Third Generation Anticonvulsants in Bipolar Disorder: A Review of Efficacy and Summary of Clinical Recommendations

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Background: To review the literature on efficacy of third generation anticonvulsants for treatment of bipolar disorder and provide clinical recommendations.

Method: Open and controlled studies, case reports, and case series on the efficacy of lamotrigine, gabapentin, topiramate, tiagabine, and zonisamide were located through electronic searches of several databases, by manual search of proceedings of international meetings, and through contacting authors of recent reports.

Results: Lamotrigine is the best studied anticonvulsant and has efficacy in acute bipolar depression and in longer term treatment of bipolar depression as well as rapid-cycling bipolar II disorder but not in acute mania. Open reports suggest usefulness of gabapentin as an adjunct in bipolar disorder, but double-blind trials failed to confirm efficacy in acute mania and treatment-resistant rapid-cycling bipolar disorder. Topiramate is reported to be effective in acute mania and rapid-cycling bipolar disorder in several open studies, but methodological problems in a double-blind study led to a failed study in acute mania. However, topiramate may lead to weight loss in some patients. Zonisamide deserves further investigation, but tiagabine does not appear to be useful in acute mania.

Conclusion: Lamotrigine clearly fills an unmet need in treating bipolar depression and rapid-cycling bipolar disorder. Other third generation anticonvulsants with the exception of tiagabine offer promise but require confirmation of their efficacy from double-blind studies.

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The term *bipolar disorder* refers to a heterogeneous group of conditions. The mood episodes that constitute bipolar disorder first appear in adolescence and early adulthood, and the disorder is characterized by different presentations, course, and response to treatment. Bipolar disorder is commonly associated with coexisting alcohol and substance abuse, anxiety disorders, psychotic symptoms, and medical disorders.[1,2] Although bipolar I disorder, with clear interepisode intervals, has been the center of classic descriptions of the condition, bipolar II disorder, mixed states, and various types of accelerated cycling are increasingly recognized as being common. Untreated bipolar disorder is associated with high recurrence rates, deterioration in psychological, interpersonal, and scholastic or work functioning, suicide, and even with increased rates of medical conditions, particularly cardiovascular disease.[3,4] Clinicians have long recognized what research has shown: the vast majority of patients will need, and quite likely benefit from, judicious use of combinations of medications, rather than monotherapy, during different phases of the disorder. In addition, there is support for Kraepelin's reports[5] of increasing amounts of cumulative time spent depressed by decade of life. Further, what works in acute phases of mania or depression may not be effective in prophylaxis and relapse prevention, particularly of depressive breakthroughs, and the side effects of and tolerance for medications have profound impact on treatment adherence and thus on morbidity.

The focus of much work, until recently, has been on the elusive search for an ideal monotherapy treatment that is effective in all types and phases of the disorder. The attitudes and expectations of major regulatory authorities in North America and Europe have driven monotherapy research at the cost of more clinically meaningful studies of combination treatments, which, interestingly enough, have won the acceptance of both researchers and regulatory authorities in the development of antiepileptic treatment. Further, although nobody would doubt the remarkable efficacy of lithium in mania, depression, and prophylaxis in a subgroup of bipolar patients, the standards and rigor of scientific research methodology and

ethics have changed since the days when lithium first received regulatory approval. These changes significantly challenge the design and completion of studies with new medications.

Valproate is as effective as lithium in acute pure mania[6] and more effective than lithium in mania accompanied by symptoms of depression.[7] In a recent small double-blind trial, valproate has been reported to be more effective than carbamazepine in acute mania.[8] Carbamazepine has been reported to have equal efficacy to lithium in acute mania in most[9–12] although not in all studies.[13] Lithium appears to have acute antidepressant properties in bipolar depressed patients, but the utility of carbamazepine and valproate in bipolar depression remains to be established with double-blind controlled trials (see Yatham et al.[14] and Srisurapanont et al.[15] for review). These compounds are relatively less effective in preventing depressive breakthroughs than manic relapses.[16] Although there is a widely held view that valproate is effective, carbamazepine less so, and lithium ineffective in rapid-cycling bipolar disorder, there are no published, controlled prospective or double-blind studies comparing these compounds to support this conclusion. However, some double-blind, placebo-controlled data suggest that lithium exerts prophylactic effect on hypomania but not on depressive episodes in patients with bipolar II disorder (some with a history of rapid cycling).[17]

The value of prophylaxis in patients with severe and recurrent bipolar disorder with a family history of the condition is well accepted. However, the debate continues about the merits of long-term treatment in patients with a relatively mild disorder without a family history of bipolar disorder and with long interepisode intervals. Lithium has the most convincing long-term data of effectiveness in prophylaxis[18]; however, these early landmark studies did not employ survival analyses. The suspected limited efficacy of lithium in the wider spectrum of bipolar disorder outside the bounds of classical bipolar I disorder has led to a search for alternatives. Valproate and lithium were not demonstrated to be superior to placebo in terms of time to any episode in the total sample of bipolar I patients in the only 1-year double-blind study of the 2 compounds in a parallel design.[19] However, the divalproex group had lower rates of discontinuation for either a recurrent mood episode or depressive episode compared with the placebo group and longer duration of successful prophylaxis in the study and less deterioration in depressive symptoms and global assessment scores compared with the lithium group. In a novel and landmark study of patients with rapid-cycling bipolar disorder, Calabrese and colleagues[20] combined lithium and divalproex in the continuation of treatment and then randomly assigned stabilized patients to a double-blind, 20-month maintenance phase of either lithium or divalproex monotherapy. During open stabilization, combined treatment (N = 215) was marked by 29% noncompliance, 18% lack of tolerability of side effects, and 26% nonresponse. Nonresponders more commonly had resistant depression as compared with resistant mania (3:1). Marked bimodal efficacy of both medications was about 50% in those completing 6 months of combination therapy, with significantly better antimanic than antidepressant efficacy. In the randomized phase of the study, where patients were treated with either lithium or divalproex monotherapy, 61% suffered a relapse into depression and 39% into hypomania/mania. Five of 47 patients in this ongoing study completed all 20 months of treatment with monotherapy. At press time, no results were available comparing the relative survival of lithium versus valproate in this ongoing study. This study demonstrates not only the value of combination treatment and the limitations of monotherapy, but also the attrition rates of patients in long-term treatment.

Along with increasing recognition and awareness of the scope and limitations of lithium, carbamazepine, valproate, antidepressants, and antipsychotics in the treatment of bipolar disorder, a surge of interest in newer treatments to fulfill the unmet needs in treating bipolar patients has developed. Newer generation anticonvulsants and atypical antipsychotics have received considerable attention and study in the last 4 years. Although the atypical antipsychotic agents all appear to have antimanic properties,[21–24] the newer anticonvulsants appear to be a heterogeneous class of psychotropic agents with markedly different spectra of efficacy.

In this article, we review and summarize the evidence from open-label as well as double-blind studies for efficacy of the third generation anticonvulsants lamotrigine, gabapentin, topiramate, tiagabine, and zonisamide in the treatment of bipolar disorder. Based on the review of evidence, we also provide clinical recommendations for use of these medications.

METHOD

MEDLINE searches were conducted for articles that reported on efficacy using the key words *lamotrigine*, *gabapentin*, *topiramate*, *tiagabine*, and *zonisamide* combined with *bipolar disorder*. References from articles were manually cross-checked to locate additional studies. Abstracts and proceedings of major international meetings of psychiatrists such as the American Psychiatric Association, the Society for Biological Psychiatry, the World Congress of Psychiatry, the College of International Neuropsychopharmacology, the American College of Neuropsychopharmacology, and so on, from 1990 to 2001, were searched, and where possible, authors of the abstracts were contacted for additional information.

Results from all case reports or series, case studies, and open-label studies are summarized for each compound. Results of double-blind studies and long-term open-label

extension phases of double-blind studies are described in greater detail as these studies provide most robust evidence for efficacy.

RESULTS: LAMOTRIGINE

Open-Label Studies

Acute mania, bipolar depression, and rapid-cycling bipolar disorder. Lamotrigine was administered in an open-label fashion to 396 patients in 19 studies on the clinical efficacy of lamotrigine.[25–43] Of the 396 patients, data on response rates were available for 371 patients. Of these, 264 (71%) patients showed improvement in their symptoms. Fifty-four patients were treated for manic, mixed, or hypomanic symptoms, and of these, 40 (85%) of 47 on whom data were available responded. Among 120 depressed patients, 74 (63%) of 117 on whom data were available responded to lamotrigine.

Data on response rates in rapid cycling were available in only 48 of 89 patients with rapid-cycling bipolar disorder. Of these 48 patients, 30 (62%) responded to the lamotrigine treatment.

Prophylaxis. Patients who participated in the 7-week double-blind study of lamotrigine monotherapy for bipolar depression[44] were offered participation in a 1-year continuation study, which consisted of 2 phases.[45] In phase 1 (a 3-week double-blind phase), patients were given either escalating doses of lamotrigine if they had previously been randomly assigned to placebo (N = 47) or lamotrigine maintenance treatment if previously randomly assigned to lamotrigine (N = 77). Phase 1 was followed by a 49-week open-label phase in which patients received open-label treatment with lamotrigine. About 56% of patients completed the study. The remaining 44% withdrew from the study for the following reasons: adverse events (14%), lack of efficacy (7%), loss to follow-up (10%), other reasons (13%). Those patients randomly assigned to the placebo group during the double-blind phase and who received open-label treatment with lamotrigine at the completion of the double-blind trial showed significant improvements in depression scores, as measured by changes in the Hamilton Rating Scale for Depression (HAM-D) and the Montgomery-Asberg Depression Rating Scale (MADRS), and improvement on the Clinical Global Impression-Improvement (CGI-I) scale. Patients randomly assigned to lamotrigine during the double-blind phase and those who received open-label treatment with lamotrigine at the completion of the trial also continued to maintain improvement that was shown in the double-blind part of the study.

In another study,[46] patients who participated in a multicenter 10-week double-blind study of lamotrigine versus placebo in bipolar depression were offered participation in a 1-year continuation study, which also consisted of 2 phases. The first phase was a 5-week double-blind phase in which patients previously randomly assigned to placebo (N = 63) were given escalating doses of lamotrigine, and those previously randomly assigned to lamotrigine (N = 64) were continued on it. This phase was followed by a 47-week open-label phase in which patients were given lamotrigine monotherapy or lamotrigine add-on therapy to other psychotropic medication. Results indicate that patients who received lamotrigine during the double-blind study continued improvement during the 52-week study period, and those previously randomly assigned to placebo showed evidence of significant improvement.

The results of these studies suggest that lamotrigine may be useful in the continuation and maintenance treatment of the depressive phase of bipolar disorder, but this needs to be confirmed in double-blind studies.

Double-Blind Placebo-Controlled Studies

Acute mania. Berk[47] examined the efficacy of lamotrigine (N = 15) up to 100 mg/day in acute mania as compared with olanzapine (N = 15) and lithium (N = 15), using a 4-week double-blind randomized design in 45 patients. The Young Mania Rating Scale (YMRS) scores declined significantly in all the groups with no significant difference in the magnitude of change in scores between the 3 groups. The results of this study suggest that lamotrigine may have some antimanic efficacy. However, the interpretation of this study's results is markedly confounded because the study was not properly powered to show equivalence. Anand et al.[48] conducted an 8-week double-blind study in 16 lithium-refractory manic or hypomanic patients to examine the efficacy of lamotrigine and found no evidence that lamotrigine was more efficacious than placebo. Of the 16 patients who participated in the study, half were randomly assigned to lamotrigine up to 200 mg/day, while the other 8 received placebo. The primary efficacy measure was a 50% or greater reduction in YMRS scores. Five of the 8 patients who were given lamotrigine either adjunctively with lithium or as monotherapy responded, while 4 of the 8 patients assigned to placebo also responded. The difference in percentage of responders between the 2 groups was not significant.

The efficacy of lamotrigine was also tested in 2 double-blind trials in acute mania.[49] In the first study, lamotrigine monotherapy was compared with placebo or lithium monotherapy for a 3-week period. In the second study, lamotrigine add-on therapy was compared with placebo or lithium add-on for a 6-week period. In these studies, lamotrigine was started at 25 mg/day and increased to 50 mg/day at week 3, 100 mg at week 5, and 200 mg at week 6. No significant differences were found between lamotrigine and placebo on the primary efficacy measure of change in Mania Rating Scale[50] scores from baseline using last-observation-carried-forward (LOCF) analysis.

In summary, 3 of 4 studies did not support the efficacy of lamotrigine in acute mania, and in the 1 study showing positive results, design issues complicated the interpretation of the data. The consensus is that there is no compelling evidence for the efficacy of lamotrigine in acute mania.

Acute bipolar depression. In a double-blind placebo-controlled study of bipolar I depression, Calabrese et al.[44] randomly assigned 195 patients with bipolar depression to lamotrigine monotherapy at doses of 50 mg/day (N = 66) or 200 mg/day (N = 63) or placebo (N = 66) for 7 weeks. Compared with those randomly assigned to placebo, patients randomly assigned to lamotrigine, 200 mg/day, did significantly better on the CGI-I and the MADRS scores, whereas those randomly assigned to lamotrigine, 50 mg/day, did better on the MADRS but not on the CGI-I. On the primary efficacy measure of change in 17-item HAM-D scores from baseline to endpoint, there was a trend toward significant improvement (p = .085) for the lamotrigine 200 mg/day group but not for the lamotrigine 50 mg/day group compared with the placebo group. Defining responders as those showing a ≥ 50% decrease in scores on the 17-item HAM-D scale or the MADRS, or a CGI-I score of 1 to 2, a significantly greater number of patients in the lamotrigine 200 mg/day group met criteria for response on the MADRS and the CGI-I compared with those in the placebo group. Those randomly assigned to lamotrigine, 50 mg/day, did significantly better on the MADRS but not on the HAM-D or the CGI-I. Treatment-emergent mania, hypomania, or mixed state was similar in patients randomly assigned to lamotrigine (5.4%) compared with those randomly assigned to placebo (4.6%), with no significant differences between the 2 groups.

In a second double-blind placebo-controlled trial of 10 weeks' duration,[49] the efficacy of lamotrigine (N = 103) was compared with placebo (N = 103) in bipolar I and bipolar II depressed patients. No differences emerged between the groups on the 17-item HAM-D scale or the MADRS using LOCF. A subgroup analysis, however, revealed that patients with bipolar I depression but not those with bipolar II depression did significantly better with lamotrigine compared with those randomly assigned to placebo on both the 17-item HAM-D scale and the MADRS using LOCF. A significant limitation of this study is that the placebo response was very high (nearly 50%), which might have obscured the true difference between the lamotrigine and placebo groups. Furthermore, reliability of diagnosis of hypomania is in general lower, and it is possible that some of the patients recruited into the study with bipolar II depression may have had unipolar major depression. Treatment-emergent mania was reported in 1% of patients receiving lamotrigine or placebo.

The selection of primary efficacy measures for studies in bipolar depression has been particularly problematic. The 17-item HAM-D scores do not capture all of the core symptoms of bipolar depression, and many researchers now feel that the MADRS might be a better alternative. Given a significant difference in favor of lamotrigine on the MADRS and a number of secondary efficacy measure in bipolar I depressed patients in both studies, we conclude that lamotrigine monotherapy is effective in the treatment of bipolar depression. Furthermore, results of these studies suggest that lamotrigine does not induce manic/hypomanic switch in bipolar patients, unlike antidepressant medications.

Prophylaxis of bipolar disorder. The long-term efficacy of lamotrigine compared with placebo and lithium was examined using a relapse prevention design in a recent double-blind trial.[51] Patients with bipolar I disorder (N = 326) who were manic or hypomanic or recently had a manic or hypomanic episode entered an open-label phase during which they were treated with addition of lamotrigine for 8 to 16 weeks. Those meeting stabilization criteria were randomly assigned to treatment with lamotrigine (N = 59) or lithium (N = 46) or placebo (N = 70) up to 18 months. Preliminary analysis indicated that lamotrigine was significantly superior to placebo on overall survival in the study and time to intervention for any mood episode, time to any bipolar event, and time to a depressive episode. Lithium was superior to placebo on time to intervention for any mood episode, time to any bipolar event, and time to manic episode but not depressive episode. Lamotrigine was well tolerated.

The results of this study suggest that lamotrigine has efficacy in longer treatment of bipolar disorder and, in particular, in the prevention of bipolar depressive episodes.

Rapid-cycling bipolar disorder. In the only placebo-controlled study of rapid-cycling bipolar disorder patients to date and the first double-blind maintenance study of lamotrigine, Calabrese et al.[52] compared the efficacy of lamotrigine to placebo during a 26-week randomized phase. Patients with bipolar I or bipolar II disorder in rapid-cycling, manic, hypomanic, mixed, or depressed states (N = 324) entered a preliminary open-label phase and were treated with the addition of lamotrigine, 100 to 300 mg/day. Concomitant medications were tapered off and those who met criteria for response (N = 182; 130 with bipolar I and 52 with bipolar II disorder) were randomized to double-blind treatment with either placebo (N = 89) or lamotrigine monotherapy (N = 93) for 26 weeks. The patients who entered the preliminary phase dropped out due to other reasons/lack of efficacy (13%), adverse effects (11%), consent withdrawn (8%), loss to follow-up (6%), or protocol violation (6%).

The primary efficacy measure was time to additional pharmacotherapy for a mood episode or emerging mood symptoms. Fifty-six percent of the placebo (N = 49) and 50% of the lamotrigine-treated patients (N = 45) met criteria for "time to intervention" and the difference between the groups was not significant (p = .177). No significant

differences existed in median survival times between the 2 groups. However, when survival is defined as any premature discontinuation, including requiring additional pharmacotherapy, the median survival time was 8 weeks for the placebo group and 14 weeks for the lamotrigine group, a difference that was statistically significant (p = .036). When subtype analysis was performed for "time to intervention," there was a trend toward a significant difference (p = .073) favoring lamotrigine for the bipolar II subtype but not for the bipolar I subtype. A significant difference (p = .015) favoring lamotrigine also existed for overall survival in the study for bipolar II patients. The percentage of patients on monotherapy who were stable without relapse for the entire study period was significantly greater (p = .03) for the lamotrigine group compared with the placebo group (41% for lamotrigine vs. 26% for placebo). The latter finding was primarily due to those patients with bipolar II disorder; 46% on lamotrigine therapy remained stable for the entire study as compared with only 18% on placebo.

Although the findings did not reach significance on a primary efficacy measure, patients randomly assigned to lamotrigine, particularly those with bipolar II subtype, did significantly better on a number of other efficacy measures, supporting the efficacy of lamotrigine.

Treatment-resistant mood disorders. Using a randomized double-blind crossover design, Frye et al.[53] examined the efficacy of lamotrigine or gabapentin monotherapy compared with placebo in 31 patients with treatment-resistant mood disorder (11 with bipolar I disorder, 14 with bipolar II disorder, and 6 with unipolar depression). Twenty-three of the 25 patients with bipolar disorder had rapid cycling. Each monotherapy trial lasted 6 weeks. The overall response rate of "much" or "very much" improved based on the CGI-I scale was 52% (16 of 31) for the lamotrigine group, 26% (8 of 31) for the gabapentin group, and 23% (7 of 31) for the placebo group. Post hoc analysis showed that the lamotrigine group did significantly better than the gabapentin and placebo groups. Lamotrigine was effective in treating depressive symptoms in 45% of patients and manic symptoms in 44% of patients compared with placebo, which was effective in treating depressive symptoms in only 19% of patients and manic symptoms in 32% of patients. The results of this study thus indicated that lamotrigine is effective in treating about 50% of patients with refractory mood disorder.

RESULTS: GABAPENTIN

Open-Label Studies

Acute mania, bipolar depression, and rapid-cycling bipolar disorder. Gabapentin was used in 20 open studies in which it was administered adjunctively or in monotherapy to 433 patients with bipolar illness, and response rates are available for 339 of them.[54–73] Of the 339 patients, 225 showed improvement for a total response rate of 66%. Ninety-nine patients presented with mania, hypomania, or mixed mania. Data were available for 82 of these patients, and 62 (76%) of them showed improvement of their symptoms. Of the 112 cases of depression, data were available for 83; 46 (55%) showed improvement in their symptoms.

Prophylaxis. Schaffer and Schaffer,[66] in an open-label follow-up study of 18 patients who were part of a larger sample in their 1997 study,[54] showed that only 7 of these 18 patients continued to maintain improvement or remission over the 3-year extension period.

Double-Blind Placebo-Controlled Studies

Acute mania. Pande et al.[74] conducted a double-blind trial to ascertain the efficacy of gabapentin add-on to a mood stabilizer in the treatment of acute mania/hypomania. Patients with bipolar I disorder presenting manic, hypomanic, or mixed state while taking lithium or valproate or the combination entered the open-label phase of the study in which the doses of these medications were optimized over a 2-week period. Patients who continued to have a score of 12 or more on the YMRS were randomly assigned to double-blind add-on treatment with either gabapentin, 900 to 3600 mg/day, or placebo for 10 weeks. The mood-stabilizer-plus-placebo group had a larger decrease in their YMRS scores from baseline to endpoint (9 points), while the mood-stabilizer-plus-gabapentin group had only a 6-point decrease; this difference was statistically significant. The differences in favor of mood stabilizer plus placebo persisted for each subgroup when patients were subdivided by severity into mild, moderate, or severe based on baseline YMRS scores, and these differences were believed to be due to dosage adjustments made to lithium during the open-label phase of the study. No significant differences emerged between the 2 groups on their HAM-D scores or other secondary efficacy measures. Hence, gabapentin is not efficacious in the treatment of mania.

Treatment-resistant mood disorders. Frye et al.[53] conducted a 6-week double-blind crossover trial of the effects of gabapentin versus lamotrigine and placebo in 31 patients with refractory mood disorders. Consistent with the findings of Pande et al.,[74] the results indicated that gabapentin was not superior to placebo in treating refractory patients. These results indicate that gabapentin lacks utility as a primary agent in the management of patients with treatment-resistant (primarily rapid cycling) mood disorders.

RESULTS: TOPIRAMATE

Open-Label Studies

Fourteen open-label studies reported on the clinical efficacy of topiramate, and these included a total of 279 patients.[75–88] Data were available on 266 subjects, 154 (58%)

of whom showed improvement in symptoms. From a total of 83 cases with data (from an original cohort of 98 cases), 52 subjects (63%) with manic, hypomanic, or mixed state showed improvement. Of 72 depressed patients, 66 had data available; of these, 41 (62%) showed improvement in their symptoms.

Ninety-four patients had rapid-cycling bipolar disorder; of the 86 on whom data were available, 46 (53%) showed improvement in their symptoms. Given these promising results, further double-bind controlled studies are warranted on the effectiveness of topiramate in the treatment of bipolar illness.

Double-Blind Placebo-Controlled Studies

Acute mania. In a preliminary 3-week randomized placebo-controlled trial, the efficacy of 2 different doses of topiramate was examined in acute mania. An interim analysis (N = 36) suggested that reduction in YMRS scores from baseline to endpoint was significantly greater in patients randomly assigned to topiramate, 512 mg/day (N = 13) or 256 mg/day (N = 11), compared with those randomly assigned to placebo (N = 12) on an intent-to-treat analysis using LOCF. When the study was completed (after increasing the sample size to 97), analysis revealed no significant between-group difference on the primary efficacy measure of YMRS change scores from baseline to endpoint using LOCF. However, a significant improvement on Global Assessment Scale (GAS) scores favoring topiramate, 512 mg/day, in comparison with the placebo group was noted.[89]

Twenty-eight patients with mania had received antidepressant treatment prior to randomization. When these subjects were excluded in a post hoc analysis, the topiramate 512 mg/day group (N = 21) but not the 256 mg/day group (N = 26) had greater reductions on primary efficacy measure (change in YMRS scores from baseline to endpoint using LOCF) compared with the placebo group (N = 22).

Topiramate was, in general, well tolerated, and headache, dizziness, and anxiety were the most common side effects noted in this study population. Further trials are currently evaluating the acute and maintenance effects of this compound in bipolar I disorder.

RESULTS: TIAGABINE

Open-Label Studies

Although case reports[90,91] suggest the usefulness of tiagabine in bipolar disorder, Grunze et al.,[92] using the Bech-Rafaelsen Mania Scale to quantify changes in manic symptoms, reported that tiagabine treatment did not lead to any significant improvement in symptoms in 8 acutely manic patients. In this open-label study, 2 patients were given tiagabine monotherapy while the other 6 received tiagabine as an add-on therapy. None of the patients showed moderate-to-marked improvement in manic symptoms. In addition to the lack of efficacy, 2 patients experienced pronounced side effects, which included severe nausea in 1 patient and a tonic-clonic (grand mal) seizure in the other. The increased side effects may have been related to rapid up-titration of the tiagabine dose in these acutely ill subjects. The investigators started tiagabine at 20 mg/day as well, 4-fold higher than the recommended starting dose for epilepsy in the product information.

Concern has been raised about GABAergic infiltration of the retina and associated visual problems with chronic tiagabine use. No plans for further systematic trials with this compound in bipolar disorder have been declared.

RESULTS: ZONISAMIDE

Open-Label Studies

In the only published study (N = 24) of the efficacy of zonisamide in the treatment of mania and acute psychotic conditions,[93] 15 patients were bipolar manic, 6 were schizoaffective manic, and 3 were schizophrenic excited. Seventy-one percent showed moderate-to-marked improvement after 4 to 5 weeks of treatment with a 100- to 600-mg/day dosage titration of zonisamide. Fifteen (71%) of 21 patients with bipolar and schizoaffective manic disorder responded to zonisamide treatment.

DISCUSSION AND CLINICAL RECOMMENDATIONS

Lithium is the preferred mood stabilizer in classic, episodic bipolar I disorder with minimal comorbidity. However, many patients are unresponsive to lithium. Although valproate and carbamazepine are useful alternatives, the vast majority of patients with bipolar disorder cannot be managed with monotherapy. Treatment-refractory patients with bipolar disorder who do not respond to multiple treatments by traditional medications require new alternatives.

The newer anticonvulsants lamotrigine, gabapentin, and topiramate offer new hope in bipolar disorder. However, lamotrigine is the only medication for which double-blind controlled data are available supporting efficacy in bipolar depression and rapid-cycling bipolar II disorder and in the prevention of mood episodes and in particular depressive episodes. The other medications discussed in this article will need further study before their routine use in bipolar disorder can be recommended.

Lamotrigine

Lamotrigine is useful in monotherapy or combination therapy with another mood stabilizer in bipolar depression and rapid-cycling bipolar disorder. Lamotrigine is also effective in prophylaxis of patients with bipolar I dis-

order, particularly for preventing depressive episodes. Lamotrigine does not appear to have significant efficacy in treating acute mania in dose ranges of 50 to 200 mg when slow up-titration is used over a 6-week period. Since it is less likely to induce a manic switch compared with antidepressants, lamotrigine may be used as a first-line agent for treating bipolar depression in patients with a previous history of severe and refractory manic episodes. Lamotrigne is also recommended as a first-line agent in those patients with rapid-cycling bipolar II disorder.

Lamotrigine should be started at a low dose (25 mg/day) and titrated up slowly during the first 6 weeks at 25-mg increments every 2 weeks to approximately 200 mg/day. It should be noted that some patients may show improvement at lower doses (50–125 mg/day) but may require higher doses (250–400 mg/day) to fully respond. Lower doses and slower titration schedules should be used when combining lamotrigine with valproate, and higher doses should be used when combining lamotrigine with carbamazepine (valproate doubles and carbamazepine halves the elimination half-life of lamotrigine).

The overall incidence of rash in lamotrigine-treated patients is 10%, which is significantly higher than the 5% incidence noted in patients receiving placebo.[94] The predictors of rash include higher-than-recommended starting dose, faster-than-recommended titration, concurrent use of valproate, use in children, and a history of prior rash. The highest risk period for rash is within the first 6 to 8 weeks of therapy. Rash induced by lamotrigine has no specific characteristics that distinguish it from rashes induced by other agents. Most rashes are benign (simple morbilliform rash). The published literature prior to the implementation of the currently recommended dosage guidelines reported a rate of severe rash in adults of 0.3% and in children of 1%. However, subsequent studies have shown that the rate of serious rash has decreased while that of the benign rash has not changed.[95] Symptoms associated with serious rashes include systemic symptoms (fever, pharyngitis, malaise, flu-like syndrome); lesions on palms, soles, or mucous membranes; and blisters or a painful rash (which can herald the onset of potentially life-threatening toxic epidermal necrolysis or Stevens-Johnson syndrome or hypersensitivity syndrome). Immediate discontinuation of lamotrigine significantly reduces the risk of toxic epidermal necrolysis and hypersensitivity syndrome. The clinical management of rash should include alerting the patient to contact medical staff about any rash, ruling out benign explanations such as contact dermatitis, poison ivy, or insect bites, and then referring the patient to a dermatologist if the rash remains unexplained or if the rash is accompanied by the above signs and symptoms.

Gabapentin

Double-blind trials of gabapentin failed to show its efficacy in patients with acute mania or in refractory bipolar disorder. Gabapentin is likely ineffective in monotherapy for acute mania or bipolar depression or as a mood stabilizer in bipolar disorder. Gabapentin is, however, effective in social phobia and most likely effective in panic disorder as well.[96,97] Thus, gabapentin may be a useful and safe agent as an adjunct to other bipolar treatments in the presence of significant anxiety.

A starting dose of 200 to 300 mg b.i.d. and increasing the dose by 200- to 300-mg increments every 2 to 3 days as tolerated would be appropriate. Doses between 1200 and 3000 mg/day may be needed to achieve therapeutic efficacy. This drug has no known clinically significant pharmacokinetic interactions and is safe to use in combination with other agents. Its sedative side effect may be beneficial for some patients.

Topiramate

Topiramate may be useful as an adjunct to other mood stabilizers in refractory mania and in ultrarapid or ultradian cycling disorder. A low starting dose, 25 to 50 mg/day, increased by 25 to 50 mg/day every 4 to 7 days, to between 200 and 500 mg/day as clinically indicated and tolerated, would be appropriate.

Its potential to cause weight loss may make it attractive as an add-on treatment. Cognitive side effects may restrict the use of this compound in some patients, but cognitive side effects are related to dose and dose escalation. Renal stones can occur in 1% of cases. Parasthesias are common with topiramate therapy, but seldom require discontinuation of the drug. Acute angle closure glaucoma with sudden loss of bilateral vision can very rarely be associated with topiramate use, but it resolves rapidly following discontinuation of topiramate.

Tiagabine and Zonisamide

At this time, with available information and without further studies of efficacy, safety, and tolerability, it is not possible to recommend the use of tiagabine or zonisamide for the treatment of patients with bipolar disorder.

Drug names: carbamazepine (Tegretol and others), divalproex sodium (Depakote), gabapentin (Neurontin), lamotrigine (Lamictal), olanzapine (Zyprexa), tiagabine (Gabitril), topiramate (Topamax), zonisamide (Zonegran).

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