Anticonvulsants and Antipsychotics in the Treatment of Bipolar Disorder

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A number of recent advances in clinical psychopharmacology regarding anticonvulsant and new antipsychotic medications have important implications with respect to the treatment of patients who have bipolar disorder. The authors reviewed the available literature on the efficacy of the anticonvulsants valproate, carbamazepine, gabapentin, and lamotrigine for the treatment of bipolar disorder. They also reviewed the use of standard and new antipsychotic medications for the treatment of various aspects of the illness. Valproate and carbamazepine have been shown to be effective in the treatment of acute mania in controlled trials. Preliminary data suggest that these agents may differ in their time course of antimanic activity and predictors of response. Neither agent has been extensively studied in controlled trials in bipolar depression or as maintenance therapy, although carbamazepine has received the most systematic study in these areas. Gabapentin and lamotrigine are only now being evaluated in controlled trials in patients who have bipolar disorder. Antipsychotics are commonly used in the treatment of patients with acute mania and as maintenance treatment. However, the use of standard antipsychotics in acute mania is associated with a number of limitations. New antipsychotic agents may possess thymoleptic as well as antipsychotic activity, but they have not been studied in controlled trials in bipolar disorder.
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Lithium was the first modern antimanic agent and has been the pharmacologic mainstay of treatment for patients who have bipolar disorder in the United States since 1970.[1] Two anticonvulsants, valproate and carbamazepine, have also been shown to be effective in the treatment of acute mania.[2,3] Prior to the availability of lithium, valproate, and carbamazepine, antipsychotic medications comprised one of the few available classes of pharmacologic agents used for the treatment of acute mania and for maintenance treatment of bipolar disorder.[4] Antipsychotic agents continue to be frequently used as adjuncts in the treatment of acute psychotic mania and psychotic bipolar depression.[5–8] A number of recent research advances have potential implications beyond the strategies described above for the treatment of patients who have bipolar disorders. First, data from recent studies[9–11] suggest that there may be important differences between valproate and carbamazepine in their time course of onset and clinical predictors of response. Second, two new anticonvulsants, lamotrigine and gabapentin, are being studied as potential treatments for patients who have bipolar disorder.[12] Third, a new generation of antipsychotic medications that may possess thymoleptic properties are now or will soon be available.[13] Finally, recent surveys indicate that, despite the availability of lithium, valproate, and carbamazepine, antipsychotics continue to be commonly prescribed as maintenance treatment for bipolar disorder.[14–17]

In this paper, my colleagues and I reviewed the available evidence supporting the efficacy of valproate and carbamazepine in the treatment of bipolar disorder, their time course of antimanic response, and the factors associated with response. We then reviewed the preliminary data regarding the potential use of lamotrigine and gabapentin and concluded by reviewing studies of standard and new antipsychotics in the acute and maintenance treatment of patients who have bipolar disorder.

ANTICONVULSANTS

Valproate

Valproate and its divalproex formulation have been shown to be effective in the treatment of acute mania in seven controlled trials.[18–24] Two of these studies[18,19] led to the recent approval of divalproex by the Food and Drug Administration for the treatment of acute mania in bipolar disorder. Pooled response rates to valproate from the three largest parallel-design, double-blind, controlled

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studies[18–20] revealed significant improvement (i.e., at least partial response or > 50% reduction in manic symptoms) in 54% of patients, superior efficacy compared with placebo,[18,19] and comparable efficacy compared with lithium.[18,20] In the single study[24] that compared oral loading of divalproex (20 mg/kg/day) with haloperidol (0.2 mg/kg/day), both agents produced comparable reductions in both manic and psychotic symptoms.

Data from the two largest placebo-controlled trials of divalproex in acute mania[18,19] indicated that the agent was well tolerated and that the therapeutic onset correlated with the achievement of therapeutic plasma concentrations.[25] These observations suggest that more rapid onset of antimanic activity might be safely achieved if alternative dosing strategies could produce therapeutic plasma concentrations earlier in treatment. This strategy has been examined in two open[26,27] and one controlled[24] study to date. In the first of these studies, Keck et al.[26] conducted a prospective, rater-blind, open trial of divalproex administered at 20 mg/kg/day in 19 patients hospitalized for acute mania. Ten (53%) of the 19 patients who received at least one complete 20 mg/kg/day dose displayed a significant (at least 50%) reduction in manic symptoms. These responders displayed the greatest improvement over the first 3 days of treatment.

Mean ± SD plasma valproate concentrations of 82 ± 21 mg/L were achieved by Day 2 of treatment in the 15 patients completing the study. Most importantly, side effects were minimal.

In the second open trial examining the safety and efficacy of valproate rapid loading, McElroy et al.[27] evaluated 13 consecutive patients hospitalized with acute mania who received divalproex at 20 mg/kg/day. In most cases (N = 11) valproate was administered concomitantly with other antimanic agents, e.g., antipsychotics or lithium. Ten (77%) patients displayed a moderate or marked response, and side effects were minor.

As previously noted, in the only controlled trial of rapid stabilization with divalproex,[24] haloperidol and divalproex were equally effective in reducing both manic and psychotic symptoms. As in the two open studies,[26,27] the greatest rate of improvement for both treatments occurred during the first 3 full days of medication administration. The findings from this initial controlled study suggest that the treatment of acute psychotic mania with divalproex may be as rapidly effective and tolerable in some patients as antipsychotic treatment. Thus, if replicated in further studies, this strategy could potentially provide a treatment alternative to antipsychotics in patients who have psychotic mania and allow earlier identification of an effective maintenance mood-stabilizer regimen.

Data from studies of valproate in the treatment of acute mania suggest that this agent is more effective than lithium in mixed mania,[20,28] rapid cycling,[18,29,30] and mania with comorbid substance use disorder.[9,31] In contrast, the presence of severe mania or comorbid personality disorder has been associated with a lower likelihood of response to valproate.[32,33]

To date, there are no controlled studies of valproate in the treatment of acute bipolar depression. In three of four open studies,[29,30,34,35] valproate appeared to be more effective in the treatment of acute mania than in depression. However, Davis et al.[36] recently reported a significant antidepressant response to an open-label trial of valproate in 33 nonbipolar patients who have major depressive disorder. In this study, 22 (66%) patients were considered responders, and the total group mean depression scores decreased by 55%. These investigators are currently conducting a double-blind, placebo-controlled study to follow up their preliminary findings.

There are no controlled studies of maintenance treatment of bipolar disorder with valproate published to date. However, Lambert and Venaud[37] reported comparable and generally favorable outcomes in patients treated with valpromide (a pro drug formulation of valproic acid) or lithium as maintenance treatment. Other retrospective and prospective case series[30] and open trials[29,35] also suggest that valproate may reduce the frequency and severity of affective episodes over time, including in patients who have rapid cycling[29,30] and mixed mania.[38] These studies also suggest that valproate, like lithium, may be more effective in the prevention of manic and mixed episodes than depressive episodes.

Carbamazepine

The results of 14 double-blind, controlled studies suggest that carbamazepine is effective in the treatment of acute mania.[3] However, only 5 of these studies are not confounded by the administration of carbamazepine combined with antipsychotics and/or lithium.[39–43] Of these studies, one was placebo-controlled,[39] two compared carbamazepine against chlorpromazine,[40,41] and two against lithium.[42,43] Carbamazepine was superior to placebo and comparable to chlorpromazine, and better tolerated in these trials. However, in comparison trials with lithium, carbamazepine response rates were low, and one study[42] reported a trend toward superior efficacy of lithium, which may have become significant with a larger sample. Nevertheless, pooled data from these 5 randomized, controlled trials of carbamazepine in acute mania revealed an overall response rate of 50% for carbamazepine-treated patients, compared with 56% for lithium-treated control groups and 61% for chlorpromazine-treated patients (differences not significant). In these studies, the time course of response to carbamazepine ranged from 1 to 2 weeks. Carbamazepine, like lithium, requires gradual dosage titration because more rapid escalation may produce intolerable, primarily neurologic, side effects.[44]

As with valproate, there are preliminary data regarding clinical features associated with response of patients to

carbamazepine in acute mania. Post et al.[45] found that four factors associated with poor response to lithium—mixed mania, rapid cycling, increased severity of acute mania, and negative family history of mood disorder—were associated with a favorable carbamazepine response. In a second study, Okuma[46] observed a more favorable response to carbamazepine in patients who had rapid cycling, early age at onset, and whose course of illness was dominated by manic episodes.

Three controlled studies[47–49] have evaluated the efficacy of carbamazepine in the treatment of patients with unipolar and bipolar depression. In the first of these studies, a placebo-controlled crossover study, Post et al.[47] reported marked improvement in 12 (34%) of 35 patients who had treatment-resistant depression. A trend toward greater improvement in patients who had bipolar (compared with unipolar) depression was observed, and the switch to placebo was associated with deterioration in carbamazepine responders. In the second study, Small[48] reported the results of a 4-week trial comparing the response of 28 patients (4 bipolar, 24 unipolar) who had treatment-resistant depression and were treated with lithium, carbamazepine, or their combination. Of patients receiving carbamazepine or the combination, 32% displayed moderate or marked improvement compared with 13% for lithium-treated patients. Finally, Kramlinger and Post[49] evaluated the efficacy of lithium versus placebo augmentation of carbamazepine and found that 6 (46%) of 13 patients responded to lithium augmentation.

Six controlled studies have assessed the efficacy of carbamazepine in the maintenance treatment of patients who had bipolar disorder.[50–55] Okuma et al.,[50] in the only placebo-controlled study, reported a 60% response rate after carbamazepine treatment for 1 year compared with 22% on placebo. In five other controlled studies,[51–55] carbamazepine was compared with lithium as a maintenance treatment. In the most recent study,[55] 50% of lithium-treated and 49% of carbamazepine-treated patients went without relapse for more than 1 year. In other studies, adjunctive treatment with antipsychotics, sedatives, and antidepressants was permitted for breakthrough episodes.[51–54] A majority of patients in these studies required adjunctive treatment, although specific data were not provided. Thus, although all five studies reported efficacy of carbamazepine in the reduction of affective episodes and prolongation of euthymic periods, this effect was incomplete for most patients. Other investigators[56] have suggested that the methodologic limitations in most of the studies that compared carbamazepine and lithium leave the question of efficacy of carbamazepine as a maintenance treatment unresolved. The findings of two naturalistic outcome studies of carbamazepine treatment underscore this uncertainty.[57,58] For example, Frankenburg et al.[57] found that only 18% of patients treated with carbamazepine for 3 to 4 years remained stable. Similarly, in a 4-year follow-up study of patients who have treatment-refractory affective disorders, Post et al.[58] found that one half of patients followed had relapsed after 4 years. In addition, the majority of patients required treatment with lithium and other agents.

Lamotrigine and Gabapentin

Although double-blind, randomized, controlled clinical trials of lamotrigine and gabapentin for the treatment of various aspects of bipolar disorder are now in progress, only anecdotal evidence is currently available regarding their potential use. Two reports of open trials of lamotrigine have recently appeared.[12,59] In the first report,[12] 50 patients received lamotrigine as adjunctive treatment to ongoing medication regimens, and 17 patients received lamotrigine as monotherapy. Nine (23%) of 39 patients who received lamotrigine for acute bipolar depression displayed moderate improvement, and 18 (46%) patients exhibited marked improvement. Of the 25 patients who received lamotrigine while manic (N = 9), hypomanic (N = 7), or mixed (N = 9), the mean reduction in manic symptoms was > 50%. Four (16%) patients exhibited moderate improvement, and 15 (60%) demonstrated marked improvement. In the second report, Calabrese et al.[59] described the successful treatment of a man with rapid cycling bipolar type I disorder who was refractory to previous trials of lithium, fluoxetine, and carbamazepine. Lamotrigine appeared to produce acute antidepressant effects and subsequent mood-stabilizing activity.

Six reports have appeared to date[60–65] regarding the use of gabapentin in the treatment of patients who have affective symptoms. In the first report, Ryback and Ryback[60] described the successful addition of gabapentin to imipramine in the treatment of behavioral dyscontrol in an adolescent patient with intermittent explosive disorder, organic mood disorder, and attention-deficit/hyperactivity disorder. Stanton et al.[61] reported the successful treatment of a patient who had acute psychotic mania with gabapentin monotherapy. Manic symptoms responded well to gabapentin but persistent delusions required the addition of haloperidol. In a third report, Schaffer and Schaffer[62] described the results of gabapentin adjunctive or monotherapy in 28 patients who had bipolar disorder refractory to treatment with lithium, valproate, or carbamazepine. Eighteen (64%) patients displayed a favorable response to gabapentin. Eight patients discontinued treatment because of side effects, primarily sedation or activation, and two because of poor response (increased rapid cycling). McElroy et al.[63] treated nine patients who had bipolar I or II disorder who were experiencing hypomanic, manic, or mixed states inadequately responsive to mood stabilizers with open-label, adjunctive gabapentin. Of the nine patients, seven displayed a moderate or marked reduction in manic symptoms by 1 month of gabapentin treatment. Another patient displayed moderate improve-

ment after 3 months. Of these eight patients, six continued to have antimanic responses for follow-up periods ranging from 1 to 7 months. Young et al.[64] described the results of an open trial of gabapentin alone or in combination with other mood stabilizers for the treatment of depression in 15 patients with bipolar I or II disorder. Eight subjects displayed a moderate (> 25%) or marked (> 50%) reduction in Hamilton Rating Scale for Depression total scores at 6 weeks compared with baseline. In contrast, Short and Cooke[65] described the occurrence of hypomanic symptoms when gabapentin was added to carbamazepine and lamotrigine in the treatment of a patient who had epilepsy. Further studies are needed to clarify the effects of gabapentin in patients who have bipolar disorder.

ANTIPSYCHOTICS

Standard Antipsychotics

Psychotic symptoms occur commonly during the manic, mixed, and depressive episodes of bipolar disorder.[1] Based on the available literature, antipsychotics appear to have two primary roles in the treatment of patients who have bipolar disorder: (1) as adjunctive agents to mood stabilizers for the management of acute psychotic mania or psychotic depression and (2) as adjunctive maintenance treatment for patients who have treatment-refractory illness.[7,8] Despite the common adjunctive use of antipsychotics in the treatment of acute mania, no study has prospectively examined the response of acute mania to antipsychotics, mood stabilizers, or their combination on the basis of presence or absence of psychotic symptoms. Thus, whether or not psychotic mania truly requires adjunctive antipsychotics for optional response more often than nonpsychotic mania remains unknown.

At least 15 double-blind, randomized, controlled trials of standard antipsychotic medications for the management of acute mania have been reported to date.[24,40,41,66–77] Five controlled trials in which chlorpromazine was compared with lithium revealed a higher overall rate of improvement by 3 weeks of treatment in patients who received lithium.[66–70] However, one study found chlorpromazine to be more effective than lithium in patients who have prominent psychomotor agitation, which may have been due to more rapid onset of action of the antipsychotic. Other studies that examined antipsychotic medications other than chlorpromazine also found a more rapid antimanic response to these agents than to lithium.[71,75] Janicak et al.,[77] in a meta-analysis of many of these studies, found significantly superior efficacy for lithium (89% responders, 11% nonresponders) compared with antipsychotics (54% responders, 46% nonresponders; $\chi^2 = 13.1$; $df = 1$; $p < .001$). As reviewed previously, three other controlled studies found comparable efficacy when antipsychotics were compared with carbamazepine[40,41] or divalproex.

There are no controlled trials investigating the efficacy and safety of antipsychotics for the treatment of psychotic bipolar depression.[7] In studies of patients who have unipolar psychotic depression, the combination of antipsychotics and antidepressants has been found to be superior to either class of agents alone.[78,79] Extrapolating from these data would suggest that adjunctive antipsychotics may be beneficial in the management of acute psychotic bipolar depression. This suggestion is supported by a report of three patients who experienced depressive relapse when antipsychotics were withdrawn or reduced, but recovered when antipsychotics were reinstituted.[80]

The use of standard antipsychotics is common in the maintenance treatment of patients who have bipolar disorder, but it is associated with several concerns.[14–17] First, there are no compelling data from controlled trials that support the efficacy of these agents as a maintenance treatment in patients who have bipolar disorder.[7,8] Second, maintenance antipsychotic treatment may be associated with the exacerbation of depressive symptoms in some patients.[81–84] Third, patients who have bipolar disorder appear to be at higher risk for developing tardive movement disorders and other neurologic side effects of standard antipsychotics than are patients who have schizophrenia.[85–87]

Surprisingly, no prospective, double-blind, randomized, parallel-design trial has been reported to date that compares antipsychotics and mood stabilizers for the maintenance treatment of patients who have bipolar disorder. Five open trials have investigated the efficacy of depot antipsychotics alone or in combination with lithium and/or carbamazepine.[81,88–91] All studies found significant reductions in the number of manic episodes and overall time patients were affectively ill during treatment with depot antipsychotics compared with prior treatment intervals when depot antipsychotics were not administered. Two open, prospective, comparative maintenance studies of depot flupenthixol use in patients who had bipolar disorder have also been reported.[92,93] In these studies, flupenthixol did not significantly reduce the frequency of affective episodes compared with the pretreatment course of illness[92] and was not significantly better than placebo when added to lithium.[93]

New Antipsychotics

Data from a number of open trials suggest that clozapine may have acute and long-term mood-stabilizing effects in patients who have bipolar disorder, including patients who have mixed mania, rapid cycling, and those refractory to treatment with mood stabilizers, electroconvulsive therapy, and standard antipsychotics.[94–97] Clozapine has also been reported to reduce manic symptoms, mixed affective symptoms, and rapid cycling in bipolar patients without psychosis.[95]

In an analysis of 10 reports of clozapine use in the treatment of patients who had severe, treatment-refractory bi-

polar disorder (N = 94), Zarate et al.[95] found that 71% of the patients displayed clinically significant improvement with clozapine and were successfully maintained on clozapine, alone or with other medications, for follow-up intervals averaging 20 months. As in acute mania, these studies, although preliminary and in need of replication in controlled trials, suggest that clozapine may be a useful maintenance treatment in patients refractory to or intolerant of standard mood stabilizers.

A small number of open trials and case reports have described the use of risperidone in the treatment of acute mania.[98–110] Several impressions emerge from these reports. First, therapeutic effects in the treatment of manic symptoms have been described for risperidone when administered with other mood stabilizers or antipsychotic agents.[99–103] Second, anecdotal reports of cases or small series of patients have described exacerbation of manic symptoms associated with risperidone, especially when given in high doses and without concomitant mood stabilizers.[104–110] Third, two reports[109,111] describe a significant improvement in depressive as well as psychotic symptoms in patients who had psychotic depression or schizoaffective disorder, depressive subtype, and were treated with risperidone.

To date, there are no reports of the efficacy of olanzapine, sertindole, quetiapine, or ziprasidone in the treatment of patients who have bipolar disorder. Preliminary data from a controlled trial comparing olanzapine with haloperidol in the acute treatment of patients who had schizoaffective disorder are of potential relevance to the role of olanzapine in the treatment of bipolar disorder.[112] In this study, olanzapine-treated patients who had schizoaffective disorder, bipolar type, displayed significantly greater improvement in measures of psychotic and depressive symptoms from baseline to endpoint compared with the haloperidol-treated group. Because the pharmacologic profile of olanzapine resembles that of clozapine,[113] and clozapine appears to have mood-stabilizing as well as antipsychotic activity, these initial findings in patients who have schizoaffective disorder suggest that olanzapine may exert thymoleptic as well as antipsychotic effects in patients who have bipolar disorder.[114]

SUMMARY

The anticonvulsants valproate and carbamazepine have established efficacy from controlled trials in the treatment of acute mania. There appear to be differences in their time course of onset with preliminary evidence suggesting that antimanic activity may occur more rapidly when valproate is administered by rapid loading. Response to valproate and carbamazepine has been associated with two similar clinical features, mixed mania and rapid cycling, which are identified with poor response to lithium.

There are substantial differences in the extent to which valproate and carbamazepine have been studied in controlled trials of bipolar depression and as maintenance treatments for bipolar disorder. No controlled trials are available regarding the efficacy of valproate in acute bipolar depression or as maintenance therapy. A small number of controlled trials of carbamazepine in bipolar depression suggest that it may have efficacy in some treatment-refractory patients. Controlled maintenance trials of carbamazepine have significant methodologic limitations. Taken altogether, these studies suggest that carbamazepine may be an effective maintenance treatment but may also be less effective overall than lithium. Only preliminary data regarding the potential efficacy and safety of two new anticonvulsants, lamotrigine and gabapentin, are available.

Standard antipsychotic agents appear to have a role as adjunctive treatment in acute psychotic mania in which they appear to exert more rapid therapeutic effects than lithium. In studies comparing standard antipsychotics with valproate or carbamazepine, no advantage has yet been found for the use of antipsychotic agents over these anticonvulsants, including the reduction of psychotic symptoms. Similarly, although standard antipsychotics are commonly used in the maintenance treatment of patients who have bipolar disorder, their efficacy in this role has yet to be established in controlled trials.

The available data suggest that clozapine and risperidone may have thymoleptic properties different from those of standard antipsychotics. These new antipsychotics may also differ from one another in their specific thymoleptic profiles. Controlled trials of clozapine, risperidone, and other new antipsychotics (e.g., olanzapine, sertindole, quetiapine, and ziprasidone) are needed to assess the efficacy of these agents in patients who have bipolar disorder and to better determine their thymoleptic activity.

CONCLUSION

Anticonvulsants and antipsychotics represent important therapeutic agents in the treatment of patients who have bipolar disorder. Although preliminary data exist, further research is needed to more firmly establish predictors of response associated with valproate and carbamazepine. Similarly, definitive evidence from controlled trials is needed to confirm the preliminary findings of a rapid onset of antimanic activity associated with rapid loading of valproate. Much work remains to be done in elucidating the efficacy of these two agents in the treatment of acute bipolar depression. Gaps also remain in our knowledge in regard to the efficacy of valproate and carbamazepine as maintenance therapies. Lamotrigine and gabapentin represent potential new treatments in need of controlled studies in all phases of bipolar disorder, e.g., acute mania and depression and as maintenance treatments.

Although standard antipsychotic medications are effective as acute (and possibly maintenance) antimanic agents, their use in patients who have bipolar disorder is associated with several concerns, including lack of antidepressant or mood-stabilizing effect, exacerbation of depressive symptoms, and increased risk of tardive movement disorders. Therefore, standard antipsychotics have clearly delineated roles in the adjunctive treatment of acute psychotic mania and as maintenance treatment for patients inadequately responsive to, intolerant of, or noncompliant with mood stabilizers.

Unlike standard antipsychotics that appear to have unidirectional antimanic properties and frequent neurologic side effects, newer antipsychotics may have different thymoleptic profiles and are associated with fewer neurologic side effects. Thus, newer antipsychotic agents are potentially useful alternative or adjunctive agents for patients who have psychotic mania and possibly nonpsychotic mania, rapid cycling, mixed affective states, and psychotic depression. As new antipsychotics become available, each with a distinctive pharmacologic profile, careful elucidation of their potential thymoleptic activity should help to define their roles in the treatment of patients who have bipolar disorder.

Drug names: carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clozapine (Clozaril), divalproex (Depakote), fluoxetine (Prozac), gabapentin (Neurontin), haloperidol (Haldol and others), imipramine (Tofranil and others), lamotrigine (Lamictal), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), sertindole (Serlect), ziprasidone (Zeldox).

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