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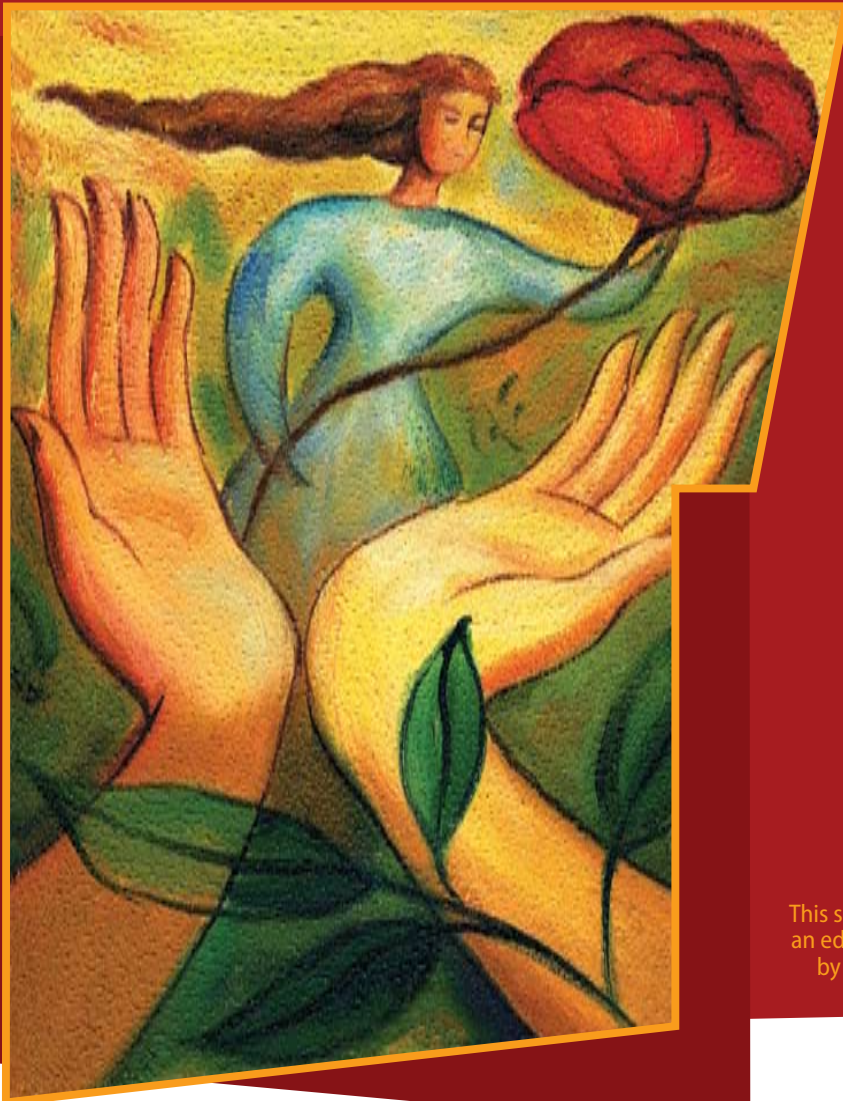
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Maintaining wellness in patients with bipolar disorder:



MOVING BEYOND
EFFICACY TO
EFFECTIVENESS

FACULTY

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TARGET AUDIENCE

This activity is designed to meet the needs of psychiatrists and other mental health care professionals interested in the management of patients with bipolar disorder.

PROGRAM OVERVIEW

Bipolar disorder (BD) is one of the most difficult psychiatric conditions to accurately recognize and diagnose because many patients report depressive, but not manic, symptoms. Additionally, BD is often comorbid with drug and alcohol abuse as well as other psychiatric illnesses, which results in symptoms that are complex and challenging to evaluate and treat. Patients with BD also experience more physical illnesses compared with the general population, and comorbid medical disorders are associated with poor functional outcomes.

Maintaining wellness in patients with BD requires consideration of the potential negative effects BD can have on functioning, quality of life, and interpersonal relationships. Since BD is a chronic disorder, long-term treatment is needed and should include both psychopharmacologic and psychosocial therapies. Evidence exists to support the use of various pharmacotherapies for the effective management of patients with depressive and/or manic symptoms of BD. Treatment optimization depends on the appropriate choice of therapies for individual patients, particularly in cases with coexisting psychiatric and medical conditions.

This activity will provide an evidence-based approach to the treatment of patients with BD using pharmacologic and psychosocial therapies. The efficacy, safety, and tolerability of various treatment interventions will be discussed based on data from the most recent clinical trials. Long-term treatment strategies will be outlined, focusing on enhancement of patient satisfaction, the minimization of adverse events, and improvement of overall patient outcomes.

LEARNING OBJECTIVES

After completing this activity, participants should be better able to:

- Develop an evidence-based approach to the treatment of patients with BD based on available treatment options
- Integrate appropriate nonpharmacologic management strategies into treatment programs for patients with BD
- Outline long-term strategies to enhance overall patient outcomes while minimizing the risk of medication-related adverse events
- Recognize the long-term consequences of the choice of pharmacotherapy on overall patient health and quality of life

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This supplement is based on the live program entitled *"Maintaining Wellness in Patients With Bipolar Disorder: Moving Beyond Efficacy to Effectiveness"*, held as a lunch symposium on April 3, 2009, at the Westin River North, Chicago, Illinois, in conjunction with the 2009 Current Psychiatry/American Academy of Clinical Psychiatrists meeting, and represents the same content material.

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Maintaining wellness in patients with bipolar disorder: moving beyond efficacy to effectiveness



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Wellness and effectiveness: key concepts in treating bipolar disorder

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At the 2009 meeting of the American Academy of Clinical Psychiatrists, a CME activity was presented entitled *Maintaining Wellness in Patients With Bipolar Disorder: Moving Beyond Efficacy to Effectiveness*. The following 2 articles are based on talks given at that meeting by Claudia Baldassano, MD, and Robert Hirschfeld, MD. This essay serves as an introduction to their articles.

Two general concepts formed the theme of the CME activity: maintaining wellness and attaining effectiveness rather than efficacy.

The concept of *maintaining* wellness is important because it can be held that our psychiatric drugs are much better at getting patients better acutely than they are at maintaining remission. When patients are depressed, antidepressants often bring them out of depression. When they are manic, neuroleptics control and end the episode. But antidepressants are not as effective in preventing depression after the patient has come out of the acute episode. In the STAR*D study, about 50% of patients with unipolar depression who responded to an antidepressant acutely were found to relapse within a year, despite staying on that same antidepressant.¹ In bipolar depression, evidence for acute efficacy with antidepressants is absent² or minimal,³ and long-term prevention has been repeatedly disproven.⁴

Similarly, neuroleptics clearly treat acute mania well, but the evidence that they prevent mania is much less convincing. The best designed study showing benefit is one with aripiprazole, where patients were initially treated with that drug for acute mania, achieved at least 2 months of remission, and then were randomized to continue or discontinue, with the long-term benefit of preventing mania (but not depression).⁵ The other neuroleptic indicated for maintenance treatment of bipolar disorder is olanzapine, yet that study was far less convincing because patients only received olanzapine for acute mania and achieved only 2 to 4 weeks of remission before being randomized to continue or discontinue that agent.⁶ Predictably, those who discontinued olanzapine relapsed within only 2 to 4 weeks of getting better. But this hardly proves long-term efficacy; rather, it reflects only short-term withdrawal. Other neuroleptics have not been individually studied for relapse prevention, although quetiapine did seem to prevent mania and depression as adjunctive treatment with reasonably well-proven preventive agents like valproate and lithium.⁷

These limited data, especially in monotherapy, should serve as a major caution against the presumption that neuroleptics will prevent mania and depression in the long term. These agents should not, in my view, be seen as mood stabilizers per se, on a par with drugs like lithium. They are adjuncts, helpers, aids, often indispensable ones, but not replacements.

The second concept is effectiveness. Contrasted with *efficacy*, which means benefit shown with a drug in a randomized clinical trial (RCT),

effectiveness refers to benefit with a drug in real world, nonrandomized clinical practice. A clinical trial is designed to isolate the effect of a drug; this is necessary but not sufficient. Often a drug may have some effect, when isolated versus nothing (placebo), but in the real world it is much less effective, either because of non-compliance, side effects, or the competing benefits of other treatments. Thus RCTs are the beginning, not the end, of drug research. We need to follow up RCTs with large effectiveness studies.

Effectiveness studies are especially relevant for many drug effects that cannot be captured in RCTs—in particular, serious and uncommon (and even sometimes common) side effects. A good example is the ongoing controversy around antidepressant-induced mania. Some researchers, focusing on RCTs, claim it does not happen. Yet all RCTs, including combinations of them in many meta-analyses,³ do not have the statistical power to distinguish between drug and placebo on important side effects. Sometimes this is because RCTs are set up to minimize side effects. In the case of antidepressant-induced mania, for instance, a major risk factor may be substance abuse,⁸ and these patients are systematically excluded from RCTs. In that case RCTs would underreport that outcome, compared with effectiveness studies.

The efficacy versus effectiveness dilemma is another reason why I believe the whole divide between clinical work and research is misguided.⁹ A harmful dichotomy has developed in our field between clinicians and researchers, stemming from the NIMH Belmont Report which sought to strictly separate research from clinical work for ethical reasons. Many clinicians are distrustful of research studies, especially when the results conflict with their own clinical experience.

If we appreciate both the strengths and the limits of efficacy and effectiveness research, we can begin to appreciate why clinicians need to be researchers and researchers need to be clinicians. Our knowledge, especially about drugs, should begin with good efficacy research but it does not end there; it should continue to be based on good effectiveness research, and both of those kinds of research should then be put to the test of clinical experience. Clinical experience alone is not enough, and it certainly should not automatically be accepted, but neither is it irrelevant; it should be used to more carefully assess the knowledge that we glean from efficacy and effectiveness studies.⁹

In the context of bipolar depression, for instance, efficacy studies show (as described in these articles) benefits with quetiapine and olanzapine/fluoxetine combination in acute mood states^{10, 11} and adjunctive prevention, as discussed above. But effectiveness studies need to assess how these benefits play out in the real world, where side effects such as sedation or metabolic syndrome will be greater because of the more at-risk populations. Also, efficacy shown in acute bipolar depression for 8 weeks in RCTs cannot legitimately be translated to effectiveness in prevention of bipolar depression for 8 years. Short-term efficacy should not be interpreted as long-term effectiveness. Efficacy in RCTs means what it means, not more nor less. Further extensions of RCTs in clinical practice need to be subject to good effectiveness research.

Edgar Allan Poe had it right, reminding us to only partly believe what we think we see, and to do the research—but also to critically analyze it:

“Believe nothing you hear, and only half that you see.”⁹ ■

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Making efficacious choices: the integration of pharmacotherapy and nonpharmacologic approaches to the treatment of patients with bipolar disorder

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INTRODUCTION

Bipolar disorder (BD) is a serious, recurrent, chronic psychiatric illness that impacts patients, their families, and communities. BD, which includes a spectrum of illnesses, has been subdivided into bipolar I (BP-I), bipolar II (BP-II), cyclothymia, and bipolar disorder not otherwise specified. Based on this broader definition, BD is more common than many people realize. The lifetime prevalence rates estimated by the National Comorbidity Survey Replication are 1.0% for BP-I, 1.1%, for BP-II, 2.4% for subthreshold BD, and 4.4% overall.¹

BD is characterized by episodes of mania or hypomania, and depression. The key difference between BP-I and BP-II is the occurrence of at least 1 manic episode in BP-I, which precludes the diagnosis of BP-II (characterized by one or more hypomanic episodes).² The fundamental problem is a dysregulation of mood. Patients with BD experience a variety of other difficulties, including impulsivity, risky behavior (eg, alcohol abuse, sexual indiscretion, excessive spending), and interpersonal problems.³ The clinical course in BP-I is primarily depressive rather than manic, and subsyndromal and minor affective symptoms predominate. In one longitudinal study, patients with BP-I were symptomatically ill 47% of the time with depressive (68%), manic (19%), and mixed (13%) symptoms.⁴

While the recognition, diagnosis, and treatment of unipolar depression have improved, patients with bipolar depression are often misdiagnosed. Identification of patients with BD is challenging due to a tendency to underreport hypomania or mania, the overlap of symptoms between bipolar and unipolar depression, and the presence of comorbid conditions. A large US population survey using the Mood Disorder Questionnaire (MDQ) revealed that unipolar depression was the most common misdiagnosis among patients with suspected BD.^{3,5} In another study of 250 patients observed in psychiatric clinics in France, 22% of patients with depression were found to have BP-II.⁶

PHARMACOTHERAPEUTIC APPROACHES

Differentiating patients with bipolar depression from other depressed patients is critical in order to appropriately administer treatment.⁷ Treatment for bipolar depression optimally should include both pharmacotherapy and psychosocial interventions. Two pharmacologic agents

have received US Food and Drug Administration (FDA) approval for the treatment of bipolar depression—quetiapine and olanzapine/fluoxetine combination (OFC). Other agents have been shown to have utility in the treatment of bipolar depression, but have not received FDA approval for this indication (FIGURE 1).

In the large US population-based survey using the MDQ, patients who screened positive for bipolar symptoms most commonly were receiving antidepressant monotherapy indicating that BD is frequently undetected or misdiagnosed.⁵ Since some studies have shown that antidepressant monotherapy has the potential to induce mania or hypomania or to cause or exacerbate rapid cycling, this approach may adversely affect outcomes. However, when antidepressants are combined with mood stabilizers such as lithium, these adverse effects may be reduced. A placebo-controlled trial involving outpatients with BD who were stabilized on lithium demonstrated beneficial effects using combination therapy with either paroxetine or imipramine in patients whose serum lithium levels were below 0.8 mEq/mL.⁸ Adding antidepressants to the treatment regimen in patients with serum lithium levels above 0.8 mEq/mL did not improve depressive symptoms compared with placebo. Combination therapy with paroxetine was associated with fewer adverse effects, including the emergence of manic symptoms, than combination therapy with imipramine.⁸

Additional studies have demonstrated efficacy and safety using antidepressants in combination with antipsychotics. In an 8-week, randomized controlled trial involving more than 800 patients with bipolar depression, both olanzapine (OLZ) monotherapy and olanzapine-fluoxetine combination therapy were more effective than placebo without increasing the risk of developing manic symptoms. Both the OLZ and OFC groups significantly reduced anxiety, improved sleep, and improved appetite. Adverse events for both groups included somnolence, weight gain, headache, dry mouth, asthenia, and insomnia; the OFC group had significantly higher rates of nausea and diarrhea (FIGURE 2 and TABLE 1).⁹ Average weight gain and percentage of patients with ≥7% weight gain

FIGURE 1

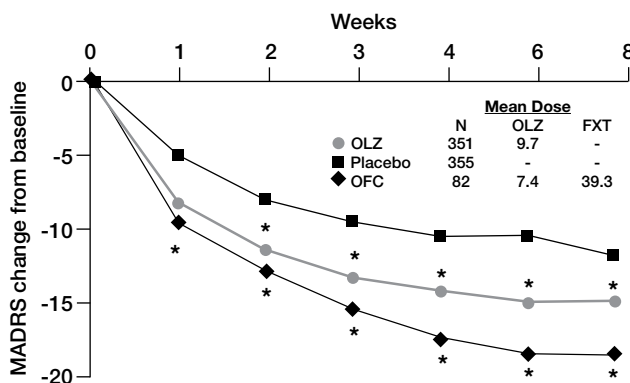
Current approved and unapproved agents for bipolar disorder

Acute Mania		Acute Depression		Maintenance		
Year	Drug	Year	Drug	Year	Drug	
1970	Lithium	2003	Olanzapine/fluoxetine combination	1974	Lithium	
1973	Chlorpromazine	Unmet need	Quetiapine	2003	Lamotrigine	
1994	Divalproex			2004	Olanzapine	
2000	Olanzapine ¹			2005	Aripiprazole	
2003	Risperidone ¹			2008	Quetiapine (Adj.)	
2004	Quetiapine ¹			2009	Risperidone LAI	
2004	Ziprasidone			Unmet need		
2004	Aripiprazole					
2004	Carbamazepine					
2005	Divalproex ER					
2009	Asenapine					

Adapted from Ketter TA, ed. Clinical Manual of Bipolar Disorder. Washington, DC: American Psychiatric Publishing, Inc. 2009. FDA approvals current at time of publication. ¹Approved as both adjunctive and monotherapy.

FIGURE 2

Olanzapine/fluoxetine combination in the acute treatment of bipolar I depression



Reprinted with permission from Tohen M et al. Arch Gen Psychiatry. 2003;60:1079-1088. *P<0.001 vs placebo; FXT=fluoxetine; OFC=olanzapine/fluoxetine combination; OLZ=olanzapine.

from baseline were significantly greater for the olanzapine and OFC groups than the placebo group.

Other studies have not demonstrated evidence of improved symptoms with combination mood stabilizer plus antidepressant therapy as compared to mood stabilizer

TABLE 1

Olanzapine/fluoxetine vs olanzapine vs placebo in acute treatment of bipolar I depression; treatment-emergent adverse events reported by $\geq 10\%$ of the patients in any group

	Olanzapine/ Fluoxetine Combination (%)	Olanzapine (%)	Placebo (%)
Somnolence	21	28*	13
Weight gain	17*	17*	3
Increased appetite	13 [†]	14*	5
Headache	14	12 [‡]	19
Dry mouth	16 [†]	11 [‡]	6
Nervousness	9	11	8
Asthenia	13*	10*	3
Insomnia	9	8 [†]	15
Diarrhea	19*	7	7
Nausea	12	4 [‡]	9

* $P \leq 0.001$; [†] $P \leq 0.01$; [‡] $P < 0.05$ vs placebo. Yellow highlighting indicates adverse events significantly greater than reported for placebo; green highlighting indicates those significantly lower than reported for placebo. Adapted from Tohen M et al. Arch Gen Psychiatry. 2003;60:1079-1088.

ers alone in patients with bipolar depression. The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) was designed to evaluate the effectiveness of treatments for BD. A 6-month controlled trial within STEP-BD investigated the use of combination therapy with a mood stabilizer plus an antidepressant. Patients with bipolar depression were treated with paroxetine or bupropion in combination with lithium, valproate, carbamazepine, or an atypical antipsychotic FDA-approved for acute mania. The primary outcome variable was durable recovery, defined as at least 8 weeks of euthymia with no more than 2 depressive/manic symptoms. There was no significant difference in effectiveness between treatment with a mood stabilizer plus adjunctive antidepressant and treatment with a mood stabilizer alone. Adverse effects, including a switch to mania, were similar (approximately 10%) in both groups.¹⁰ In summary, these results do not support the use of antidepressants as add-on therapy with mood stabilizers in bipolar depression.

Data were analyzed from the Bipolar Collaborative Network (formerly the Stanley Foundation Bipolar Network) to determine the factors associated with the emergence of mania in patients with BD treated with antidepressants. Baseline Young Mania Rating Scale (YMRS) scores, particularly increased motor activity, speech, and thought content, were higher in the group

with increased rates of treatment-emergent mania. Nonpredictors of mania included age, gender, age at onset of symptoms, number of prior episodes, rapid cycling, family history, and comorbid disorders. These results indicate that careful assessment of the presence of manic symptoms is important when considering treatment with antidepressants for patients with bipolar depression.¹¹

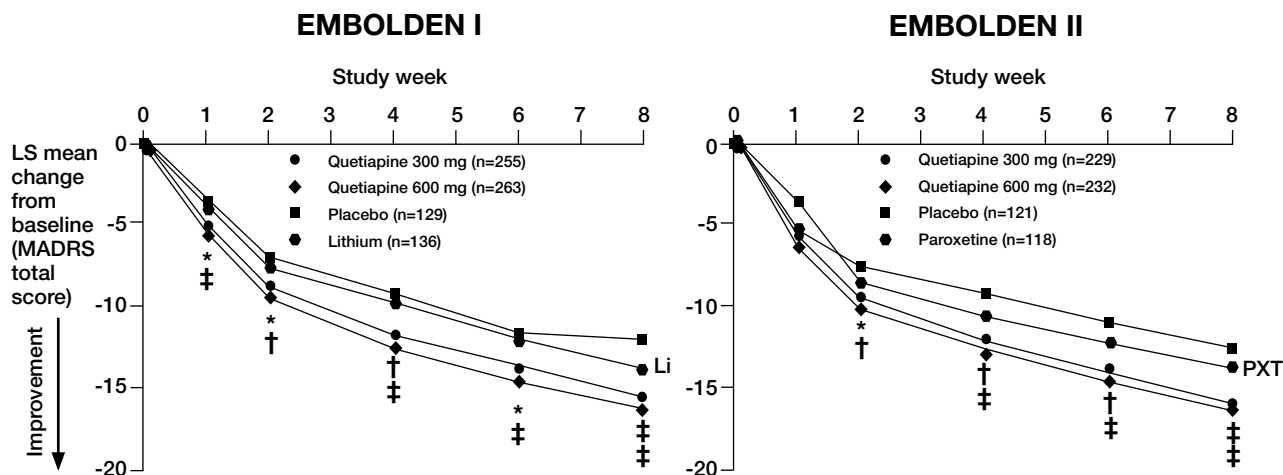
A recent 8-week, placebo-controlled study investigated paroxetine monotherapy in the acute treatment of bipolar depression as part of a larger study including quetiapine monotherapy. No significant difference in improvement on the Montgomery-Asberg Depression Rating Scale (MADRS) was found with paroxetine compared with placebo. Surprisingly, there were similar low switch rates for paroxetine and placebo,¹² and it is unknown whether the 20-mg paroxetine dosage was sufficient.

Other pharmacotherapeutic options for bipolar depression have been investigated. Use of the anticonvulsant, lamotrigine, for the acute treatment of bipolar depression has shown mixed results. A 7-week placebo-controlled study demonstrated that lamotrigine monotherapy was both effective and well tolerated.¹³ However, 4 other studies found that, although lamotrigine monotherapy was well tolerated, measures of efficacy were not greater than placebo.¹⁴ The results from the 5 randomized, placebo-controlled trials were included in a pooled analysis of more than 1000 patients. This analysis found that lamotrigine was significantly better than placebo ($P=0.002$; Number needed to treat = 11) for response to treatment. The difference in response rates was more pronounced among more severely depressed patients (Number needed to treat = 7).¹⁵ Lamotrigine also has demonstrated efficacy as add-on treatment to lithium for acute bipolar depression.¹⁶

In 2 identical, 8-week, placebo-controlled trials using aripiprazole monotherapy in outpatients with bipolar depression, statistically significant improvements in depression rating scales were seen for the first 6 weeks; however, the effect was not superior to placebo during the last 2 weeks of the studies. In addition, aripiprazole was associated with a higher incidence of akathisia, insomnia, nausea, fatigue, restlessness, and dry mouth compared with placebo.¹⁷

FIGURE 3

Quetiapine monotherapy in the acute treatment of bipolar I and II depression



Young AH et al. Presented at: 3rd Biennial Conference of the International Society for Bipolar Disorders; January 27-28, 2008; Delhi, India; and January 30, 2008; Agra, India. Abstract; McElroy S et al. Presented at: 3rd Biennial Conference of the International Society for Bipolar Disorders; January 27-28, 2008; Delhi, India. Abstract. * $P < 0.05$ vs placebo; † $P < 0.01$ vs placebo; ‡ $P < 0.001$ vs placebo; Intent-to-treat (ITT) population; Last Observation Carried Forward (LOCF); Li=Lithium; LS=least square; MADRS=Montgomery-Åsberg Depression Rating Scale; PXT=Paroxetine.

In 2006, quetiapine was approved by the FDA for the treatment of bipolar depression. Two 8-week, randomized controlled trials (BOLDER I and II) involving more than 1000 patients with bipolar depression who were treated with either quetiapine monotherapy or placebo demonstrated significantly greater improvements in mean MADRS scores for the quetiapine groups. The incidence of treatment-emergent mania was lower with quetiapine than placebo in one study and low, but similar to placebo, in the other study.^{18,19} The most common adverse events reported with quetiapine were dry mouth, sedation, somnolence, and dizziness (TABLE 2). Recently, 2 additional trials (EMBOLDEN I and II) investigating the use of quetiapine monotherapy compared to lithium, paroxetine, or placebo confirmed the superior efficacy of quetiapine over placebo for the treatment of bipolar depression (FIGURE 3).^{12,20}

Several studies have evaluated the efficacy of lithium for the depressive symptoms in patients with BD. Eight placebo-controlled trials, all completed prior to 1980, demonstrated an overall response rate of 79%; however, the unequivocal response rate, defined as patients with “good” or “moderate” (but not “partial”) responses to lithium, was 36%.²¹ A recent 8-week study of lithium monotherapy, which was part of a quetiapine study, demonstrated no significant improvement in MADRS scores using lithium

TABLE 2

Combined BOLDER studies: most common adverse events associated with quetiapine treatment $\geq 10\%$ of patients and 2 times placebo

Adverse Event	Quetiapine 300 mg (%) (N=350)	Placebo (%) (N=347)
Dry mouth	43	13
Sedation	31	8.1
Somnolence	29	6.6
Dizziness	15	6.9

Data on file. AstraZeneca Pharmaceuticals LP, Wilmington, DE.

monotherapy compared to placebo in patients with bipolar depression.²⁰ In addition lithium has been shown to reduce the risk of suicide in bipolar patients.²²

Three small placebo-controlled studies evaluated the use of divalproex in the acute treatment of bipolar depression. One study demonstrated a trend that favored divalproex, which was not statistically significant,²³ whereas the other two studies showed significant improvements in depression rating scores.^{24,25}

The dopamine agonist, pramipexole, has shown safety and efficacy as an antidepressant add-on in patients with bipolar depression. Significant improvements in depressive symptoms compared to placebo

TABLE 3

Psychosocial interventions in the treatment of bipolar disorder: commonly-used techniques and goals

	Goals	Techniques
Psychoeducation	<ul style="list-style-type: none"> • Illness awareness • Treatment compliance • Early detection of prodromal symptoms and recurrences • Lifestyle regularity 	<ul style="list-style-type: none"> • Education, including pamphlets, books, web sites • Exercises related to issues (eg, life chart, writing list of triggers) • Discussion
Family-Focused Psychoeducation	<ul style="list-style-type: none"> • Accept the notion of a vulnerability to future episodes • Accept a dependency on mood-stabilizing medication for symptom control • Distinguish between the patient's personality and his/her bipolar disorder • Recognize and cope with stressful life events that trigger relapse • Reestablish functional relationships after a mood episode 	<ul style="list-style-type: none"> • Education about symptoms, course, treatment, and self-management of bipolar disorder • Communication enhancement, including rehearsal of effective speaking and listening strategies • Problem solving, including identifying specific problems, and the teaching of problem-solving skills
Cognitive Therapy	<ul style="list-style-type: none"> • Challenge the patient's beliefs or assumptions about his or her self, the world, and the future that contribute to vulnerability to bipolar disorder 	<ul style="list-style-type: none"> • Monitor, examine, and change dysfunctional thinking and behavior associated with undesirable mood states • Monitor moods and early signs of relapse • Develop a plan to deal with prodromal activities • Emphasize the need for combined medication and psychological therapies • Promote the importance of regular sleep and routine
Interpersonal and Social Rhythm Therapy	<ul style="list-style-type: none"> • Stabilize daily routines and sleep-wake cycles • Gain insight into relationships between moods and interpersonal events • Ameliorate interpersonal problems 	<ul style="list-style-type: none"> • Review history of illness • Track and identify connections between wake time, sleep time, activities, and mood • Develop a plan to stabilize social and circadian rhythms by maintaining consistent sleep and wake times and reducing irregular bursts of social stimulation • Explore and resolve key interpersonal problems

Adapted from Lam DH et al. Arch Gen Psychiatry. 2003;60:145-152; Colom F et al. Arch Gen Psychiatry. 2003;60:402-407; Miklowitz DJ et al. Arch Gen Psychiatry. 2003;60:904-912; Frank E et al. Arch Gen Psychiatry. 2005;62:996-1004.

were demonstrated when pramipexole was added to a mood stabilizer.^{26,27}

Modafinil, which is currently approved by the FDA to improve wakefulness in patients with excessive sleepiness, has been studied as an adjunct to mood stabilizers in patients with bipolar depression. Significant improvements on the Inventory of Depressive Symptoms and the Clinical Global Impression-Bipolar Version scales were noted in patients treated with modafinil compared with placebo.²⁸

NONPHARMACOLOGIC APPROACHES

Psychosocial interventions are important, efficacious components in the treatment of bipolar disorder, and studies have demonstrated their importance when used as adjuncts in patients receiving pharmacotherapies

(**TABLE 3**). Psychoeducation focuses on illness awareness, treatment compliance, early detection of prodromal symptoms and recurrences, and lifestyle regularity.²⁹ Family-focused psychoeducation teaches patients and their families about the signs and symptoms of BD and helps them understand vulnerability to recurrent episodes. By accepting a dependency on mood-stabilizing medication for symptom control and learning to recognize and cope with stressful life events that might trigger relapse, psychoeducation improves drug adherence in patients with BD.³⁰

Cognitive therapy is another useful tool used in conjunction with mood stabilizers for the treatment of BD. Patients are taught to monitor, examine, and change the dysfunctional thinking and behavior associated with undesirable mood states as well as recognize early signs of relapse. Patients receiving cognitive therapy in conjunction with mood stabilizers have significantly fewer

bipolar episodes and hospitalizations than patients who receive pharmacotherapy alone.³¹

Interpersonal and social rhythm therapy (IPSRT) aims to regulate social routines, stabilize sleep-wake cycles, and gain insight into interpersonal relationships. Circadian rhythm instability, in vulnerable individuals, can lead to affective episodes. IPSRT used in the acute treatment phase of BD increases the survival time without a new affective episode and reduces the likelihood of recurrence during the maintenance phase.³²

In summary, various classes of pharmacotherapeutic agents have shown efficacy in treating the depressive symptoms of BD. Quetiapine monotherapy has demonstrated efficacy in the treatment of both BP-I and BP-II depression, and OFC has demonstrated efficacy in the treatment of BP-I depression in several studies. Limited evidence supports the use of antidepressants in

combination with mood stabilizers. Indeed, addition of these agents may be harmful, with the exception of OFC, which has been approved by the FDA for bipolar depression. Although paroxetine monotherapy may not be associated with risk of treatment-emergent mania, as previously thought, its efficacy has not been consistently demonstrated. Lamotrigine monotherapy is particularly effective in severely depressed patients and has shown efficacy in combination with lithium. The effectiveness of atypical antipsychotics for bipolar depression is variable depending on the agent. Aripiprazole has not shown efficacy. Other classes of pharmacotherapeutic agents may be beneficial in the treatment of bipolar depression, but limited clinical trial data are available. Psychosocial interventions, in combination with pharmacotherapy, result in fewer relapses and recurrences as well as longer survival intervals in patients with BD. ■

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Promoting wellness in patients with bipolar disorder: strategies to move beyond maintaining stability and minimizing adverse events in effective long-term management

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INTRODUCTION

Bipolar disorder (BD) is an episodic illness that requires a multifaceted management strategy in order for patients to maintain wellness. Patients with bipolar disorder experience mood symptoms nearly half of the time. Depressive symptoms predominate and also predict greater future illness burden than mania. More than half of the depressive symptoms are moderate or severe in nature.¹ Patients with bipolar I disorder experience depressive or mixed symptoms 80% of the time and mania or hypomania only 20% of the time that they are symptomatic.² In bipolar II disorder, patients experience depressive or mixed symptoms during more than 95% of symptomatic time.³

Patients with BD typically experience recurrent symptoms for many years. Prospective data obtained from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study were analyzed to determine clinical features associated with the risk of recurrence. Almost half of the patients experienced recurrences within 2 years, with more than twice as many participants developing depressive episodes as those who developed manic, hypomanic, or mixed episodes. The median time to recurrence was 87 weeks, with 24% of patients experiencing an episode by 6 months, 36% by 1 year, and 61% by 4 years. Patients who had >20 previous episodes of depression or (hypo)mania had a significantly greater risk of recurrence compared to patients with <5 previous episodes. Greater number of days depressed or anxious in the year preceding recovery—as well as residual mood symptoms early in recovery—predicted recurrence, particularly for depression.⁴ These results highlight the importance of targeting residual symptoms in maintenance treatment in order to reduce the risk of recurrence.

The management of patients with BD involves long-term treatment strategies, with an emphasis on the depressive symptoms that predominate throughout the course of the illness. Several issues arise, particularly when patients are treated for long periods of time, including suicide risk, management of subsyndromal symptoms, treatment resistance, comorbidities, and adverse events associated with therapies. These concerns will be addressed within the context of maintaining wellness for patients with BD.

PREVENTING SUICIDE

Increased mortality is one of the major consequences in individuals with mood disorders compared with the general population. Cardiovascular disease is responsible for the majority of excess premature deaths in patients with BD⁵ but the highest standardized mortality rate in patients with BD is for suicide.⁶ The suicide rate is approximately 1% annually, which is 30 to 60 times greater than the rate in the general population, and accounts for 15% to 20% of deaths among patients with BD worldwide.⁷ Suicide attempts usually occur early in the course of the disease,^{8,9} and are more lethal in BD than in the general population.⁷

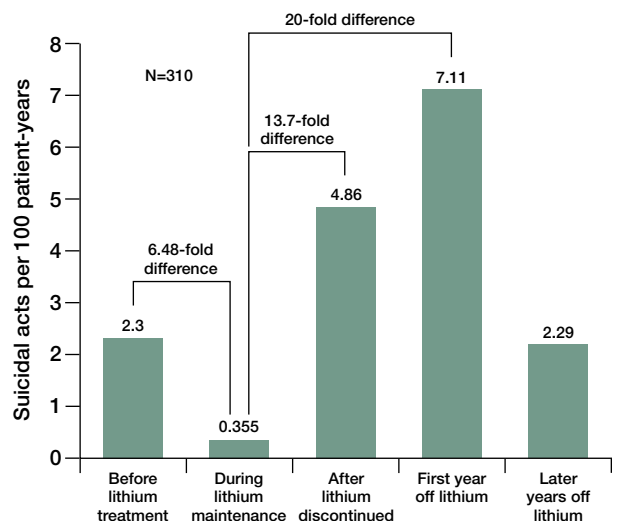
Therefore, reduction of the suicide rate in patients with BD is an important therapeutic goal. However, the ethical issues surrounding potential lethality when treatments are withheld or removed have resulted in relatively few studies that have investigated treatment effectiveness in the prevention of suicide or other causes of early mortality in patients with BD. Only lithium has shown efficacy in the long-term prevention of suicide. An observational study demonstrated a nearly 7-fold reduction in suicidal acts, which includes attempts and fatalities, per year during lithium maintenance monotherapy compared to the time at risk before treatment was initiated. In addition, the cumulative risk of a life-threatening suicide attempt was reduced by more than 8-fold over 15 years of follow-up with lithium maintenance. Suicide rates increased 20-fold within the first year after discontinuation of lithium, and returned to pretreatment levels after 12 months of follow-up (FIGURE 1).⁹ Based on clinical trial evidence, lithium treatment should strongly be considered in patients with either a personal history of suicide attempts or a strong family history of suicide.

SUBSYNDROMAL SYMPTOMS

Functional disabilities in patients with BD affect their lives at work, at home, with friends, and with family. These social and occupational deficits have become a significant public health issue with a profound economic impact on society. Subsyndromal symptoms, which do not meet the full DSM IV diagnostic criteria for mood episodes, are present in 70% of patients with BD and have been associated with functional impair-

FIGURE 1

Lithium decreases risk of suicide



Adapted from Baldessarini RJ et al. *J Clin Psychiatry*. 1999;60(suppl 2):77-84.

ment in multiple domains (TABLE 1).¹⁰ In addition, the presence of these subthreshold symptoms increases the risk of relapse.¹¹ The frequency of subsyndromal symptoms has been reported in 25% to 60% of patients with BD in various studies.^{12,13} Therefore, awareness of subsyndromal symptoms is an important consideration for maintaining wellness in patients with BD. Unfortunately, there have not been any published controlled studies evaluating treatment options for subsyndromal symptoms. It is important for clinicians to recognize the symptoms and maximize treatment options.

TREATMENT RESISTANCE

Although few studies have addressed treatment-resistant depression, it is an important concern in the long-term management of patients with BD. A 16-week open-label randomized trial within STEP-BD, which was designed to evaluate the effectiveness of treatments for BD, investigated the efficacy and safety of augmentation with lamotrigine, inositol, or risperidone in patients with treatment-resistant bipolar depression. Overall, the response rates were low and there were no statistically significant between-group differences

TABLE 1

Subsyndromal symptoms are associated with functional impairment in 50% to 75% of patients

Role Function	Not Depressed (n=292)	Subsyndromally Depressed (n=291)	Syndromally Depressed (n=176)	P-value
Duties at work/school	64 (31)	108 (64)	61 (87)	<0.0001
Duties at home	107 (38)	209 (75)	142 (93)	<0.0001
With family	90 (34)	151 (59)	112 (77)	<0.0001
With friends	48 (18)	144 (56)	116 (81)	<0.0001
Total—all domains	91 (32)	205 (70)	157 (92)	<0.0001

Altshuler LL et al. *J Clin Psychiatry*. 2006;67:1551-1560.

when any pair of treatments were compared regarding the rate of recovery (defined as no more than 2 DSM IV mood symptoms present for 8 weeks). However, patients who received lamotrigine had lower Clinical Global Impression severity scores and greater Global Assessment of Functioning scores than patients in the other 2 groups.¹⁴

COMORBIDITIES

Another key issue in the management of patients with BD is the presence of comorbidities, which are commonly multiaxial, and include both psychiatric and medical conditions. Studies have shown that patients with BD are twice as likely to have comorbid psychiatric conditions compared with BD alone. These comorbidities include anxiety, impulse control problems, attention deficit hyperactivity disorder, personality disorder, and eating disorders.¹⁵ The prevalence of comorbid substance abuse in patients with bipolar I and bipolar II disorder is as high as 61% and 48%, respectively, which is greater than the prevalence of comorbid substance abuse seen with any other psychiatric conditions, including schizophrenia, panic disorder, dysthymia, and unipolar depression.¹⁶ Many patients with BD have multiple comorbidities, which presents an even greater challenge for the management of the disease. Data from the Stanley Foundation Bipolar Treatment Outcome Network indicate that approximately one-quarter of patients with BD have ≥ 3 axis I comorbidities during their lifetime.¹⁷

The presence of psychiatric comorbidities affects both diagnosis and treatment in patients with BD. In general, these patients have earlier onset of illness, delayed short- and long-term recoveries, and worsening course of disease and outcomes.^{15,17} Psychiatric comorbidities in patients with BD are associated with more mixed features, depressive episodes, and suicide attempts.¹⁸ In addition, patients who have

comorbid BD with anxiety disorders have greater severity of bipolar illness, which manifests as a reduced likelihood of recovery, diminished functioning, and decreased quality of life. There are fewer total days and generally shorter periods of euthymia. In addition, there is a greater likelihood of suicide attempts in patients with comorbid anxiety compared to patients with BD alone.¹⁹

There have been relatively few large-scale controlled studies that address specific management issues for patients with BD and comorbidities, so treatment is largely empirical. Patients with BD and comorbid anxiety are treated with antidepressants more commonly than patients with BD without this comorbidity.²⁰

Medical comorbidities in patients with BD pose additional challenges for disease management. The prevalence of migraine, diabetes, other endocrinopathies, and cardiovascular disease is higher in patients with BD than in the general population.^{6,21,22} Patients with BD are typically overweight or obese due to a variety of factors, including sedentary lifestyle, poor eating habits, and weight gain associated with psychotropic medications. Similar to other individuals with abdominal obesity, patients with BD are at increased risk for developing the metabolic syndrome. In a study of 171 patients with BD, 74% were overweight or obese, and 30% met the criteria for the metabolic syndrome.²³ In addition to medical comorbidities in patients with BD, some medical disorders may cause mania. This so-called secondary mania is common in patients with brain injuries involving right-sided subcortical areas as well as cortical areas linked to the limbic system.²⁴

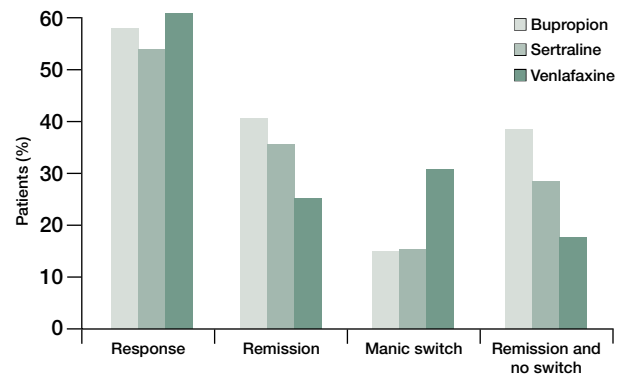
LONG-TERM MAINTENANCE THERAPY

Although a variety of pharmacotherapeutic agents have been approved for the treatment of acute mania in patients with BD, fewer options are available for the treatment of acute bipolar depression and/or maintenance therapy. Many patients with BD are treated with antidepressants for long periods of time. A recent study compared long-term continued use of antidepressants added to mood stabilizers vs discontinuation of antidepressants in patients who received mood stabilizers. Moderate improvement in subsyndromal depressive symptoms was observed in the patients treated with antidepressants plus mood stabilizers for 1 year compared to the patients treated with mood stabilizers alone. Additionally, the patients treated with antidepressants had longer periods of time until their first depressive episodes. However, further data analysis showed that in a subgroup of patients with rapid cycling, antidepressant-treated patients had a 3-fold excess of depressive recurrences compared to patients treated with mood stabilizers alone.²⁵ Another recent placebo-controlled trial demonstrated favorable long-term results with antidepressants in patients who had an initial positive response. After 1 year of continued treatment with either bupropion, sertraline, or venlafaxine, 69% of the acute positive responders maintained positive responses and 53% achieved remission.²⁶ A meta-analysis of studies involving long-term use of antidepressants in patients with BD suggested an unfavorable risk-to-benefit ratio. Overall, there was a 27% reduction in risk for depressive relapses when antidepressants were included in long-term treatment compared with either mood stabilizers alone or no treatment. However, the pooled risk of new manic or hypomanic episodes was >72% with long-term use of antidepressants than without these agents. When studies comparing antidepressant monotherapy vs no treatment were excluded, there was very little difference in the risk of depressive relapses and no significantly increased risk of new mania in patients treated with antidepressants plus mood stabilizers compared to patients treated with mood stabilizers alone.²⁷

Data were analyzed from the Stanley Foundation Bipolar Network to compare the risks of switches in mood polarity to hypomania or mania in patients with BD who were treated with mood stabilizers plus venlafaxine, sertraline, or bupropion. Adjunctive antidepressant treatment was associated with an increased risk

FIGURE 2

Stanley randomized controlled trial: first maintenance study with new antidepressants



Adapted from Leverich G et al. *Am J Psychiatry*. 2006;163:232-239. Response and remission used Inventory of Depressive Symptomatology (IDS) criterion only; manic switch and remission/no switch used Young Mania Rating Scale (YMRS) or Clinical Global Impressions Scale for Bipolar Disorder (CGI-BP).

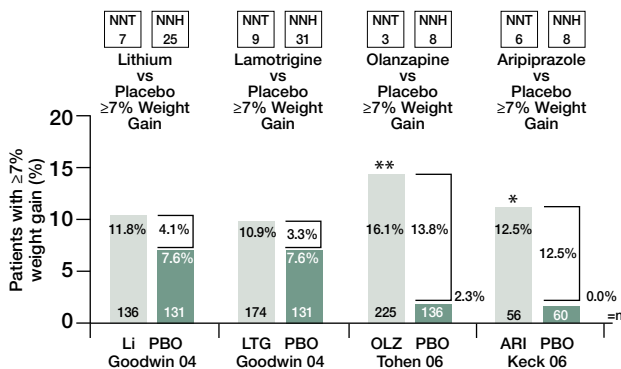
of threshold switches to full-duration hypomania or mania in both acute and long-term maintenance trials. Although switch rates were not significantly different among the 3 antidepressants in the continuation trials, the ratio of threshold switches to subthreshold hypomanias was highest for venlafaxine compared with the other antidepressants. Overall, only 23% of the patients had sustained antidepressant responses with long-term maintenance treatment in the absence of a threshold switch (FIGURE 2).²⁸

ADVERSE EVENTS

Adverse events are relatively common with the use of psychotropic agents and must be considered when prescribing these drugs. Unwanted side effects may contribute to poor medication adherence, particularly when used for maintenance therapy. Lithium has a narrow therapeutic window, which necessitates frequent drug level monitoring. Adverse events associated with lithium include weight gain, gastrointestinal disturbances, polyuria, impaired cognition, sedation, and other neurotoxic effects, which result in poor coordination and muscle weakness. The American Psychiatric Association recommends that serum lithium levels be measured every

FIGURE 3

Overview of bipolar maintenance studies: numbers needed to treat and harm ($\geq 7\%$ weight gain rates) — contemporary registration studies



Mood stabilizers compared to antipsychotics—slightly less efficacy, but better tolerability

Adapted from Ketter TA, ed. *Clinical Manual of Bipolar Disorder*. Washington, DC: American Psychiatric Publishing, Inc. (2009). * $P < 0.01$ vs placebo, ** $P < 0.0001$ vs placebo; ARI=Aripiprazole; LTG=Lamotrigine; Li=Lithium; NNH=Number needed to harm; NNT=Number needed to treat; OLZ=Olanzapine; PBO=Placebo.

6 months and that patients be monitored for clinical signs and symptoms of toxicity including tremor, nausea and diarrhea, blurred vision, vertigo, confusion, and increased deep tendon reflexes.²⁹ Carbamazepine is associated with gastrointestinal side effects, cognitive impairment, and skin rash as well as hepatic enzyme autoinduction, which can affect the metabolism of concomitant medications. The most serious side effects associated with carbamazepine are blood dyscrasias, including agranulocytosis and aplastic anemia. Sodium divalproex has fewer gastrointestinal side effects than valproic acid but has been associated with hair loss, tremor, sedation, cognitive impairment, pancreatitis, polycystic ovarian syndrome, and thrombocytopenia.³⁰⁻³² The most common adverse events reported in maintenance studies with lamotrigine are headache, nausea, infection, and insomnia. In rare cases, lamotrigine treatment has been associated with skin rash including mild Stevens-Johnson syndrome.³³

In general, mood stabilizers used for maintenance therapy in patients with BD may have slightly less efficacy but better tolerability than some antipsychotics. Antipsychotic medications have been associated with a variety of adverse effects. Analysis of weight gain data from maintenance studies using the mood stabilizers lithium and lamotrigine showed higher numbers needed to harm

compared with studies using the atypical antipsychotics olanzapine and aripiprazole (FIGURE 3).³⁴ Although some atypical antipsychotics have lesser propensity to weight gain than conventional antipsychotics, patients receiving olanzapine, clozapine, risperidone, and quetiapine should be closely monitored. Additional adverse effects associated with the use of antipsychotics include somnolence, extrapyramidal symptoms (EPS), dyslipidemia, and hyperprolactinemia. Many of these effects are less common and/or less severe when second-generation antipsychotics are used compared with first-generation agents. Risperidone, olanzapine, and ziprasidone are more likely to cause dose-dependent EPS than quetiapine, aripiprazole, and clozapine. Somnolence is more commonly observed with olanzapine, clozapine, and quetiapine than with the other atypical antipsychotics.³⁰

TREATMENT ADHERENCE

Although new treatment strategies have shown improved efficacy compared with some of the traditional therapies, patient adherence is key to effectiveness and remains a challenge in patients with BD. A study investigating non-adherence with mood stabilizers in patients with BD found that one-third of the participants did not take at least 30% of their prescribed medication doses and over 60% of these partially adherent patients had subtherapeutic serum levels of mood stabilizers.³⁵ Another survey involving veterans with BD found that 22% of the participants either discontinued all medications or missed more than half of their prescribed doses.³⁶

Unfavorable side-effect profiles are a significant impediment to treatment adherence.^{37,38} Medication-associated weight gain can lead to impaired quality of life, both socially and physically, as well as poor treatment adherence. This was confirmed in a study of patients with schizophrenia treated with atypical antipsychotics, which showed that weight gain is a predictor of medication noncompliance (FIGURE 4).³⁹

Up to 85% of patients with BD complain of disturbing medication side effects and many do not receive information from their physician regarding strategies to manage these events.⁴⁰ In addition to medication side effects, several other factors can negatively impact treatment adherence in patients with BD, including comorbid substance use disorder, barriers to health care access, poor provider-patient relationships, poor patient insight, and

negative patient attitudes about their illness, the benefits of treatment, and the potential impact on their lives.^{35,36}

Perceptions of clinicians and patients differ regarding reasons for treatment nonadherence. A study was performed to determine if clinicians are aware of the reasons why patients discontinue medications. Practicing psychiatrists and patients receiving mood stabilizers were surveyed and several discrepancies were noted between the 2 groups. For example, psychiatrists believed that patients discontinue medications when they feel well and no longer see the need to take medications. Conversely, patients cited the hassle involved in taking medications as one of the main reasons for discontinuation. In addition, psychiatrists believed that patients miss the “highs” associated with BD, whereas the patients were most concerned about feeling depressed.⁴¹

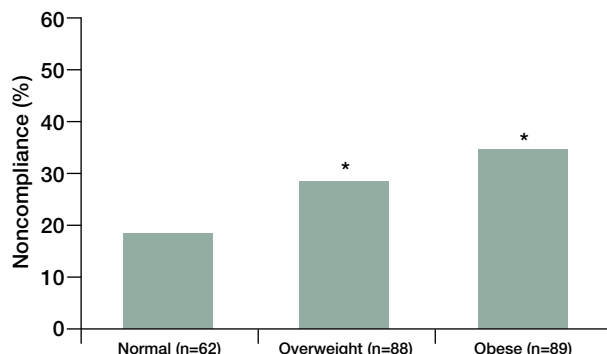
PSYCHOTHERAPIES

In order to maintain wellness in patients with BD, pharmacotherapy should be supplemented with psychotherapy, which may include psychoeducation, cognitive-behavioral therapy, family-focused therapy, as well as interpersonal and social rhythm therapy. Evidence supports the use of these adjunctive modalities. One efficacy study demonstrated that group psychoeducation was useful in preventing recurrences in patients with BD. Patients in remission who received group psychoeducation in conjunction with standard pharmacologic treatment had fewer relapses, increased time to depressive, manic, hypomanic, and mixed recurrences as well as fewer and shorter hospitalizations compared with patients who received standard pharmacotherapy and attended non-structured group meetings (FIGURE 5).⁴²

In summary, maintaining wellness in patients with BD requires consideration of many factors. Following correct diagnosis, it is of paramount importance that patients accept their diagnosis, and ongoing patient education is critical in this process. Development of strategies to manage the symptoms of BD should be based on patients’ individual needs and social situations. In prescribing therapies, it is important to consider efficacy as well as side effects and tolerability. Recognition and treatment of subsyndromal symptoms, which can impact functioning, are important aspects of long-term management. Simplifying complex medication regi-

FIGURE 4

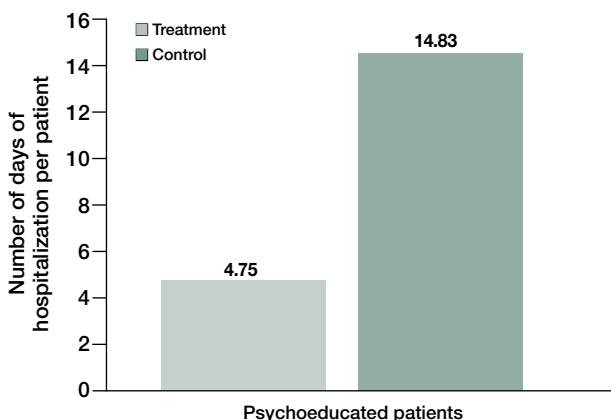
Obesity as a risk factor for antipsychotic noncompliance



Noncompliant respondents according to BMI category (schizophrenia population). Adapted from Weiden PJ et al. *Schizophr Res.* 2004;66:51-57. * $P=0.01$ vs normal; Chi-square: $P=0.03$; Test for linearity: $P=0.01$.

FIGURE 5

Group psychoeducation in the prophylaxis of recurrences in bipolar disorder



Adapted from Colom F et al. *Arch Gen Psychiatry.* 2003;60:403-407.

mens may reduce the side-effect burden experienced by some patients and is an important approach to consider, particularly in patients who are not responding well to therapy. Identifying stressors and triggers that contribute to relapses and recognizing warning signs of impending depressive or manic episodes enables treatment intervention and potentially prevents full relapse.⁴³ Mood charting and assessing sleep-wake cycles also are useful components of management strategies and provide opportunities for patient control. ■

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POSTTEST QUESTIONS

Select the single letter response that best answers the question, and complete the answer key on page S22.

1. Which of the following conditions is the most common misdiagnosis among patients with bipolar disorder?

- a) Anxiety
- b) Personality disorder
- c) Depression
- d) Schizophrenia or schizoaffective disorder

2. Patients with bipolar disorder most frequently relapse into which of the following episodes?

- a) Depressive
- b) Manic
- c) Hypomanic
- d) Mixed

3. Which of the following statements is true concerning the treatment of bipolar depression?

- a) Optimal treatment should include both pharmacotherapy and psychosocial interventions.
- b) Mood stabilizers such as lithium, anticonvulsants such as valproate, and several antipsychotic medications have been approved by the US Food and Drug Administration for this indication.
- c) The use of mood stabilizers with antidepressants carries a significantly increased risk of treatment-emergent mania compared with the use of antidepressants alone.
- d) All of the atypical antipsychotics have demonstrated similar effectiveness.

4. Which of the following statements is true concerning psychiatric comorbidities in patients with bipolar disorder?

- a) Substance abuse is less common in patients with bipolar disorder compared to patients with other psychiatric conditions like schizophrenia and unipolar depression.
- b) Psychiatric comorbidities are associated with earlier onset of bipolar illness, delayed short- and long-term recoveries, and worse outcomes.
- c) Patients with bipolar and comorbid anxiety disorders have a greater likelihood of recovery, improved functioning, and increased quality of life compared to patients with bipolar disorder alone.
- d) Less than 5% of patients with bipolar disorder have ≥ 3 axis I comorbidities during their lifetime.

5. Which of the following statements is true concerning long-term maintenance therapy in patients with bipolar disorder?

- a) More therapeutic options have been approved for maintenance therapy than for acute mania.
- b) Patients with rapid cycling who are treated long-term with mood stabilizers plus antidepressants have a higher incidence of depressive relapses compared to patients treated with mood stabilizers alone.
- c) Studies have suggested a favorable risk-to-benefit ratio concerning the long-term use of antidepressants.
- d) More than half of patients who receive long-term maintenance treatment with mood stabilizers plus antidepressants have sustained antidepressant responses without switches in mood polarity.

EVALUATION FORM

SciMed respects and appreciates your opinion. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form, and **fax it to 212-661-8338, ATTN: CME Department.** For questions about this activity, or to mail in this evaluation and request for credit, please contact SciMed, 420 Lexington Avenue, Suite 902, New York, NY 10170

Circle the appropriate response: 5 = outstanding/extremely; 4 = good/very; 3 = satisfactory; 2 = fair/not very; 1 = poor/not at all

1. Extent to which activity met the identified objectives

How much did participation in this activity enhance your ability to:

Develop an evidence-based approach to the treatment of patients with bipolar disorder based on available treatment options	5	4	3	2	1
Integrate appropriate nonpharmacologic management strategies into treatment programs for patients with bipolar disorder	5	4	3	2	1
Outline long-term strategies to enhance overall patient outcomes while minimizing the risk of medication-related adverse events	5	4	3	2	1
Recognize the long-term consequences of the choice of pharmacotherapy on overall patient health and quality of life	5	4	3	2	1

2. Overall effectiveness of the activity

The content presented:

Was timely and will influence how I practice	5	4	3	2	1
Will assist me in improving patient care	5	4	3	2	1
Fulfilled my educational needs	5	4	3	2	1
Avoided commercial bias or influence	5	4	3	2	1

If you rated "1" or "2" regarding commercial bias, please provide comment(s).

Logistically:

The format and materials were useful	5	4	3	2	1
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What was the most positive part of this activity?

3. Impact of the activity

Will your practice change as a result of participating in this activity?

Yes No

Please describe any change(s) you plan to make in your practice as a result of this activity.

How committed are you to making these changes?

5 4 3 2 1

4. Future activities

Do you feel future activities on this subject matter are necessary and/or important to your practice?

5 4 3 2 1

Please suggest educational needs or practice-related problems in which you have interest for future activities.

What method of learning do you most prefer?

Live meeting (eg, symposium)

5 4 3 2 1

Enduring materials (eg, monograph, journal supplement)

5 4 3 2 1

Multimedia (eg, CD-ROM, Web-based activities)

5 4 3 2 1

5. Follow-up

As part of our continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

- Yes**, I would be interested in participating in a follow-up survey
- No**, I would not be interested in participating in a follow-up survey

Additional comments about this activity:

REQUEST FOR CREDIT

If you wish to receive acknowledgement for participating in this activity, please complete the posttest (select the best answer to each question), along with this evaluation form verifying your participation.

The posttest and evaluation form can be faxed to 212-661-8338, ATTN: CME Department.

Posttest answer key

Enter posttest answers: 1. 2. 3. 4. 5.

Participant Information: (PLEASE PRINT CLEARLY)

Last Name First Name Degree(s)

Academic Title

Affiliation

Specialty

Address (No PO Boxes, please)

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Last four digits of your Social Security Number OR AMA ME Number

I certify that I have participated in the CME activity entitled

Maintaining Wellness in Patients With Bipolar Disorder:

Moving Beyond Efficacy to Effectiveness for a total of _____ hours.

Signature Date

Yes, I am interested in receiving future educational materials.

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SUPPLEMENT TO

Current PSYCHIATRY

October 2009

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patients with

bipolar disorder:

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EFFICACY TO
EFFECTIVENESS

