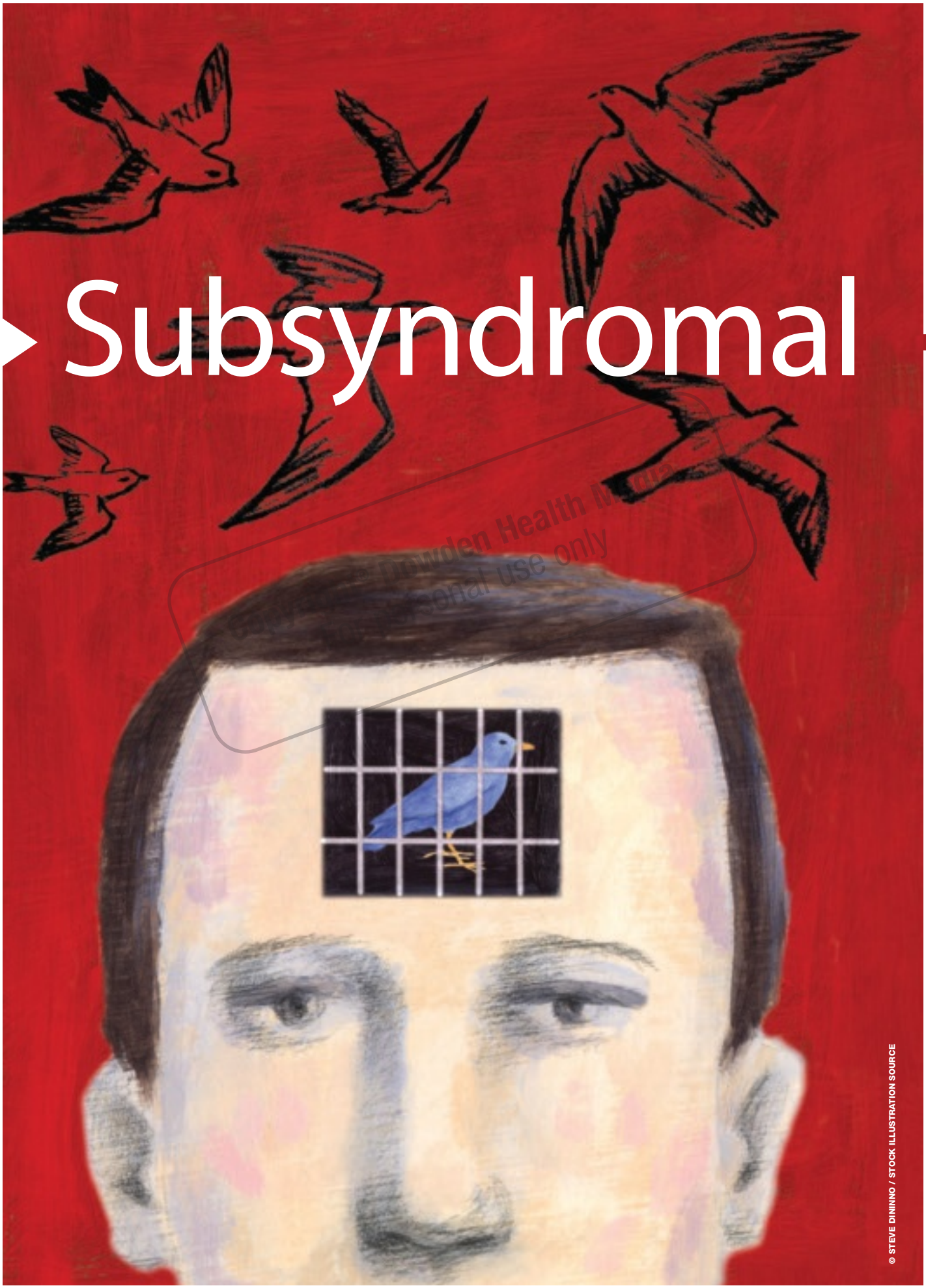
Subsyndromal



Current PSYCHIATRY

depression

Help your bipolar patients feel better

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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-

Subsyndromal depression

Clinical Point

Most patients in STEP-BD never recovered from a depressed episode despite 2 years of optimal care

Table 1

How to minimize bipolar subsyndromal depression

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

toms of major depression, with or without depressed mood or anhedonia. Subsyndromal depressive symptoms predict relapse to depression,[5] and depressive symptoms are disproportionately responsible—compared with manic symptoms—for the impact of bipolar illness on patients and their families.[9]

This article offers clinically useful strategies to minimize subsyndromal depression in patients with bipolar disorder (***Table 1***). These strategies include an evidence-based approach to medication, the use of validated psychotherapies, regular sleep and socialization schedules, and careful monitoring of mood symptoms.

Persistent depression

Randomized, controlled trials designed to obtain FDA approval of bipolar medications inadequately reflect the disabling, confounding nature of bipolar illness. 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.[10] 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.[5,8,11]

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.[5]

Collaborative Depression study. Longitudinal data from the National Institute of Mental Health's Collaborative Depression Study[6,7] 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.[5]

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.[8] Poor social and occupational functioning predicted poor outcomes, suggesting an interplay between subsyndromal depression, poor functioning, and relapse.

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LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

(5% and 4%); Fatigue (5% and 2%). **Psychiatric Disorders:** Insomnia (9% and 4%); Somnolence (6% and 2%); Appetite Decreased (3% and 1%); Libido Decreased (3% and 1%). **Respiratory System Disorders:** Rhinitis (5% and 4%); Sinusitis (3% and 2%). **Urogenital:** Ejaculation Disorder[1,2] (9% and <1%); Impotence[2] (3% and <1%); Anorgasmia[3] (2% and <1%).*Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo ≥ Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety. [1]Primarily ejaculatory delay. [2]Denominator used was for males only (N=225 Lexapro; N=188 placebo). [3]Denominator used was for females only (N=490 Lexapro; N=404 placebo). **Generalized Anxiety Disorder Table 3** enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see **TABLE 3**). **TABLE 3: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder* (Percentage of Patients Reporting Event) Body System/Adverse Event [Lexapro (N=429) and Placebo (N=427)]: Autonomic Nervous System Disorders:** Dry Mouth (9% and 5%); Sweating Increased (4% and 1%). **Central & Peripheral Nervous System Disorders:** Headache (24% and 17%); Paresthesia (2% and 1%). **Gastrointestinal Disorders:** Nausea (18% and 8%); Diarrhea (8% and 6%); Constipation (5% and 4%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Flatulence (2% and 1%); Toothache (2% and 0%). **General:** Fatigue (8% and 2%); Influenza-like symptoms (5% and 4%). **Musculoskeletal:** Neck/Shoulder Pain (3% and 1%). **Psychiatric Disorders:** Somnolence (13% and 7%); Insomnia (12% and 6%); Libido Decreased (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (3% and 1%); Lethargy (3% and 1%); Yawning (2% and 1%). **Urogenital:** Ejaculation Disorder[1,2] (14% and 2%); Anorgasmia[3] (6% and <1%); Menstrual Disorder (2% and 1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo ≥ Lexapro: inflicted injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. [1]Primarily ejaculatory delay. [2]Denominator used was for males only (N=182 Lexapro; N=195 placebo). [3]Denominator used was for females only (N=247 Lexapro; N=232 placebo). **Dose Dependency of Adverse Events** The potential dose dependency of common adverse events (defined as an incidence rate of ≥ 5% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). **Table 4** shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group. **TABLE 4: Incidence of Common Adverse Events* in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=125): Insomnia** (4%, 7%, 14%); **Diarrhea** (5%, 6%, 14%); **Dry Mouth** (3%, 4%, 9%); **Somnolence** (1%, 4%, 9%); **Dizziness** (2%, 4%, 7%); **Sweating Increased** (<1%, 3%, 8%); **Constipation** (1%, 3%, 6%); **Fatigue** (2%, 2%, 6%); **Indigestion** (1%, 2%, 6%).*Adverse events with an incidence rate of at least 5% in either of the Lexapro groups and with an incidence rate in the 20 mg/day Lexapro group that was approximately twice that of the 10 mg/day Lexapro group and the placebo group. **Male and Female Sexual Dysfunction with SSRIs** Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. **Table 5** shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. **TABLE 5: Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials** [In Males Only: **Adverse Event: Lexapro** (N=407) **and Placebo** (N=383)]: Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%); Libido Decreased (6% and 2%); Impotence (2% and <1%). [In Females Only: **Lexapro** (N=737) **and Placebo** (N=636)]: Libido Decreased (3% and 1%); Anorgasmia (3% and <1%) There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes** Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes** Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes** Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Events Observed During the Premarketing Evaluation of Lexapro** Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the **ADVERSE REACTIONS** section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in **Tables 2 & 3**, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients. Cardiovascular - *Frequent:* palpitation, hypertension. *Infrequent:* bradycardia, tachycardia, ECG abnormal, flushing, varicose vein. Central and Peripheral Nervous System Disorders - *Frequent:* light-headed feeling, migraine. *Infrequent:* tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased. Gastrointestinal Disorders - *Frequent:* heartburn, abdominal cramp, gastroenteritis. *Infrequent:* gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. General - *Frequent:* allergy, pain in limb, fever, hot flushes, chest pain. *Infrequent:* edema of extremities, chills, tightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall. Hemic and Lymphatic Disorders - *Infrequent:* bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. Metabolic and Nutritional Disorders - *Frequent:* increased weight. *Infrequent:* decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. Musculoskeletal System Disorders - *Frequent:* arthralgia, myalgia. *Infrequent:* jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. Psychiatric Disorders - *Frequent:* appetite increased, lethargy, irritability, concentration impaired. *Infrequent:* jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruxism, carbohydrate craving, confusion, depersonalization, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency. Reproductive Disorders/Female* - *Frequent:* menstrual cramps, menstrual disorder. *Infrequent:* menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. *% based on female subjects only: N=905 Respiratory System Disorders - *Frequent:* bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. *Infrequent:* asthma, breath shortness, laryngitis, pneumonia, tracheitis. Skin and Appendages Disorders - *Frequent:* rash. *Infrequent:* pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, lipoma, furunculosis, dry lips, skin nodule. Special Senses - *Frequent:* vision blurred, tinnitus. *Infrequent:* taste alteration, earache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. Urinary System Disorders - *Frequent:* urinary frequency, urinary tract infection. *Infrequent:* urinary urgency, kidney stone, dysuria, blood in urine. **Events Reported Subsequent to the Marketing of Escitalopram** - Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during post marketing spontaneous and clinical trial experience and were not observed during the premarketing evaluation of escitalopram: Blood and Lymphatic System Disorders: hemolytic anemia, leukopenia, thrombocytopenia. Cardiac Disorders: atrial fibrillation, cardiac failure, myocardial infarction, torsade de pointes, ventricular arrhythmia, ventricular tachycardia. Endocrine Disorders: diabetes mellitus, hyperprolactinemia, SIADH. Eye Disorders: diplopia, glaucoma. Gastrointestinal Disorders: gastrointestinal hemorrhage, pancreatitis, rectal hemorrhage. General Disorders and Administration Site Conditions: abnormal gait. Hepatobiliary Disorders: fulminant hepatitis, hepatic failure, hepatic necrosis, hepatitis. Immune System Disorders: allergic reaction. Investigations: electrocardiogram QT prolongation, INR increased, prothrombin decreased. Metabolism and Nutrition Disorders: hypoglycemia, hypokalemia. Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis. Nervous System Disorders: akathisia, choreoathetosis, dysarthria, dyskinesia, dystonia, extrapyramidal disorders, grand mal seizures (or convulsions), hypoaesthesia, myoclonus, neuroleptic malignant syndrome, nystagmus, seizures, serotonin syndrome, tardive dyskinesia. Pregnancy, Puerperium and Perinatal Conditions: spontaneous abortion. Psychiatric Disorders: acute psychosis, aggression, anger, delirium, delusion, nightmare, paranoia, visual hallucinations. Renal and Urinary Disorders: acute renal failure. Reproductive System and Breast Disorders: priapism. Respiratory, Thoracic and Mediastinal Disorders: pulmonary embolism. Skin and Subcutaneous Tissue Disorders: angioedema, ecchymosis, erythema multiforme, photosensitivity reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis, urticaria. Vascular Disorders: deep vein thrombosis, hypotension, orthostatic hypotension, phlebitis thrombosis.

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Risk factors

Rapid cycling may be a marker for persistent, subsyndromal symptoms. Rapid cycling is defined clinically as 4 distinct mood episodes—switching to the opposite pole or 2 episodes of the same pole separated by ≥8 weeks of partial or full recovery—in the previous 12 months. Rapid cycling usually is diagnosed retrospectively—introducing patients' recall bias—but may be more of a marker for symptom persistence than for defined episodes.

In STEP-BD, 32% of study entrants reported ≥4 mood episodes in the previous year, yet only 6% of that subgroup had ≥4 episodes after 1 year of prospective follow-up.[12] This suggests:

- patients who retrospectively report rapid cycling may be chronically and persistently ill, rather than experiencing multiple discrete episodes
- rapid cycling is a marker for symptom persistence, subsyndromal depression, and lack of sustained remission.

Treatment resistance in bipolar disorder is characterized by symptom persistence, more frequent episodes, and less time spent being healthy. Well-known factors increase the probability of treatment resistance:

- comorbid anxiety disorders (present in ≤50% of patients with bipolar I and II disorder)
- active and past substance use disorders (including nicotine dependence)
- early age of onset of the mood disorder.[13-16]

Less documented is the likely association between treatment resistance and environmental stress, disrupted social rhythms, and irregular sleep. Clinical experience suggests, however, that patients feel better and stay in remission longer if they sleep regular hours, increase contact with a support network, and adhere to a daily structure. Hypnotics are not well-studied in bipolar disorder, but there is no evidence to suggest that they are not safe. Improved sleep hygiene, nonetheless, is a cornerstone of regularizing sleep, and pharmacologic treatment of sleep difficulties is not likely a replacement for it.

continued

Subsyndromal depression

Clinical Point

Minimizing antidepressant use in bipolar depression hastens rather than delays patients' recovery, in my clinical experience

Table 2

Subsyndromal bipolar depression: Recommended medications*

Medication	Initial and maximum dosages	Clinically important side effects
Quetiapine	Start at 50 mg and titrate to 300 mg within 4 to 7 days; maximum 600 mg	Sedation, somnolence, weight gain, gastrointestinal side effects, lipid abnormalities, increased fasting glucose, increased risk of diabetes
Olanzapine/ fluoxetine	Start at 6 mg/25 mg; maximum 12 mg/50 mg	Weight gain, sedation, gastrointestinal side effects, lipid abnormalities, increased fasting glucose, increased risk of diabetes
Lamotrigine	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	Rash, headache, balance difficulties, clumsiness; Stevens-Johnson syndrome or toxic epidermal necrolysis are rare but potentially fatal
Lithium	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	Tremor, nausea, diarrhea, increased thirst, increased urination, hair loss, thyroid abnormalities, weight gain, acne, worsening of psoriasis, diabetes insipidus, renal insufficiency
Divalproex	Start at 500 to 750 mg and increase to 15 to 20 mg/kg; usual target blood levels are >50 mg/dL	Nausea, abnormal liver function tests, weight gain, hair loss
Olanzapine	Start at 5 mg; maximum 30 mg	Weight gain, sedation, somnolence, lipid abnormalities, increased fasting glucose, increased risk of diabetes
Modafinil	Start at 50 to 100 mg and increase to 200 mg; higher dosages have not been systematically studied in bipolar disorder	Nervousness, insomnia

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 methylphenidate 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.[17] 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.[18] 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.[19]

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.[20]
- A trial that compared risperidone with lamotrigine and inositol for treatment-resistant bipolar depression suggested that risperidone may have hindered recovery.[21]

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.[22] 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

Clinical Point

Some psychodynamic psychotherapies are thought to increase anxiety and mood instability in bipolar disorder patients

Subsyndromal depression

Clinical Point

Advise patients to regularize their sleep-wake cycle and adopt predictable daily schedules with planned social contact and activities

Table 3

Tools for monitoring subsyndromal symptoms

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

(CBT) 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[23,24]—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.[23,25] 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.[26] 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.

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Related Resources

- Otto M, Reilly-Harrington N, Kogan JN, Henin A. *Managing bipolar disorder: a cognitive behavior treatment program therapist guide (treatments that work)*. Oxford, UK: Oxford University Press; 2008.
- 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	Olanzapine • Zyprexa
Carbamazepine • Tegretol	Olanzapine/fluoxetine • Symbyax
Divalproex • Depakote	Propranolol • Inderal
Lamotrigine • Lamictal	Quetiapine • Seroquel
Lithium • various	Valproate • Depacon
Methylphenidate • various	Venlafaxine • Effexor
Modafinil • Provigil	Zolpidem • Ambien

Disclosure

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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.

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Clinical Point

The care of most patients with bipolar disorder must be optimized over years, not weeks or months