

CURRENT AND EMERGING TREATMENTS FOR ACUTE MANIA AND LONG-TERM PROPHYLAXIS FOR BIPOLAR DISORDER

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The range of available medications for the acute treatment of bipolar mania and maintenance treatment of bipolar disorder (BD) has expanded rapidly in recent years. Data regarding medications with established antimanic efficacy are growing and a number of new agents with putative mood-stabilizing properties are under study. These developments are fortunate because recent studies also indicate that the long-term outcome of many patients with BD remains poor (43,45,100).

Data from randomized, controlled clinical trials supporting the efficacy of lithium, valproate (VPA), carbamazepine (CBZ), and typical antipsychotics as antimanic and mood-stabilizing agents are reviewed in the following. Studies of two other important drug classes under active study for patients with BD, atypical antipsychotics and novel antiepileptics, are also reviewed (62). Finally, the development of signal transduction modifiers and regulators of neuroplasticity and cellular resiliency as truly novel agents for the treatment of BD is discussed.

LITHIUM

Acute Mania

Lithium was superior to placebo in the treatment of acute mania in five controlled studies (8,31,55,85,93). Only one of these studies utilized a parallel design (8). The remaining four studies were crossover trials of varying duration (31,55,85,93). These crossover studies may have been vulnerable to carry-over, period, and abrupt treatment discontinuation

effects, which may have deflated placebo response rates, and contamination of the study blind (16,49). In addition, two studies utilized nonrandom assignment (31,93). Finally, many of the early landmark lithium studies used diagnostic criteria to define BD that may not be comparable to those of DSM-III-R1 or DSM-IV (2,10,62). Although Bowden and associates used lithium as an active control (8), data from this parallel-design study are the most methodologically rigorous. In this study, 17 (49%) of 35 lithium-treated patients displayed more than 50% reduction in manic symptoms as measured by the Mania Rating Scale (MRS) total score from the Schedule for Affective Disorders and Schizophrenia (SADS-C) compared with 24% of placebo-treated patients at 3 weeks. The lithium-placebo effect size was a moderate 0.4 (48). Further analysis of data from this study revealed that mania characterized by predominantly elevated or elated mood was associated with lithium response, whereas depressive symptoms during mania and multiple prior affective episodes were associated with poor response to lithium (95,96). These findings are similar to those of earlier reports, which found that patients with mixed mania had a lower likelihood of lithium response compared with classic mania (64). In studies in which response of psychotic symptoms was also assessed, lithium also produced significant improvement in these symptoms (8,31,55,93).

Lithium has also been compared with standard antipsychotic agents in nine controlled trials in patients with acute mania (30,40,75,78,86,87,90,97). Of these studies, three found lithium to be comparable to chlorpromazine (40,90) or haloperidol (86) over treatment intervals ranging from 1 to 3 weeks; four found lithium superior to chlorpromazine (40,75,87,97) or haloperidol (86) over 1 to 5 weeks; and one study found haloperidol plus placebo and haloperidol plus lithium superior to lithium plus placebo after 1 and 2 weeks (30). In the largest and most rigorous study compar-

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ing lithium and a typical antipsychotic in acute bipolar mania, Prien and colleagues (78) assessed the efficacy of lithium versus chlorpromazine in 225 patients divided into "highly active" or "mildly active" groups. In the mildly active group, both medications produced significant and comparable improvement. However, chlorpromazine-treated patients experienced more frequent and severe side effects. In contrast, chlorpromazine produced more rapid reduction in measures of agitation, grandiosity, hostility, and psychotic disorganization than lithium in the highly active group over the first week of treatment. In this latter group, dropouts were higher for lithium (38%) than chlorpromazine (8%). At the end of 3 weeks of treatment, both drugs were significantly and comparably effective.

In summary, the studies reviewed indicate that lithium is superior in efficacy to placebo and comparable or possibly superior to standard antipsychotics for the normalization of affective symptoms in mania. These studies also indicate that lithium exerts antipsychotic effects in patients with psychotic mania. On the other hand, standard antipsychotics appear to have a more rapid onset of action and, therefore, may be more effective initially, especially in severely manic or agitated patients.

Maintenance

The prevention of affective episodes is the essential goal of the maintenance treatment of patients with BD. Double-blind, placebo-controlled studies conducted during the late 1960s and 1970s demonstrated that lithium was superior to placebo in preventing recurrent affective episodes (3,19, 21,25,27,38,41,67,79,83,92). A recent analysis of six parallel group, placebo-controlled lithium maintenance treatment trials in patients with bipolar I disorder found an odds ratio favoring relapse in patients receiving placebo of 4.1 (95% CI: 2.1, 7.7) at both 6 and 12 months of treatment (49). However, more recent data from five naturalistic long-term studies of patients maintained on lithium for greater than 1 year suggest that a substantial number of patients do not respond adequately to lithium prophylaxis (36,56, 69,73,81). Baldessarini and Tondo recently reviewed 24 reports on long-term lithium treatment published between 1970 and 1996 and also analyzed its clinical efficacy in 360 patients at a single center who began lithium maintenance monotherapy after 1970 (4). There were no significant differences in lithium response, defined either as percentage of patients displaying more than 50% improvement or percentage episode-free, among patients treated in the 1970s, 1980s, or 1990s. The specific response rates are of clinical interest: Approximately 66% of patients displayed more than 50% improvement and only 33% were episode-free. Not surprisingly, patients with mixed episode, psychotic features or rapid cycling were less treatment responsive. Other studies also found that mixed mania or rapid cycling were associated with a poor lithium response (24,64).

VALPROATE

Acute Mania

The efficacy of VPA in the treatment of acute bipolar mania was established in six double-blind, randomized controlled trials (8,11,26,28,37,76). These studies include comparisons of VPA versus placebo in crossover trials (11,26) versus placebo in a parallel group trial in lithium-refractory or intolerant patients (76), versus placebo and lithium in a parallel group trial⁸ and against lithium in two parallel group trials (28,37), one of which also compared rapid loaded of divalproex (30 mg/kg per day) with gradual titration (37). Two of these trials led to approval by the United States Food and Drug Administration (USFDA) of divalproex for the treatment of manic episodes associated with BD (8,76). In these two studies, response to divalproex as defined by more than 50% reduction in total manic symptoms was comparable, with 53% (76) and 48% (8) of patients responding, respectively. Similarly, among responders in these two studies significant improvement was evident by day 7 and 10 of treatment, respectively, using a gradual divalproex titration schedule beginning with an initial dose of 750 mg per day. Divalproex exerted therapeutic effects on psychotic and manic symptoms in both studies. In the study by Bowden and colleagues (8), all patients with rapid cycling ($n = 8$) were randomly assigned to divalproex; four (50%) displayed at least 50% improvement on the MRS, which was comparable to the overall response of the divalproex-treated group. This finding is consistent with two other reports from open trials suggesting efficacy of divalproex in patients with rapid cycling (13,63). In a subsequent analysis of response according to several definitions of depressive (mixed) mania, Swann and associates found that the presence of even mild depressive symptoms was associated with a poor antimanic response to lithium, but had no significant effect on VPA response (95). Divalproex was well tolerated in this study and significantly more lithium-treated patients dropped out of this trial owing to side effects than patients receiving divalproex or placebo.

VPA and lithium were comparable in efficacy in two other head-to-head comparison trials, although the relatively small sample sizes in these trials makes them vulnerable to a type II error (28,37). As in the Bowden and colleagues study (8), Freeman and colleagues also found that the presence of depressive symptoms during mania was associated with a greater likelihood of VPA than lithium response (28). VPA was compared with haloperidol in an open randomized trial in patients with psychotic mania (65). In that study, 36 inpatients with bipolar I disorder in a manic or mixed episode with psychotic features received either divalproex rapid loading (20 mg/kg per day) or haloperidol (0.2 mg/kg per day) for 6 days. Divalproex and haloperidol were equally effective in reducing both manic and psychotic symptoms (8,76). The improvement in psy-

chosis with divalproex treatment was consistent with findings in two other studies and with improvement in manic psychosis produced by lithium in earlier studies (8,31,55,93). Several other studies investigated the efficacy and tolerability of divalproex rapid loading (20 to 30 mg/kg per day) (37,46,65) and one recent pilot 5-day trial explored intravenous VPA administration (1,200 to 1,800 mg per day) (35). Although all four studies reported rapid improvement (within 3 days) in manic symptoms among responders, only one of these studies was a double-blind, randomized trial (37). In this controlled trial, the study was designed to assess the tolerability of divalproex loading (30 mg/kg per day \times 2 days, then 20 mg/kg per day) and was not powered sufficiently to detect differences in efficacy. VPA has also been compared against placebo as adjunctive therapy to standard antipsychotics in acute mania (68). In a multicenter, double-blind, parallel design, 3-week trial conducted in Europe, 136 patients receiving standard antipsychotics were randomized to VPA or placebo. By study termination, significantly more VPA-treated patients displayed a decrease in concomitant antipsychotic treatment. In summary, these studies suggest that VPA has a broad spectrum of efficacy in acute mania, mixed mania, and rapid cycling, and appears to be comparable to lithium and haloperidol in overall antimanic efficacy.

Maintenance

Open maintenance trials of VPA in patients with BD reported that approximately 45% to 50% of patients experienced a recurrent affective episode in follow-up periods ranging from 6 to 24 months (15,52,82). A randomized, open comparison of lithium and VPA found generally good efficacy for both drugs over an 18-month period (52). Bowden and associates recently reported the results of the largest, prospective, double-blind, randomized maintenance trial of pharmacological treatment in patients with BD using survival analysis to assess time to and rates of relapse (9). In this study, 38% of patients receiving placebo relapsed, compared with 31% on lithium and 24% on divalproex (differences not significant). It is instructive to compare the results of this study with those of the other large maintenance study that compared lithium to placebo (79). In this latter study, 68% of patients receiving placebo relapsed compared with 36% of patients on lithium by 1 year (79). Thus, the drug relapse rates were very similar between studies but the placebo relapse rate was much lower in the Bowden and coworker study (9). This disparity in placebo relapse rates is probably owing to several factors. First, although both studies standardized enrollment by an index manic episode, it is likely that patients in the Bowden and associates study were less severely ill because only 18% had been hospitalized during the index episode, whereas all patients in the Prien and colleagues study had been hospitalized. Second, the definition of relapse differed between the studies. In the

Prien and colleagues study (79), a relapse was an event that required hospitalization or supplemental drug treatment; in the Bowden and associates study (9), it was the occurrence of any affective episode. Finally, the Prien and colleagues study consisted of a more homogeneous sample of lithium responders diagnosed by more conservative diagnostic criteria (80).

As described, many patients with BD have symptomatic or syndromic recurrences on monotherapy with lithium or VPA. The addition of a second mood-stabilizer is a common strategy to enhance maintenance treatment efficacy. Unfortunately, only one controlled trial has examined this approach using the combination of lithium and divalproex in maintenance treatment (89). In this pilot study, 12 patients with bipolar I disorder receiving lithium plasma concentrations (0.8 to 1.0 mEq/L) were randomized to adjunctive maintenance treatment with divalproex (plasma concentrations 50 to 125 mg/L) or placebo and followed for 1 year. Patients who received the combination of lithium and divalproex were significantly less likely to experience a relapse but significantly more likely to suffer at least one moderate or severe adverse event. It is possible that adverse events might be reduced by using doses of lithium and/or divalproex at the lower end of the therapeutic range for each agent.

CARBAMAZEPINE

Acute Mania

Although 14 double-blind controlled studies have found CBZ to be effective in the treatment of acute mania, only five of these studies are not confounded by the use of concomitant agents with antimanic effects (reviewed in Keck and associates 1992) (44). In the only placebo-controlled trial, 19 patients were crossed over between CBZ or placebo (5). During CBZ treatment, 63% of patients displayed significant improvement on global nursing measures of mania, depression, anxiety, anger, and psychosis. Relapse typically occurred on placebo.

Two studies compared CBZ with lithium (53,88). In the first study, 34 inpatients were randomized to lithium or CBZ for up to 4 weeks (53). Twenty-eight patients (14 per treatment group) completed the study and were included in the data analysis. There were no significant differences in improvement between the two drugs on the BPRS and the Beigel-Murphy Manic State Rating Scale. However, lithium-treated patients showed significantly greater improvement in CGI change scores. In addition, only four (29%) of 14 CBZ-treated patients were considered responders, whereas 11 (79%) of 14 lithium-treated patients responded. In the second lithium comparison study (88) 70% of 52 hospitalized patients randomized to lithium or CBZ dropped out of the trial by 8 weeks owing to lack of efficacy.

Of the study completers, 36% who received CBZ and 37% who received lithium were rated as improved (defined as at least partial remission of manic symptoms). Two studies compared CBZ with chlorpromazine in the treatment of acute mania (34,71). In the first comparison trial, 60 acutely manic patients were randomized to either agent in a 6-week trial (71). There were no significant differences in efficacy between the two drugs, with moderate to marked improvement in 70% of the 32 patients treated with CBZ and 60% of 28 patients receiving chlorpromazine. In the second study (34,37) patients were randomized to CBZ ($n = 15$) or chlorpromazine ($n = 19$) in a 3-week trial. Response was assessed in 26 patients who completed the trial. Patients treated with CBZ ($n = 15$) or chlorpromazine ($n = 11$) had comparable improvement. In the CBZ group, 67% were rated as displaying at least moderate improvement and 59% for the chlorpromazine group. In summary, data from these five trials suggest that CBZ is superior to placebo and comparable to lithium and chlorpromazine in the treatment of acute bipolar mania.

Maintenance

The efficacy of CBZ in the prevention of recurrent affective episodes has been a matter of controversy (22,77). This controversy rests in part on the heterogeneity among the early controlled maintenance studies (22,54,74,101), and the availability of only one placebo-controlled maintenance trial (70). Interpretation of this latter study is also limited by the use of adjunctive rescue medications other than lithium and CBZ to treat breakthrough symptoms. The liberal use of these adjunctive treatments thus limits the degree to which relapse rate can be directly attributed to CBZ or placebo in this study.

Two recent large prospective, double-blind, long-term maintenance studies provide new data comparing the efficacy of CBZ with lithium (23,33). In the first study (33), 144 patients were randomized to lithium ($n = 74$; mean \pm SD serum level, 0.6 ± 1 mEq/L) or CBZ ($n = 70$; mean \pm SD) dose, 621 ± 186 mg per day) and followed for 2.5 years. Affective relapse, hospitalization, need for supplemental medication, and adverse events requiring treatment discontinuation were used to define treatment failure. Using survival analysis, there were no statistically significant differences between the two treatment groups in time to episode recurrence or hospitalization. However, significantly more patients receiving CBZ required supplemental medications for symptomatic recurrences and experienced adverse events requiring treatment discontinuation. In a secondary analysis of predictors or response, patients with classical features (bipolar I patients without mood-incongruent delusions and comorbidity) had a lower rehospitalization rate with lithium than with CBZ (32). For patients with nonclassical features (mixed states, bipolar II, and NOS) a trend in favor of CBZ was found.

In the second lithium comparison study, 52 outpatients with bipolar I and II disorder were randomly assigned for an initial year of treatment with lithium or CBZ, a crossover to the alternate drug in the second year, followed by a third year on the combination (23). Among evaluable patients, 13 (31%) of 42 lithium-treated patients relapsed within 1 year compared with 13 (37%) of 35 CBZ-treated patients. Seven (24%) of 29 remaining patients relapsed on combination therapy. As in the previous study, a higher percentage of patients receiving CBZ withdrew because of adverse events. The percentage of patients who had moderate or marked improvement on the CGI was not significantly different: 33% on lithium, 31% on CBZ, 55% on the combination; however, on a variety of measures of mania, lithium was more effective than CBZ. Finally, patients with a history of rapid cycling responded significantly better to the combination (56% response) compared with lithium (28%) or CBZ (19%).

STANDARD ANTIPSYCHOTICS

Acute Mania

There is one double-blind, placebo-controlled study of a standard antipsychotic in the treatment of acute bipolar mania (50). In that study, 13 patients were randomized to chlorpromazine (1,200 mg per day), imipramine (300 mg per day), or placebo for 7 weeks. Response was assessed using a global scale ranging from -9 to $+9$. Chlorpromazine was significantly superior to placebo and imipramine on global outcome (6.1 versus 2.0 and -2.8 , respectively). Studies comparing standard antipsychotics with lithium, VPA, and CBZ are reviewed in the preceding.

Maintenance

There are no parallel group, double-blind randomized maintenance trials of standard antipsychotics in the maintenance treatment of patients with BD.

ATYPICAL ANTIPSYCHOTICS

Clozapine

Acute Mania

No double-blind, randomized controlled trials of clozapine in the treatment of acute bipolar mania have been published. Clozapine has been reported to be an effective anti-manic agent in three open-label, prospective studies (6,14, 18). The first two studies evaluated treatment-refractory bipolar patients. In the first (6), 13 (87%) of 15 acutely manic patients who had failed to respond to a minimum 6-week antipsychotic trial of 500 mg per day chlorpromazine-equiv-

alents in combination with lithium (mean serum level 0.8 mEq/L) were rated as moderate or marked responders to clozapine. In the second study (14), 25 acutely manic patients with bipolar or schizoaffective disorder, all of whom had failed to respond to or tolerate lithium, VPA, or CBZ, and at least two standard antipsychotics, received a 13-week trial of clozapine (mean \pm SD, 194 ± 145 mg per day) following a 1-week washout. Eighteen (72%) patients displayed marked improvement on the YMRS and eight (32%) on the BPRS, defined as more than 50% reduction in total score on either scale. Bipolar patients compared with schizoaffective patients, and non-rapid cyclers compared with rapid cyclers, exhibited significantly greater improvement on the BPRS. In the third study (18), 30 hospitalized acutely manic patients were randomized to clozapine (mean 166 mg per day) or chlorpromazine (mean 310 mg per day) in a 3-week trial. Although clozapine-treated patients displayed significantly lower YMRS scores after 2 weeks, there were no significant differences between the two groups at the end of the trial.

Maintenance

There are no randomized double-blind controlled studies of clozapine in the maintenance treatment of BD. Suppes and co-workers randomized 85 patients with DSM-IV criteria for schizoaffective or BD with treatment-refractory illness to add-on clozapine or treatment as usual (94). After 1 year, patients receiving clozapine displayed significant reductions in measures of mania, psychosis, and global improvement compared with patients receiving treatment as usual. In addition, total medication use decreased significantly in the clozapine group. This open-label, randomized trial confirmed earlier reports suggesting that clozapine exerted long-term mood-stabilizing effects in patients with treatment-refractory BD (102).

Olanzapine

Acute Mania

The efficacy of olanzapine in the treatment of acute bipolar mania has been established in three double-blind, controlled trials (7,98,99). In the first of two placebo-controlled studies, 139 inpatients with bipolar I disorder were randomized to olanzapine ($n = 70$) or placebo ($n = 69$) for up to 3 weeks (99). Olanzapine was begun at 10 mg per day and adjusted by 5-mg per day increments within a range of 5 to 20 mg per day; the median modal dose was 15 mg per day. Concomitant lorazepam up to 4 mg per day was permitted for the first 7 days as needed for agitation; 2 mg per day was permitted for the subsequent 3 days. The olanzapine group displayed significant improvement on the YMRS, CGI-BP severity of mania, and the PANSS total and positive symptom scores compared with the placebo group.

Olanzapine also produced a significantly higher response rate (defined as $\geq 50\%$ improvement in YMRS score) of 49% compared with placebo at 24%. However, olanzapine did not separate from placebo on the YMRS until the third week of treatment.

In the second placebo-controlled trial, 115 bipolar I inpatients were randomized to olanzapine ($n = 55$) or placebo ($n = 60$) for up to 4 weeks (98). This study used a higher initial starting dose of olanzapine, 15 mg per day, and concomitant lorazepam use was further restricted to 2 mg per day for the first 10 days. The olanzapine group again displayed significant improvement on the YMRS, CGI-BP severity of mania, PANSS total and positive symptom scores compared with the placebo group. These differences were evident by week one (the time of the first rating) and sustained throughout the trial. Olanzapine-treated patients also exhibited significantly higher response (65% versus 43%, respectively) and remission (61% versus 36%, respectively) rates than placebo-treated patients. In addition, patients presenting with prominent depressive symptoms during mania (HamD-21 scores \geq baseline) showed a significant reduction in HamD-21 total scores with olanzapine compared with placebo.

In the third controlled trial, 30 inpatients with acute mania were randomized to olanzapine ($n = 15$) or lithium ($n = 15$) for 4 weeks (7). Olanzapine was administered as a fixed dose of 10 mg per day and lithium at 400 mg BID (mean serum level 0.74 mEq/L). Concomitant lorazepam 4 to 12 mg per day was permitted throughout the 4-week trial. There were no significant differences between the two treatment groups on any of the primary outcome measures—the Mania Scale and BPRS total scores and the CGI improvement scale. However, olanzapine-treated patients displayed significantly greater improvement than lithium-treated patients on the CGI severity scale at the end of 4 weeks of treatment.

Maintenance

There are no controlled trials of olanzapine in the maintenance treatment of BD published to date. In an open-label 52-week extension trial following the initial placebo-controlled acute mania study, none of the 98 patients who participated developed tardive dyskinesia during long-term treatment (99).

Risperidone

Acute Mania

There are two double-blind randomized active comparator studies of risperidone in the treatment of acute bipolar mania (84,86). In the first study, 45 inpatients were randomized to risperidone 6 mg per day ($n = 15$), haloperidol 10 mg per day ($n = 15$), or lithium 800 to 1,200 mg per

day (with levels ranging from 0.6 to 1.2 mEq/L) ($n = 15$) for up to 4 weeks (86). There were no significant differences among the three treatment groups in reductions on the YMRS, BPRS, CGI, and GAF from baseline to endpoint (LOCF). In the second trial, 158 inpatients receiving lithium or VPA were randomized to adjunctive therapy with risperidone 1 to 6 mg per day ($n = 52$), haloperidol ($n = 53$), or placebo ($n = 51$) for up to 3 weeks (84). Patients receiving risperidone or haloperidol displayed significantly greater improvement at 1 week, 2 weeks, and at endpoint (LOCF), but not at 3 weeks of treatment on the YMRS compared with patients receiving placebo. There were no significant differences between the risperidone and placebo groups from baseline to endpoint in BPRS and HamD total scores. There are no controlled trials of risperidone in the maintenance treatment of patients with BD.

Ziprasidone

Acute Mania

Ziprasidone has been studied in placebo-controlled trials in the treatment of acute mania in patients with BD and schizoaffective disorder, bipolar type (42,47). In a 3-week acute treatment trial of inpatients with bipolar I disorder, manic or mixed, 199 patients were randomized to ziprasidone 80 to 160 mg per day or placebo (42). Ziprasidone produced significant reductions on the Manic Rating Scale (MRS) total score (from the SADS-C) at day two and throughout the remainder of the trial compared with placebo. Based on a $\geq 50\%$ reduction in MRS total scores, significantly more ziprasidone-treated patients responded (50%) compared with placebo-treated patients (36%). This study confirmed the findings of an earlier study that found that ziprasidone produced significant reductions in manic symptoms compared with placebo in patients with schizoaffective disorder (47). There are no controlled maintenance trials yet published of ziprasidone in BD. Finally, there are no controlled trials of quetiapine in the acute or maintenance treatment of BD.

NEW ANTIEPILEPTICS

Four new antiepileptic agents, gabapentin, lamotrigine, topiramate, and tiagabine are being investigated as potential antimanic agents (62). To date, no controlled trials have been reported for topiramate or tiagabine. However, two controlled studies evaluated gabapentin in the treatment of bipolar mania (29,72). In the first study, 117 outpatients with bipolar I disorder who displayed breakthrough manic symptoms (defined as a YMRS total score ≥ 12), whereas on therapeutic doses of lithium, VPA, or the combination, were randomized to adjunctive treatment with gabapentin 600 to 3,600 mg per day ($n = 55$) or placebo ($n = 59$)

(72). Patients receiving placebo exhibited significantly greater improvement in YMRS total scores compared with patients receiving gabapentin.

In the second controlled trial, 28 patients with bipolar I ($n = 13$) or bipolar II ($n = 15$) disorder received 6-week crossover trials of gabapentin, lamotrigine, or placebo (29). The reduction in manic symptoms as measured by the CGI-BP was not significantly different among the three treatments. However, manic symptoms were quite low at baseline, raising the possibility that meaningful differences among the three groups might not have been detected. Lamotrigine was also compared with lithium in a 4-week double-blind, randomized trial in 30 inpatients with bipolar I disorder (39). Patients received lithium 800 mg per day or lamotrigine 25 mg per day for the first week, 50 mg per day during the second, then 100 mg per day for the final 2 weeks of the trial. At the conclusion of the study, both agents produced significant reductions in mean Mania Rating Scale, BPRS, and CGI total scores from baseline to endpoint. There were no significant differences between the two treatment groups. The small sample size, low lithium dose, use of as needed lorazepam throughout the trial, and absence of a placebo control group limit the results of this trial.

Lamotrigine is the only new antiepileptic agent studied to date in a randomized controlled trial in the maintenance treatment of bipolar disorder (12). In this study, bipolar I ($n = 130$) and bipolar II ($n = 52$) patients who were stabilized on initial open-label lamotrigine monotherapy were randomized to lamotrigine or placebo in a 26-week prevention trial. There were no significant differences between the lamotrigine and placebo groups in time to drop out for any reason and time to need for additional medication among bipolar I patients. However, in bipolar II patients, treatment with lamotrigine was associated with significantly lower relapse rates on these measures compared with placebo.

THE RATIONAL DEVELOPMENT OF TRULY NOVEL TREATMENTS FOR BD

Signal Transduction Modifiers

Although the large number of anticonvulsants and atypical antipsychotic agents in the pharmacopeia has greatly enhanced our ability to treat patients with BD, there is still clearly a real need to develop truly novel agents to adequately treat this devastating illness, and modify the long-term outcome for millions of sufferers. A major impediment in the development of truly novel agents has been the dearth of knowledge pertaining to the underlying pathophysiology of the illness. A true understanding of the pathophysiology of an illness as complex as BD must clearly address its neurobiology at different physiologic levels (i.e., molecular, cellular, systems, and behavioral). Abnormalities in gene expres-

sion undoubtedly underlie the neurobiology of the disorder at the molecular level; this will become evident as we identify the susceptibility and protective genes for BD in the coming years. Once this has been accomplished, however, the even more difficult work must begin to examine the impact of the faulty expression of these gene products (proteins) on integrated cell function. It is at these levels that critical signaling molecules recently have been identified as candidate targets for the development of truly novel agents for the treatment of BD.

Multicomponent, cellular signaling pathways interact at various levels, thereby forming complex signaling networks that allow the cell to receive, process, and respond to information (58). The high degree of complexity generated by these signaling provides neurons with the flexibility to generate the wide range of responses observed in the nervous system. These pathways are undoubtedly involved in regulating such diverse vegetative functions as mood, appetite, and wakefulness, as well as higher cognitive functions—systems that are all affected in BD—and thus represent attractive putative mediators of mood stabilization. Over the last decade, there have been major advances in our understanding of the critical role of the protein kinase C (PKC) signaling pathway as a therapeutically relevant target for the long-term actions of mood stabilizers (57,59). The preponderance of the data indicates that chronic lithium attenuates PKC responses and down-regulates specific PKC isozymes (57). Studies in rodents and cultured cells have demonstrated that chronic (but not acute) lithium produces an isozyme-selective reduction in PKC α and ϵ . Moreover, the structurally highly dissimilar antimanic agent VPA produces strikingly similar effects on the PKC signaling pathway, as does lithium (17,57). In view of the pivotal role of the PKC signaling pathway in the regulation of neuronal excitability, and neurotransmitter release (57), it was postulated that the attenuation of PKC activity might play a major role in the antimanic effects of lithium and VPA. There is currently only one relatively selective PKC inhibitor available for human use—tamoxifen (20). Tamoxifen, a synthetic nonsteroidal antiestrogen, is also a potent PKC inhibitor at therapeutically relevant concentrations (20). Therefore, a pilot study was initiated to investigate the efficacy of tamoxifen in the treatment of acute mania, and it was found that tamoxifen did indeed possess antimanic activity (57,58). Clearly, the results have to be considered preliminary owing to the small sample size thus far. Nevertheless, the significant (and in some cases rapid and striking) results that have been observed are intriguing. In view of the preliminary data suggesting the involvement of the PKC signaling system in the pathophysiology of BD (17,57), these results suggest that PKC inhibitors may be very useful agents in the treatment of BD. Larger, double-blind placebo-controlled studies of tamoxifen and novel selective PKC inhibitors in the treatment of mania are clearly warranted.

In recent years, a hitherto completely unexpected target

for the action of lithium has been identified. Klein and Melton (51) were the first to demonstrate that lithium, at therapeutically relevant concentrations, inhibits glycogen synthase kinase 3B (GSK3B). GSK3B is now known to play a critical role in the CNS, by regulating various cytoskeletal processes, synaptic plasticity, and long-term gene expression (51,59). Interestingly, VPA (but not CBZ) also concentration-dependently inhibits GSK-3B *in vitro*, with significant effects observed at concentrations of VPA similar to those attained clinically (17,60). Most recently, it has been demonstrated that the chronic (3- to 4-week) administration of lithium and VPA also increase B-catenin levels in rodent brain (Chen and Manji, unpublished observations), compatible with inhibition of GSK3B during chronic *in vivo* administration of the agents under therapeutic paradigms. Overall, GSK-3B appears to play a critical role in regulating neuroplastic events in the CNS, and there is considerable excitement about the possibility of developing novel GSK-3B modulators as potential new therapeutics for both BD and neurodegenerative diseases (60).

NEUROTROPHIC AND NEUROPROTECTIVE AGENTS FOR THE OPTIMAL LONG-TERM TREATMENT OF BD

Recent studies investigating potential structural brain changes in mood disorders have demonstrated reductions in regional CNS volume and cell numbers (both neurons and glia) in many patients (61). It is thus noteworthy that lithium and VPA have recently been demonstrated to robustly increase the expression of the cytoprotective protein bcl-2 in the CNS (59,61). Chronic lithium not only exerts neuroprotective effects in several preclinical paradigms, but also enhances hippocampal neurogenesis (61). VPA robustly promotes neurite outgrowth and activates the ERK MAP kinase pathway, a signaling pathway utilized by many endogenous neurotrophic factors (61). Consistent with its preclinical neurotrophic/neuroprotective effects, chronic lithium treatment of patients with BD increases brain N-acetylaspartate (NAA, a putative marker of neuronal viability and function) levels, effects that are localized almost exclusively to gray matter (61). To determine if lithium was producing neuropil increases, quantitative three-dimensional MRI studies were undertaken that revealed that chronic lithium significantly increases total gray matter volume in the human brain of patients with BD (61). The evidence demonstrating the neurotrophic effects of lithium, VPA, and antidepressants, the enhancement of hippocampal neurogenesis in the adult mammalian brain, as well as the growing appreciation that mood disorders are associated with cell loss and atrophy, suggest that these effects may be very relevant for the long-term treatment of mood disorders. It is perhaps useful to conceptualize the cell death and atrophy that occurs in mood disorders as arising from an impair-

ment of “cellular resiliency.” In this context, it is noteworthy that a variety of strategies to enhance cellular resiliency via effects on molecules involved in cell survival and cell death pathways are currently under investigation.

CONCLUDING REMARKS

The growing body of data implicating signaling pathways in the pathophysiology and treatment of BD suggests that compounds with potent effects distal to the receptor may represent truly novel treatments for BD. The rapid technological advances in molecular and cellular biology have greatly enhanced our ability to understand the complexities of the regulation of neuronal function; these advances are leading to an increasing number of avenues to modulate transmembrane signaling pathways, and hold much promise for the development of truly novel and improved therapeutics. Emerging results from a variety of clinical and preclinical experimental and naturalistic paradigms also suggest that optimal long-term treatment of BD may only be achieved by the early use of agents with neurotrophic/neuroprotective effects, irrespective of the primary, symptomatic treatment. The development of new treatments that regulate molecules involved in cell survival and cell death pathways, such as CREB, BDNF, Bcl-2, and MAP kinases remains an exciting prospect for the future.

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