbid psychiatric disorders

Patients with bipolar disorders have high rates of comorbid anxiety, substance use, eating, and personality disorders.^{11,15,16} For example, lifetime comorbid anxiety disorders were found in more than 50% and current anxiety disorders in 31% of the first 500 patients enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study.²³ Further, the lifetime risk of anxiety disorders in bipolar I disorder has been reported to be 93%, compared with 58% in unipolar depression.²⁴ Bipolar disorder with comorbid anxiety disorders is associated with more severe symptoms, more frequent episodes, decreased likelihood of recovery, longer time to remission, poorer role functioning and quality of life, less time euthymic, and a higher incidence of substance abuse and suicide attempts.^{16,23-25} Anxiety disorders may be more likely to occur in patients with mixed episodes.^{16,24} Bipolar disorder with comorbid substance abuse is associated with fewer and slower remissions, higher rates of suicide attempts and suicide, and poorer outcomes.^{19,20,24} Patients with bipolar disorder and comorbid substance abuse should be aggressively treated for both disorders.²⁰ Because patients with comorbid psychiatric

FIGURE 1

Sample checklist for psychiatrist's report of psychiatric evaluation to PCP

Referring physician name and address _____

Patient name, address, phone _____

Preferred mode(s) of communication

Letter _____

Telephone _____

 During the hours of _____

 Emergency number _____

Copy of medical records _____

In-person discussion _____

E-mail _____

Online chat _____

 During the hours of _____

Initial Evaluation

Psychiatric diagnosis or diagnoses _____

Results of psychological or neuropsychological testing _____

Results of imaging or laboratory studies _____

Treatment prescribed or recommended _____

Recommendations for specific actions/treatments by PCP _____

Educational information provided to patient and family _____

Referral made to advocacy or support groups _____

Plans for follow-up _____

disorders may be more difficult to treat, they are especially likely to be referred by PCPs for specialized psychiatric assessment.

Comorbid medical conditions

Patients with bipolar disorder have higher rates of conditions that increase their risk of cardiovascular disease and type 2 diabetes mellitus, including obesity, smoking, hyperglycemia, hypertension, and dyslipidemia.^{17,26} In one sample, 30% of patients with bipolar disorder met criteria for the metabolic syndrome, 49% had abdominal obesity, and 48% had hypertriglyceridemia or

were taking a lipid-lowering medication.²⁷ Obesity and the metabolic syndrome contribute to a worse prognosis for bipolar disorder through their negative effect on general physical well-being and functioning, quality of life, and self-esteem.^{25,27,28}

Certain psychotropic medications, including some of the newer second-generation antipsychotics (SGAs), as well as lithium, valproic acid, and carbamazepine, can contribute to weight gain, and some of the SGAs also increase the risk of metabolic abnormalities.^{16,17,27} If weight gain and metabolic problems are a concern, clinicians may want to select an agent that is less likely to cause these problems.¹⁷ Among available SGAs, olanzapine is associated with the greatest increase in weight and metabolic problems and ziprasidone and aripiprazole with the least.^{12,17}

If a patient with bipolar disorder does gain weight during treatment, the following additional options should be considered: dietary advice and support; advising regular aerobic exercise; referral to specific programs for weight management; and referral to a dietitian (especially if the person has complex comorbid medication problems).¹⁸ It may be particularly useful for the PCP and the psychiatrist to collaborate in developing such programs and helping patients follow through. However, the practitioners must both be clear on who is ordering which monitoring tests, on sharing any results that might signal a health problem, and on how any changes in psychiatric medications—if needed—will be undertaken.

Other conditions reported at elevated rates in patients with bipolar disorder include human immunodeficiency virus (HIV) and hepatitis C (possibly reflecting increased risk-taking or impulsive behaviors in this population), chronic fatigue syndrome, migraine, asthma, chronic bronchitis, multiple chemical sensitivities, and gastric ulcer.^{29,30}

Physical health monitoring

A collaborative approach to treating patients with mental illness can also improve the regularity of their physical health monitoring. Initial treatment plans should clearly outline the frequency of health monitoring as well as a mechanism for regular communication of results. Although it is not always possible to follow all guidelines in every setting, keeping the

following recommendations in mind can help promote the best use of resources and guide discussions with patients about disease management and the need for adherence.

Initial physical assessment of a patient with bipolar disorder should include personal and family history; measurement of weight, height, and blood pressure; calculation of body mass index (BMI); assessment of tobacco and alcohol use; thyroid, liver, and renal function tests; full blood cell count; blood glucose and lipid levels; and cardiovascular history.^{2,18} If clinically warranted, drug screening, a chest x-ray, an electrocardiogram, an electroencephalogram, a computed tomography scan, or a magnetic resonance imaging scan can be ordered.¹⁸

When initiating treatment with an antipsychotic, it is recommended that height, weight, waist circumference, fasting plasma glucose and lipid levels, and blood pressure be measured.¹²

During ongoing SGA treatment, patients' weight should be reassessed at 4-, 8-, and 12-week intervals after initiating or changing treatment and quarterly thereafter. For patients who gain 5% or more of baseline body weight, switching to a different antipsychotic should be considered.¹² It is, of course, important to be cautious in making changes if a patient is doing well, since a switch can expose the patient to long periods of drug transition and a whole new set of potential side effects. At the same time, patients who gain significant amounts of weight and develop lipid and glucose abnormalities can be at risk for serious health problems and health crises. Therefore, it is important to conduct a careful review of side effects and their potential causes when deciding what to do.⁶ Fasting plasma glucose level and blood pressure should be assessed 3 months after initiating an SGA and annually thereafter (more frequently if the patient has an elevated baseline risk for diabetes or hypertension). For patients with normal lipid levels, testing should be repeated every 5 years or more frequently if clinically indicated.^{12,28} As mentioned, patients with serious mental illness have an increased risk for diabetes and heart disease; therefore, this monitoring is particularly important.³¹

Prolactin levels should be measured in patients taking risperidone or other SGAs if they develop low libido, sexual dysfunction, menstrual abnormalities, gynecomastia, or galactorrhea.¹⁸

Thyroid function should be assessed since patients, especially those taking lithium, may have normal thyroid-stimulating hormone levels but low or low-normal free thyroid (T4 or T3) levels. Raising T3 or T4 levels, usually using L-thyroxine, can often improve response to lithium or other mood-stabilizing agents.²⁰

An annual examination should be performed in patients with bipolar disorder to assess plasma glucose levels, weight, smoking, alcohol use, and blood pressure, as well as lipid levels (including cholesterol) in patients older than 40 years.¹⁸

Psychiatrists may find it helpful to refer their patients with bipolar disorder to a PCP for the physical health monitoring described here. If a patient being treated with an SGA gains substantial weight or develops metabolic abnormalities and a change of medications is not possible, a referral to a PCP for medical management of these problems can be useful. The psychiatrist and the PCP should coordinate responsibility for medication prescriptions and follow-up laboratory tests (eg, serum drug levels, lipid and glucose levels).¹⁵

Principles of shared management and collaboration

Developing collaborative relationships

One model of psychiatrist-PCP collaboration would be for psychiatrists to be part of a multidisciplinary care team within the primary care setting.³² Each physician could refer patients to the other as needed for further psychiatric or medical assessment; ideally the psychiatrist would be immediately available when necessary.¹ Although such a partnership has the potential to improve patient care, decrease morbidity, reduce health care costs, and enhance patient satisfaction and adherence, it is relatively rare in current treatment settings.³²⁻³⁵ For such a system to work effectively, PCPs need to increase their knowledge of psychiatric diagnosis and treatment to better understand when referral is indicated and to provide follow-up care for psychiatric disorders in their own practices. Likewise, given the increasing focus on the overall health and wellness of psychiatric patients, psychiatrists need to gain a better understanding of the types of medical problems that their patients are vulnerable to, both due to the disorder itself and as a result of the treatments they

are receiving.^{18,36} Telemedicine and telepsychiatric consultations also have the potential to improve care for chronic psychiatric conditions.^{4,37}

A recent, 3-year study at 11 Veterans Affairs hospitals compared a collaborative care model for bipolar disorder with continued usual care. The intervention consisted of improving patients' self-management skills through psychoeducation, supporting providers' decision making through simplified practice guidelines, and enhancing access to and continuity of care and flow of information through the use of a nurse care coordinator. In this study, the collaborative care intervention significantly reduced the number of weeks in an affective episode, primarily mania. Broad-based improvements were demonstrated in social role function, mental quality of life, and treatment satisfaction.³⁸ These findings are similar to those of other studies of collaborative care of patients with bipolar disorder.^{36,39}

Improving communication between care providers

There is room for improvement in communication between PCPs and psychiatrists. For example, the Study of Outpatient Referral Patterns found that only 51% of psychiatrists who saw patients referred by other physicians, mainly PCPs, often or always received the reason for the referral; only 33% often or always received the patient's demographic information; only 26% often or always received the patient's medical history before the visit; and only 17% often or always received the patient's treatment history. One third of the surveyed psychiatrists indicated that they often or always receive no information from the referring physician before the first patient visit.⁵ Although the majority of the respondents reported that the accessibility of PCPs and their level of satisfaction with the overall quality of interactions with PCPs were very good or excellent, 68% reported that communication with PCPs regarding follow-up care was poor to fair.⁵ Psychiatrists identified medical and treatment histories and the referring doctor's expectations as especially inadequate.⁵ When referring a patient, PCPs need to provide as complete information as possible, including reasons for the referral, urgency of the referral, medical and psychiatric history, medication allergies, current therapies and changes in medications, and results of imaging and

laboratory studies. If this information is not provided, the psychiatrist should request it from the referring PCP. Best outcomes are also achieved when individuals with bipolar disorder have continuity of care.^{4,18}

Working as a team: Primary care providers, psychiatrists, patients, and families

It is important that patients perceive their care providers as a team working together to achieve the best outcomes. Thus, psychiatrists and PCPs should communicate regularly, so that they are both aware of the patient's current status and of the recommendations the other physician has made for ongoing care. It can be helpful for PCPs to provide copies of the educational materials on such issues as weight, lipids, and exercise that they have given patients, and likewise for psychiatrists to give PCPs copies of educational materials on bipolar disorder.

A supportive therapeutic alliance between physicians and the patient with bipolar disorder can increase the patient's willingness to remain in and adhere to treatment. Essential components of such an alliance include expressing concern for the individual's suffering and communicating appropriate optimism about the potential for successful treatment while avoiding raising unrealistic expectations. To this end, patients should be told that they may need to try several different medication regimens before they find one that works.^{2,6,20} Patients and their families/caregivers should be encouraged to work collaboratively with their health care providers and to take an active role in treatment decisions.^{6,18} Health care professionals should show respect for the patient's knowledge and experience of his or her own illness and provide relevant information about diagnosis and treatment, including proper use instructions and side effect profiles of prescribed medications.^{6,18} In addition, educating patients about the reasons for psychiatric consultation and reassuring them that there will be communication among the team are important for encouraging the patient to follow through with referrals.⁴ Families of patients with bipolar disorder also experience stress and increased burdens. Among primary caregivers of 500 patients enrolled in the STEP-BD study, 89% experienced moderate or high burden related to patient problem behaviors, 52% experienced role dysfunction,

and 61% experienced disruption of household routine.⁴⁰ Educating family members about the biological nature of the disorder and referring them to national and community-based support and advocacy groups can help them cope with their own burden and help them to avert future crises related to the patient's illness-related behavior.^{6,14,15,18,41}

Psychosocial interventions

Psychosocial interventions are key components in effectively managing bipolar disorder, especially during depressive or hypomanic episodes and continuation and maintenance treatment, as patients are more capable of taking in and using new information at these times than they are during manic or mixed episodes.^{6,42} Psychotherapy for bipolar disorder involves a combination of psychoeducation and other types of therapy, including cognitive-behavioral therapy, family-focused therapy, interpersonal therapy, and interpersonal and social rhythm therapy.^{1,43} Combined with medication, these strategies can help prolong time to relapse, reduce symptom severity, and increase adherence.^{14,41,42,44} Effective psychosocial interventions for bipolar disorder encourage patients to be active collaborators in their own treatment; emphasize the need for medication to prevent relapse; stress education for patients and families about medications, adherence, early warning signs of relapse, and lifestyle changes and stress management; and target comorbid psychiatric illnesses.^{14,25}

Although a detailed discussion of specific psychotherapeutic techniques for bipolar disorder is beyond the scope of this chapter, psychiatrists should ensure that PCPs are informed about any psychotherapy that patients are receiving, including the underlying principles, so that the PCP can encourage the patient to follow through. Psychiatrists may also be able to assist PCPs in learning more about these techniques so that they can incorporate them into their own practices.¹ Mood charting (discussed further in chapter 4) is especially useful as a monitoring tool that helps patients see their progress while providing the clinician with important and accurate information about a patient's disease course.

Conclusion

Clinicians who treat patients with serious and persistent mental illnesses such as bipolar disorders have become increasingly aware of the need to focus on their patients' overall well-being. It is not enough to treat the symptoms of the mental disorder while ignoring signs of other health problems that can compromise patients' social and occupational functioning and put them at risk for long-term adverse consequences. Given this focus on treating the "whole" person, a collaborative model in which psychiatrists and PCPs work together seems likely to promote the best outcomes for patients. ■

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PART 4

Treatment by phase: Pharmacologic management of bipolar disorder

Bipolar disorder is a lifelong illness with a broad spectrum of presentations. The overall goals of bipolar disorder treatment are to control acute episodes as quickly as possible, prevent or reduce further episodes, decrease or eliminate inter-episode symptoms, and provide support and education to the patient about management of the disorder.¹ Given the complex nature of bipolar disorder, it is difficult for the patient, who is experiencing depression and mania (sometimes concurrently), to manage and control the illness without the help of a strong and supportive therapeutic alliance.²

Pharmacologic therapy

The primary goal of pharmacologic treatment for bipolar disorder is mood stabilization. Drugs usually considered mood stabilizers include lithium and the anticonvulsants carbamazepine, valproic acid, and, more recently, lamotrigine; increasingly, second-generation antipsychotics (SGAs) are being prescribed for this purpose. First-generation antipsychotics may be effective primarily for mania but are not as well tolerated as the SGAs, and some studies suggest that they may exacerbate depressive symptoms.³

An ideal mood stabilizer would alleviate acute manic, mixed, and depressive symptoms; not induce the alternate mood symptoms; and prevent relapses into manic, mixed, or depressive episodes—all without causing significant side effects or toxicity. In reality, this is rarely accomplished by one medication alone. Successful treatment of bipolar disorder often requires use of either different drugs for different phases of the illness or a combination regimen. In one study of a voluntary registry of 457 patients with bipolar disorder, less than

20% of the group was receiving monotherapy for the disease. Half of those who were on a combination regimen were taking 3 or more medications, and almost one quarter of the patients in the survey were taking 4 or more drugs for their illness.⁴

Managing bipolar disorder is something of a balancing act. It is important to effectively treat acute episodes and current mood symptoms, and it is also essential to keep in mind the chronic and cyclical nature of the disease.² **TABLE 1** lists medications currently approved by the US Food and Drug Administration (FDA) for treatment of the different phases of bipolar disorder.

The depressive phase

The issue of controlling the acute symptoms of a bipolar mood episode while also considering long-term management is particularly pronounced in the depressive phase of the illness, in which patients tend to spend a majority of time.⁵ As mentioned previously, patients in the depressive phase of bipolar disorder are frequently misdiagnosed as having unipolar depression, an error that can have unwanted clinical consequences because the recommended treatments for the 2 disorders are substantially different.⁶

Antidepressants for unipolar depression may not be effective for the depressive symptoms of bipolar disorder. In a recent study by Sachs et al that is part of the Systemic Treatment Enhancement Program for Bipolar Disorder (STEP-BD), a large effectiveness trial funded by the National Institute of Mental Health, adjunctive antidepressant therapy did not significantly improve depressive symptoms of bipolar depression compared with mood stabilizers alone.⁷ Furthermore, some studies have suggested that antidepressants can hasten manic episodes and contribute to rapid cycling in patients with bipolar disorder, although the findings of Sachs et al do not support this when antidepressants are used in conjunction with mood stabilizers. In addition, 2 European reviews have reported that patients with bipolar depression responded favorably to antidepressant therapy.^{2,8,9} Still, it is considered prudent to prescribe an antidepressant for a patient with bipolar disorder only when other treatment strategies have failed and the benefits are determined to outweigh the risks. It is worth noting that, according to a small study by Altshuler et al, there may be a subset of patients for whom

TABLE 1

Medications approved by the FDA for the treatment of bipolar disorder

Phase	Medications
Depressive	Olanzapine/fluoxetine Quetiapine
Maintenance	Aripiprazole Lamotrigine Lithium Olanzapine
Manic	Aripiprazole Carbamazepine ER Chlorpromazine Divalproex ER Divalproex Lithium Olanzapine Quetiapine Risperidone Ziprasidone
Mixed	Aripiprazole Carbamazepine ER Divalproex ER Olanzapine Risperidone Ziprasidone
Manic and mixed episodes with or without psychotic symptoms	Aripiprazole Divalproex ER Olanzapine Risperidone Ziprasidone

FDA, US Food and Drug Administration.
Source: Manufacturers' US prescribing information for drugs listed.

ongoing antidepressant use—together with a mood stabilizer regimen—is effective, does not precipitate mania, and conveys some protection against another depressive episode.¹⁰ However, continued antidepressant efficacy in bipolar depression remains controversial and is considered by many to be unproven, especially in light of the longer-term risk of worsening cycling. It is generally recommended, therefore, that antidepressants be tapered and discontinued once bipolar depression is controlled.² Despite these recommendations, antidepressants are one of the most commonly prescribed classes of drugs for bipolar disorder in the United States.¹¹

Traditional mood stabilizers have been shown to have only limited efficacy in the depressive phase of bipolar disorder. Lithium, for example, is somewhat

effective, but its time to onset during bipolar depression is 6 to 8 weeks, and the response is less robust than that seen during mania.¹ Lamotrigine has been shown to be effective in both preventing and treating depressive episodes, and it has been recommended as first-line therapy for this phase of the disease.¹²⁻¹⁵

Important new options for treating bipolar depression are emerging from among the SGAs. Currently, quetiapine and an olanzapine/fluoxetine combination are the only medications with FDA approval for the treatment of patients with bipolar depression (TABLE 1). In placebo-controlled trials, both regimens have shown significant efficacy in improving depressive symptoms in patients in this phase of the disorder. Patients treated with the olanzapine/fluoxetine combination showed improvement compared with those taking placebo, starting at week 1 and continuing through the 8-week end point. Patients who received olanzapine alone also showed greater improvement than did those who received placebo during all 8 study weeks, but the response for olanzapine alone was numerically more modest than for the combination regimen.¹⁶ Quetiapine at 300 and 600 mg/d was studied in patients with bipolar I and bipolar II depression in an 8-week, double-blind, placebo-controlled study. At both doses, quetiapine was superior to placebo from baseline through week 8, and these findings have recently been replicated.^{17,18}

Two recent studies of aripiprazole showed that when the drug was administered as monotherapy (10 mg/day titrated to 5-30 mg/day) to patients with bipolar I disorder who were having a major depressive episode, it was no more effective than placebo.¹⁹ Ziprasidone is under investigation by its manufacturer to determine whether clinical experience, case reports, and open-label work that suggest efficacy in bipolar depression can be reproduced in more stringent, blinded, multicenter trials.

The manic phase

The effectiveness of lithium in the manic phase of bipolar disorder has been documented over more

than 50 years of testing. The use of valproate and carbamazepine is also supported by some 20 years of clinical study.²⁰ More recently, the SGAs have proven to be effective for treating the manic phase of this disorder. Aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone are FDA-approved for the treatment of bipolar manic episodes. All 5 medications have shown efficacy in treating acute manic episodes compared with placebo; however, their times to first separation from placebo range from 2 to 7 days. TABLE 2 presents each medication's earliest day of significant separation from placebo, measured in controlled studies.²¹⁻³¹

In cases of severe mania, it is often recommended that a combination of an antipsychotic with either lithium or valproate be used.¹ Benzodiazepines, while not thought to have an antimanic effect, can be a useful addition in the treatment of mania by providing extra sedation, restoring sleep patterns, and easing anxiety.^{1,3}

Mixed episodes

Acute mood episodes that include significant symptoms of both depression and mania are categorized as mixed episodes.³² These episodes are difficult to identify and present a particular challenge to both primary care providers (PCPs) and psychiatric clinicians. PCPs sometimes refer patients experiencing mixed episodes to psychiatrists for "treatment-refractory depression,"

TABLE 2

Time to onset of effect of second-generation antipsychotics in bipolar mania

Oral Medication	Onset of Effect*	
	First Assessment	First Significant Separation from Placebo
Ziprasidone	Day 2 ^{21,22}	Day 2 ^{21,22}
Aripiprazole	Day 2 ²³ or 4 ²⁴	Day 4 ^{23,24}
Risperidone	Day 3 ^{25,26} or 7 ²⁷	Day 3 ²⁵ or 7 ^{26,27}
Olanzapine	Day 7 ^{28,29}	Day 7 ²⁹ or 21 ²⁸
Quetiapine	Day 4 ^{30,31}	Day 4 ³¹ or 7 ³⁰

This table is *not* derived from head-to-head studies. It is derived from the pivotal studies accepted by the US Food and Drug Administration in support of the indication.

*Studies assessed first significant separation from placebo at different days.

as they do not always recognize these patients as having bipolar disorder.

Mixed states are common, troublesome, and underdiagnosed, and present unique treatment concerns. It is estimated that approximately 33% to 40% of patients with bipolar disorder experience mixed states.³³ Clinicians usually are able to identify depressive symptoms far more readily than manic symptoms in patients with bipolar disorder, but screening for both hypomania and mania, especially in the context of a depressed episode, is an important step in distinguishing mixed mood from pure depression.² Even when properly diagnosed and treated, patients who experience mixed episodes tend to have a slower recovery time and a shorter time to relapse than do patients with pure manic or depressive episodes.³³ For example, in a 5-year prospective study, median time to recovery for mixed episodes or rapid cycling episodes was 17 weeks, compared with 6 weeks for manic episodes and 11 weeks for depressive episodes.³⁴ The cumulative probability of relapse at 6 months after the first episode was 36% for patients with mixed episodes or rapid cycling, 20% for patients whose last episode was manic, and 33% for patients with depressive episodes.³⁴

Patients who experience mixed episodes also have higher rates of both suicidality and substance abuse. For instance, in a pooled study of more than 500 patients with bipolar or other major affective disorders who had a history of at least 1 hospitalization, 29.2% of patients with mixed episodes had had a recent suicide attempt, compared with 20.3% of patients with a depressive episode and 2% of manic patients (a statistically significant difference).³⁵ In addition, an incidence of substance abuse was observed in 38.2% of patients with mostly mixed episodes, compared with 30.3% in the rest of the bipolar population.³⁵

Patients with mixed episodes respond more slowly to and experience less improvement with lithium than do patients experiencing pure mania.³ Anticonvulsants such as valproate may be more effective than lithium for the treatment of mixed states.^{1,33} Recent efforts to identify other treatment options that will rapidly relieve both the manic and the depressive symptoms of mixed episodes have led to the increased use of SGAs in this context.³³ As with mania, rapid control of mixed states is an important objective.

Treatment issues when psychotic symptoms are present

Psychotic features most frequently appear in manic episodes of bipolar disorder but may occur during any phase. More than half of manic episodes have psychotic features, and as many as 58% of patients with bipolar disorder have experienced at least 1 psychotic episode.^{1,36} Psychotic symptoms that typically occur in bipolar disorder are grandiose delusions, such as an unrealistically inflated sense of worth, power, or knowledge, and depressive delusions, such as personal inadequacy and disease, paranoid and bizarre delusions, and hallucinations. Patients who experience psychotic symptoms during an acute episode may benefit from the use of an antipsychotic agent.¹

Maintenance therapy

According to expert consensus guidelines, once an acute episode has been identified and controlled, the same medication should be continued at the same dose that achieved remission.¹⁴ After a depressive episode, any antidepressants being used as adjunctive therapy should be tapered and discontinued when possible.¹⁴

Key points in the overall pharmacologic management of bipolar disorder

Several organizations publish treatment and medication algorithms for bipolar disorder (**TABLE 3**).^{1,14,15,32,37} Thus, even if the first medication or dosage prescribed for a particular patient is not effective, there are many pharmacologic options and steps in the management of bipolar disorder.³⁸ Important management components to keep in mind are medication adherence, level of response to the treatment regimen, and possible adverse reactions.

Before changing therapies for a nonresponsive patient, the clinician must ensure that medications are being taken as directed. Nonadherence is high among patients with bipolar disorder, who have long periods of normal functioning and may be in denial about their illness. Patients with only hypomanic symptomatology may not consider their symptoms problematic, and those with mania may be reluctant to give up the euphoric feelings and high self-esteem that can come with it.¹ Thus, follow-up and patient education about medication adherence are vital.

If the patient is following medication schedules and directions correctly but improvement is still insufficient, optimizing dosing is the next step in pharmacologic management. **TABLE 4** gives the recommended dosages of agents for various phases of bipolar disorder.

If response is still less than optimal, treatments may be switched or augmented. It is important during this process to keep patients hopeful, for example, by informing them that if they have not responded to a certain class of drugs, they may be more likely to respond to a different class.³⁸

Most of the traditional mood stabilizers used for bipolar disorder can cause significant side effects; thus, periodic patient monitoring is crucial during long-term treatment. Interactions with other psychiatric and non-psychiatric medications may push a mood stabilizer into either a subtherapeutic or a toxic range, and the consequences of overdosage can be serious and even lethal.¹ Therefore, serum levels of lithium, valproate, and carbamazepine should be checked regularly and dosages adjusted accordingly to ensure that they are in the therapeutic range.²⁰ Lithium treatment has been associated with weight gain and thyroid toxicity,³⁹ and renal and thyroid function should be checked every 6 months to 1 year during treatment.^{1,39} Side effects of valproate can include transaminase elevations, hepatic failure (in pediatric patients), and, rarely, thrombocytopenia; while not required, it is recommended that tests of hematologic and hepatic function be performed every 6 months during valproate treatment.¹ Treatment with carbamazepine calls for complete blood cell counts, platelet measurements, and liver function tests every 2 weeks for the first 2 months of treatment. Thereafter, if laboratory results are normal, blood cell counts and liver function tests should be performed every 3 months.¹ Carbamazepine may decrease levels of valproate, lamotrigine, oral contraceptives, protease inhibitors, benzodiazepines, and certain antipsychotics and antidepressants; monitoring of serum levels of these drugs is, thus, required during carbamazepine therapy.¹

After reviewing data on the metabolic implications of SGAs, the American Diabetes Association (ADA) and the American Psychiatric Association (APA) issued a joint consensus statement concluding that clozapine and olanzapine have a pronounced risk of metabolic syndrome, risperidone and quetiapine exhibit discrepancies

TABLE 3

Guidelines and algorithms for bipolar disorder treatment

American Psychiatric Association Practice Guideline for Bipolar Disorder¹

- Comprehensive
- For all aspects of treatment

Expert Consensus Guideline for Bipolar Disorder¹⁴

- Developed by an independent group of psychiatrists
- Focused primarily on psychopharmacology
- Survey of experts

Texas Implementation of Medication Algorithms for Bipolar Disorder¹⁵

- Flowcharts as treatment algorithms for medication management

Mt. Sinai Guidelines³⁷

- Physical health monitoring of patients taking antipsychotics

Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)³²

- Decision tree for differential diagnosis of mood disorders, including bipolar disorder

in the data, and aripiprazole and ziprasidone show minimal impact on metabolic indices (**TABLE 5**).⁴⁰ The organizations nevertheless advocate that a patient taking any SGA be monitored for metabolic syndrome upon initiation of treatment and then periodically, as shown in **TABLE 6**.⁴⁰ An individual patient with an elevated level of risk may require more frequent monitoring.⁴⁰

If a patient's metabolic condition deteriorates due to medication (eg, weight gain >5%, increased glycemia, or dyslipidemia), the ADA/APA consensus statement recommends switching to an SGA with a more favorable metabolic profile, thus reinforcing the importance of considering the overall health needs of a patient when choosing a treatment approach.⁴⁰ However, because antipsychotics are very different medications with distinctive receptor profiles, changing from one to another can be problematic. Therefore, it is prudent to follow a protocol for switching, such as the gradual approach recommended by the ADA/APA consensus statement. It calls for cross-titration, avoidance of abrupt discontinuation of the current

TABLE 4

Recommended dosage and administration of FDA-approved bipolar medications

Medication	Bipolar Depression	Maintenance/ Continuation	Mania	Mixed Episodes
Olanzapine/ fluoxetine	<ul style="list-style-type: none"> Take with or without food: initiate 6 mg/25 mg capsule; adjust to optimal clinical response \leq18 mg/75 mg (once daily pm) 	NA	NA	NA
Quetiapine	<ul style="list-style-type: none"> Take with or without food: initiate 50 mg/d; adjust daily to reach 300 mg/d on day 4 (once daily pm) 	NA	<ul style="list-style-type: none"> Take with or without food: initiate 100 mg/d; adjust by 100 mg/d (max 400 mg/d on day 4) and then by 200 mg/d (max 800 mg/d on day 6) to optimal clinical response 400 to 800 mg/d (divided dose) 	NA
Divalproex	NA	NA	<ul style="list-style-type: none"> Take with food: initiate 750 mg/d (divided dose); adjust to optimal clinical response \leq60 mg/kg/d 	NA
Divalproex ER	NA	NA	<ul style="list-style-type: none"> Take with food: initiate 25 mg/kg/d; adjust to optimal clinical response \leq60 mg/kg/d (once daily) 	<ul style="list-style-type: none"> Take with food: initiate 25 mg/kg/d; adjust to optimal clinical response \leq60 mg/kg/d (once daily)
Lamotrigine	NA	<ul style="list-style-type: none"> Take with or without food: escalate slowly; target dose for monotherapy is 200 mg/d; adjust downward or upward during coadministration with other drugs; therapeutic plasma concentration not established; read prescribing information carefully 	NA	NA
Lithium	NA	<ul style="list-style-type: none"> Usually 900 to 1200 mg/d bid, tid or qid; dosage must be individualized and serum levels monitored at 1- or 2-week intervals to maintain optimal clinical response between 0.6 and 1.2 mEq/L; during uncomplicated remission, monitor every 2 months 	<ul style="list-style-type: none"> Usually 1800 mg/d in divided doses; dosage must be individualized and serum levels monitored twice weekly until stabilized to optimal clinical response between 1.0 and 1.5 mEq/L 	NA
Aripiprazole	NA	<ul style="list-style-type: none"> Take once daily with or without food: 15 or 30 mg/d in patients whose acute symptoms have been stabilized on aripiprazole 	<ul style="list-style-type: none"> Take with or without food: initiate 30 mg/d oral tablets, 25 mg/d oral solution; may decrease to 15 mg/d if not well tolerated (once daily) 	<ul style="list-style-type: none"> Take with or without food: initiate 30 mg/d oral tablets, 25 mg/d oral solution; may decrease to 15 mg/d if not well tolerated (once daily)

Continued on page S25

TABLE 4 Continued from page S24

Recommended dosage and administration of FDA-approved bipolar medications

Medication	Bipolar Depression	Maintenance/ Continuation	Mania	Mixed Episodes
Olanzapine	NA	<ul style="list-style-type: none"> Take once daily with or without food: 5-20 mg/d in patients whose acute symptoms have been stabilized on olanzapine 	<ul style="list-style-type: none"> Take with or without food: initiate 10 to 15 mg/d; adjust by 5 mg/d to optimal clinical response ≤20 mg/d (once daily) 	<ul style="list-style-type: none"> Take with or without food: initiate 10 to 15 mg/d; adjust by 5 mg/d to optimal clinical response ≤20 mg/d (once daily)
Carbamazepine ER	NA	NA	<ul style="list-style-type: none"> Take with or without food: initiate 400 mg/d; adjust by 200 mg/d to optimal clinical response ≤1600 mg/d (divided dose) 	<ul style="list-style-type: none"> Take with or without food: initiate 400 mg/d; adjust by 200 mg/d to optimal clinical response ≤1600 mg/d (divided dose)
Risperidone	NA	NA	<ul style="list-style-type: none"> Take with or without food: initiate 2 to 3 mg/d; adjust by 1 mg/d to optimal clinical response ≤6 mg/d (once daily) 	<ul style="list-style-type: none"> Take with or without food: initiate 2 to 3 mg/d; adjust by 1 mg/d to optimal clinical response ≤6 mg/d (once daily)
Ziprasidone	NA	NA	<ul style="list-style-type: none"> Take with food: initiate 80 mg/d; target 120 to 160 mg/d by day 2 (divided dose) NOTE: Absorption doubles when taken with food 	<ul style="list-style-type: none"> Take with food: initiate 80 mg/d; target 120 to 160 mg/d by day 2 (divided dose). Absorption doubles when taken with food

NA, not applicable
Source: US Food and Drug Administration; Manufacturers' US prescribing information for drugs listed.

drug, and dosage determined by the profile of the new drug.⁴⁰ Also, there are times when switching may not be appropriate. For example, if the drug causing the metabolic problem is the only one to which the patient has responded clinically, efforts should be made to maintain symptom control and address metabolic concerns.

Beyond pharmacotherapy

Psychotherapy is another important component of bipolar treatment. Studies of several psychotherapeutic models have shown that family-focused, cognitive, psychoeducational, and interpersonal social rhythm therapies—which combine interpersonal therapy with simple techniques to help the patient follow daily routines—can all be effective in treating bipolar disorder.^{1,41,42} These interventions allow for dialogue about ongoing disease management, educate the patient

TABLE 5

Metabolic effects of second-generation antipsychotics

Drug	Weight Gain	Risk for Diabetes	Worsening Lipid Profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole	+/-	-	-
Ziprasidone	+/-	-	-

+ = increase effect; - = no effect; D = discrepant results
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TABLE 6

Monitoring schedule for patients taking second-generation antipsychotics

Assessment	Start	4 Weeks	8 Weeks	12 Weeks	3 Month	Annually	5 Years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting glucose	X			X		X	
Fasting lipid profile	X			X			X

BMI, body mass index.
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about medications and the need for adherence, and provide information about the importance of sticking to a routine and getting enough sleep.¹¹

Psychotherapy can increase medication adherence, reduce relapse rates, shorten recovery times from depression, and improve overall patient functioning.¹¹ Although the best setting for psychotherapy is the office of a psychiatrist or psychologist (ideally one experienced in the treatment of bipolar disorder), the patient can benefit greatly if the PCP incorporates the messages from psychotherapy at key junctures during primary care visits.⁴¹

An especially important tool is daily mood charting, which enables the patient and the physician together to recognize subtle mood changes and symptoms, identify possible triggers and warning signs that might herald an acute episode, and graphically and efficiently monitor treatment response. Mood charts (available, for example, from <http://www.manicdepressive.org/moodchart.html>) can provide the clinician with important and accurate information about a patient's disease course.^{2,11}

A strong collaborative team that includes both the psychiatrist and the PCP is also needed to optimally address the psychiatric and medical comorbidities that occur in up to 70% of patients with bipolar disorder.⁶ A particularly prevalent comorbidity in this patient population is obesity. In one multicenter study, 45% of patients with bipolar disorder were considered obese

(based on body mass index) compared with 30.5% of the general population.⁴³ Obesity is a risk factor for many medical conditions, including diabetes and cardiovascular disease. In addition, obese patients can have significantly shorter times to recurrence of depressive episodes, more acute episodes over their lifetime (both manic and depressive), and more severe and difficult-to-treat index episodes.⁴⁴ It is important to keep in mind that many medications for bipolar disorder—including lithium, valproate, and many of the SGAs—are associated with weight gain.^{40,45}

The prevalence of smoking (another risk factor for cardiovascular disease) is also high in the bipolar population: an estimated 54% to 68% compared with 21.5% in the general population.^{46,47} Obesity and smoking are considered modifiable risk factors for cardiovascular disease and represent a target for intervention with exercise, nutrition, and lifestyle counseling.⁴³

Conclusion

Optimal management of bipolar disorder involves maximizing patient functioning in both the short and the long term. Together with psychosocial interventions, today's pharmacologic treatment options for bipolar disorder offer greater possibilities for successful outcomes for these patients than ever before. ■

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PART 5

Recognizing bipolar disorder on initial presentation: A case study with decision points

The diagnosis and treatment of bipolar disorder poses challenges to both primary care providers (PCPs), whose patients often present with a variety of physical rather than psychological complaints, and psychiatric clinicians, whose patients' initial presenting symptoms often are nonspecific.¹⁻⁴ The following is a case in point.

INITIAL PRESENTATION

Susan D, a 32-year-old overweight married woman without children, presents to her PCP. As she paces, she remarks: "I came to see you because I just can't sleep. I might get 3 or 4 hours of sleep a night. It's been like that for about a week now. It's affecting everything, and I'm snapping at everyone. I think I need a sleeping pill."

Decision point:

- What is the value of a good history in a case such as this one? How can the patient interview be structured to elicit a good history?

Careful questioning can aid the clinician in drawing a more accurate picture of the patient and tailoring treatment accordingly. At first glance, the solution to a sleep disturbance may seem obvious. However, several red flags have prompted the clinician to probe further. The clinician responds, "First let's discuss the problem. How are you handling the lack of sleep?" Susan D replies:

"I normally need 7 or 8 hours of sleep in order to function. But it's funny, even though I've been getting only 3 or 4 hours of sleep every night, I still have enough energy during the day. I even cleaned out the garage the other night because my husband wasn't doing it right. It's not like I feel I really need to sleep, but this insomnia for the past week or so has been driving me crazy."

The clinician continues to probe, “What troubles you the most about this?” Susan D replies:

“Maybe it’s more than just the sleep. At the same time, I’ve been feeling incredibly sad. I cry over everything and anything. I just keep thinking about things. At home and at work, I snap at the slightest thing. I’ve been losing patience with my husband. I yell at him over silly issues. I can’t concentrate at work. I eat, gain weight, feel guilty, and eat some more.”

Decision points:

- What are the indications that this could be more than a problem with sleep?
- What general medical conditions (including substance abuse) must the clinician rule out? Is the patient currently taking any medications that could be contributing to her problems?
- Are there any lifestyle or interpersonal issues contributing to sleep disturbance that should be considered?
- What evidence leads the clinician to suspect a mood disorder? What are the criteria for a major depressive episode? What are the criteria for a manic episode?

Insomnia may be due to one or more environmental or medical conditions.⁵ In this case, the clinician needs a more detailed history, because Susan D’s sleep symptoms have persisted for at least a week, she has been distractible and irritable, and she has clear mood disturbances with depressive symptoms.

Susan D states that she has occasional headaches and she denies substance abuse. Recent laboratory results, including a thyroid workup, were unremarkable. With no contributory medical history in this case, medical causes of insomnia can be ruled out. Susan D takes no medications, has a history of good sleep hygiene despite her current sleep issues, and reports no recent major changes in her lifestyle.

Her symptoms point to a mood disorder: depressed mood, significant weight gain, insomnia, psychomotor agitation, and diminished ability to concentrate are all indicative of a major depressive episode.⁵ Irritated mood, decreased need for sleep, racing thoughts, and an increase in goal-directed activity/psychomotor agitation are symptoms of a manic episode.⁵

To further clarify the diagnosis, the clinician asks about a history of mood episodes, including periods of depression, irritability, or mania. The clinician asks,

“Have you ever had a period in your life when you felt overly sad?” Susan D responds:

“A few years back, when I lived in Atlanta, I was so sad I couldn’t get out of bed and I was crying all the time. My doctor put me on an antidepressant. I had to stop it because it made me really hyper. My mind was racing and I wasn’t getting any sleep so I stopped taking the medication and I felt better. There was also a period in college when I felt depressed, but it wasn’t as bad as the time in Atlanta.”

Decision points:

- What is the significance of feeling “hyper” or agitated when taking an antidepressant?
- How should the clinician elicit information about previous experience with such symptoms?

Many patients who have bipolar disorder may be misdiagnosed as having unipolar depression. If an antidepressant is prescribed to such patients, they may experience a switch to mania or a mixed state, as evidenced by Susan’s agitation—her “hyper” symptoms.^{6,7}

The clinician asks an open-ended question, “Tell me about other times when you’ve had no sleep and increased energy...” Susan D replies:

“In college there was a period when I didn’t sleep, but that was different, since I got all of my work done. I remember that it lasted most of the spring semester.”

Decision points:

- What is the significance of a prior experience with sleeplessness?
- What is the significance of Susan D’s memory of a positive experience (ie, completion of her work)?
- How does this information align with the current symptoms?
- Is a referral to a psychiatric clinician necessary, or can this be managed by a PCP?

Susan’s history of episodes suggestive of mania following antidepressant treatment and while in college allows the clinician to rule out major depressive disorder and to diagnose Susan with bipolar disorder. It might appear from the patient’s history that she has bipolar depression, but the clinical assessment is not complete. Now the clinician has to determine the phase. Currently, Susan is experiencing a depressed mood, sleeplessness, hopelessness, and racing thoughts.

Sleeplessness may be a symptom of either mania or depression. An increase in goal-directed activity, such as seen currently (cleaning out the garage) and in the past (getting all of her work done during a period with little sleep), is present in mania but not in depression.

The clinician concludes that Susan D is most likely experiencing bipolar disorder, current episode mixed. Patients having a mixed episode of bipolar disorder meet the criteria for both a manic episode and a major depressive episode nearly every day for at least 1 week.⁵ (Note that many bipolar disorder cases seen in primary care may not meet the strict criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* [DSM-IV-TR] for duration; such cases are classified in the DSM-IV-TR as “bipolar disorder not otherwise specified.”)⁵ With its alternating moods, a mixed episode may well be one of the most disabling forms of this disorder.

Susan D has had a positive perception of her previous manic episode. Compliance with medication is something that she and her clinician should discuss, as Susan may be among those with bipolar disorder who believe that some symptoms of mania are needed for personal success.

The PCP is faced with deciding whether to refer this patient for psychiatric consultation or to retain the management of her care in the primary care setting.⁸ He determines through direct questioning that Susan has not thought about or attempted suicide. Though agitated, she seems able to discuss and understand her disorder and her treatment. Through direct questioning and observation during the office visit, the clinician determines that Susan is not experiencing hallucinations and judges that she does not require hospitalization.⁵ She appears to be a suitable candidate for outpatient management. This decision will vary depending on a clinician’s level of comfort, experience, and psychiatric resources available.⁸

Treatment recommendations

Based on a diagnosis of bipolar disorder, current episode mixed, and a phone consultation with a psychiatric colleague, the PCP determines that the appropriate way to treat Susan D is to prescribe a

medication for mixed episodes of bipolar disorder. An important step in treatment selection is to review the characteristics of the options and select the one most appropriate for the individual patient.

Decision points:

- What makes an agent a good first choice for Susan D?
- How do Susan D’s weight and metabolic risk affect the choice of agent?
- How does Susan D’s previous history of noncompliance affect the choice of agent?

As there are many medications with indications for mania, a good choice is to start with a medication that has a specific indication for mixed episodes, namely, aripiprazole, carbamazepine extended release, divalproex extended release, olanzapine, risperidone, or ziprasidone (See **TABLE**).⁹⁻²¹

In addition, Susan D needs a medication that can be started immediately and will work quickly. Ziprasidone has shown separation from placebo at day 2 in two pivotal trials, and aripiprazole has shown separation from placebo at day 4 in two pivotal trials.⁹⁻¹² This may be a benefit in Susan’s case. However, rapidity of effect cannot be the only factor in the decision. As an overweight woman, Susan D is already at increased diabetes, cardiovascular, and cerebrovascular risk.²² The use of ziprasidone or aripiprazole is associated with minimal risk of weight gain; in addition, both drugs have a metabolically neutral profile.²² Because patients with bipolar disorder may be at increased risk for overweight and obesity, therapy with agents that are associated with lower rates of weight gain is recommended in the joint consensus statement issued in 2004 by the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, and the North American Association for the Study of Obesity.^{21,23} This patient already has a history of noncompliance, albeit as a legitimate response to side effects. It has been noted that of all side effects, treatment-associated weight gain is the most common reason for noncompliance.²⁴

Since bipolar disorder is a chronic, lifelong illness, it is important to consider medications that patients can live with, ones that they can and will take consistently through future episodes.²⁵

TABLE
FDA-approved medications for mixed episodes

Oral Medication	FDA Approved for Mixed Episode	Onset of Effect*		Neutral Mean Effect on Weight ^c	Dosing Regimen ^a
		Day of 1st Assessment	Day of 1st Significant Separation From Placebo ^b		
Ziprasidone	√	Day 2 ^{9,10}	Day 2 ^{9,10}	Yes ^c	Take with food: initiate 80 mg/d; target 120-160 mg/d by day 2 (divided doses)
Aripiprazole	√	Day 2 ¹² or 4 ¹¹	Day 4 ^{11,12}	Yes ^c	Take with or without food: initiate 30 mg/d oral tablets, 25 mg/d oral solution; may decrease to 15 mg/d if not well tolerated (once daily)
Risperidone	√	Day 3 ^{14,15} or 7 ¹³	Day 3 ¹⁴ or 7 ^{13,15}	No ^c	Take with or without food: initiate 2-3 mg/d; adjust by 1 mg/d to optimal clinical response ≤6 mg/d (once daily)
Divalproex extended release	√	Day 5 ¹⁶	Day 5 ¹⁶	No ^{16,b}	Take with food: initiate 25 mg/kg/d; adjust to optimal clinical response ≤60 mg/kg/d (once daily)
Carbamazepine extended release	√	Day 7 ^{17,18}	Day 7 ¹⁸ or 14 ¹⁷	Yes ^{17,18,b}	Take with or without food: initiate 400 mg/d; adjust by 200 mg/d to optimal clinical response ≤1600 mg/d (divided doses)
Olanzapine	√	Day 7 ^{19,20}	Day 7 ²⁰ or 21 ¹⁹	No ^c	Take with or without food: initiate 10-15 mg/d; adjust by 5 mg/d to optimal clinical response ≤20 mg/d (once daily)

This table is *not* derived from head-to-head studies. It is derived from (a) the US prescribing information for each drug, (b) the pivotal studies accepted by the FDA in support of the indication, and (c) the ADA/APA 2004 Consensus Statement
*Studies assessed *first* significant separation from placebo at different days.

Follow-up

The clinician prescribed medication to treat a mixed episode. After weighing the pros and cons of prescribing a sleep medication as well as the available options, he also wrote a prescription for a benzodiazepine prn for 2 weeks. The practitioner showed Susan D how to complete a mood chart. The PCP had a staff member call her 2 days later to check on how she was doing. Susan D stated:

“I’m feeling less hyper and irritable. I had a good night’s sleep last night, so I was able to concentrate at work today. My husband thinks there’s already been a change in my behavior.”

Susan D returns to her practitioner 1 week later. She is calmer and does not complain of any mood symptoms. Together, she and the clinician review her mood chart, and the clinician asks directly about each mood symptom. He confirms that her irritability continues to decrease and that she is not becoming depressed. As recommended with all atypical antipsychotics, the clinician rechecks her vitals and laboratory results and asks about her benzodiazepine use. He also asks if she is experiencing any medication side effects, to determine if a medication adjustment is needed.

Decision points:

- Evaluation of treatment outcome
- Is the patient at risk of discontinuing medication when she feels “well”?

The clinician is pleased with Susan D’s response to medication but counsels her to remain on the medication even after she feels she is back to normal. Patients with bipolar disorder are known to have difficulty in

remembering to take a medication when they are not experiencing symptoms.²⁴ He makes sure she understands the chronic nature of the condition and the cycling that occurs with bipolar disorder and urges her to continue to update her mood chart. He asks her to return in 1 week and makes arrangements to refer her for counseling to a clinician with expertise in bipolar disorder. ■

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Drug Brand Names
Aripiprazole • Abilify
Carbamazepine ER • Equetro ER
Chlorpromazine • various
Divalproex • Depakote
Divalproex ER • Depakote ER
Lamotrigine • Lamictal
Lithium • Lithobid
Olanzapine • Zyprexa
Olanzapine/fluoxetine • Symbyax
Quetiapine • Seroquel
Risperidone • Risperdal
Ziprasidone • Geodon