Subsyndromal
Mr. W, a 53-year-old divorced entrepreneur, presents to you for evaluation of poor concentration, decreased self-esteem, and difficulty making decisions that are interfering with his work. A longtime patient of another psychiatrist, Mr. W has a 26-year history of bipolar I disorder. He has not had a manic episode for 5 years but has had several depressive episodes.

During his last manic episode, Mr. W was hospitalized with expansive and irritable mood, racing thoughts, impulsive sexual behavior, psychomotor agitation, elevated self-esteem, marked distractibility, and paranoid ideas about his business partners. His discharge regimen included lithium titrated to 0.9 mEq/L and divalproex sodium, 1,500 mg/d, with lamotrigine, 200 mg/d, added to reduce depressive relapse risk. After several years of stable treatment, Mr. W complained of cognitive impairment. His psychiatrist discontinued lithium and added a low-dose stimulant—methylphenidate, 20 mg bid—to address Mr. W’s complaints of poor concentration.

Mr. W also is taking zolpidem, 10 mg as needed for onset insomnia, and receives weekly psychodynamic psychotherapy. His work performance problems persist despite these treatments, and his company is failing.

A poor course in bipolar disorder—as in Mr. W’s case—is frequently characterized by persistent or relapsing depression. Bipolar disorder is diagnosed by a manic, mixed, or hypomanic episode, but depression and depressive symptoms are most prominent in clinical practice. Likewise, major observational studies blame depression for most of the time spent ill in bipolar types I and II.1-8

A good deal of bipolar symptom burden is associated with subsyndromal depression—defined as having >2 but <5 DSM-IV-TR symp-
How to minimize bipolar subsyndromal depression

<table>
<thead>
<tr>
<th>Monitor</th>
<th>symptoms using validated clinician- and patient-rated tools at all visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use</td>
<td>evidence-based treatments first</td>
</tr>
<tr>
<td>Eliminate</td>
<td>ineffective medications</td>
</tr>
<tr>
<td>Use</td>
<td>adequate doses of medications for different mood states</td>
</tr>
<tr>
<td>Monitor and treat adverse effects of successful treatments</td>
<td></td>
</tr>
<tr>
<td>Monitor</td>
<td>and minimize medications that can worsen symptoms</td>
</tr>
<tr>
<td>Watch</td>
<td>for the impact of medical conditions on mood</td>
</tr>
<tr>
<td>Be</td>
<td>attentive to alcohol and substance use (including caffeine, nicotine, and energy drinks)</td>
</tr>
<tr>
<td>Monitor</td>
<td>psychotherapies for symptom worsening</td>
</tr>
<tr>
<td>Address</td>
<td>comorbid psychiatric conditions</td>
</tr>
<tr>
<td>Regularize</td>
<td>social rhythms</td>
</tr>
<tr>
<td>Initiate</td>
<td>validated psychosocial treatments</td>
</tr>
<tr>
<td>Engage</td>
<td>the patient as a active participant in treatment</td>
</tr>
</tbody>
</table>

Nearly all of these large studies of acute treatments for mood episodes are placebo-controlled trials with narrow inclusion and broad exclusion criteria. Eliminating subsyndromal symptoms is not their goal, and they are of little help in understanding how to manage residual symptoms.

A more realistic view of bipolar disorder comes from large observational studies that have examined its longitudinal course in outpatients under more or less ideal treatment conditions. These studies show that bipolar disorder is almost always recurrent and relapsing, but full recovery and functioning between episodes is not the norm. Most patients never achieve prolonged recovery, complete symptom relief, or return to full functioning.

**STEP-BD.** Most patients in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) never recovered from a depressed episode during 2 years of prospective follow-up under optimal care. Only 58% of patients who entered the study during an episode of illness achieved 8 consecutive weeks of euthymia.

**Collaborative Depression study.** Longitudinal data from the National Institute of Mental Health’s Collaborative Depression Study showed:

- patients with bipolar I disorder had depressive symptoms in approximately three-quarters of the weeks in which they reported significant symptoms
- patients with bipolar II disorder were depressed in nearly all sick weeks.

These findings are consistent with STEP-BD data that showed nearly three-quarters of relapses (72%) occurred with depressed episodes and one-quarter (28%) with manic, mixed, or hypomanic episodes.

**The Stanley Foundation Bipolar Network** had similar findings, with bipolar disorder patients reporting 3 times as much time spent with depressed mood as with elevated mood. Poor social and occupational functioning predicted poor outcomes, suggesting an interplay between subsyndromal depression, poor functioning, and relapse.

Persistent depression

Randomized, controlled trials designed to obtain FDA approval of bipolar medications inadequately reflect the disabling, confounding nature of bipolar illness.
LEXAPRO® (escitalopram oxalate) TABLETS/TORAL/SOLUTION

(5% and 20%), Fatigue (5% and 20%), Psychotic Disorders: Inocencer (5% and 20%), Somnolence (5% and 20%), Aplasia (5% and 20%), Leukopenia (5% and 20%), Decreased (5% and 20%).

Risk factors

Rapid cycling may be a marker for persistent, subsyndromal symptoms. Rapid cycling clinically defines as distinctly 4 distinct mood episodes separated by 2 weeks or partial recovery in the previous 12 months. Rapid cycling usually is diagnosed retrospectively and may or may not be a factor seen in patients who are not taking lithium or carbamazepine. Rapid cycling may be a marker for persistent, subsyndromal symptoms, and pharmacological treatment of sleep difficulties may not be a likelihood for it to continue.

continued from page 40
Subsyndromal depression

Clinical Point
Minimizing antidepressant use in bipolar depression hastens rather than delays patients’ recovery, in my clinical experience.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Initial and maximum dosages</th>
<th>Clinically important side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine</td>
<td>Start at 50 mg and titrate to 300 mg within 4 to 7 days; maximum 600 mg</td>
<td>Sedation, somnolence, weight gain, gastrointestinal side effects, lipid abnormalities, increased fasting glucose, increased risk of diabetes</td>
</tr>
<tr>
<td>Olanzapine/fluoxetine</td>
<td>Start at 6 mg/25 mg; maximum 12 mg/50 mg</td>
<td>Weight gain, sedation, gastrointestinal side effects, lipid abnormalities, increased fasting glucose, increased risk of diabetes</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Must be titrated per package labeling; start at 25 mg and titrate to 200 mg (12.5 mg titrated to 100 mg if patient is on valproate, 50 mg titrated to 400 mg if on carbamazepine or other enzyme inducer); maximum (per label) 500 mg</td>
<td>Rash, headache, balance difficulties, clumsiness; Stevens-Johnson syndrome or toxic epidermal necrolysis are rare but potentially fatal</td>
</tr>
<tr>
<td>Lithium</td>
<td>Start at 300 to 600 mg and use moderate blood levels (0.4 to 0.7 mEq/L); if no improvement in 4 to 8 weeks, titrate to 0.8 to 1.1 mEq/L</td>
<td>Tremor, nausea, diarrhea, increased thirst, increased urination, hair loss, thyroid abnormalities, weight gain, acne, worsening of psoriasis, diabetes insipidus, renal insufficiency</td>
</tr>
<tr>
<td>Divalproex</td>
<td>Start at 500 to 750 mg and increase to 15 to 20 mg/kg; usual target blood levels are &gt;50 mg/dL</td>
<td>Nausea, abnormal liver function tests, weight gain, hair loss</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Start at 5 mg; maximum 30 mg</td>
<td>Weight gain, sedation, somnolence, lipid abnormalities, increased fasting glucose, increased risk of diabetes</td>
</tr>
<tr>
<td>Modafinil</td>
<td>Start at 50 to 100 mg and increase to 200 mg; higher dosages have not been systematically studied in bipolar disorder</td>
<td>Nervousness, insomnia</td>
</tr>
</tbody>
</table>

EPS: extrapyramidal symptoms

* Medications are listed in from most to least evidence supporting their use in treating bipolar depression

CASE CONTINUED
Restoring the cornerstone
You review Mr. W’s records. Recent lab values were essentially normal, with thyroid stimulating hormone 2.3 mIU/mL and stable renal function. He scores 11 on the Quick Inventory of Depressive Symptoms—self-rated version (QIDS-SR), indicating mild to moderate depressive symptom burden.

His mood chart and interview reveal that he has been depressed and anhedonic most of the day for 4 of the last 10 days. By systematically asking the depression questions in the DSM-IV-TR, you find that he does not meet criteria for depressed mood or anhedonia but has difficulty concentrating most of the day, persistent low self-esteem, and feeling “slowed.”

After you discuss lithium’s pros and cons with Mr. W, he agrees to try this mood stabilizer again. You explain the importance of preventing relapse to mania and of monitoring his cognitive performance at work.

Over time, you titrate lithium to a moderate serum level (0.5 to 0.7 mEq/L) and treat a resulting mild tremor with propranolol, 20 to 40 mg/d. Mr. W is tolerating lamotrigine well, so you continue this medication because of its potential to decrease the probability of relapse to depression. You also continue zolpidem, as needed, but discontinue methyphenidate because you think it may be contributing to sleep difficulties.

Managing medication
Nine drugs are FDA-approved for acute bipolar mania, but treatments for bipolar
depression, maintenance treatment, and relapse prevention are far fewer, often partially effective, or effective for a limited number of patients. When depressive symptoms fail to resolve, a reasonable approach is to review patients’ medications and suggest alternatives with proven efficacy for bipolar disorder (Table 2). Patients can then accept or reject various options based on personal preference.

**Combination strategies.** Antimanic treatment is the cornerstone of treating bipolar I disorder, and preventing manic episodes should be a primary treatment goal. Thus, consider continuing treatments that have prevented mania for your patient—as lithium did in Mr. W’s case—while adding treatments aimed at depression. For example, adding lamotrigine to any antimanic agent is reasonable, especially if doing so does not add substantially to your patient’s side-effect burden.

**Minimize antidepressants.** Given the predominance and persistence of depressive symptoms in bipolar disorder, one can understand why clinicians and patients might try standard antidepressants without clear evidence supporting this practice. Antidepressants—especially venlafaxine and tricyclic antidepressants—are the most common and likely suspects when patients experience switching to mania, rapid cycling, and symptom persistence. Antidepressants’ negative effect has not been clearly defined, however, and may be patient-specific (related to patient factors rather than intrinsic to the compound).

In my clinical experience, minimizing antidepressant use in bipolar depression hastens rather than delays patients’ recovery. A prudent approach would be to use the minimum dose necessary and discontinue the antidepressant if possible. Also minimize medical pharmacotherapies—including corticosteroids and oral contraceptives—that may worsen mood symptoms, especially in patients with this history.

**Avoid under-dosing.** Inadequate dosing and duration often are overlooked as causes of treatment resistance in bipolar disorder and other illnesses. Bipolar disorder medications are hardly benign; every drug approved for any phase of bipolar disorder has a black-box warning. Understandably, clinicians and patients try to choose medications and dosages perceived to be most tolerable. Full-dose treatment trials may be warranted, however, given the high probability of incomplete recovery, impaired functioning, and risk of relapse with ineffective dosing.

**Address iatrogenic causes.** In addition, identify and eliminate medications and treatments that may be perpetuating patients’ bipolar symptoms. Stimulants such as methylphenidate and amphetamines may contribute to sleep disturbance and manic relapse and might be minimized or eliminated in a patient with continued symptoms and sleep disturbance.

**Antipsychotics.** Quetiapine and the combination olanzapine/fluoxetine are FDA-approved for acute bipolar depression episodes, but not all atypical antipsychotics show antidepressant effects in bipolar disorder:

- Two trials of aripiprazole for bipolar depression failed to show benefit.
- A trial that compared risperidone with lamotrigine and inositol for treatment-resistant bipolar depression suggested that risperidone may have hindered recovery.

**Other agents.** Lamotrigine’s benefit in acute bipolar depression is controversial, as no trial has shown unequivocally that it is more effective than placebo. Modafinil, 100 to 200 mg/d, was significantly more effective than placebo as an adjunct to mood stabilizer therapy in a 6-week study of bipolar depression. This result in a cohort of 85 patients has not been replicated, however, and modafinil’s long-term safety in bipolar disorder is unknown.

**Case Continued**

**Distressed by psychotherapy**

You ask Mr. W about his psychodynamic psychotherapy, and he says that exploring his early life experiences and his work difficulty is increasing his anxiety. You recommend switching to cognitive-behavioral therapy.
Table 3

Tools for monitoring subsyndromal symptoms

<table>
<thead>
<tr>
<th>Encourage</th>
<th>patient to keep a daily mood chart, including sleep-wake times</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use</td>
<td>standardized depression rating scales to monitor symptom changes:</td>
</tr>
<tr>
<td></td>
<td>• Montgomery Åsberg Depression Rating Scale (MADRS)</td>
</tr>
<tr>
<td></td>
<td>• Hamilton Depression Rating Scale (HAMD)</td>
</tr>
<tr>
<td></td>
<td>• Quick Inventory of Depressive Symptoms –self-rated version</td>
</tr>
<tr>
<td>Use</td>
<td>the Structured Clinical Interview for DSM-IV, Mood Module to verify whether or not the patient is in a mood episode</td>
</tr>
<tr>
<td>Use</td>
<td>the Clinical Global Impression Severity Scale (BP version) as a measure of illness severity</td>
</tr>
<tr>
<td>Monitor</td>
<td>use of caffeine, nicotine, alcohol, and other drugs of abuse by asking about the frequency and amounts used</td>
</tr>
<tr>
<td>Calculate</td>
<td>body mass index at each visit to monitor for weight gain</td>
</tr>
</tbody>
</table>

Subsyndromal depression

Clinical Point

Advise patients to regularize their sleep-wake cycle and adopt predictable daily schedules with planned social contact and activities to work on delegating tasks that are not his strong areas and focusing on his marketing talents. You also encourage him to maintain regular sleep-wake cycles.

Some psychodynamic psychotherapies are thought to increase anxiety and mood instability in bipolar disorder patients. Examine the form and content of psychosocial approaches for their role in worsening your patients’ symptoms. As with medications, validated psychotherapeutic interventions—such as CBT for bipolar disorder, family-focused treatment, interpersonal social rhythm therapy, and long-term group psychotherapy—are preferred over those not specifically studied in bipolar disorder.

In clinical practice, medication management of bipolar disorder is more effective when combined with psychoeducation and psychosocial interventions. Advise patients to:

- Establish a social rhythm that includes a regularized sleep-wake cycle and predictable daily schedules, with planned contact with people and organized activities.
- Decrease behaviors associated with mood fluctuation, such as substance use, irregular hours of sleep, conflicts in relationships and work, poor adherence to medications, and lack of regard for physical health.

Include psychoeducation about bipolar disorder’s course and treatment when communicating with patients and their families. Behavior change may come slowly, but monitor the patient’s progress and focus on that goal.

CASE CONTINUED

Changes for the better

After several months of CBT and medication changes, Mr. W is continuing to work and shows some symptom improvement. His QIDS-SR scores have decreased to 6, indicating minimal to mild depressive symptom burden. He reports that most weeks he has no depressive symptoms, but he remains unable to focus on specific tasks for long periods. He continues to have difficulties when his work requires detailed, intensive activities.

Mr. W has developed a new relationship but gives high priority to keeping a regular schedule. Before going to sleep most nights, he records his mood in a diary to monitor his progress.

Mr. W may show additional improvement in work performance with continued daily mood monitoring and a regularized routine. The care of most patients with bipolar disorder must be systematically optimized over years, not weeks or months. Because medication adherence during well periods is essential, discuss and address adverse effects such as weight gain or urinary symptoms.

Measure treatment response. Effectively managing subsyndromal depression requires medication and appropriate cognitive therapy and psychoeducation to engage patients in behavioral change. Measuring treatment response (Table 3) and managing care based on this information allows you to:

- minimize or eliminate ineffective and harmful treatments
- continue effective treatments, whether psychopharmacologic or psychosocial.
Related Resources

- Inventory of Depressive Symptomatology (IDS) and Quick Inventory of Depressive Symptomatology (QIDS). Validity, reliability, administration, and scoring. www.ids-qids.org.
- Bipolar Clinic and Research Program, Massachusetts General Hospital. Resources for clinicians and patients, plus links to information on bipolar disorder. www.manicdepressive.org.

Drug Brand Names

- Aripiprazole • Abilify
- Carbamazepine • Tegretol
- Divalproex • Depakote
- Lamotrigine • Lamictal
- Lithium • various
- Methylphenidate • various
- Modafinil • Provigil
- Olanzapine • Zyprexa
- Olanzapine/Fluoxetine • Symbyax
- Propranolol • Inderal
- Quetiapine • Seroquel
- Valproate • Depacon
- Venlafaxine • Effexor
- Zolpidem • Ambien

Disclosure

Dr. Ostacher is a speaker for AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, and Pfizer Inc.

References

12. Schneck C. What is the best treatment for rapid cycling? Presented at: Annual Meeting of the American Psychiatric Association; May 21-26, 2005, Atlanta, GA.

Bottom Line

Continuously monitor patients with subsyndromal bipolar depression to address all aspects of care and eliminate ineffective treatments. Provide adequate dosing of mood stabilizer therapy, cognitive-behavioral therapy, and psychosocial treatments, and measure responses to treatment changes.