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Recognizing, managing and treating bipolar disorders at the interface of primary care and psychiatric medicine

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PRIMARY EDUCATION
ON BIPOLAR DISORDER



Recognizing, managing and treating bipolar disorders at the interface of primary care and psychiatric medicine

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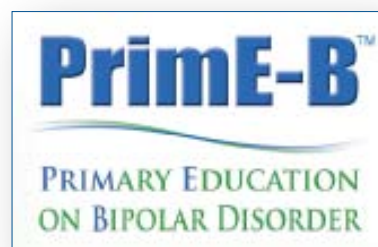
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PART 1

Defining the challenge: Recognizing and treating bipolar disorders 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.^{1,2,3} In psychiatric settings, too, bipolar disorder may be undetected or may be recognized only after a long delay,⁴ possibly because of evolving criteria for diagnosing the disorder.^{3,5,6,7}

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.^{1,2,3,8,9} 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.^{11,12,13}

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 *Current Psychiatry*, is the end result of a meeting of an editorial planning board of expert 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

Recognizing and understanding bipolar disorders

CASE DISCUSSION. Mr. R, a 23-year-old man, is brought into the primary care provider's office by his mother, who accompanies him into the examining room. Mr. R states he has come because his mother said he could not continue to live at home if he did not get help. Mr. R's mother reports the following history: During Mr. R's third year of college, he began to drink heavily and smoke marijuana. His grades, which had initially been good, began to plummet and he was placed on academic probation. During his fourth year, Mr. R shared a house off campus with several other students, who were also heavy drinkers. One evening, Mr. R created a disturbance in the neighborhood and the police charged him with disorderly conduct and resisting arrest. The charges were dropped on the condition that Mr. R would seek help at the university counseling center. Mr. R received substance abuse counseling there and was entered into a clinical trial for alcohol abuse treatment. His grades improved somewhat, but at the end of the study, he dropped out of treatment, began drinking heavily again, and stopped going to classes. He failed all of his courses during the last semester and was told he could not return to the university. He then returned home to live with his parents, where he has been for the past 3 months.

Mr. R's mother reports that he shows no initiative and refuses to look for a job despite his parents' urging. He sleeps excessively and the rest of the time just sits around watching television, drinking beer, and smoking and "snaps our heads off" if his parents say anything to him about his behavior. When his parents questioned him, he told them he feels depressed and like a failure and that he just wants to sleep and does not care about anything. When the physician asks him why he drinks so much, he says it is the only thing that makes him feel better.

The doctor makes a tentative diagnosis of major depression and prescribes a selective serotonin reuptake inhibitor (SSRI) antidepressant. He asks Mr. R to return in 1 week for follow-up.

BOX

Recognizing bipolar disorder —key points

- The initial presentation of patients with bipolar disorder is almost always depression.^{1,2}
- Bipolar depressive episodes tend to occur more frequently and to last longer than hypomanic or manic episodes.³
- Pure mania or hypomania usually presents as part of a mixed mood state, in which depression is accompanied by irritable, restless, driven energy.¹
- The symptomatic criteria for major depressive disorder and bipolar depression are identical, except that bipolar depression includes a history of manic, hypomanic, or mixed episodes.¹
- Patients with bipolar disorder frequently have comorbid substance abuse problems.^{1,3,4}
- Before prescribing an antidepressant, look for signs that the patient may have a bipolar disorder rather than a unipolar depression.^{2,3}
- For patients with mixed episodes, treatment with selective serotonin reuptake inhibitor (SSRI) antidepressants alone can be particularly risky, amplifying both the mania and the depression.^{5,6}

At the follow-up visit, Mr. R reports that he is feeling much better, has more energy, and is thinking of going back to school at the local community college. The doctor provides a refill for the SSRI and schedules Mr. R for a return appointment in 4 weeks, telling him to call if he has any problems with the medication before then.

Four days later, the physician receives an urgent phone call from Mr. R's mother. She says that Mr. R has been staying up all night, waking his parents and younger sister by playing music loudly and talking to his friends on long distance calls for hours. She reports a crisis the night before: When Mr. R's father told Mr. R he was going to cancel his credit card because Mr. R was using it to buy beer and cigarettes, Mr. R became extremely angry and began to smash furniture in the house. A family friend whom Mr. R respects was called and was able to calm him down. Mr. R's mother asks if the doctor can see Mr. R right away.

When seen in the doctor's office later that day and asked about the incident, Mr. R says that he just saw red and could not stop himself from smashing the furniture. He says he is sorry and scared about what he did. He reports that he often feels angry and irritable and just

wants to "smash stuff up." He says he has had similar outbreaks in the past but nothing as bad as this. The physician makes a mental note that it is difficult to interrupt Mr. R with follow-up questions.

The PCP then asks both Mr. R and his mother to complete the Mood Disorder Questionnaire (MDQ). With further questioning and the responses to the MDQ, the following information emerges. Mr. R has tended to have very rapidly shifting moods since his early teens, which his parents had attributed to the normal ups and downs of being a teenager. Mr. R reports that he used to feel angry and irritable with his teachers and parents a lot and that these feelings were much stronger than those his friends seemed to feel. Mr. R responded affirmatively to 9 of the 13 items on the MDQ. When questioned directly, Mr. R's mother reluctantly admitted that Mr. R's paternal grandfather had been "manic depressive" and had committed suicide when Mr. R's father was a young man. Mr. R had not known this "family secret." He had always been told his grandfather died of cancer. With this additional information, the physician revises the diagnosis to bipolar disorder. He starts Mr. R on a mood-stabilizing agent, and the SSRI is gradually tapered and discontinued. Mr. R responds well to the mood-stabilizing agent.

Recognition of bipolar disorder

As many as 4% of American adults may suffer from bipolar I disorder and bipolar II disorder.⁴ This was the prevalence found in a large-scale community screening study by Hirschfeld and colleagues that used the MDQ, a validated self-report screening instrument for bipolar disorders. This questionnaire, which can be completed by patients in about 5 minutes, identifies up to 7 in 10 psychiatric patients and 6 in 10 patients in general populations with bipolar disorder, and it screens out 9 in 10 patients who do not have this disorder (**FIGURE 1**)^{7,8} It is notable in the Hirschfeld study that only 19.8% of the individuals with positive screens for bipolar I and II disorders reported that they had previously received a diagnosis of bipolar disorder from a physician, whereas 31.2% reported receiving a diagnosis of unipolar depression. The remaining 50% reported not receiving either diagnosis.⁴

When 1157 patients seeking primary care at an urban general medicine clinic were screened for bipolar

FIGURE 1

Mood disorder questionnaire

	Yes	No
1. Has there ever been a period of time when you were not your usual self and...		
• you felt so good or so hyper that other people thought you were not your normal self or you were so hyper that you got into trouble?		
• you were so irritable that you shouted at people or started fights or arguments?		
• you felt much more self-confident than usual?		
• you got much less sleep than usual and found you didn't really miss it?		
• you were much more talkative or spoke faster than usual?		
• thoughts raced through your head or you couldn't slow your mind down?		
• you were so easily distracted by things around you that you had trouble concentrating or staying on track?		
• you had much more energy than usual?		
• you were much more active or did many more things than usual?		
• you were much more social or outgoing than usual; for example, you telephoned friends in the middle of the night?		
• you were much more interested in sex than usual?		
• you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?		
• spending money got you or your family into trouble?		
2. If you checked YES to more than one of the above, have several of these ever happened during the same period of time?		
3. How much of a problem did any of these cause you like being unable to work; having family, money, or legal troubles; getting into arguments or fights? <input type="checkbox"/> No Problem <input type="checkbox"/> Minor Problem <input type="checkbox"/> Moderate Problem <input type="checkbox"/> Serious Problem		
4. Have any of your blood relatives (ie, children, siblings, parents, grandparents, aunts, uncles) had manic-depressive illness or bipolar disorder?*		
5. Has a health professional ever told you that you had manic-depressive illness or bipolar disorder?*		
<small>© 2000 Dr. Robert M.A. Hirschfeld; Licensed by Compact Clinicals Kansas City, MO. This instrument is designed for screening purposes only and is not to be used as a diagnostic tool. A score of at least 7/13 on the MDQ, with several of the symptoms occurring during the same period and causing moderate to severe problems for the patient, has shown good sensitivity and very good specificity in screening for bipolar spectrum disorders in outpatients. *Questions 4 and 5 are often included when the MDQ is administered. The MDQ is available to download at www.epocrates.com/products/medtools/bipolarscreening.html</small>		

disorder, 1 in 10, or approximately 116 patients, screened positive for a lifetime history of the disease,⁹ but only 8% of these patients reported having received a diagnosis of bipolar disorder in the past, whereas nearly 80% reported a previous diagnosis of depression.⁹ Yet the medical records for these patients from primary care visits during the previous 6 months identified depressive symptoms in only 49% of cases and made no mention of bipolar disorder. In another investigation of patients being treated for depression with antidepressants at a family medicine clinic, about 1 in 5 screened positive for bipolar disorder on the MDQ.⁸ In addition, a study by the Depression and Bipolar Support Alliance found that the time from first presentation to correct diagnosis of bipolar disorder was, on average, 8 years.¹⁰

These results, taken together, indicate that bipolar disorder frequently is either misdiagnosed or missed altogether, and further highlight the importance of screening for bipolar disorder in primary care settings to increase identification and treatment of the disease. Additionally, bipolar II disorder may be more likely than bipolar I disorder to go unrecognized because the hypomania characteristic of bipolar II disorder, although much more common than classic pure mania, is also more difficult to identify and diagnose.²

As mentioned, one reason for the frequent misdiagnosis of bipolar disorder as depression is that as many as 60% of first episodes of bipolar disorder present with depressive symptoms.^{11,12} For example, in a cohort of individuals born in 1940 or later taken from a registry of more than 1200 patients with bipolar illness, major depression was the type of episode at onset in 55% of the patients. A manic episode was observed in 23% of patients, and a mixed episode was observed in 22%. Women were more likely to experience major depression as the first episode, and men were more likely to present with mania.¹¹

More than 90% of individuals who have a first manic episode have future episodes, and patients with bipolar I disorder generally have more episodes, both depressive and manic, over their lifetime than patients with recurrent major depressive disorder.¹³ Yet almost 40% of patients with bipolar disorder are diagnosed as having unipolar major depressive disorder, even after having a manic or hypomanic episode.^{2,12,14}

Unipolar major depressive disorder and bipolar disorder differ substantially in their underlying genetics, prognosis, disease course, outcomes, and recommended treatment.² As illustrated in the case presented here, the clinical implications of missing a diagnosis of bipolar disorder are serious, since use of an antidepressant without a mood stabilizer may lead to worsening symptoms and increased mood cycling.^{2,14,15,16} Unfortunately, it is often only after this worsening has occurred that a patient is correctly diagnosed.

A majority of patients with bipolar disorder experience chronic interpersonal or occupational difficulties between acute episodes.¹³ In addition, the presence of bipolar disorder can have a negative effect on the expression, course, and management of comorbid medical conditions (eg, obesity, diabetes mellitus, cardiovascular and cerebrovascular disease, metabolic syndrome), as prevention and treatment programs are difficult to implement in the bipolar population.¹⁷ Patients with bipolar disorder also have high rates of suicidal ideation and attempted suicide, with some 10% to 15% completing suicide, usually when in a depressive or a mixed state.¹³ Thus, not recognizing bipolar disorder has significant implications for the patient's long-term health and welfare and may even be life-threatening. Fortunately, a number of features have been identified that can help clinicians make this important differential diagnosis.

Diagnosing bipolar disorder

For diagnostic purposes, primary mood disorders are divided into 4 major categories: depressive disorders, bipolar disorders, mood disorders due to a general medical condition (eg, depression due to Parkinson's disease), and substance-induced mood disorders (eg, depression due to alcohol abuse).¹³ Here, our focus is on the question of how to distinguish unipolar depressive disorder and bipolar disorder from each other. Simply

put, the key to distinguishing them is the presence or a history of a manic, mixed, or hypomanic episode. If a patient has experienced any of these, the diagnosis is bipolar disorder.¹³ In practice, however, this distinction may not be easy to make.

Patients with mood disorders can experience a widely varying pattern of mood episodes. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR®), presents criteria for each category of mood episode, ie, major depressive, manic, mixed, and hypomanic. Diagnosis is not based on the presenting episode alone. Rather, the different types of mood episodes serve as "building blocks" of information that one uses to arrive at the diagnosis. The diagnosis is thus derived from the pattern of episodes that a patient experiences.¹³

Depressive Episodes

Most PCPs are familiar with the criteria for a major depressive episode and recognize its symptoms. However, it is crucial to not automatically diagnose a patient whose symptoms meet criteria for a major depressive episode as having major depressive disorder (ie, unipolar depression). An assessment to rule out a bipolar disorder should be a routine part of any workup for such a patient.^{2,3,15} Although depression is fairly easy for a physician to recognize, it is extremely difficult to distinguish unipolar depression from bipolar depression on the basis of the current clinical features alone. Therefore, the differential diagnosis rests on a careful assessment of past manic or hypomanic symptoms, as well as a careful investigation of family history.¹⁵

In addition, a constellation of characteristics and behavior patterns can alert clinicians to the possibility of a bipolar illness in a patient with depressive symptoms (**TABLE**)⁵. These include recurrent interpersonal conflicts, extreme extroversion that causes interpersonal problems, legal difficulties, sexual promiscuity, other types of impulsive behaviors, poor judgment that produces destructive consequences, reduced need for sleep, sudden or frequent job or career changes, and severe or recurrent financial difficulties or indiscretions.^{15,18}

Manic and hypomanic episodes

Pure mania is characterized by abnormally and persistently elevated, expansive, or irritable mood for at least 1

TABLE

Five keys to diagnosing bipolar disorder: A primary care approach

When you suspect a patient has bipolar disorder, consider...

1. Sleep disruption	<ul style="list-style-type: none"> • Patient has trouble falling asleep because thoughts are racing.
2. Family history	<ul style="list-style-type: none"> • Patient has a relative with bipolar disorder, or • Patient has 3 or more first-degree relatives diagnosed with any of the following: depression, obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, anxiety, or panic disorder, or • The family history contains many instances of suicide, incarceration, drug or alcohol abuse, or mental breakdowns.
3. Personal history	<ul style="list-style-type: none"> • What were patient's childhood and adolescence like? • Ever depressed prior to this episode? • Experienced postpartum psychosis or depression? • Attempted suicide? • Abused drugs or alcohol? • Exhibited cutting behaviors? • Have a history of migraine headaches? • Have a history of job loss? (How many times changed jobs?) • Left a job without another lined up? • Had unexpected result or misadventures with antidepressants? <p>Rule of threes: If the patient has had 3 jobs or 3 marriages or has had a failed response to 3 different antidepressants, suspect bipolar disorder.</p>
4. Instability	<ul style="list-style-type: none"> • Patient has had episodes of mania or hypomania, or • Patient is not always "the same person" from one day to the next, or • Patient is irritable, easily flies off the handle, or is unpredictable.
5. Atypical depression	<ul style="list-style-type: none"> • Distinguishing features are sleepiness and rapid onset and rapid remission of symptoms.

Adapted with permission from Grieco R, Edwards L. *The Other Depression: Bipolar Disorder*. Beaver Falls, Pa: McKinley Press; 2006.5

week accompanied by at least 3 additional characteristic symptoms, including inflated self-esteem or grandiosity, decreased need for sleep, pressured speech, flight of ideas, distractibility, increased involvement in goal-directed activities or psychomotor agitation, and excessive involvement in pleasurable activities with a high potential for painful consequences.¹³ Although PCPs

will almost certainly recognize full-blown mania, they are unlikely to encounter a patient in this phase, as it is much rarer than a hypomanic or a mixed episode.¹⁵

The characteristics of hypomania are similar to those of mania, but they are less intense and of a shorter duration (ie, at least 4 days).¹³ Patients having a hypomanic episode often feel quite well and may not recognize that there is anything abnormal occurring. Therefore, it can be difficult to differentiate normal elevated mood from mild manic symptoms.¹⁹ By definition, a patient with hypomania does not have psychotic symptoms and is not hospitalized, so there may be no record of a previous hypomanic episode. Obtaining additional history from a patient's family or a close friend (with the patient's permission) can help the PCP identify hypomania.¹² For example, having a family member complete the MDQ about the patient can be helpful in identifying symptoms, especially hypomania, that the patient might not consider a problem.^{2,18}

The duration of the manic or hypomanic episodes of many patients seen in primary care does not meet the criteria of either bipolar I or bipolar II disorder; for these patients, the diagnosis would be bipolar disorder not otherwise specified.¹³

Mixed episodes

It may seem contradictory that a person can be manic and depressed at the same time. However, in a mixed state, the high level of energy and mental activation associated with mania may be coupled with sadness, dark thoughts, intense dysphoria, worry, despair, guilt, or self-loathing. The result can manifest as restlessness, agitation, irritability, anger, or even rage and can lead to particularly dangerous and destructive activities.⁵ A mixed episode is one that meets the criteria for both a manic episode and a major depressive episode (except for duration) nearly every day for at least a 1-week period.¹³

Mixed episodes may be difficult to identify, particularly when a clinician has not seen them before or when the patient's symptoms only partially meet the criteria for a mixed episode. But family practitioners need to be able to make this identification, because it is more common to see mixed episodes in family practice than mania.²⁰

Further complicating the differential diagnosis—sense of well-being may be suffering from mild hypomania, rather than a mixed episode.²

Bipolar I and Bipolar II Disorders

Key to differentiating between bipolar I and bipolar II disorders is the presence or absence of mixed or manic episodes. If a patient has or has had 1 or more manic episodes or 1 or more mixed episodes, the diagnosis is bipolar I disorder.¹³ If a patient has had 1 or more major depressive episodes and 1 or more hypomanic episodes, but no mixed or manic episodes, the diagnosis is bipolar II disorder.¹³

CASE DISCUSSION. As noted, the PCP's 2 main challenges in diagnosing bipolar disorder are (1) distinguishing unipolar depression from bipolar depression or a mixed episode and (2) eliciting a history of manic or hypomanic symptoms.¹⁵ In the case presented here, although

Mr. R was initially diagnosed with depression, it eventually became clear that his condition had a number of features suggestive of bipolarity, such as substance abuse, excessive sleeping, and irritability combined with depressive symptoms. Other important aspects of Mr. R's current and past symptoms and of the family history of bipolar disorder came to light only when the doctor probed further and administered the MDQ. A score of 7 or greater on this questionnaire is considered a reliable indicator of the presence of manic or hypomanic symptoms, and Mr. R's score was 9. The building blocks of Mr. R's presentation strongly suggest a mixed episode. However, as has been illustrated here, mixed episodes do not necessarily present with the classic euphoric mood of mania but may involve depression associated with restless energy and irritability. ■

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PART 3

Clinical management of bipolar disorder: Role of the primary care provider

Primary care providers (PCPs) are frequently relied on to initially manage psychiatric disorders and to determine the subsequent need for specialized care.¹ A Several factors have contributed to increased PCP involvement in the detection, diagnosis, and treatment of patients with bipolar disorder in recent years. The most important of these is the markedly increased participation of PCPs in psychiatric care in general and the increased number of safe and effective treatments for bipolar disorder. Another is that patients frequently fail to follow through with referrals to psychiatrists because of insurance restrictions, limited physician availability or waiting lists, and the stigma associated with psychiatric care.²

Successful primary management of bipolar disorder involves addressing issues related to comorbidities, referrals, treatment goals, medication, psychosocial interventions, and family concerns that are unique to the disease and that will need continued attention over multiple office visits (TABLE 1).³⁻¹⁹

Evaluating comorbidity in the patient with bipolar disorder

Comorbid psychiatric conditions

Patients with bipolar disorders have high rates of comorbid anxiety disorders. 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).²⁰ The lifetime risk of anxiety disorders in bipolar I disorder has been reported to be 93% compared with 58%

TABLE 1

Key principles in managing bipolar disorder in primary 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)³
Referral	<ul style="list-style-type: none"> • In deciding to refer a patient for specialized mental health care, PCPs should evaluate their comfort level in treating each patient, depending on the complexity of the case, suicidality, psychosis, and their familiarity with the medications and other interventions indicated.^{2,4} • The best results are often obtained when PCPs work collaboratively with a psychiatric provider and/or a psychotherapist.^{4,5}
Treatment goals	<ul style="list-style-type: none"> • 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.^{4,6} Specific goals include establishing and maintaining a therapeutic alliance, monitoring the patient's psychiatric status, providing education about bipolar disorder, promoting treatment adherence and regular patterns of activity and sleep, anticipating stressors, identifying new episodes early, and minimizing functional impairments.⁶
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.⁴ 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.⁴ • Antidepressants, used alone without a mood stabilizer, can exacerbate mood symptoms or cause rapid cycling in patients with bipolar disorders.^{2,8-10} • 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.^{4,11} • 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.¹¹
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.^{4,12,13}
Psychiatric comorbidity	<ul style="list-style-type: none"> • Patients with bipolar disorder have high rates of comorbid psychiatric disorders, especially anxiety disorders, which need to be taken into account in treatment planning.^{2, 14-16} • Patients with comorbid substance abuse are prime candidates for collaborative care with a substance abuse team that includes a psychiatric provider.¹⁷
Medical comorbidity	<ul style="list-style-type: none"> • Patients with bipolar disorder have elevated rates of obesity and metabolic abnormalities^{4,18} that are therapeutic targets and need to be considered in selecting psychiatric medications. • Bipolar disorder, like depression, may have an adverse impact on the expression, progression, and management of many comorbid illnesses. Such effects need to be addressed in an effort to optimize the patient's global health. • Regular monitoring of the physical health of patients with bipolar disorder is essential in promoting the best outcomes.¹⁹

in unipolar depression.²¹ 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 with a normal mood, and a higher incidence of substance abuse and suicide attempts.^{15,20,21,22} These disorders may be more likely to occur in patients with mixed episodes.^{15,21}

Patients with bipolar disorder also have higher rates of substance abuse than the general population, with about 60% meeting criteria for substance abuse at some point in their lives.²³ Bipolar disorder with comorbid substance abuse is associated with fewer and slower remissions, higher rates of suicide and suicide attempts, and poorer outcome.^{7,21} Patients with bipolar disorder and comorbid substance abuse should

be aggressively treated for both disorders.¹⁷ Comorbid eating and personality disorders are important therapeutic targets as well for patients with bipolar disorder.¹⁵

Comorbid medical disorders

Patients with bipolar disorder have elevated rates of conditions that increase their risk of cardiovascular disease and type 2 diabetes mellitus, such as obesity, smoking, hyperglycemia, hypertension, and dyslipidemia.^{18,24,25} In one sample, 30% of patients with bipolar disorder met criteria for the metabolic syndrome²⁶ and nearly 50% had abdominal obesity or hypertriglyceridemia or were receiving a lipid-lowering medication.²⁶ Obesity and the metabolic syndrome contribute to a worse prognosis for bipolar disorder through their negative impact on general physical well-being and functioning, quality of life, and self-esteem.^{22,26,27} 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,^{18,26} and some of the SGAs also increase the risk of metabolic abnormalities.^{15,18} If weight gain and metabolic problems are a concern, clinicians may want to select an agent that is less likely to cause these problems.¹⁸ Among available SGAs, olanzapine is associated with the greatest increase in weight and metabolic problems and ziprasidone and aripiprazole with the least.^{11,18}

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),²⁵ chronic fatigue syndrome, migraine, asthma, chronic bronchitis, multiple chemical sensitivities, and gastric ulcer.²⁸

Physical health monitoring

An advantage of primary care evaluation of patients with bipolar disorder is that many

FIGURE 1

Sample checklist for PCP referral for a specialized psychiatric evaluation

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: _____

Provide as complete information as possible on the following (attach any relevant reports or laboratory printouts)

Reason for referral

Expectations from referral (eg, Confirm diagnosis and return patient to primary care? Advise primary care provider of what to do? Develop a shared treatment plan? Take over treatment of patient entirely?) _____

Demographic

Medical history

Psychiatric history: pattern and duration of symptoms, previous diagnoses

Treatment history

Current medications, dosage, duration, symptom response, side effects

Past medications, dosage, duration, symptom response, side effects

Medication allergies

Results of imaging and laboratory studies

Exposure to stressful life events

Suicidal ideation/suicide potential/suicide attempts

Alcohol/substance use

Family psychiatric history

Relevant family medical history

Patient's health plan

Expectations regarding follow-up care

FIGURE 2

Sample checklist for psychiatrist 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 (attach any relevant reports or laboratory printouts)

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 _____

of the elements of the initial assessment, including medical history, physical examination, and laboratory testing, may already have been addressed. If these have not been recently performed or documented in the chart, the initial evaluation of a patient with bipolar disorder should include a review of family history for diabetes, lipids, cholesterol, and stroke; weight, height, and blood pressure measurement; body mass index (BMI) calculation; evaluation of tobacco and alcohol use; assessments of thyroid, liver, and renal function and blood glucose and lipid levels; complete blood cell count; and cardiovascular history.^{3,19} If clinically warranted, drug screening, a chest X-ray, an electrocardiogram (ECG), an electroencephalogram (EEG), a computed tomography (CT) scan, or a magnetic resonance imaging (MRI) scan can be ordered.¹⁹

When initiating pharmacologic treatment (*addressed in Part 4*), height, weight, waist circumference, BMI, fasting plasma glucose or glycated hemoglobin (HbA1c) and lipid levels, and blood pressure should be measured.¹¹ Patients being treated with SGAs as well as their family members should be educated about symptoms and risks of diabetes mellitus and diabetic ketoacidosis and hyperlipidemia.¹¹

An annual examination should be performed in patients with bipolar disorder to assess plasma glucose levels, weight, smoking, alcohol use, and blood pressure. Lipid levels, including cholesterol, should be assessed annually in patients older than 40 years of age.¹⁹ For most patients, this examination can be efficiently integrated into their ongoing preventive medical care or other primary care visits.

During long-term SGA therapy, patients' weight should be reassessed at 4, 8, and 12-week intervals after initiating or changing treatment with an SGA, and quarterly thereafter. For patients who are not at elevated risk for metabolic syndrome, diabetes mellitus,

or hypertension and who do not experience significant weight gain on SGA therapy, fasting plasma glucose level and blood pressure should be assessed 3 months after initiating an SGA and annually thereafter. For patients with normal baseline lipid levels, follow-up fasting lipid profile testing should be repeated at 5-year intervals unless there is a significant weight gain associated with the SGA therapy or it is otherwise clinically indicated.^{11,27} For patients who have a 5% or greater increase in baseline body weight, switching to a different antipsychotic should be considered.¹¹ Patients with metabolic syndrome, hypertension, dyslipidemia, cardiovascular disease, or type 2 diabetes mellitus or those who experience the emergence or progression of such diseases but are not candidates for a switch to another SGA, must be monitored scrupulously according to current guidelines for these diseases.¹¹ Patients with serious mental illness have an increased risk for diabetes and heart disease; therefore, this monitoring is particularly important.²⁹

Prolactin levels should be measured in patients taking SGAs, particularly if they are taking risperidone, and if they develop low libido, sexual dysfunction, menstrual abnormalities, gynecomastia, or galactorrhea.¹⁹

If a patient is not responding to a drug used for bipolar disorder treatment, such as lithium or quetiapine,^{30,31} thyroid function should be assessed, since such patients may have normal thyroid-stimulating hormone levels but low or low-to-normal free thyroid (T4 or T3) values. Correction of this subclinical hypothyroidism, usually using L-thyroxine, can often improve long-term response to these agents.¹⁷

Provision and coordination of care

Considerations for referral to psychiatric care

Whenever a PCP does not feel comfortable treating a patient with bipolar disorder, it is appropriate to consult or refer the patient to a psychiatric specialist for further evaluation and follow-up. A referral is also indicated if the patient has a very complex presentation, treatment-refractory illness, psychosis, or significant suicidal ideation or behavior. A patient who presents with symptoms of acute mania and/or appears to be a danger to self or others should be referred to a

TABLE 2

Interventions to manage side effects of bipolar medications

Side Effect	Intervention
Tremor	<ul style="list-style-type: none"> • Low doses of propranolol or other β-blocking agents
Cognitive/Memory Problems	<ul style="list-style-type: none"> • Dose decrease • Bedtime dosing • Addition of B vitamins • Correction of low-normal thyroid function
Weight Gain	<ul style="list-style-type: none"> • Dietary changes—especially, restriction of simple sugars, frequent small feedings, and L-glutamine supplementation for lithium treatment • Thyroid supplementation • Change in medication

Source: Reference 17

psychiatrist/advanced practice psychiatric nurse, psychiatric hospital, or emergency department, as indicated, for urgent evaluation.^{14,19} Although a rare occurrence in the primary care setting, extremely ill patients may need to be transported to the hospital, often by the police.¹⁴

Collaboration with mental health care providers

Communication between PCPs and psychiatric providers is often inadequate. To provide effective treatment for mental illness, PCPs need to develop broader psychiatric diagnostic and referral skills³² and collaborative relationships with local psychiatrists/psychiatric specialists and psychotherapists to whom they can refer patients for further evaluation and treatment.^{4,14}

As with any referral to a specialist, when referring a patient for a specialized mental health evaluation, PCPs should provide as complete information as possible⁵ (see **FIGURE 1**). The referring physician should notify the patient as to what information will be shared and obtain the patient's permission to disclose this information.

As with the care provided by other specialists, when the main health care provider for a patient with bipolar disorder is the psychiatrist, the PCP should expect the psychiatrist to initiate and maintain communication of the details necessary for the PCP to manage the

patient's overall care (**FIGURE 2**). When necessary, the PCP should communicate this expectation to the psychiatrist; if the response is inadequate, the PCP should consider an alternate psychiatric referral.

Such communication is accomplished easily by placing a phone call or leaving a message alerting the collaborating clinician that a patient has been referred, along with a brief overview of the problem and pertinent patient information. Telemedicine and telepsychiatric consultations have the potential to improve care for patients with chronic psychiatric conditions.^{5,33} Together, the psychiatric provider and the PCP should coordinate responsibility for medication prescriptions and follow-up laboratory tests (eg, serum drug levels and lipid and glucose levels).¹⁴ The best outcomes are achieved when individuals with bipolar disorder have continuity of care and see the same health care professional regularly. When this is not possible, coordination of care becomes even more important.

Working with patients to achieve best outcomes

This section describes various aspects of care for patients with bipolar disorder and the way that such care can be optimized to improve outcomes. The total delivery of the care implied by this section may be beyond the capabilities of most PCP practices. However, as with other specialty areas, PCPs often deliver portions of such care, with the amount determined by their level of interest, expertise, and resources. In addition, again, as with the care delivered for comorbidities (ie, diabetes mellitus), the supplemental use of effective patient education materials, support groups, and ancillary providers—in this case, psychotherapists—can allow PCPs to provide comprehensive but time-efficient care.

Therapeutic alliance

A supportive therapeutic alliance between the clinician 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 are (1) expressing concern for the individual's suffering, (2) communicating appropriate optimism about the potential for successful treatment, while (3) avoiding

raising unrealistic expectations by educating patients that they may need to try several different medication regimens before they find one that works.^{3,17} Patients and families/caregivers should be encouraged to work collaboratively with health care providers and to take an active role in treatment decisions.^{6,19}

Patients and families are part of the treatment team

Psychoeducation involves providing patients and families/caregivers with accurate, easy-to-understand information about bipolar disorder, available medications, and potential side effects of those medications. It is helpful to explain to the patient and family that bipolar disorder is a real medical condition, legitimate and worthy of treatment, but that management is likely to be ongoing over the course of the patient's life.^{6,19} Encouraging patients with bipolar disorder to draft an advance directive stating their preferred treatment in the event of a health crisis can help reduce confusion and stress for the patient and caregivers and facilitate timely delivery of effective care.¹⁹

Patients and families should also be informed about advocacy and support groups, early warning signs of relapse, and lifestyle changes to reduce relapses and minimize side effects of medications.^{4,19} Lifestyle changes that can improve outcomes include avoiding alcohol, nicotine, caffeine, and illegal drugs.⁴ Additionally, patients should be encouraged to get regular sleep, since disruptions in sleep patterns can precipitate mood disturbance.^{24,17}

Because patients with bipolar disorder have increased rates of obesity and other medical conditions that can increase health risks, clinicians should educate patients about dietary restrictions and exercise to limit weight gain, which can improve the long-term prognosis for bipolar disorder, as well as overall health and wellness.²⁶ When a patient does gain weight during treatment, the clinician should review the medication regimen and refer the patient to specific programs for weight management or to a dietitian, especially if the patient has complex comorbid medical problems.¹⁹ The clinician should also alert patients to the dangers of sexually risky behavior and monitor patients for sexually transmitted diseases.¹⁴

Improving adherence

Poor adherence to the medication regimen is one of the most common causes of relapse or poor response to treatment.^{17,34} High rates of nonadherence have been reported in patients with bipolar disorder.³⁵ Although data are limited, published studies suggest that adherence rates may be better with SGAs than with typical antipsychotics.³⁵

The most common reason for nonadherence is side effects, especially weight gain, sedation, cognitive slowing, and decreased energy, as well as tremor with lithium, hair loss with valproate,¹⁷ and stigmatizing extrapyramidal symptoms (EPS) associated with some antipsychotic medications.³⁵ Other common reasons are negative attitudes about medications, lack of insight about being ill, and missing the “highs” of a manic or hypomanic episode.^{34,35,36}

There are several ways to improve adherence. First, most drug side effects can be effectively treated with dose adjustments or changes in medication and/or the use of adjunctive treatments (see **TABLE 2**).¹⁷ Simplifying dosing regimens (ie, once-a-day dosing or dosing that fits into regular activities such as meal times.^{6,17,37,38} focusing on a patient’s subjective perceptions of medications and their effects,^{34,39} and addressing comorbid substance abuse and other psychiatric conditions and psychosocial stressors (eg, homelessness, financial problems)^{35,40} can all improve treatment adherence, as can involving the patient in decisions about his or her treatment and in monitoring the course of the illness.^{4,6,17} Studies also suggest that extra time, effort, and contact in the first 30 to 45 days of treatment can increase long-term adherence rates. Clinicians should contact the patient by phone soon after the initial visit; a follow-up visit should be scheduled for 1 to 2 weeks later to ensure adherence.^{41,42}

Psychosocial interventions

Psychosocial interventions are key components in the effective management of bipolar disorder, especially during depressive or hypomanic episodes and during 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.^{6,38} Combined with medication, these strategies can help prolong time to relapse, reduce symptom severity, and increase adherence.^{13,34,38,40}

Effective psychosocial interventions for bipolar disorder encourage patients to be active collaborators in their own treatment;¹³ emphasize the need for medication to prevent relapse; stress education for patients and families about medications, adherence,^{13,22} early warning signs of relapse, and lifestyle changes and stress management; and target comorbid psychiatric illnesses.^{13,22}

Special issues in working with families

Families of patients with bipolar disorder experience stress and increased burdens. Among primary caregivers of 500 patients enrolled in STEP-BD, 89% experienced moderate or high burden related to patient problem behaviors. Caregivers with high burden reported more physical health problems, depressive symptoms, health risk behavior and health service use, and less social support than those with fewer burdens. Psychosocial interventions targeting caregiving burden are thus needed.⁴³

Educating family members about bipolar disorder and its treatment, as discussed above, can help avert future crises.^{14,34} For example, if the patient displays reckless financial behavior, strategies such as putting the house in the spouse’s name, limiting access to credit, creating a trust fund, or using financial planning services may be helpful.¹⁴ Furthermore, alerting family members to the warning signs of suicide and the importance of contacting the PCP or psychiatric provider if they believe the patient is at risk can be life saving.¹⁴ PCPs working with patients with bipolar disorder should inform and support family members about the possible need to petition the court for psychiatric admission and attempt to allay any guilt about this potential necessity.¹⁴ Finally, PCPs need to remember that bipolar disorder is familial and may even be genetic. There is a reasonable chance that family members who could normally be expected to provide support to the patient may themselves be afflicted with the disorder.³⁸ Clinicians should be prepared for family members to be fearful and to want to know their own risk of developing or transmitting the disorder.

Sources of information and support

Patients and family members often feel devastated by the stigma that is associated with mental illness.

Education about the biological nature of the disorder and referral to national and community-based support and advocacy groups can be very helpful.^{5,6,13,14,19} Some resources that may be helpful for patients and families

are listed in **TABLE 3**. Two groups that may be helpful for patients and families are the Depression and Bipolar Support Alliance, www.DBAlliance.org, and the National Alliance on Mental Illness, www.nami.org. ■

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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 somewhat 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 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,⁶ an error that can have unwanted clinical consequences because the recommended treatments for the 2 disorders are substantially different.

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 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 episodes² and contribute to rapid cycling in patients with bipolar disorder,² although Sachs et al's findings 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.^{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 ongoing antidepressant use—together with a mood stabilizer regimen—is

TABLE 1

Medications approved for the treatment of bipolar disorder

Phase	Medications
Depressive	Olanzapine/fluoxetine (Symbyax [®]) Quetiapine (Seroquel [®])
Maintenance	Aripiprazole (Abilify [®]) Lamotrigine (Lamictal [®]) Lithium (Lithobid [®]) Olanzapine (Zyprexa [®])
Manic	Aripiprazole (Abilify [®]) Carbamazepine ER (Equetro ER [®]) Chlorpromazine Divalproex ER (Depakote ER [®]) Divalproex (Depakote [®]) Lithium (Lithobid [®]) Olanzapine (Zyprexa [®]) Quetiapine (Seroquel [®]) Risperidone (Risperdal [®]) Ziprasidone (Geodon [®])
Mixed	Aripiprazole (Abilify [®]) Carbamazepine ER (Equetro ER [®]) Divalproex ER (Depakote ER [®]) Olanzapine (Zyprexa [®]) Risperidone (Risperdal [®]) Ziprasidone (Geodon [®])
Manic and Mixed Episodes With or Without Psychotic Symptoms	Aripiprazole (Abilify [®]) Divalproex ER (Depakote ER [®]) Olanzapine (Zyprexa [®]) Risperidone (Risperdal [®]) Ziprasidone (Geodon [®])

Source: Manufacturers' US prescribing information for drugs listed.

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 preventing¹² and treating depressive episodes,¹³ and it has been recommended as first-line therapy for this phase of the disease.^{14,15}

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). Both regimens have shown significant efficacy in placebo-controlled trials 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 endpoint. Patients who received olanzapine alone also showed greater improvement than 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 8,¹⁷ and these findings have recently been replicated.¹⁸

Two recent studies of aripiprazole showed that when the drug was administered as monotherapy (10mg/day titrated to 5-30mg/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 2²¹⁻³¹ presents each medication's earliest day of significant separation from placebo, measured in controlled studies.

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,³ can be a useful addition in the treatment of mania¹ by providing extra sedation, restoring sleep patterns, and easing anxiety.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," as they do not always recognize these patients as having bipolar disorder.

TABLE 2

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

Oral medication generic name (trade name)	Onset of effect*	
	First assessment	First significant separation from placebo
Ziprasidone (Geodon®)	Day 2 ^{21,22}	Day 2 ^{21,22}
Aripiprazole (Abilify®)	Day 2 ²⁴ or 4 ²³	Day 4 ^{23,24}
Risperidone (Risperdal®)	Day 3 ^{26,27} or 7 ²⁵	Day 3 ²⁶ or 7 ^{25,27}
Olanzapine (Zyprexa®)	Day 7 ^{28,29}	Day 7 ²⁹ or 21 ²⁸
Quetiapine (Seroquel®)	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 FDA in support of the indication.

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

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,² 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. 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 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,³⁵ 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 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,¹ and as many as 58% of patients with bipolar disorder have experienced at least 1 psychotic episode.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**).^{1,14,32,37} 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 and 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 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

<p>American Psychiatric Association (APA) Practice Guideline for Bipolar Disorder¹</p> <ul style="list-style-type: none"> • Comprehensive • For all aspects of treatment
<p>Expert Consensus Guideline for Bipolar Disorder¹⁴</p> <ul style="list-style-type: none"> • Developed by an independent group of psychiatrists • Focused primarily on psychopharmacology • Survey of experts
<p>Texas Implementation of Medication Algorithms for Bipolar Disorder¹⁵</p> <p>Flowcharts as treatment algorithms for medication management</p>
<p>Mt. Sinai Guidelines³⁷</p> <p>Physical health monitoring of patients taking antipsychotics</p>
<p>Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)³²</p> <ul style="list-style-type: none"> • 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,⁴⁰ thus reinforcing the importance of considering the overall health needs of a patient when choosing a treatment approach. 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 drug and dosage determined by the profile of the

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 ≤18 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 100mg/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 ≤60 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 ≤60 mg/kg/d (once daily) 	<ul style="list-style-type: none"> Take with food: initiate 25 mg/kg/d; adjust to optimal clinical response ≤60 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 25

TABLE 4 Continued from page 24

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

Source: Manufacturers' US prescribing information for drugs listed.

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-focused¹, cognitive,¹ psychoeducational,¹ and interpersonal social rhythm therapies¹—which combines interpersonal therapy with simple techniques to help the patient follow daily routines—can all be effective in treating bipolar disorder.^{41,42} These interventions allow for dialogue about ongoing disease management, educate the patient about medications and the need for adherence, and

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

Metabolic Effects of 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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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,² 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,¹¹ 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

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,⁴⁵ valproate,⁴⁵ and many of the SGAs⁴⁰—are associated with weight gain.

The prevalence of smoking (another risk factor for cardiovascular disease) is also high in the bipolar population: an estimated 54% to 68%⁴⁶ compared with 21.5% in the general population.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 PCPs, whose patients often present with a variety of physical rather than psychological complaints,^{1,2} and psychiatric clinicians³, whose patients' initial presenting symptoms often are non-specific.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 points:

- 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 is 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 littlest 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,^{6,7} as evidenced by Susan’s agitation—her “hyper” symptoms.

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 DSM for duration; such cases are classified in the DSM 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,^{9,10} and aripiprazole has shown separation from placebo at Day 4 in two pivotal trials.^{11,12} 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;²² in addition, ziprasidone has a metabolically neutral profile.²² Because patients with bipolar disorder may be at increased risk for overweight and obesity,²³ 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 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,²⁵ it is important to consider medications that patients can live with, ones that they can and will take consistently through future episodes.

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,

TABLE

Medications FDA-Approved for Mixed Episodes

Oral Medication Generic Name (Trade Name)	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 (Geodon [®])	√	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 (Abilify [®])	√	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 (Risperdal [®])	√	Day 3 ^{14,15} or 7 ¹³	Day 3 ¹⁴ or 7 ^{13,15}	no ^c	Take with/without food: initiate 2-3 mg/d; adjust by 1 mg/d to optimal clinical response ≤6 mg/d (once daily)
Divalproex extended release (Depakote ER [®])	√	Day 5 ¹⁶	Day 5 ¹⁶	no ^{b 16}	Take with food: initiate 25 mg/kg/d; adjust to optimal clinical response ≤60 mg/kg/d (once daily)
Carbamazepine extended release (Equetro ER [®])	√	Day 7 ^{17,18}	Day 7 ¹⁸ or 14 ¹⁷	yes ^b	Take with or without food: initiate 400 mg/d; adjust by 200 mgd to optimal clinical response ≤1600 mg/d (divided doses)
Olanzapine (Zyprexa [®])	√	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 first assessed significant separation from placebo at different days.

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 has a staff member call her 2 days later to check on how she is doing. Susan D states:

“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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