Bipolar disorder: Current treatments and new strategies

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Bipolar disorder is a complex, potentially lethal, chronic disease. The diversity of its symptoms presents clinicians with an ongoing challenge to make the correct diagnosis, to successfully manage the acute episodes, and to decide on a course for prophylaxis. Lithium, the first effective drug for bipolar disorder, is still considered the drug of choice for treatment of the acute phase and for maintenance. Although lithium has been the mainstay of bipolar treatment for half a century, the problem of managing many bipolar patients is unresolved, and other therapeutic agents are being investigated.

This paper will review issues concerning the diagnosis and epidemiology of bipolar disorder, discuss the unique problems of treating bipolar patients, and address the question of why lithium has not been working for many of them. It will analyze recent studies on the efficacy of anticonvulsants in the treatment of bipolar disorder and evaluate their use in prophylaxis and as mood stabilizers.

BIPOLAR DISORDER

Clinical presentation

Bipolar disorder, also known as manic depression, is characterized by recurrent periods of abnormal mood elevation alternating with periods of depression. During manic periods of euphoria and agitation, patients may display impaired judgment and irresponsible and frenzied behavior that is possibly injurious to themselves and others.[1] Each phase lasts from days to weeks. Rapid cycling individuals have at least 4 episodes of mood disturbances in a 12-month period. Some patients may suffer from mixed episodes, presenting simultaneously with both depression and mania.[1] The Massachusetts General Hospital (MGH) Bipolar Clinic defines continually cycling patients as those who go from one phase to another three or more times in a month without intermittent periods of euthymia.

Individuals with bipolar disorder can be a risk to themselves and to society. They are prone to child abuse and spousal abuse, and 10% to 15% of patients commit suicide. Other associated problems include school failure, occupational failure, divorce, and substance abuse.[1] The multiplicity of symptoms presented by bipolar patients complicates the process of diagnosis and the charting of treatment.

Epidemiology

Many symptoms characteristic of bipolar illness, like grandiose and persecutory delusions, impulsivity, and irritability are common to those observed in other psychotic disorders.[1] Therefore, cases of bipolar disorder are underdetected, with reported prevalence rates varying: 0.46% in the Old Order Amish Study,[2] 0.7% to 1.6% in a study of five communities,[3] and 0.9% to 2.1% reported in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM).[1] In addition, Weissman et al[3] reported no significant gender differences in either the prevalence or the age of onset of bipolar disorder.

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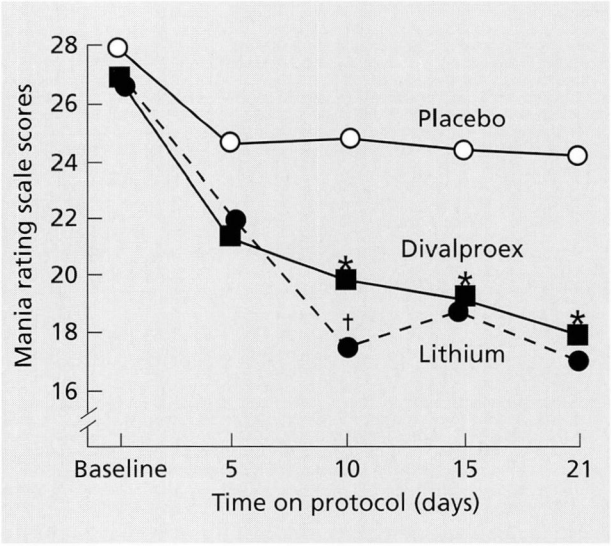

FIGURE 1. Changes from baseline to final evaluation in Mania Rating scale score, Schedule for Affective Disorders and Schizophrenia. Numbers on the vertical axis indicate the sum of all items on this subscale of the SADS-C. Asterisks and dagger indicate time points at which a significant difference ($P < .05$) was observed between divalproex and lithium, respectively, and placebo. Adapted from Bowden et al, 1994.[10]

Issues facing psychiatrists

Left untreated, bipolar disorder is dangerous for patients and for society. However, millions of bipolar patients receive no mental health care.[4] One approach for improving public health is to increase diagnosis and ensure that patients stay with treatment.

The major goal of treatment is to induce and sustain remission. Although the objective is the same as for any other mental disorder, treatment of bipolar disorder presents a unique set of problems. Effective treatment addresses both acute mania and acute depression and attempts to prevent both from recurring. A need for acute treatment may compete with a long-range goal of minimizing exposure to cycle-promoting agents. Treatment of a manic episode with antimanic agents may increase the risk of treatment-emergent depression. Treatment of a major depressive episode with antidepressants may induce mania.

LITHIUM TREATMENT

The use of lithium for the treatment of depression goes back to the 1880s. Lithium fell into disrepute because of toxicity associated with its misuse, but it was rediscovered by Cade in 1949 as an effective treatment for acute mania. Lithium was extensively used in Europe in the 1950s and 1960s.[5] In the United States, lithium was approved by the FDA as treatment for acute mania only in 1970, on the strength of placebo-controlled clinical studies demonstrating its efficacy.[6] In 1974 the FDA approved lithium as a maintenance drug for bipolar disorder.[7] In 1985 the NIH/NIMH Consensus Development Panel[8] recommended lithium as the drug of choice in the prevention of recurrent bipolar disorder, and the Expert Consensus Guidelines suggested lithium as the only first-line antidepressant to be used as a mood stabilizer in monotherapy.[9] Taking note of recent reports casting doubt on the efficacy of lithium as an antidepressant, the Expert Consensus Guidelines note that other mood stabilizers are even weaker.[9]

Efficacy for mania patients

More recent data suggest that the problem of treating bipolar patients has not been solved by the use of lithium. Bowden et al compared the efficacy of divalproex versus lithium and placebo in hospitalized, acutely manic patients in a randomized, double-blind, parallel-group study.[10] As shown in *Figure 1*, there was a significant improvement at 21 days for patients receiving either lithium or divalproex compared with patients receiving placebo. By the end of 21 days, patients' average score on the mania rating scale was 16. However, patients entering into the study were required to have a washout score of at least 14.[10] This indicates that after 21 days of treatment, they still were considered ill enough to enter the study.[10] Thus, although lithium and divalproex were efficacious, the benefit patients derived from them was not sufficient.

Prophylactic efficacy

A number of prospective studies suggest that the majority of bipolar patients do not benefit from the prophylactic agents in current use.

In a double-blind, multicenter, long-term follow-up study, the NIMH collaborative study group evaluated the prophylactic effects of lithium and imipramine in 117 bipolar patients.[11] Only 33% of patients receiving lithium monotherapy remained well for the 2-year duration of the study.[11] A 1-year follow-up study with patients receiving lithium

monotherapy in our MGH Bipolar Clinic showed that only 4% of patients remained well for the entire year. In addition, similar results were obtained in an evaluation of patients in private practice, ruling out the possibility that the poor outcome in the clinic was because the clinic patients were more seriously ill.[12]

Gitlin et al[13] noted that naturalistic studies of populations treated for bipolar disorder suggest greater morbidity and less evidence for successful prophylaxis with mood stabilizers than do earlier control studies. For a mean of 4.3 years, Gitlin et al prospectively followed 82 bipolar patients who were prescribed mood stabilizers in an uncontrolled manner in order to evaluate the efficacy of mood stabilizers in a clinic setting.[13] Analysis of the data showed 37% probability that a manic or depressive episode would occur within 1 year, 55% likelihood of a relapse within 2 years, and 73% chance of relapse within 5 years. Moreover, more than 70% of the patients who relapsed had multiple episodes.[13]

In a 5-year prospective study, Maj et al[14] interviewed 359 bipolar patients given lithium prophylaxis. Of the 247 patients still taking lithium at the 5-year follow-up, 15.4% showed no improvement, 46.6% had partial improvement, and 38.1% had no recurrence of a major depressive or manic episode. However, more than one third of this group had a subsyndromal affective morbidity during the treatment period. Only 14.2% of the patients evaluated had no affective morbidity.[14]

The contradictory results of early placebo-controlled studies of lithium and the more recent open studies, as well as evidence that divalproex alleviates acute mania, stimulated Bowden et al to design a 1-year outcome study comparing the effects of prophylactic treatment with lithium, divalproex, and placebo in bipolar patients.[15] Patients who had a manic episode within 3 months of randomization and had achieved remission within 3 months of enrollment, with or without any open treatment indicated by their physicians, were enrolled in this randomized, double-blind, parallel-group study.[15]

By the end of 1 year, 24% of patients on divalproex, 33% on lithium, and 39% on placebo suffered either mania or depression. These differences were not significant. Occurrence of mania alone was not significantly different among groups either; mania occurred in 18%, 22%, and 23% of the enrollees on divalproex, lithium, and placebo groups, respectively. Divalproex (6%) had a better prophylactic effect than lithium (10%) and placebo (17%) only in depression.[16] The high dose of lithium prescribed (1.0 ± 0.48 mmol/L) may account for the increased level of depression in the lithium group.

Taken together, the naturalistic and the controlled studies suggest that prophylactic medication is helpful for only 4% to 33% of bipolar patients.

Noncompliance

A major problem in lithium treatment is noncompliance, some of which is related to the perceived toxicity of lithium.[5] Although the prescribed doses are not toxic, the gap between the therapeutic and the toxic doses of lithium is the narrowest of any drug prescribed to psychiatric patients, and an overdose could cause severe damage.[10] The noncompliance rate in outpatients ranges from 12% to 60%.[17] Maj et al[14] found that 112 of 359 (31%) patients in longitudinal studies stopped taking lithium, and 85% of these did so on their own.

The most discouraging report on noncompliance in the use of lithium is the 6-year longitudinal cohort study by Johnson and McFarland of 1,594 patients enrolled for 6 months in a health maintenance organization (HMO).[18] Seventy-four patients in a random sample of the large group took lithium for an average of 34% of the days they were enrolled in the HMO, and only 8% of the patients were using it for 90% of their days of eligibility.[18] Reasons for noncompliance include uncomfortable side effects, stigma, patients' beliefs that they are well, and beliefs that treatment is unhelpful.[14,17]

Nonresponding patients

Patients who discontinue treatment with lithium because they feel well often relapse. Their sense of well-being may, in fact, be the prodrome: hypomania before mania. Rather than increase the lithium dose, which may exacerbate deterioration and drive compliance further down, clinicians should consider the possibility that these patients do not respond to lithium. The use of lithium adjuncts or substitutes should be considered.

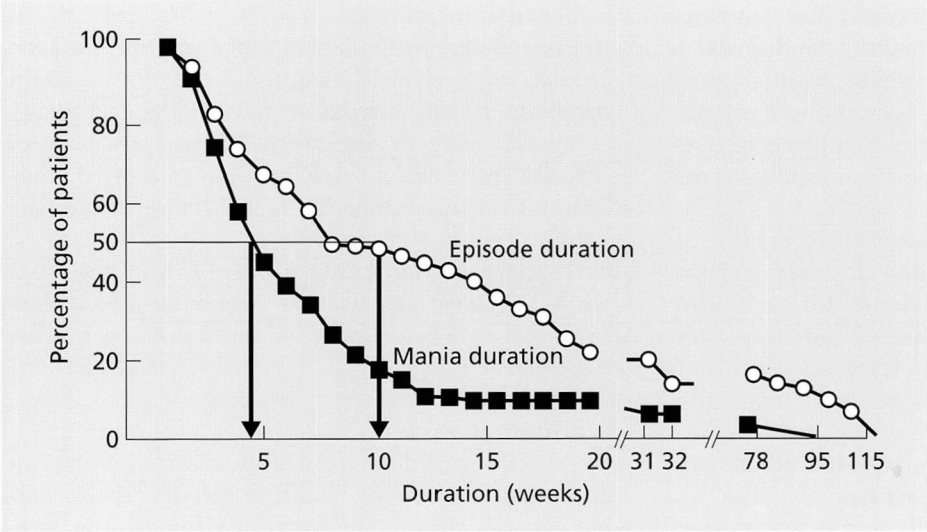

FIGURE 2. Duration of manic phases and episodes in bipolar patients at Massachusetts General Hospital Bipolar Clinic.

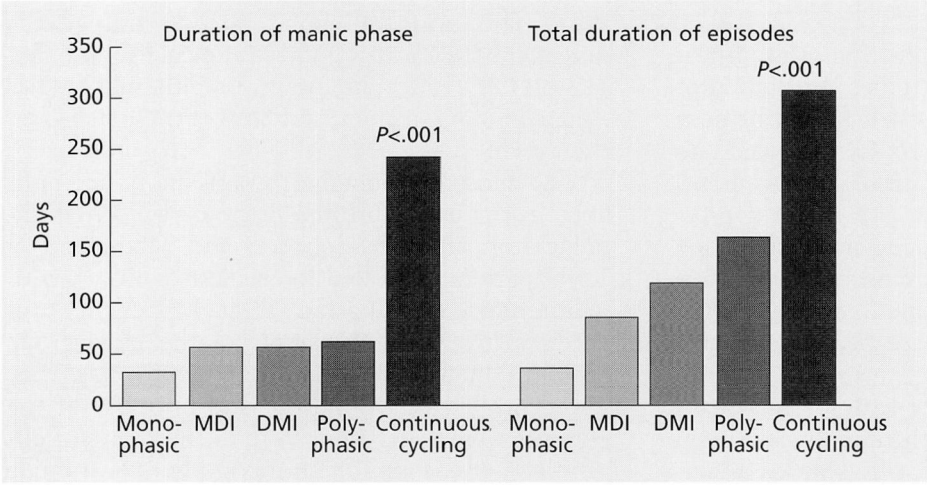

FIGURE 3. Episode pattern influence on episode duration. MDI = mania phase followed by depression, and interval of well-being; DMI = depression phase followed by mania, and interval of well-being. *P* values indicate difference between continuous cycling and any of the other four patterns.

The data from our MGH Bipolar Clinic (*Figure 2*) clearly illustrate the problems clinicians face. The manic phase in 50% of our patients persists for fewer than 5 weeks. Here, good outcome reflects good treatment. However, many of these patients suffer a relapse within a year. On the other hand, 15% to 20% of the episodes persist for 1 to 2 years. What can we do for these individuals?

Pattern of episodes as an indicator of treatment outcome

Dunner and Fieve[19] observed that bipolar patients on lithium prophylaxis with at least four affective episodes in a year (rapid cyclers) had a disproportionately high rate of relapse. Although the rate of treatment failure was 41% in nonrapid cyclers (18/44), the rate of relapse in the rapid cyclers was 82% (9/11).[19]

In our bipolar clinic at MGH we found correlations between the pattern of episodes, the duration of episodes (*Figure 3*), and the prognosis. Some groups of patients tend to have good prognoses—people who have monophasic episodes of mania, people with biphasic episodes that start high and go to depression (MDI) or begin with depression and go to mania (DMI), and people who have a chain of phases lasting at least 2 weeks each. The episodes of individuals who are continuously cycling last significantly longer ($P < .001$) than the episodes in patients presenting with any of the other four patterns. The prognosis for continuously cycling patients is not good. As soon as we identify such a pattern, we immediately follow our treatment algorithm and add other medications.[20]

As psychiatrists, we are faced with a great challenge: How can we help our bipolar patients who do not respond to lithium or divalproex? Antidepressants are often a poor option. Ideally, we would like to use mood stabilizers.

MOOD STABILIZERS

I would like to present a definition for what a mood stabilizer should be. A mood stabilizer should be efficacious for one or more of the primary therapeutic objectives in treating bipolar patients:

- Treating acute mania
- Treating acute depression
- Prophylaxis.

When administered during any phase of the illness, a mood stabilizer:

- Should not make the patient acutely worse
- Should not increase the switch rate between phases.

Agreeing on a definition for a mood stabilizer still does not help us in our quest for the ideal treatment. As much as we like to practice polypharmacy, not much data are present to tell us which drugs are mood stabilizers. The published guidelines in the *Journal of Clinical Psychiatry*[9] and our own guideline[20] show an approximate 93% agreement about how to manage acute mania, mixed, hypomanic episodes, depression, and continued maintenance.[9]

The agreed-upon primary mood stabilizing agents include lithium, divalproex, carbamazepine, and bilateral electroconvulsive therapy. The recommended adjunctives include thyroxine, clonazepam, lorazepam, and psychotherapy.[20] However, we do not have a clear guideline for treating refractory bipolar patients.

TREATMENT OF REFRACTORY BIPOLAR PATIENTS

Lamotrigine and gabapentin are two of the most recent anticonvulsants under investigation for their efficacy in treating refractory bipolar patients. Studies indicate that lamotrigine may be a useful antidepressant and that gabapentin may be beneficial for treating mania. Early studies on topiramate suggest that it may have some antimanic effects.

Lamotrigine

In a double-blind, placebo-controlled study, we evaluated the effect of 50-mg and 200-mg lamotrigine monotherapy in depressed bipolar patients. As demonstrated in *Figure 4*, the groups receiving lamotrigine did better than the placebo group, with those taking 200 mg doing the best.[21] Our data suggest that lamotrigine offers useful therapy for depressed bipolar

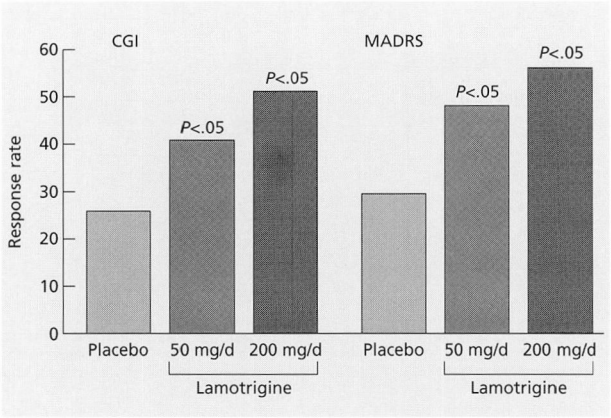

FIGURE 4. The response rate of depressive bipolar patients to monotherapy treatment with lamotrigine and placebo treatment in a double-blind, placebo-controlled study. Patients were evaluated on: Clinical Global Impression (CGI) and Montgomery-Asberg Depression Rating Scale (MADRS).

patients. However, more subjects in the 200-mg lamotrigine group switched from depression to mania than those taking placebo. Thus, while this study suggests that lamotrigine may be an effective antidepressant, the data shed doubt on its efficacy as a mood stabilizer.

An intriguing aspect of this study was the observation that side effects were reported by 92% of the placebo group, compared with only 76% of the lamotrigine patients. There was no difference between the control group and the experimental group in incidence of rash.

Dosing at Massachusetts General Hospital. Our dosing of lamotrigine differs from the recommended dosing in the *Physicians' Desk Reference* (PDR) (*Figure 5*).[22] Patients who are not taking divalproex or carbamazepine begin with a daily dose of 25 mg lamotrigine the first week and increase their dose weekly in increments of 25 mg until they reach 100 mg per day. Thereafter, we increase the dose from 25 to 50 mg on alternate weeks. We usually end up with a daily dose of 75 to 250 mg lamotrigine. Although the PDR recommends starting lamotrigine at 50 mg per day when used with an enzyme inducer,[22] we prefer starting with the lower dose because of the severe, potentially life-threatening rashes that have been associated with lamotrigine use. Potential risk factors for rashes include young age (lamotrigine is not approved for use in patients under 16 years), starting with a high dose, and fast rate of titration.[22]

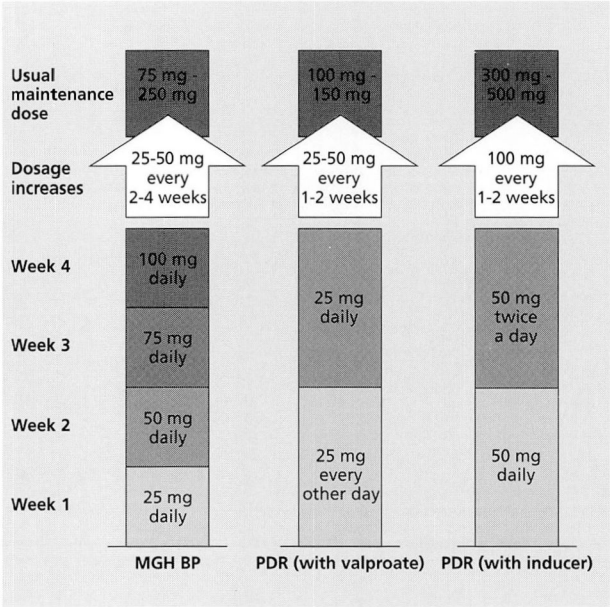

FIGURE 5. Lamotrigine dosing at Massachusetts General Hospital Bipolar Clinic (MGH BP), and the dosing suggested in the *Physicians' Desk Reference* (PDR).[22]

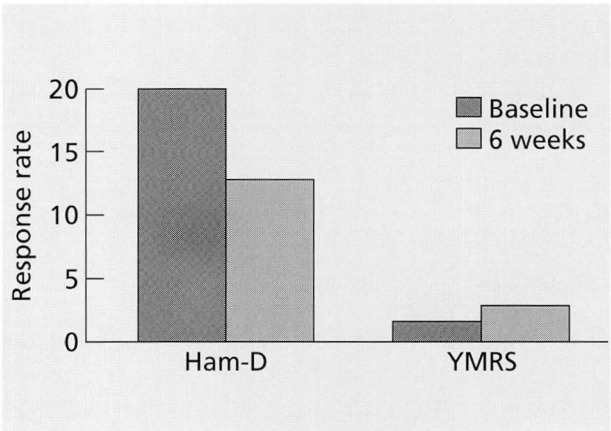

FIGURE 6. Gabapentin open treatment of refractory, depressed patients with bipolar disorder (N = 30). For 6 weeks, individuals received daily 1000 to 2000 mg gabapentin. HamD = Hamilton Depression scale; YMRS = Young Mania Rating Scale. After Young LT,[23] with permission.

Gabapentin

In an open trial, Young[23] gave gabapentin as adjunctive therapy to refractory patients suffering from bipolar depression. The participants received oral doses twice or three times a day, with the target dose between 1000 and 2000 mg. The mean dose was 1000 to 2000 mg.[23] After 6 weeks (*Figure* 6), the patients showed a significant decrease in Hamilton Depression Scale (HamD) scores but no clinically significant change in Young Mania Rating Scale (YMRS) scores. This suggests that gabapentin may be an effective treatment for mania in bipolar patients.

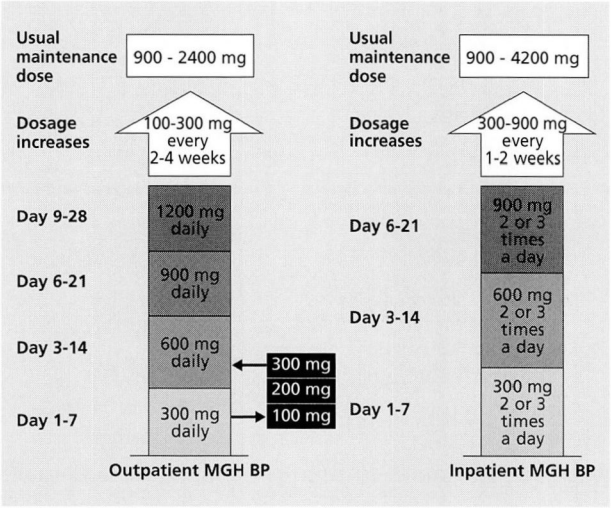

FIGURE 7. Gabapentin dosing of outpatients and inpatients at Massachusetts General Hospital Bipolar Clinic (MGH BP). qd = every day; bid = twice a day; tid = three times a day.

Dosing at Massachusetts General Hospital. We treat manic patients with gabapentin. Our goal in treating outpatients with gabapentin is usually improving their sleep patterns and reducing their agitation. Our inpatients are usually treatment-refractory manic patients, and we try to bring their agitation under control. We start outpatients on 300 mg per day; if a patient cannot tolerate 300 mg, we cut back to 100 mg per day and then slowly increase the dose to the recommended effective dose of 900 mg per day to 1800 mg per day (*Figure 7*).[24] Inpatients are treated more aggressively, starting with 300 mg two or three times a day. We increase the dose until we bring the agitation under control.

Topiramate

Open treatment of acute manic patients with topiramate did not change their depression score.[25] There was, however, some drop in the average mania score in individuals treated with doses up to 1600 mg per day.

Major side effects of topiramate are somnolence and fatigue.[26] In general, patients initially thrive on topiramate. Within 2 to 3 weeks, however, many

report severe fatigue and psychomotor retardation. Thus, using this drug can be challenging.

In conclusion, the recently available anticonvulsants lamotrigine and gabapentin seem to be useful in treating both depression and mania in some treatment-resistant patients. However, it is too early to predict whether either of them will be a good mood stabilizer.

REFERENCES

1. **American Psychiatric Association.** Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994;350–362.
2. **Egeland JA.** Bipolarity: the iceberg of affective disorders? Compr Psychiatry 1983; 24:337–344.
3. **Weissman MM, Leaf PJ, Tischler GL, Blazer DG, Karno M, Bruce ML, et al.** Affective disorders in five United States communities. Psychol Med 1988;18:141–153.
4. **Regier DA, Narrow WE, Rae DS, Manderscheid RW, Locke BZ, Goodwin FK.** The de facto US mental and addictive disorders service system. Epidemiologic catchment area prospective 1-year prevalence rates of disorders and services. Arch Gen Psychiatry 1993; 50:85–94.
5. **Lenox RH, McNamara RK, Papke RL, Manji HK.** Neurobiology of lithium: an update. J Clin Psychiatry 1998; 59(suppl 6):37–47.
6. **Bowden CL.** Key treatment studies of lithium in manic-depressive illness: efficacy and side effects. J Clin Psychiatry 1998;59(suppl 6):13–19.
7. **Jefferson JW, Greist JH, Ackerman DL, Carroll JA.** Lithium encyclopedia for clinical practice. 2nd edition. Washington, DC: American Psychiatric Press, Inc; 1987:2.
8. **Consensus Development Panel.** Mood disorders: pharmacologic prevention of recurrences. Am J Psychiatry 1985; 142:469–476.
9. **Frances AJ, Kahn DA, Carpenter D, Docherty JP, Donovan SL.** The expert consensus guidelines for treating depression in bipolar disorder. J Clin Psychiatry 1998; 59(suppl 4):73–79.
10. **Bowden CL, Brugger AM, Swann AC, Calabrese JR, Janicak PG, Petty F, et al.** Efficacy of divalproex vs lithium and placebo in the treatment of mania. JAMA 1994; 271:918–924.
11. **Prien RF, Kupfer DJ, Mansky PA, Small JG, Tuason VB, Voss CB, et al.** Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. Report of the NIMH Collaborative Study Group comparing lithium carbonate, imipramine, and a lithium carbonate imipramine combination. Arch Gen Psychiatry 1984; 41:1096–1104.
12. **Truman C, Sachs GS, Baldassano C, Ghaemi SN.** Pattern of illness and duration of mania in bipolar disorder. Presented at the 148th annual meeting of the American Psychiatric Association; 1995; Miami, Florida.
13. **Gitlin MJ, Swendsen J, Heller TL, Hammen C.** Relapse and impairment in bipolar disorder. Am J Psychiatry 1995; 152:1635–1640.
14. **Maj M, Pirozzi R, Magliano L, Bartoli L.** Long-term outcome of lithium prophylaxis in bipolar disorder: a 5-year prospective study of 402 patients at a lithium clinic. Am J Psychiatry 1998; 155:30–35.
15. **Bowden CL, Swann AC, Calabrese JR, McElroy SL, Morris D, Petty F, et al.** Maintenance clinical trials in bipolar disorder: design implications of the divalproex-lithium-placebo study. Psychopharmacol Bull 1997; 33:693–699.
16. **Bowden CL.** Long-term prophylaxis treatment: priorities in bipolar disorder. Eur Neuropsychopharmacol 1997; 7:S2–S123.
17. **Keck PE Jr, McElroy SL, Strakowski SM, Stanton SP, Kizer DL, Balistreri TM, et al.** Factors associated with pharmacologic noncompliance in patients with mania. J Clin Psychiatry 1996; 57:292–297.
18. **Johnson RE, McFarland BH.** Lithium use and discontinuation in a health maintenance organization. Am J Psychiatry 1996; 153:993–1000.
19. **Dunner DL, Fieve RR.** Clinical factors in lithium carbonate prophylaxis failure. Arch Gen Psychiatry 1974; 30:229–233.
20. **Sachs GS.** Bipolar mood disorder: practical strategies for acute and maintenance phase treatment. J Clin Psychopharmacol 1996; 16(suppl 1):32S–47S.
21. **Sachs GS, Guille C, Demopulos C, Desan P.** Atypical antipsychotics: use in bipolar disorder clinic. Presented at the 21st Collegium International Neuropsychopharmacologicum Congress; 1998; Glasgow, Scotland.
22. Lamictal (lamotrigine). Physicians' Desk Reference. 52nd ed. Montvale, NJ: Medical Economics Co Inc; 1998:1043–1048.
23. **Young LT.** An open trial of gabapentin in bipolar disorder. In: Syllabus and proceedings summary of the American Psychiatric Association Annual Meeting; May 30 June 4, 1998; Toronto, Ontario, Canada. Abstract 77C:150.
24. Neurontin (gabapentin). Physicians' Desk Reference. 52nd ed. Montvale, NJ: Medical Economics Co Inc; 1998:2110–2113.
25. **Calabrese JR, Shelton MD, Keck PE, McElroy SL, Werkner JE.** Emerging trends in the management of psychiatric illness. In: Syllabus and proceedings summary of the annual meeting of the American Psychiatric Association; May 30–June 4, 1998; Toronto, Ontario, Canada. Abstract NR202.
26. Topamax (topiramate). Physicians' Desk Reference. 52nd ed. Montvale, NJ: Medical Economics Co Inc; 1998:2058–2061.