Challenges in the Management of Bipolar Depression

Trisha Suppes, M.D., Ph.D.; Dorothy I. Kelly, M.A.; and Jessica M. Perla, B.S.

Bipolar depression has started to receive more attention in clinical trials only relatively recently, despite the fact that patients spend more time in the depressed phase than in the manic phase of bipolar disorder. The diagnosis and management of bipolar depression are challenging, and many patients are undiagnosed or misdiagnosed due to symptom similarities with unipolar depression or other illnesses and/or comorbidities. Untreated or inappropriately treated bipolar depression adds to the burden of illness and is associated with a greater risk of suicide. Treatment options include lithium, lamotrigine, atypical antipsychotics, and traditional antidepressants, such as the selective serotonin reuptake inhibitors. However, traditional antidepressants are recommended with caution due to their potential risk of switching patients into mania. Some atypical antipsychotics have shown efficacy in bipolar depression, although longer-term studies are warranted. The choice of treatment for different subgroups of patients with bipolar depression, including those with comorbid anxiety, may vary and also needs further study. Other important issues that require further investigation include the recognition of the core features of bipolar depression and the threshold symptoms for treatment, as well as the optimal treatment choices for monotherapy or combination therapy, and acute versus long-term management of bipolar depression. *(J Clin Psychiatry 2005;66[suppl 5]:11–16)*

Bipolar disorder is a debilitating and usually chronic psychiatric illness that appears to be more prevalent than originally appreciated, with a recent community-based estimate suggesting an adjusted lifetime prevalence rate of more than 3% for the spectrum of bipolar disorders,[1] and conservative estimates from larger epidemiology studies of 1.3% to 2%.[2,3] Despite the relatively high prevalence rate of bipolar disorder and its significant personal and societal burden, it continues to be poorly recognized by the general public, primary care physicians, and even psychiatrists.[4,5]

From the Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas.

This article is derived from the roundtable "The Burden of Bipolar Illness," which was held April 30, 2004, in New York, NY, and supported by AstraZeneca Pharmaceuticals, LP.

The authors would like to acknowledge the editorial assistance of Tanwen Evans, Ph.D. (PAREXEL Medical Marketing Services [MMS], Uxbridge, U.K.). AstraZeneca provided financial support for this assistance.

Dr. Suppes has received grant/research support from Abbott, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, the National Institute of Mental Health, Novartis, the Robert Wood Johnson Pharmaceutical Research Institute, and the Stanley Medical Research Institute and has been a consultant to and has participated in speakers/advisory boards for Abbott, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Johnson & Johnson Pharmaceutical Research & Development, Novartis, Pfizer, the Pharmaceutical Research Institute, Ortho McNeil, Shire, Solvay, and UCB Pharma. Mss. Kelly and Perla report no other affiliation or financial relationship relevant to the subject of this article.

Corresponding author and reprints: Trisha Suppes, M.D., Ph.D., Bipolar Disorders Research Program, University of Texas Southwestern Medical Center, Department of Psychiatry, 5323 Harry Hines Blvd., Room MC5.262, Dallas, TX 75390-9121 (e-mail: trisha.suppes@utsouthwestern.edu).

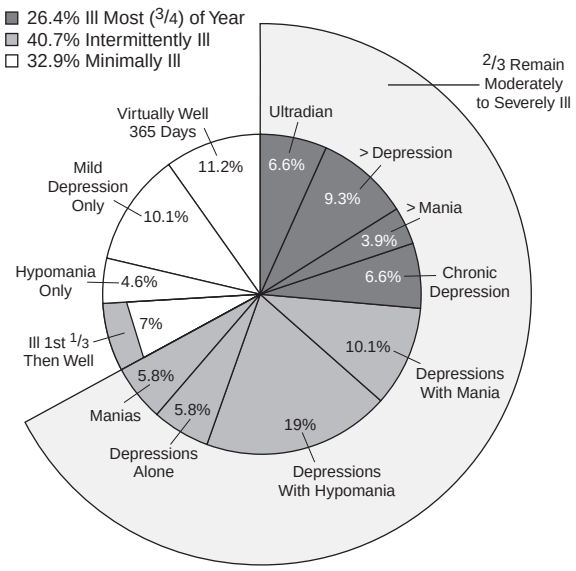
To date, most research has focused on the acute treatment of manic symptoms of bipolar disorder. However, it is now clear that, for a large proportion of patients, depression is the predominant clinical feature of their illness (Figure 1).[6] A large percentage of patients with bipolar disorder may spend at least half of their lives with some degree of depressive symptomatology,[7,8] and approximately 20% of such patients are at increased risk of suicide.[9] In addition, patients experience significant and sustained functional impairment[10,11] even after the symptoms of the acute episodes have resolved. The depressive phase of bipolar disorder is particularly difficult to treat, and the objectives of treatment are not fully met by currently available pharmacotherapies.[12] Patients often receive combination therapy to treat the spectrum of symptoms associated with this illness.

The aim of this article is to review current challenges in the management of bipolar depression and the specific complexities associated with managing certain bipolar subgroups, including those with bipolar I versus bipolar II depression, those with medical and psychiatric comorbidities, and those with a rapid-cycling disease course.

UNDERRECOGNITION AND UNDERDIAGNOSIS OF BIPOLAR DEPRESSION

Since bipolar disorder, and in particular bipolar depression, may be poorly recognized, patients frequently experience a considerable delay before an accurate diagnosis. For a large proportion of patients, the delay before a correct diagnosis is made and appropriate treatment is initiated can be up to 10 years, and as few as one third of patients with

Figure 1. A 12-Month Pattern-of-Illness Study of 258 Patients Receiving Intensive Treatment for Bipolar Disorder[a,b]



[a]Reprinted with permission from Post et al.[6]
[b]Refractory breakthrough depression is a greater problem than mania in the long-term treatment of bipolar disorder, even in patients with bipolar I disorder.

bipolar disorder receive a correct initial diagnosis.[1,4,13] Overlapping symptomatology—particularly with major depressive disorder (unipolar depression)—and comorbidities all confound the diagnostic process. Failure to accurately identify and diagnose patients with bipolar disorder may worsen their long-term prognosis as complications, morbidities, and comorbid psychiatric conditions, such as drug and alcohol abuse, increase. Furthermore, some studies suggest that appropriate mood-stabilizing treatment and psychosocial interventions for bipolar disorder may be less effective in patients who have experienced several untreated or inappropriately treated episodes.[14,15]

It is important to exclude the possibility of a bipolar diagnosis in all patients who present initially with depressive symptoms prior to initiation of unimodal antidepressant monotherapy. There are several signs to be aware of and measures that can be taken by clinicians to improve recognition and diagnosis of bipolar disorder. Table 1 outlines potential distinguishing clinical features of unipolar and bipolar depression.[16] Bipolar depression typically emerges before the age of 25 years, while the onset of unipolar depression generally occurs later in life. A thorough history of symptoms and past responsiveness to antidepressant therapy may also assist the clinician in identifying patients with bipolar depression rather than unipolar depression. A history of treatment resistance or failure, treatment-emergent mania, or activation symptoms should raise suspicion of bipolarity. Table 2 outlines the clinical features that may assist in the diagnostic process and point toward bipolarity in patients initially presenting with depressive symptoms.[16] Routine use of a self-report screening tool, such as the Mood Disorder Questionnaire (MDQ),[17] can also help to identify patients who need a full diagnostic assessment for bipolar disorder, as well as provide education to the patient about the illness. It should be noted, however, that a negative MDQ must still be followed by a full assessment, as patient insight may be limited.

OPTIMIZING PHARMACOTHERAPY FOR BIPOLAR DEPRESSION

Although there is general agreement among current treatment guidelines for bipolar depression, there remain some discrepancies in the recommendations for treating patients in this phase of the illness.[18–22] For patients with severe depressive episodes, the American Psychiatric Association[18] recommends first-line treatment with lithium or lamotrigine, with combination of an antidepressant with a mood stabilizer as a second-line approach if symptoms persist. In contrast, the World Federation of Societies for Biological Psychiatry guidelines recommend an antidepressant and mood stabilizer combination as a first-line approach for all patients with bipolar disorder presenting with an acute depressive episode.[21]

Antidepressant monotherapy is recommended with caution due to the risk of treatment-emergent hypomania or mania and cycle acceleration.[23,24] The coadministration of a traditional mood-stabilizing agent decreases the risk of treatment-emergent mania or cycle acceleration associated with antidepressant use in bipolar disorder[24–26]; however, this does not completely eliminate the risk, and this approach continues to be debated.[27,28] While this approach may be seen as the standard, new data suggest that other options may be effective.

Data showing that several newer agents are useful in the management of bipolar depression have emerged in the past 5 years. A double-blind, placebo-controlled study of the anticonvulsant lamotrigine, given as monotherapy in outpatients with bipolar I depression,[29] resulted in its inclusion in many guidelines as a first-line option for patients with bipolar depression, but with moderate clinical confidence because the evidence is derived from only 1 qualifying clinical study. In 2 later studies, 18 months of maintenance therapy with lamotrigine was shown to be superior to placebo in prolonging time to or delaying intervention for a depressive relapse in recently manic/hypomanic or recently depressed patients, respectively.[30,31] Although lamotrigine had numerical superiority over lithium for this parameter, there was no statistically significant difference between the 2 agents. Currently, lamotrigine is U.S. Food and Drug Administration (FDA) recommended as maintenance therapy for patients with bipolar depression but not for the treatment of acute depressive episodes.

Table 1. Clinical Features That May Distinguish Between Major Depressive Disorder (unipolar depression) and Bipolar Depression[a]

Unipolar Depression	Bipolar Depression
Typically emerges after the age of 25 years	Typically emerges before the age of 25 years
May be preceded by an extended period of gradually worsening symptoms	Episodes may be abrupt in onset (hours or days)
No history of mania or hypomania	Often periodic or seasonal
	Treatment-emergent mania/hypomania during antidepressant monotherapy may be suggestive of bipolarity
	Highly heritable. Bipolar disorder often runs in families, and a thorough family history is a vital diagnostic step
	A history of mania, hypomania, or increased energy and decreased need for sleep

[a]Based on Manning.[16]

Table 2. Clinical Features That May Suggest Bipolarity in Patients Presenting With Depressive Symptoms[a]

Clinical Feature	Explanation
A history of antidepressant failures	Failure to respond to 3 or more adequate trials of unimodal antidepressants
Antidepressant-induced activation	Activation of symptoms such as restlessness, irritability, and insomnia, particularly in patients initially diagnosed with panic disorder or generalized anxiety disorder
Behavioral disruptions	Patients exhibiting disruptive behavioral patterns should be assessed for both bipolar disorder and Axis II personality disorder
History of manic/hypomanic symptoms	Patients presenting with depressive symptoms often fail to recall or recognize periods of mania/hypomania, and input from significant others/caregivers may prove useful. Education directed at helping patients recognize past or current hypomania is important

[a]Based on Manning.[16]

Olanzapine (alone and in combination with fluoxetine) and quetiapine monotherapy have also been shown to improve the depressive symptoms of bipolar disorder.[32–34] The combination of olanzapine and fluoxetine recently became the first strategy to receive FDA approval for the treatment of bipolar I depression. Although olanzapine monotherapy was also superior to placebo in the pivotal trial, the effect was not as robust as that achieved with the olanzapine-fluoxetine combination, and the combination strategy was superior to olanzapine monotherapy for almost all outcomes.[32] Recent evidence also suggests that quetiapine has significantly greater efficacy compared with placebo in the treatment of acute bipolar depression when given as monotherapy.[33,34] The magnitude of effect with quetiapine monotherapy appears to be larger than with olanzapine monotherapy.[32–34]

A considerable research effort is still required to further elucidate the underlying pathology of bipolar depression, and indeed, bipolar disorder, so that the effects of individual agents can be better understood and predicted. Future research in this area may assist clinicians in selecting the most appropriate agent(s) for individual patients. Key challenges for the future include defining which patients are likely to benefit most from which treatments, identifying which symptoms of bipolar depression are improved by the different treatment options (e.g., dimensions of mood, sleep, quality of life), determining whether polypharmacy needs to be considered from the outset, and gaining evidence-based consensus on the appropriate first-line treatment options.

Although no head-to-head trials have yet been performed to compare the newer agents that have shown efficacy in treating bipolar depression, there appear to be important clinical differences between them. Clinical choice is likely to be guided not only by differences in efficacy, but also by differences in tolerability profiles. Given the chronic course of bipolar disorder and the considerable proportion of patients' lives spent experiencing depressive symptoms and receiving treatment, it is essential to define the long-term treatment needs of these patients and reach a consensus as to which pharmacotherapeutic agents offer optimal prophylaxis with minimal side effects.[35]

IMPROVING OUTCOMES IN BIPOLAR DEPRESSION

Patients with bipolar disorder are heterogeneous with respect to symptom profile and severity, clinical course, and psychiatric comorbidity. Thus, treatment has to be individualized and requires consideration of the needs of subgroups of patients with bipolar disorder as well as awareness and appropriate management of the factors that may precipitate acute episodes.

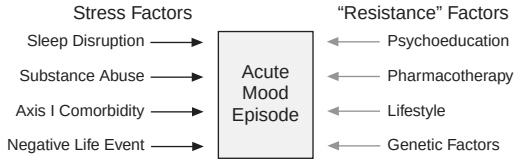
Identification and Management of Life Stressors

In patients with bipolar disorder, stress and negative life-events (e.g., death of relatives, family conflicts) have been linked to symptomatic worsening and episode precipitation (Figure 2),[36–40] particularly precipitation/worsening of depressive symptomatology.[39] Early identification of, and intervention for, basic life stresses that may contribute to symptomatic worsening (e.g., insomnia) is becoming increasingly recognized as a valuable approach to improving long-term outcomes for patients with bipolar disorder.[18]

© Copyright 2005 Physicians Postgraduate Press, Inc.

Psychosocial interventions, such as psychoeducation, are an important component of the integrated package of care and are especially useful in addressing these issues (see Vieta[41]). When a multidisciplinary approach is employed, however, it becomes important to define the clinical point at which to consider amending the prescribed pharmacotherapy (i.e., consider new or additional medications); for example, are there key depressive or manic symptoms that physicians should monitor to determine when intervention is required?[42]

Figure 2. Stressors Known to Impact on Bipolar Symptomatology Versus Current Treatment Options[a]



[a]Based on Hlastala,[38] Christensen et al.,[39] and Kessing et al.[40]

Bipolar I Versus Bipolar II Depression

Patients with bipolar I disorder experience severe acute manic symptoms, while those with bipolar II disorder are more likely to suffer a chronic disease course predominated by depressive symptoms.[43,44] In addition, patients with bipolar I disorder are more likely to be hospitalized during acute mania and experience more psychotic symptoms. Bipolar II patients appear to have shorter periods of euthymia/subsyndromal symptoms between acute episodes than patients with bipolar I disorder as well as more hospitalizations due to depression (Table 3).[43,45] While patients with bipolar I disorder are more likely to experience hypomania, patients with bipolar I or II disorder are equally likely to experience mixed or dysphoric hypomania a greater percent of the time than euphoric mania.[46]

There also appear to be differences between patients with bipolar I and bipolar II depression in terms of response to treatment and sensitivity to treatment-induced side effects, although few controlled studies have examined this discrepancy directly. As patients with bipolar II disorder appear to experience a predominantly depressive course, defining differences in response patterns between patients with bipolar I and II depression as well as identifying the most appropriate long-term treatment strategies for each subgroup are important research needs (Table 4).

Comorbid Symptoms in Bipolar Depression

A significant proportion of patients with bipolar disorder experience comorbid psychiatric conditions during their lifetime, including other Axis I disorders, such as anxiety disorders and alcohol and drug abuse.[47–50] In fact, comorbidity may be the norm within the bipolar population, rather than representing a subgroup of patients.[6,51] Patients with more than 1 comorbid psychiatric diagnosis generally have a poorer long-term prognosis and present a significant treatment challenge, as appropriate treatment for one disorder may exacerbate the symptoms of the comorbid condition.[51]

Bipolar depression with comorbid symptoms and disorders can often be more challenging to treat and manage over the long term.[47,48,51] Anxiety disorders and substance abuse disorders are the most frequently encountered comorbidities. Developing appropriate treatment strategies to optimize outcomes for patients with comorbid symptoms and disorders is a major clinical challenge for the future. For example, unimodal antidepressants are often used in the treatment of anxiety disorders, but it is recommended that patients with bipolar depression who are taking antidepressants be monitored due to the increased risk of treatment-emergent mania and cycle acceleration. Studies targeted at defining the most appropriate treatment strategies in patients with common comorbidities are currently lacking and are urgently needed given the high prevalence of comorbidities among patients with bipolar disorder (Table 4).

Gender Differences

There are clinically relevant differences between men and women in the presentation, symptom expression, comorbidities, and course of bipolar disorder.[46,49,52,53] Bipolar II disorder is more common in women.[44,54] Female patients with bipolar disorder appear to have a greater risk for depressive episodes and symptomatology as well as mixed or dysphoric hypomania.[46,53] Women may also be more susceptible to a rapid-cycling course of illness[52,55,56] and more sensitive than men to the negative effects of stressful life events, making them more susceptible to symptomatic relapse.[39] Moreover, life events unique to women, including pregnancy, menstruation, lactation, and menopause, all present additional challenges in the management of women with bipolar disorder.

At present, there is little evidence to suggest that gender affects response to treatment with mood stabilizers. However, given that women are more likely to follow a depressive course of illness and experience more periods of mixed hypomania, there is a need to determine differential treatment response in men and women with the newer agents for the treatment of bipolar depression. Identifying and understanding these differences between men and women should help guide treatment and long-term management strategies (Table 4).

The Rapid-Cycling Patient

Patients with rapid cycling generally have a poorer response to pharmacotherapy, particularly lithium.[57,58] These patients also appear to experience more severe and more frequent depressive episodes.[57,59,60] Controlled trials

Table 3. Clinical Differences Between Bipolar I and Bipolar II Disorder[a]

Clinical Feature	Bipolar I	Bipolar II
Symptom profile	More severe symptoms Hospitalization due to mania	Less severe acute symptoms Depressive symptoms likely to predominate Hospitalization due to depression
Clinical course	More likely to experience hypomania	More chronic course with more episodes of longer duration
Comorbidity	More comorbidities than the general population	More comorbidities than the general population May be more likely to experience comorbid anxiety
Switching frequency	May be less frequent than bipolar II	May be more frequent than bipolar I

[a]Based on Judd et al.[43] and Vieta et al.[45]

Table 4. Challenges in the Management of Bipolar Subgroups—Considerations for Future Research

- Bipolar I Versus Bipolar II
  - Are patients with bipolar II disorder more sensitive to treatment side effects than patients with bipolar I disorder?
  - Does the predominating depression in patients with bipolar II disorder affect willingness to tolerate side effects?
  - What should be the first-line treatment for patients with bipolar II disorder?
  - How often is cotherapy needed, and should initial monotherapy studies allow add-on continuation phases to address this issue?
- Treatment of Patients With Bipolar Disorder and Comorbid Disorders
  - What are the preferred pharmacotherapeutic choices for patients with different comorbid conditions, given that appropriate treatment for one disorder may exacerbate the symptoms of a comorbid condition?
- Treatment of Men and Women With Bipolar Disorder
  - Are women with bipolar disorder more sensitive to certain treatment side effects, such as weight gain?
  - Are women more susceptible to a rapid-cycling course of illness, and if so, what implications does this susceptibility have on treatment choices, if any?
  - If women are more likely to follow a depressive course of illness, is there a differential treatment response between men and women using the newer agents emerging for the treatment of bipolar depression?
  - Are gender differences between men and women with bipolar disorder culturally determined or truly international?

to guide treatment choice for patients with rapid-cycling bipolar depression are limited, and there is a pressing need to define treatment strategies that address depressive symptoms.[57] Quetiapine monotherapy has demonstrated efficacy in improving symptoms in patients with rapid-cycling bipolar I and II depression in a large, controlled clinical trial,[61] but further large studies with this and other agents are needed to confirm treatment effects in this population.

CONCLUSION

Despite the predominance of, link to increased risk of suicide with, and resulting considerable functional impairment from depressive symptoms in bipolar disorder, their characteristics and treatment have not been as well studied as those of the manic phase of this illness. Important issues that remain unresolved include the recognition of the core features of bipolar depression and the threshold symptoms for treatment, optimal treatment choices for monotherapy or combination therapy, and optimal treatment for acute and long-term management.

Olanzapine in combination with fluoxetine is a new strategy recently added to the range of treatment options for the acute treatment of bipolar depression, although no head-to-head trials with the more conventional treatment approaches have yet been performed. There is now also promising evidence that quetiapine monotherapy may be efficacious in treating acute bipolar depression. Further study of the risks and benefits of using an antimanic and antidepressant combination, in comparison to lithium and newer agents and anticonvulsants, is still needed.

An integrated approach combining pharmacotherapy and management of life stressors and underlying trigger factors through psychosocial intervention is important in the improvement of long-term outcomes for patients with bipolar depression as well as acute treatment to improve symptoms and minimize suicidal impulses. Future studies of acute and long-term treatment of bipolar depression should focus not only on bipolar I disorder but also bipolar II disorder and on patients with rapid cycling and comorbid conditions. Understanding the characteristics and treatment response profiles of these subgroups of patients with bipolar depression, and taking into account individual patient histories, preferences, and likely treatment durations, will assist clinicians in developing appropriate management strategies.

Drug names: lamotrigine (Lamictal), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), olanzapine-fluoxetine (Symbyax), quetiapine (Seroquel).

REFERENCES

1. Hirschfeld RMA, Calabrese JR, Weissman MM, et al. Screening for bipolar disorder in the community. J Clin Psychiatry 2003;64:53–59
2. Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse: results from the Epidemiologic Catchment Area (ECA) Study. JAMA 1990;264:2511–2518
3. Regeer EJ, ten Have M, Rosso ML, et al. Prevalence of bipolar disorder in the general population: a Reappraisal Study of the Netherlands Mental Health Survey and Incidence Study. Acta Psychiatr Scand 2004;110: 374–382
4. Suppes T, Leverich GS, Keck PE, et al. The Stanley Foundation Bipolar Treatment Outcome Network: demographics and illness characteristics of the first 261 patients. J Affect Disord 2001;67:45–49
5. Hirschfeld RMA, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar

disorder. J Clin Psychiatry 2003;64:161–174
6. Post RM, Leverich GS, Altshuler LL, et al. An overview of recent findings of the Stanley Foundations Bipolar Network, pt 1. Bipolar Disord 2003;5:310–319
7. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002;59:530–537
8. Judd LL, Akiskal HS, Schettler PJ, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry 2003;60:261–269
9. Simpson SG, Jamison KR. The risk of suicide in patients with bipolar disorders. J Clin Psychiatry 1999;60(suppl 2):53–56
10. Altshuler LL, Gitlin MJ, Mintz J, et al. Subsyndromal depression is associated with functional impairment in patients with bipolar disorder. J Clin Psychiatry 2002;63:807–811
11. Calabrese JR, Hirschfeld RMA, Reed M, et al. Impact of bipolar disorder on a US community sample. J Clin Psychiatry 2003;64:425–432
12. Hlastala SA, Frank E, Mallinger AG, et al. Bipolar depression: an underestimated treatment challenge. Depress Anxiety 1997;5:73–83
13. Dunner DL. Clinical consequences of under-recognized bipolar spectrum disorder. Bipolar Disord 2003;5:456–463
14. Post RM. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. Am J Psychiatry 1992;149:999–1010
15. Swann AC, Bowden CL, Morris D, et al. Depression during mania: treatment response to lithium or divalproex. Arch Gen Psychiatry 1997;54: 37–42
16. Manning JS. Bipolar disorder in primary care. Curr Psychiatry 2003; (suppl):6–9
17. Hirschfeld RMA, Williams JB, Spitzer RL, et al. Development and validation of a screening instrument for bipolar disorder: the Mood Disorder Questionnaire. Am J Psychiatry 2000;157:1873–1875
18. American Psychiatric Association. Practice Guidelines for the Treatment of Patients With Bipolar Disorder [Revision]. Am J Psychiatry 2002;159 (suppl 4):1–50
19. Suppes T, Dennehy EB, Swann AC. Report of the Texas Consensus Conference Panel on Medication Treatment of Bipolar Disorder 2000. J Clin Psychiatry 2002;63:288–299
20. Goodwin GM, Young AH. The British Association for Psychopharmacology guidelines for treatment of bipolar disorder: a summary. J Psychopharmacol 2003;17:3–6
21. Grunze H, Kasper S, Goodwin G, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of bipolar disorders, pt 2: treatment of bipolar depression. World J Biol Psychiatry 2002;3:115–124
22. Keck PE, Perlis RH, Otto MW, et al. The Expert Consensus Guideline Series: Treatment of Bipolar Disorder 2004. Postgrad Med 2004:1–122
23. Altshuler LL, Post RM, Leverich GS, et al. Antidepressant-induced manic and cyclic acceleration: a controversy revisited. Am J Psychiatry 1995;152: 1130–1138
24. Goldberg JF, Truman CJ. Antidepressant-induced mania: an overview of current controversies. Bipolar Disord 2003;5:407–420
25. Baldessarini RJ, Tondo L, Hennen J, et al. Is lithium still worth using? an update of selected recent research. Harv Rev Psychiatry 2002;10:59–75
26. Thase ME, Sachs GS. Bipolar depression: pharmacotherapy and related therapeutic strategies. Biol Psychiatry 2000;48:558–572
27. Ghaemi SN, Sachs GS, Goodwin FK. What is to be done? controversies in the diagnosis and treatment of manic-depressive illness. World J Biol Psychiatry 2000;1:65–74
28. Grunze H. Reevaluating therapies for bipolar depression. J Clin Psychiatry 2005;66(suppl 5):17–25
29. Calabrese JR, Bowden CL, Sachs GS, et al. A double-blind, placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression. J Clin Psychiatry 1999;60:79–88
30. Bowden CL, Calabrese JR, Sachs G, et al. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently manic or hypomanic patients with bipolar I disorder. Arch Gen Psychiatry 2003;60: 392–400
31. Calabrese JR, Bowden CL, Sachs G, et al, for the Lamictal 605 Study Group. A placebo-controlled 18-month trial of lamotrigine and lithium maintenance treatment in recently depressed patients with bipolar I disorder [Comment in: Evid Based Ment Health 2004;7:48]. J Clin Psychiatry 2003;64:1013–1024
32. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry 2003;60:1079–1088
33. Calabrese JR, Keck PE Jr, MacFadden W, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. Am J Psychiatry. In press
34. Calabrese JR, Elhaj O, Gajwani P, et al. Clinical highlights in bipolar depression: focus on atypical antipsychotics. J Clin Psychiatry 2005; 66(suppl 5):26–33
35. Suppes T, Dennehy EB, Hirschfeld RMA, et al. The Texas Implementation of Medication Algorithms: update to the algorithms for treatment of bipolar I disorder. J Clin Psychiatry. In press
36. Hammen C, Gitlin M. Stress reactivity in bipolar patients and its relation to prior history of disorder. Am J Psychiatry 1997;154:856–857
37. Hlastala SA, Frank E, Kowalski J, et al. Stressful life events, bipolar disorder, and the "kindling model." J Abnormal Psychol 2000;109:777–786
38. Hlastala SA. Stress, social rhythms, and behavioral activation: psychosocial factors and the bipolar illness course. Curr Psychiatry Rep 2003;5:477–483
39. Christensen EM, Gjerris A, Larsen JK, et al. Life events and onset of a new phase in bipolar affective disorder. Bipolar Disord 2003;5:356–361
40. Kessing LV, Agerbo E, Mortensen PB. Major stressful life events and other risk factors for first admission with mania. Bipolar Disord 2004;6:122–129
41. Vieta E. The package of care for patients with bipolar depression. J Clin Psychiatry 2005;66(suppl 5):34–39
42. Calabrese JR, Vieta E, El-Mallakj R, et al. Mood state at study entry as predictor of risk of relapse and spectrum of efficacy in bipolar maintenance studies. Biol Psychiatry 2004;56:857–873
43. Judd LL, Akiskal HS, Schettler PJ, et al. The comparative clinical phenotype and long term longitudinal episode course of bipolar I and II: a clinical spectrum or distinct disorders? J Affect Disord 2003;73:19–32
44. Suppes T, Dennehy EB. Evidence-based long-term treatment of bipolar II disorder. J Clin Psychiatry 2002;63(suppl 10):29–33
45. Vieta E, Gasto C, Otero A, et al. Differential features between bipolar I and bipolar II disorder. Compr Psychiatry 1997;38:98–101
46. Suppes T, Mintz J, McElroy SL, et al. Mixed hypomania in 908 patients with bipolar disorder evaluated prospectively in the Stanley Bipolar Treatment Network: a gender-specific phenomenon. Arch Gen Psychiatry. In press
47. Freeman MP, Freeman SA, McElroy SL. The comorbidity of bipolar and anxiety disorders: prevalence, psychobiology, and treatment issues. J Affect Disord 2002;68:1–23
48. Henry C, Van den Bulke D, Bellivier F, et al. Anxiety disorders in 318 bipolar patients: prevalence and impact on illness severity and response to mood stabilizer. J Clin Psychiatry 2003;64:331–335
49. Frye MA, Altshuler LL, McElroy SL, et al. Gender differences in prevalence, risk, and clinical correlates of alcoholism comorbidity in bipolar disorder. Am J Psychiatry 2003;160:883–889
50. McElroy SL, Altshuler LL, Suppes T, et al. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. Am J Psychiatry 2001;158:420–426
51. Sasson Y, Chopra M, Harrari E, et al. Bipolar comorbidity: from diagnostic dilemmas to therapeutic challenge. Int J Neuropsychopharmacol 2003;6: 139–144
52. Hendrick V, Altshuler LL, Gitlin MJ, et al. Gender and bipolar illness. J Clin Psychiatry 2000;61:393–396
53. Arnold LM. Gender differences in bipolar disorder. Psychiatr Clin North Am 2003;26:595–620
54. Benazzi F. Gender differences in bipolar II and unipolar depressed outpatients: a 557-case study. Ann Clin Psychiatry 1999;11:55–59
55. Coryell W, Endicott J, Keller M. Rapid cycling affective disorder: demographics, diagnosis, family history, and course. Arch Gen Psychiatry 1992;49:126–131
56. Tondo L, Baldessarini RJ. Rapid cycling in women and men with bipolar manic-depressive disorders. Am J Psychiatry 1998;155:1434–1436
57. Calabrese JR, Shelton MD, Bowden CL, et al. Bipolar rapid cycling: focus on depression as its hallmark. J Clin Psychiatry 2001;62(suppl 14):34–41
58. Grunze H, Amann B, Dittmann S, et al. Clinical relevance and treatment possibilities of bipolar rapid cycling. Neuropsychobiology 2002;45 (suppl 1):20–26
59. Calabrese JR, Shelton MD, Rapport DJ, et al. A 20-month, double-blind, maintenance trial of lithium vs divalproex in rapid-cycling bipolar disorder. Am J Psychiatry. In press
60. Coryell W, Solomon D, Turvey C, et al. The long-term course of rapid-cycling bipolar disorder. Arch Gen Psychiatry 2003;60:914–920
61. Vieta E, Calabrese JR, Macfadden W, et al. Quetiapine for the treatment of rapid-cycling bipolar depression [abstract]. Acta Psychiatr Scand 2004; 110(suppl):41