Therapeutic Approaches

Pharmacologic Agents for the Treatment of Acute Bipolar Mania

Susan L. McElroy and Paul E. Keck, Jr.

The knowledge base regarding the medical treatment of acute bipolar mania is rapidly expanding. Information about agents with established antimanic properties is increasing, and more agents with putative antimanic properties are being identified. We first review the controlled studies supporting the efficacy of the established antimanic agents lithium, valproate, and carbamazepine and standard antipsychotics. We then review available research on two important classes of drugs that are emerging as potential treatments for acute mania: the novel antipsychotics, which include clozapine, olanzapine, quetiapine, risperidone, and ziprasidone, and the new antiepileptics, which include gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate, and zonisamide. We conclude that although controlled data are accumulating to support the efficacy of several atypical antipsychotics in the treatment of acute bipolar mania, particularly olanzapine, ziprasidone, and risperidone, the new antiepileptics need more extensive study before it can be concluded that any of them possess specific antimanic properties. We also conclude that as the medical options for acute bipolar mania expand, treatment guidelines must remain both evidence based and flexible, so that they represent cutting edge medical science yet can be tailored to the specific needs of individual patients.

Established Antimanic Agents

Lithium

Lithium was the first drug approved by the United States Food and Drug Administration (FDA; in 1970) for the treatment of “manic episodes of manic-depressive illness” (Goodwin and Jamison 1990). Five controlled studies have demonstrated that lithium is superior to a placebo for the treatment of acute mania (Bowden et al 1994; Goodwin et al 1969; Maggs 1963; Schou et al 1954; Stokes et al 1971; Table 1). Summarized below, several methodological limitations should be considered in interpreting these studies. First, only one study (conducted after lithium was granted its approval by the FDA for the treatment of acute mania (Bowden et al 1994; Goodwin et al 1969; Maggs 1963; Schou et al 1954; Stokes et al 1971; Table 1). Summarized below, several methodological limitations should be considered in interpreting these studies. First, only one study (conducted after lithium was granted its approval by the FDA for the treatment of acute mania) employed a parallel design (Bowden et al 1994); the four earlier studies essentially performed completer analyses; last observation carried forward (LOCF) analyses were not conducted. Completer analyses, which only evaluate patients who receive a treatment for a specified duration of their reputations as having established antimanic efficacy, we limit our review of these agents to double-blind, controlled monotherapy and placebo-controlled add-on or dual therapy studies. We then review available research on two important classes of drugs that are emerging as potential treatments for acute mania: the novel antipsychotics, which include clozapine, olanzapine, quetiapine, risperidone, and ziprasidone, and the new antiepileptics, which include gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate, and zonisamide. We conclude that as the medical options for acute bipolar mania expand, treatment guidelines must remain both evidence based and flexible, so that they represent cutting edge medical science yet can be tailored to the specific needs of individual patients.

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Table 1. Double-Blind, Placebo-Controlled Studies of Lithium Monotherapy in Acute Bipolar Mania

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Duration (days)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schou et al 1954</td>
<td>Random, crossover^a</td>
<td>38^b</td>
<td>“Usually” 14 for Li and PBO</td>
<td>14 (37%) positive effect,^d 18 (47%) possible effect, 6 (16%) negative effect</td>
</tr>
<tr>
<td>Maggs 1963</td>
<td>Random, crossover, ABA vs. BAB</td>
<td>28</td>
<td>14 for Li and PBO</td>
<td>Li superior to PBO for 18 patients who completed entire 6-week study</td>
</tr>
<tr>
<td>Goodwin et al 1969</td>
<td>Nonrandom, crossover</td>
<td>12</td>
<td>ND</td>
<td>9 (75%) response to Li,^c 3 (25%) worse with Li</td>
</tr>
<tr>
<td>Stokes et al 1971</td>
<td>Nonrandom, crossover</td>
<td>28</td>
<td>7–10 for Li and PBO</td>
<td>42 (75%) 36 response to Li,^d</td>
</tr>
<tr>
<td>Bowden et al 1994</td>
<td>Random, parallel-group, VPA comparison</td>
<td>Li 35, PBO 73, VPA 68</td>
<td>21</td>
<td>17 (41%) 42 response to PBO^d</td>
</tr>
<tr>
<td>Overall monotherapy response^e</td>
<td></td>
<td>85</td>
<td></td>
<td>33 (48%) response to VPA (p = .004)</td>
</tr>
</tbody>
</table>

^a Lithium sometimes administered as “open treatment for a certain period.”
^b Includes 30 patients with “typical” and 8 patients with “atypical” (schizoaffective) manic–depressive illness.
^c Worsening with PBO substitution part of definition of response to Li.
^d Refers to number of treated periods of mania.
^e Includes those studies in which Li response rate is quantifiable (Bowden et al 1994; Goodwin et al 1969; Schou et al 1954).

Time, may be biased toward showing efficacy, as opposed to LOCF analyses, which evaluate all patients who receive a treatment for any duration of time. Fourth, the diagnostic criteria used to define bipolar disorder in the early lithium studies were not necessarily comparable to those of DSM-III-R (American Psychiatric Association 1987) or DSM-IV (American Psychiatric Association 1994).

In the first placebo-controlled, crossover study (Schou et al 1954) a definite response based on global impression of improvement was reported in 12 (40%) and a probable response in 15 (50%) of 30 patients with typical bipolar disorder. Response was less robust in eight patients with atypical features (which implied a schizoaffective diagnosis), with two (25%) displaying a probable response. In the second crossover trial (Maggs 1963), which was the first study to use formal rating scales (i.e., the Wittenborn Scale) and to analyze data statistically, 28 inpatients with mania were randomized to three consecutive 14-day periods of lithium–rest–placebo or placebo–rest–lithium. Nine patients did not complete their 6-week cycles of treatment, and results were based on the 18 patients who completed their trials. In these 18 patients, lithium was superior to a placebo during the second week of treatment on the Wittenborn Scale measures of “manic states” and “schizophrenic excitement.”

In the first United States study (Goodwin et al 1969) the longitudinal efficacy of lithium was compared with a placebo in 12 patients with mania; eight (67%) displayed a complete response and one (8%) a partial response. A complete response was defined as complete remission of all manic symptoms within 2 weeks of starting lithium and return of symptoms during placebo periods; a partial response was defined as a decrease in mean mania ratings of at least three points within 2 weeks of starting lithium, but not complete remission of symptoms, and an increase in symptoms during placebo periods. In the fourth study (Stokes et al 1971) 38 inpatients with “typical manic depressive illness” were evaluated in a crossover design with alternating 7- to 10-day periods on lithium or a placebo. Although 7- to 10-day trial periods may have limited the patients’ ability to display a more robust lithium response, the equally brief placebo periods may have been confounded by residual lithium effects. Despite these caveats, mania ratings decreased in 75% of lithium treatment periods, as compared with 41% of placebo treatment periods.

In the only randomized, double-blind, placebo-controlled, parallel-design trial of lithium published to date in acute bipolar mania (Bowden et al 1994) lithium was used as an active control substance in a study designed primarily to assess the antimanic efficacy of valproate. In this study, 17 (49%) of 35 patients receiving lithium displayed at least 50% improvement on the Mania Rating scale (MRS) of the Schedule for Affective Disorders and Schizophrenia (SADS-C) at 3 weeks, as compared with 18 (25%) of 73 patients receiving a placebo and 33 (48%) of 68 patients receiving valproate. Regarding onset of response, both lithium and valproate first separated from the placebo on the MRS on day 10 of treatment. On day 8 of treatment, the mean lithium and valproate serum concentrations were 1.0 mmol/L and 77 mg/mL, respectively.

In summary, these studies showed that lithium is superior in efficacy to a placebo in acute bipolar mania, usually requiring a 1- to 3-week trial at therapeutic levels to exert significant antimanic effects. The pooled response rate from the three placebo-controlled studies in which patient response...
rate to lithium monotherapy was quantifiable revealed that 58 (68%) of 85 acutely manic patients experienced at least partial improvement with lithium (Bowden et al 1994; Goodwin et al 1969; Schou et al 1954; Table 1). Further analysis of the Bowden et al (1994) study showed that a history of previous lithium response and pure mania, or of mania with predominantly elevated or elated mood and without depressive symptoms (Swann et al 1997), were associated with favorable response to lithium. In those studies in which response of psychotic symptoms was assessed, lithium also produced significant improvement in these symptoms (Bowden et al 1994; Goodwin et al 1969; Maggs 1963; Stokes et al 1971); however, psychotic symptoms in the absence of manic symptoms (Schou et al 1954), depressive symptoms during mania (Swann et al 1997), and a greater number (approximately 10 or more) of prior mood episodes (Swann et al 1999) were associated with poor antimanic response to lithium.

Lithium has also been compared with standard antipsychotic agents in nine controlled trials in the treatment of acute bipolar mania (Garfinkel et al 1980; Johnson et al 1968, 1971; Platman 1970; Prien et al 1972; Segal et al 1998; Shopsin et al 1975; Spring et al 1970; Takahashi et al 1975; Table 2). Interpretation of the results of virtually all of these studies is limited because of the inclusion of manic patients with schizoaffective disorder, lack of placebo comparison groups, lack of standardized rating scales for mania, lack of performance of LOCF analyses, and/or the possibility of occurrence of a Type II error (the failure to find a significant difference between treatments because of a small sample size; Table 2). Nonetheless, of these nine studies, three involving 58 patients found lithium comparable to chlorpromazine (Johnson et al 1971; Spring et al 1970) or haloperidol (Segal et al 1998) over periods of 1 to 4 weeks; four studies involving 160 patients found lithium superior to chlorpromazine (Johnson et al 1968; Platman 1970; Shopsin et al 1975; Takahashi et al 1975) and/or haloperidol (Shopsin et al 1975) over periods of 1 to 5 weeks; and one study (Garfinkel et al 1980) involving 21 patients found haloperidol plus a placebo and haloperidol plus lithium superior to lithium plus a placebo (and equivalent to one another) after 1 and 2 weeks.

In the ninth study, the largest and most rigorous comparison of lithium and an antipsychotic conducted in acute bipolar mania to date, Prien et al (1972) evaluated the response of 225 manic inpatients to lithium versus chlorpromazine according to degree of psychomotor agitation by dividing patients into “highly active” (N = 125) or “mildly active” (N = 130) groups. The dosage of lithium ranged from 500 to 4000 mg/day, with a mean of 1800 mg/day; the median lithium level was 1.4 mEq/L for the highly active group and 1.2 mEq/L for the mildly

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**Table 2. Controlled Studies of Lithium and Standard Antipsychotics in Acute Bipolar Mania**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Duration (days)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson et al 1968</td>
<td>Random, parallel-group</td>
<td>Li 18</td>
<td>21–28</td>
<td>14 (78%) response to Li,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPZ 11</td>
<td></td>
<td>4 (36%) response to CPZ</td>
</tr>
<tr>
<td>Platman 1970</td>
<td>Random, parallel-group</td>
<td>Li 13</td>
<td>21</td>
<td>Li superior to CPZ after 3 weeks (ns)</td>
</tr>
<tr>
<td>Spring et al 1970</td>
<td>Random, parallel-group, crossover of nonresponders</td>
<td>Li 7</td>
<td>21</td>
<td>6 (86%) response to Li,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPZ 5</td>
<td></td>
<td>3 (60%) response to CPZ (ns)</td>
</tr>
<tr>
<td>Johnson et al 1971</td>
<td>Random, parallel-group</td>
<td>Li 13</td>
<td>21</td>
<td>5 CPZ and 6 Li completers showed significant and equal improvement on BPRS and CGI; Li superior to HAL on “major component” of TRAM; overall, ns</td>
</tr>
<tr>
<td>Prien et al 1972</td>
<td>Random, parallel-group</td>
<td>Mildly active 130</td>
<td>21</td>
<td>Li = CPZ in mildly active group at weeks 1, 2, and 3; CPZ superior to Li in highly active group at weeks 1 and 2, equivalent to Li at week 3</td>
</tr>
<tr>
<td>Shopsin et al 1975</td>
<td>Random, parallel-group</td>
<td>Li 10</td>
<td>21</td>
<td>7 (70%) response to Li,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPZ 10</td>
<td></td>
<td>1 (10%) response to CPZ,</td>
</tr>
<tr>
<td>Takahashi et al 1975</td>
<td>Random, parallel-group</td>
<td>Li 37</td>
<td>35</td>
<td>25 (68%) response to Li,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CPZ 34</td>
<td></td>
<td>17 (50%) response to CPZ (p = .05)</td>
</tr>
<tr>
<td>Garfinkel et al 1980</td>
<td>Random, parallel-group</td>
<td>Li + PBO 7</td>
<td>21</td>
<td>HAL + PBO = HAL + Li; both superior to Li + PBO in improving global clinical ratings on days 8, 15, and 22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HAL + PBO 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Li + HAL 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Segal et al 1998</td>
<td>Random, parallel-group, HAL comparison</td>
<td>Li 15</td>
<td>28</td>
<td>Li = HAL in decreasing manic symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HAL 15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Li, lithium; CPZ, chlorpromazine; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression; HAL, haloperidol; TRAM, Treatment Response Assessment Method; PBO, placebo.
active group. Chlorpromazine doses ranged from 200 to 3000 mg/day, with a mean of 1000 mg/day. In the mildly active group, LOCF analysis showed that both medications produced significant and comparable improvement on the Brief Psychiatric Rating Scale (BPRS), the Inpatient Multidimensional Psychiatric Scale, and the Psychotic Inpatient Profile; however, side effects were more frequent and severe among the chlorpromazine-treated patients. By contrast, in the highly active group LOCF analysis showed that chlorpromazine produced more significant reductions in measures of agitation, excitement, grandiosity, hostility, and psychotic disorganization than did lithium during the first week of treatment. In addition, dropouts in the lithium-treated group were higher (38%) than in the chlorpromazine-treated group (8%). By 3 weeks of treatment both drugs were significantly and comparably effective. The authors concluded that chlorpromazine was superior to lithium in the initial treatment of highly active patients, but that the two drugs were equally effective in mildly active patients. Of relevance when interpreting other lithium–antipsychotic comparator trials, a completer analysis of the highly active group showed no differences between the lithium- and chlorpromazine-treated patients.

In summary, these data suggest that lithium is comparable and possibly superior to antipsychotics in the short term (i.e., 3- to 6-week treatment of acute bipolar mania). They also suggest that lithium exerts antipsychotic effects in mania; however, these data also indicate that antipsychotics may have a more rapid onset of action in mania and, therefore, may be more effective initially (i.e., within the first week), especially in severely manic or highly agitated patients.

It is important to note that the response rates in the above studies were to lithium monotherapy, and that these rates would be expected to be more robust with the use of adjunctive antimanic agents. Although there are controlled add-on trials in which other potential antimanic agents are added to lithium, we were unable to locate any such trials in which lithium was added to another antimanic agent. Nonetheless, numerous open reports suggest the antimanic effects of lithium may be augmented by other mood stabilizers, standard antipsychotics, and atypical antipsychotics (Freeman and Stoll 1998).

**Valproate**

Five controlled trials have shown valproate to be efficacious as monotherapy for the short-term treatment of acute bipolar mania (Bowden et al 1994; Brennan et al 1984; Emrich et al 1981; Freeman et al 1992; Pope et al 1991; Table 3). These studies include comparisons of valproate and a placebo in crossover trials without concomitant psychotropics (Brennan et al 1984; Emrich et al 1981), valproate and a placebo in a parallel-group trial in lithium-refractory or intolerant patients (Pope et al 1991), valproate and lithium in a parallel-group trial (Freeman et al 1992), and valproate and a placebo and lithium in a...
parallel-group trial (Bowden et al 1994). The last three studies (Bowden et al 1994; Freeman et al 1992; Pope et al 1991), which enrolled the largest patient samples, allowed as-needed lorazepam at low dosages during the initial week of 3-week trials. Two of these trials (Bowden et al 1994; Pope et al 1991) led to valproate being the second drug approved by the FDA for the treatment of the manic episodes associated with bipolar disorder.

In the first double-blind, placebo-controlled, parallel-group study (Pope et al 1991) 36 inpatients with DSM-III-R bipolar disorder, manic phase, who were either lithium refractory or lithium intolerant, were randomly assigned to valproate (N = 17) or to a placebo (N = 19) for 7 to 21 days. Compared with placebo-treated patients, valproate-treated patients displayed statistically significant improvement on all three measures used to assess response: the Young Mania Rating Scale (YMRS), the BPRS, and the Global Assessment of Functioning Scale (GAF). Of the 17 patients receiving valproate, nine (53%) displayed a 50% or greater reduction on the YMRS, compared with two (10%) of the 19 patients receiving a placebo. Patients receiving valproate required significantly less lorazepam, and there was no statistically significant difference in the frequency of side effects between the two groups. Further, in responders the onset of antimanic response to divalproex was prompt, with significant improvement occurring within the first week of treatment despite use of a gradual titration schedule (the beginning valproate dose was 750 mg/day).

In the second double-blind, parallel-group, controlled study (Freeman et al 1992) 27 patients with DSM-III-R bipolar disorder, manic phase were randomized to valproate or lithium. Both drugs produced significant and comparable improvement as measured by the MRS of the SADS-C, the BPRS, and the GAF. Twelve (92%) of 13 patients assigned to the lithium group were rated as responders, compared with nine (64%) of 14 patients assigned to the valproate group. Although the response rate to lithium exceeded that to valproate in this study, the difference was not statistically significant (p = .20 by Fisher exact test, two-tailed). Unlike the case with lithium, favorable response to valproate was associated with high pretreatment depression scores.

In the second double-blind, placebo-controlled, parallel-group study (Bowden et al 1994) 179 inpatients meeting Research Diagnostic Criteria for manic disorder were randomized to valproate (N = 68), lithium (N = 35), or a placebo (N = 73) for up to 3 weeks. Both valproate- and lithium-treated patients had statistically significantly greater improvement on the primary measure—the MRS of the SADS-C—than placebo-treated patients by day 10 of the study, beginning with an initial valproate dose of 750 mg/day and using a gradual titration schedule. The proportions of patients improving at least 50% on the MRS were comparable for valproate (48%) and lithium (49%) and superior to a placebo (25%). 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 rate of the divalproex-treated group. This response rate, though limited by the small number of patients, is notable because rapid cycling is associated with poor lithium response (Dunner and Fieve 1974). In addition, analysis of response according to several definitions of depressive mania based on the SADS-C depression subscale measure showed that the presence of even mild depressive symptoms was associated with a poor antimanic response to lithium, but had no significant effect on valproate response (Swann et al 1997). (There was a trend, however, toward more improvement with valproate with the narrowest definition of depressive mania.) Finally, significantly more lithium-treated patients dropped out of this study due to side effects than did patients receiving valproate or a placebo.

One study has compared valproate monotherapy with a standard antipsychotic in the treatment of acute bipolar mania. In that study, 36 inpatients with bipolar I disorder, manic or mixed phase with psychotic features by DSM-III-R criteria, were randomized to receive either valproate (20 mg/kg/day) or haloperidol (0.2 mg/kg/day) in single (rater)-blind fashion for 6 days (McElroy et al 1996). There was no placebo group. Lorazepam up to 4 mg/day was the only other permitted psychotropic for the management of agitation. Valproate and haloperidol were equally effective in acutely reducing manic and psychotic symptoms as assessed by the YMRS and the Scale for Assessment of Positive Symptoms, respectively. Ten (48%) of 21 patients receiving valproate and five (33%) of 15 patients receiving haloperidol were classified as responders. The greatest rate of improvement for both drug regimens occurred over the first 3 days of treatment. Adverse effects were infrequent and minor for both drugs, except for extrapyramidal side effects, which were significantly more common with haloperidol.

In summary, pooled response rates to valproate from the three parallel-design, double-blind, controlled, parallel-design monotherapy studies (Bowden et al 1994; Freeman et al 1992; Pope et al 1991) revealed significant improvement (i.e., at least a partial response or a 50% or greater reduction in manic symptoms) in 54% of patients, as well as efficacy superior to that of a placebo (Bowden et al 1994; Pope et al 1991) and efficacy equivalent to that of lithium (Bowden et al 1994; Freeman et al 1992). These studies further suggest that valproate may have a broad spectrum of efficacy in acute mania, with effectiveness in mania with and without psychotic features, with and
without depressive features, with and without rapid cycling, and with and without numerous prior mood episodes (Bowden et al 1994; McElroy et al 1991). Indeed, the Bowden et al (1994) study suggests that valproate may be more effective than lithium for acute mania with depressive features (Swann et al 1997) and acute mania associated with many (10 or more) prior mood episodes (Swann et al 1999).

As with the controlled studies of lithium for bipolar acute mania, the response rates in the above studies were attributable to valproate monotherapy and might be expected to be more robust with the use of adjunctive agents. Indeed, valproate has recently been compared with a placebo as add-on therapy to standard antipsychotics in the treatment of acute bipolar mania. In a multicenter, parallel-group, double-blind, 3-week study from Europe, 136 hospitalized patients with acute mania by ICD-10 criteria were randomized to receive carbamazepine (haloperidol and/or perazine) were randomized to receive add-on therapy with valproate (20 mg/kg/day) or a placebo (Müller-Oerlinghausen et al 2000). The primary outcome measure was the mean dose of antipsychotic received for the 21-day treatment period, converted into haloperidol equivalents. The mean antipsychotic dose declined continuously in the valproate group, whereas only slight dose variations were observed in the placebo group; the difference in antipsychotic dose was statistically significant for study weeks 2 and 3 ($p = .0007$). The proportion of responders (response was defined as 50% or greater improvement on the YMRS) was higher for the group receiving the combination (70%) than for the group receiving antipsychotics alone (46%; $p = .005$). The authors concluded that the combination of valproate and an antipsychotic was superior to an antipsychotic alone in treating acute mania.

Many open reports indicate that valproate can be successfully combined with other typical antipsychotics, other mood stabilizers, and atypical antipsychotics in the treatment of acute manic, mixed, and rapid-cycling states (Freeman and Stoll 1998). In addition, valproate has been administered via the oral loading strategy of 20 to 30 mg/kg/day (Keck et al 2000a; McElroy et al 1996) as well as intravenously (1200 or 1800 mg/day; Grunze et al 1999a) to acutely manic patients with rapid onset of response (within 1 to 3 days) and minimal side effects.

**Carbamazepine**

At least 14 double-blind, controlled studies published to date have shown carbamazepine to be effective in acute mania (Keck et al 1992); however, only five of these studies were not confounded by the simultaneous coadministration of carbamazepine with lithium and/or standard antipsychotics (Table 4). One of these studies was placebo controlled, two compared carbamazepine with lithium, and two compared carbamazepine with chlorpromazine.

In the placebo-controlled study ($N = 19$), which utilized a crossover (BABA) design, 63% of patients receiving carbamazepine (from 11 to 56 days; mean dose 1242 mg/day; mean plasma level $10.4 \pm 2.2$ mg/mL) displayed significant improvement on nursing staff global ratings of mania on the Bunney–Hamburg scale (Ballenger and Post 1978; Post et al 1984, 1987). Eight of nine responders who received placebo discontinuation trials displayed a “relapse in manic or psychotic symptomatology.” Factors significantly associated with favorable antimanic response to carbamazepine were greater severity of mania and presence of rapid cycling; greater dysphoria during mania and family history negative for mood disorder tended to be associated with carbamazepine response.

In the first study comparing carbamazepine with lithium (Lerer et al 1987) 34 inpatients with bipolar disorder, manic phase, by DSM-III criteria were randomized to either drug for up to 4 weeks. Twenty-eight patients (14 on each drug) completed the 4-week study period and were included in the data analysis. Although the overall response to treatment was not significantly different between the two groups, a more consistent level of improvement was seen in the lithium-treated group, as compared with a minority of robust responders in the carbamazepine-treated group. Specifically, both groups displayed significant and comparable improvement on the BPRS and the Beigel–Murphy Manic State Rating Scale, and trends toward superior improvement with lithium on both scales were not significant; however, the Clinical Global Impression (CGI) change scores for the lithium-treated group showed statistically significant improvement, as compared with those for the carbamazepine group. Specifically, only four (29%) of 14 patients receiving carbamazepine were evaluated as having a good response, compared with 11 (79%) of 14 patients receiving lithium.

In the second lithium comparison study (Small et al 1991) two thirds of 52 hospitalized patients with treatment-refractory mania randomly assigned to lithium or carbamazepine had dropped out by 8 weeks of treatment because of lack of efficacy or refusal to continue. Of the 48 patients who remained in the study for at least 3 weeks, 33% of 24 carbamazepine-treated patients were rated as improved (defined as at least partial remission of symptoms), as were 33% of 24 lithium-treated patients. Double-blind assessments revealed no statistically significant factors associated with response to either drug.

In the first carbamazepine–chlorpromazine comparison study (Okuma et al 1979) 60 acutely manic patients were randomized to receive carbamazepine ($N = 32$) or chlorpromazine ($N = 28$) in a 6-week trial. The two drugs were
equally effective: moderate to marked improvement was seen in 65% of 26 carbamazepine-treated patients and 52% of 23 chlorpromazine-treated patients at week 3, and 71% of 28 carbamazepine-treated patients and 56% of chlorpromazine patients at week 6. In addition, carbamazepine was better tolerated than chlorpromazine. In the second comparison (Grossi et al. 1984) 37 bipolar patients with acute mania by DSM-III criteria were randomized to carbamazepine ($N = 18$) or chlorpromazine ($N = 19$) for up to 3 weeks. Response was evaluated in the 26 patients who completed the entire 3-week treatment period. The mean ± SD (range) carbamazepine dose was 655.5 ± 295.5 (200–1200) mg/day; that for chlorpromazine was 362.5 ± 166.83 (200–800) mg/day. Carbamazepine- and chlorpromazine-treated patients displayed comparable improvement, with similar reductions in Manic State Rating Scale scores and similar response rates. Specifically, 67% of patients receiving carbamazepine ($N = 15$) and 76% of those receiving chlorpromazine ($N = 11$) showed at least moderate improvement. The incidence of side effects for the two drugs did not differ (61% for carbamazepine and 79% for chlorpromazine).

Pooled data from these five randomized, controlled trials suggest carbamazepine is superior to a placebo and comparable to lithium and standard antipsychotics in the treatment of acute bipolar mania, with an overall response rate for carbamazepine of 52%, as compared with 50% for lithium-treated control subjects and 63% for chlorpromazine-treated control subjects (differences not significant; Table 4). Several small double-blind, placebo-controlled trials (Desai et al. 1987; Klein et al. 1984; Möller et al. 1989; Müller and Stoll 1984; Table 4) and a large clinical literature (Freeman and Stoll 1998) further suggest that carbamazepine’s antimanic properties may be augmented by the coadministration of lithium, antipsychotics, and possibly valproate; however, Post and colleagues’ finding (Post et al. 1987) that rapid cycling was associated with acute antimanic response to carbamazepine has not been supported by subsequent clinical reports that many rapid-cycling patients respond inadequately to carbamazepine.

Table 4. Double-Blind, Controlled Studies of Carbamazepine in Acute Bipolar Mania

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>$N$</th>
<th>Duration (days)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo controlled</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post et al. 1984, 1987</td>
<td>Random, crossover</td>
<td>19</td>
<td>11–56</td>
<td>12 (63%) response to CBZ, 8 (89%) of 9 relapse on PBO substitution</td>
</tr>
<tr>
<td>Klein et al. 1984</td>
<td>Random, parallel-group, add-on to HAL</td>
<td>CBZ 14</td>
<td>21</td>
<td>10 (71%) response to CBZ + HAL, 7 (53%) response to PBO + HAL</td>
</tr>
<tr>
<td>Müller and Stoll 1984</td>
<td>Random, parallel-group, add-on to HAL</td>
<td>CBZ 6</td>
<td>28</td>
<td>CBZ + HAL improvement superior to PBO + HAL</td>
</tr>
<tr>
<td>Desai et al. 1987</td>
<td>Random, parallel-group, add-on to Li</td>
<td>CBZ 5</td>
<td>28</td>
<td>CBZ + Li superior to CBZ + PBO on BRMS ($p &lt; .05$) and CGI ($p &lt; .05$), but = on BPRS</td>
</tr>
<tr>
<td>Möller et al. 1989</td>
<td>Random, parallel-group, add-on to HAL, LEV</td>
<td>CBZ 11</td>
<td>21</td>
<td>CBZ + HAL = PBO + HAL in reducing manic symptoms, CBZ + HAL group needed less LEV</td>
</tr>
<tr>
<td>Lithium controlled</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lerer et al. 1987</td>
<td>Random, parallel-group</td>
<td>CBZ 15</td>
<td>28</td>
<td>4 (29%) of 14 response to CBZ, b 11 (79%) of 14 response to Li ($p &lt; .05$)</td>
</tr>
<tr>
<td>Small et al. 1991</td>
<td>Random, parallel-group</td>
<td>Li 19</td>
<td>21–56</td>
<td>8 (33%) of 24 response CBZ, c 8 (33%) of 24 response Li (ns)</td>
</tr>
<tr>
<td>Antipsychotic controlled</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Okuma et al. 1979</td>
<td>Random, parallel-group</td>
<td>CBZ 32</td>
<td>42</td>
<td>17 (65%) of 26 response to CBZ, b 12 (52%) of 23 response to CPZ at week 3 (ns), 20 (71%) of 28 response to CBZ, 14 (56%) of 25 response to CPZ at week 6 (ns)</td>
</tr>
<tr>
<td>Grossi et al. 1984</td>
<td>Random, parallel-group</td>
<td>CBZ 18</td>
<td>21</td>
<td>10 (67%) of 15 response to CBZ, b 13 (76%) of 17 response to CPZ (ns)</td>
</tr>
<tr>
<td>Overall monotherapy response</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CBZ, carbamazepine; PBO, placebo; HAL, haloperidol; Li, lithium; BRMS, Bech-Rafaelsen; CGI, Clinical Global Impression; BPRS, Brief Psychiatric Rating Scale; LEV, levo-nepromazine; CPZ, chlorpromazine.

*Indicates number of patients randomized to controlled treatment.

bOutcome evaluated only in completers.

cOutcome evaluated in patients who completed at least 3 weeks of treatment.
over the long term (Denicoff et al 1997; Okuma 1993; Wehr et al 1988).

**Standard Antipsychotics**

There is one double-blind, placebo-controlled study of a standard antipsychotic in the treatment of acute bipolar mania. In that study (Klein 1967), 13 manic–depressive patients with “manic excitement” were randomized to chlorpromazine (1200 mg/day), imipramine (300 mg/day), or a placebo for 7 weeks. Response was assessed with a global outcome scale that ranged from 2 to 9. Chlorpromazine was statistically significantly superior to a placebo and imipramine in producing good global outcome (6.1 vs. 2.0 and 2.8, respectively).

Most controlled studies of standard antipsychotics in acute bipolar mania, which used chlorpromazine or haloperidol, have been comparisons with lithium and were reviewed above (Table 2). Four other controlled monotherapy studies found comparable efficacy when standard antipsychotics were compared with carbamazepine (Grossi et al 1984; Okuma et al 1979; Table 4), valproate (McElroy et al 1996), or risperidone (Segal et al 1998; Table 5). In a recently presented study (Sachs and Risperidone Bipolar Study Group 1999), 156 patients with bipolar mania receiving lithium or valproate were randomized to add-on therapy with haloperidol (2–12 mg/day; \( N = 53 \)), risperidone (1–6 mg/day; \( N = 52 \)), or a placebo (\( N = 51 \)) for up to 3 weeks. Although haloperidol-treated patients’ results were not statistically analyzed, they displayed comparable improvement compared with those of risperidone-treated patients, who showed significantly greater improvement on the YMRS than placebo-treated patients at 1 week, 2 weeks, and end point (LOCF).

**Novel Antipsychotics**

**Clozapine**

No double-blind, controlled studies of clozapine in the treatment of acute bipolar mania have been published. Numerous open reports, however, suggest that clozapine may have acute and long-term antimanic (as well as antipsychotic) properties in bipolar disorder, including in patients with pure and mixed features, those with rapid and nonrapid cycling, those with and without psychotic features, and those refractory to treatment with mood stabilizers, standard antipsychotics, and electroconvulsive therapy (Frye et al 1998; Suppes et al 1999; Zarate et al 1995).

The successful use of clozapine in acute bipolar mania has been reported in at least three prospective open-label studies (Barbini et al 1997; Calabrese et al 1996; Green et al 2000). In the first study (Calabrese et al 1996) 25 acutely manic patients with DSM-III-R bipolar or schizoaffective disorder refractory to or unable to tolerate lithium, valproate, or carbamazepine and at least two standard antipsychotics received a 13-week clozapine monotherapy trial after a 7-day washout period. The mean ± SD (range) peak dose of clozapine was 494 mg/day ± 145 (250–800). Eighteen (72%) patients exhibited marked improvement on the YMRS and eight (32%) exhibited marked improvement on the BPRS, defined as a 50% or greater decrease in score on either scale. Bipolar patients and nonrapid cyclers, as compared with schizoaffective pa-
tients and rapid cyclers, respectively, displayed significantly greater improvement in total BPRS scores.

In the second study (Barbini et al. 1997) 30 hospitalized patients with mania were randomized to receive clozapine or chlorpromazine for 3 weeks. Although clozapine-treated patients displayed significantly lower YMRS scores after 2 weeks of treatment, there were no significant differences between the two groups at the end of the trial. A limitation of this study was the lower mean dose of clozapine (166 mg/day) relative to that of chlorpromazine (310 mg/day). The authors nonetheless concluded that onset of response for acute mania was more rapid for clozapine than for chlorpromazine.

In the third study (Green et al. 2000) 22 bipolar inpatients with treatment-refractory psychotic mania received a 12-week trial of clozapine monotherapy. Treatment refractoriness was defined as a history of manic and psychotic symptoms that had not improved after a 6-week trial of chlorpromazine (500 mg/day) or its equivalent and a 6-week or longer trial of lithium (with a plasma level of at least 0.8 mEq/L). Clozapine was begun at 25 mg/day and increased 25 mg/day as tolerated to a maximum of 550 mg/day. Seventeen (77%) of the 22 subjects displayed a response, defined as a 20% or greater decrease on the YMRS, CGI, and BPRS. Ten (46%) subjects showed at least 50% improvement on all three scales. All 14 subjects who completed the trial had at least 20% improvement on all three scales; 10 (71%) had at least 50% on all three scales.

**Olanzapine**

Three double-blind, controlled studies of olanzapine in the treatment of acute bipolar mania have been completed (Table 5). Two were comparisons with a placebo (Tohen et al. 1999, in press) and the third was a comparison with lithium (Berk et al. 1999). The two placebo comparisons led to olanzapine being the third drug approved by the FDA (in 2000) for bipolar mania—specifically, for the “short-term treatment of acute manic episodes associated with Bipolar I Disorder.”

In the first placebo-controlled trial (Tohen et al. 1999) 139 hospitalized patients with bipolar I disorder, manic or mixed episodes with or without psychotic features by DSM-IV criteria and total YMRS scores of 20 or greater, were randomized to receive olanzapine (N = 70) or a placebo (N = 69) for up to 3 weeks. Olanzapine was begun at 10 mg/day and thereafter adjusted upward or downward by 5 mg/day within the allowed dosage range of 5 to 20 mg/day. The mean modal and median modal doses were 14.9 (± 5.0) mg/day and 15 mg/day, respectively. Concomitant lorazepam up to 4 mg/day during the first 7 days was the only allowed adjunctive medication for agitation; during the next 3 days, 2 mg/day was permitted. Olanzapine-treated patients displayed statistically significant improvement on the YMRS, the CGI for use in bipolar illness (CGI-BP) severity of mania (Spearling et al. 1997), and the Positive and Negative Syndrome Scale (PANSS) total and positive symptom scores. Olanzapine separated from the placebo on the YMRS at week 3 of treatment. Significantly more patients responded to olanzapine (49%) than to the placebo (24%), with response defined as displaying a 50% or greater decrease on the YMRS from baseline to end point. Of note, patients with and without psychotic features and those with and without rapid cycling displayed similar reductions in YMRS scores. Also, the two groups showed no differences in treatment-emergent extrapyramidal side effects.

In the second placebo-controlled trial (Tohen et al., in press) 115 hospitalized bipolar I patients with manic or mixed episodes with or without psychotic features by DSM-IV criteria were randomized to olanzapine (N = 55) or a placebo (N = 60) for up to 4 weeks. Olanzapine was begun at 15 mg/day and adjusted upward or downward by 5 mg/day within the allowed dosage range of 5 to 20 mg/day. The mean modal and median modal doses of olanzapine were 16.4 mg/day and 20 mg/day, respectively. Concomitant lorazepam up to 2 mg/day was the only allowed adjunctive medication, and it was permitted for the first 10 study days. Olanzapine was statistically significantly superior to the placebo on the YMRS, the CGI-BP severity of mania, the CGI-BP severity of overall bipolar illness, and the total and positive PANSS scores. These differences were evident at week 1 and maintained throughout the course of the 4-week trial. Olanzapine-treated patients demonstrated significantly higher rates of response (65% vs. 43%, respectively) and remission (61% vs. 36%, respectively) than placebo-treated patients at their final evaluation; rates were defined, a priori, as a 50% or greater improvement from baseline to end point and as an end point score of ≤12 on the YMRS, respectively. Patients with and without psychotic features showed similar reductions in manic symptoms on the YMRS, as did those with manic and mixed episodes. Patients presenting with depressive symptoms (21-item Hamilton Rating Scale for Depression [HAMD-21] scores of ≥20 at baseline) displayed a statistically significant reduction in HAMD-21 scores with olanzapine treatment, as compared with placebo treatment. The two groups showed no differences in extrapyramidal side effects.

In the third controlled trial (Berk et al. 1999) 30 inpatients with bipolar disorder, manic episodes by DSM-IV criteria, were randomized to receive olanzapine (N = 15) or lithium (N = 15) for 4 weeks. The doses were 10 mg/day, olanzapine, and 400 mg b.i.d., lithium. The mean lithium level in the lithium-treated group was 0.74
mmol/L. Lorazepam, 4 to 12 mg/day, was the only allowed concomitant medication. Olanzapine- and lithium-treated patients did not differ on any of the primary outcome measures, which included the Mania Scale, the BPRS, and the CGI improvement scale; however, olanzapine (2.29) was significantly superior to lithium (2.83) on the CGI severity scale at week 4 of treatment ($p = .025$). The two drugs did not differ regarding treatment-emergent extrapyramidal side effects. Limitations of this study included lack of a placebo arm, small sample size, and the low mean plasma lithium level in the lithium group. (Lithium levels generally considered therapeutic for acute bipolar mania and used in most pivotal comparator trials have been in the range of 0.8–1.4 [Bowden et al 1994; Prien et al 1972].)

Open reports further suggest olanzapine may be effective in bipolar mania when used in combination with mood stabilizers such as lithium and valproate (Weisler et al 1997), and in various forms of bipolar disorder inadequately responsive to standard agents, including mixed states and rapid cycling (McElroy et al 1998; Zarate et al 1998); however, case reports of hypomania and mania associated with olanzapine treatment have been described (John et al 1998; Lindenmayer and Klebanov 1998; Pozo and Alcantara 1998; Reeves et al 1998).

**Risperidone**

No double-blind, placebo-controlled monotherapy studies of risperidone in the treatment of acute bipolar mania have been published. Two controlled comparisons, however, have been conducted (Table 5).

In the first (Segal et al 1998), 45 inpatients with DSM-IV bipolar disorder, manic phase, were randomized to receive 6 mg/day of risperidone ($N = 15$), 10 mg/day of haloperidol ($N = 15$), or 800 to 1200 mg/day of lithium (with levels between 0.6 and 1.2 mmol/L; $N = 15$) for up to 28 days. All three treatment groups showed similar improvement on day 28 (LOCF) on all rating scales—the YMRS, the BPRS, the CGI, and the GAF; however, the extrapyramidal side effects of risperidone and haloperidol were not significantly different. Also, this trial was limited by its small sample size and the low day 28 mean lithium level (0.72 mmol/L) in the lithium comparison group.

In the second study (Sachs and Risperidone Bipolar Study Group 1999) 156 inpatients with bipolar I mania by DSM-IV criteria on lithium or valproate were randomized to the placebo ($N = 51$) for up to 3 weeks. Risperidone-treated patients displayed statistically significantly greater improvement of treatment on the YMRS, as compared with placebo-treated patients, after 1 week, 2 weeks, and at end point (LOCF), but not at 3 weeks. Haloperidol patients showed similar improvement, but statistical analyses of their results were not provided.

Increasing numbers of open reports support risperidone’s effectiveness in acute mania, particularly when used in combination with mood stabilizers (Frazier et al 1999; Ghaemi et al 1997; Jacobsen 1995; Keck et al 1995; McIntyre et al 1997; Tohen et al 1996), but also when used alone (Goodnick 1995; Singh and Catalan 1994). In addition, patients with treatment-refractory bipolar disorder, including those with mixed states and rapid cycling, have been reported to respond to risperidone (Fras and Major 1995; Vieta et al 1998). As with olanzapine, however, cases of hypomania and mania associated with risperidone treatment have been reported (Barkin et al 1997; Dwight et al 1994; O’Croinin et al 1995; Sajatovic et al 1996; Schaffer and Schaffer 1996; Schnierow and Graebner 1996; Tomlinson 1996).

**Quetiapine**

There are no reports of controlled trials in the treatment of acute bipolar mania using quetiapine, the most recent atypical antipsychotic to be approved by the FDA in the United States; however, case reports have described bipolar patients with treatment-resistant manic symptoms responding to the addition of quetiapine to their existing medication regimens (Dunayevich and Strakowski, in press; Ghaemi and Katzow 1999).

**Ziprasidone**

Ziprasidone, an atypical antipsychotic currently under review by the FDA, has been evaluated in one randomized, placebo-controlled, double-blind, parallel-group study in 195 patients with DSM-IV bipolar manic or mixed episodes (Keck and Ice 2000; Table 5). Ziprasidone (80–160 mg/day) was superior to a placebo on the MRS of the SADS-C at all time points beginning on day 2 ($p < .01$). Fifty percent of 131 patients randomized to ziprasidone displayed a response (defined as a 50% or greater reduction in MRS scores), as compared with 36% of 64 patients randomized to the placebo.

**New Antiepileptics**

**Gabapentin**

Gabapentin is a new antiepileptic drug designed to mimic the synaptic effects of γ-aminobutyric acid (GABA); however, it does not affect GABA receptors and its mechanism of action in epilepsy remains unknown. Pharmacologic properties of the drug include alteration of synthesis and release of GABA in the brain, interaction...
with the system L amino acid transporter, high-affinity binding to the α2δ subunit of voltage-activated calcium channels, blockade of voltage-activated sodium channels, and alteration of monoamine neurotransmitter release (Taylor et al 1998). Two controlled studies have evaluated the response of bipolar manic symptoms to treatment with gabapentin (Table 6). In the first (Pande et al, in press), 114 outpatients with bipolar I disorder with manic, hypomanic, or mixed-state symptoms and a total YMRS score of 12 or greater despite ongoing therapy with lithium, valproate, or the combination were randomized to the addition of gabapentin (N = 55; 600–3600 mg/day) or a placebo (N = 59) for up to 10 weeks, after completing a 2-week, single-blind, placebo-controlled lead-in period. During the lead-in period, doses of lithium and/or valproate were adjusted to achieve maximal clinical benefit and plasma levels equal to or greater than 0.5 mEg/L and 50 mg/mL, respectively. Both treatment groups displayed a decrease in YMRS scores from baseline to end point, but this decrease was significantly greater in the placebo group (−9) than the gabapentin group (−6; p < .05). Regarding the possibility of gabapentin exacerbating manic symptoms, three (43%) gabapentin-treated patients and four (57%) placebo-treated patients were assessed to have manic reactions (N = 6) or psychosis (N = 1) as serious adverse events while receiving randomized medication. Gabapentin- and placebo-treated patients did not differ on any other efficacy variables, including the Internal States Scale, CGI severity, CGI change, HAM-D, and Hamilton Anxiety Scale. The authors concluded that this study did not demonstrate gabapentin to be an effective adjunctive treatment in bipolar outpatients with manic, hypomanic, or mixed-state symptoms.

Of note, this study did have several methodological limitations possibly biasing its results against gabapentin. First, more patients in the placebo group had changes made to their ongoing lithium treatment (N = 12), compared with the gabapentin group (N = 4), during the 2-week lead-in phase (p < .01). When these patients were removed from the efficacy analysis, the YMRS treatment difference still favored the placebo but was no longer statistically significant. Second, plasma gabapentin levels at study termination suggested that some patients did not take the drug as prescribed (eight patients had plasma drug levels below the limit of detection of 0.5 mg/mL).

In the second study (Frye et al, in press) 28 patients with refractory bipolar I (N = 13) or bipolar II (N = 15) disorder were evaluated in a double-blind, randomized, crossover series of three 6-week monotherapy trials of gabapentin (900–4800 mg/day over 6 weeks), lamotrigine, and a placebo using the CGI-BP as the primary efficacy measure. The rate of CGI-BP response for manic symptoms did not differ among the three drugs for the 25 patients who completed all three trials: gabapentin (20%), lamotrigine (44%), and the placebo (32%); however, this study was limited by the extremely low mean ± SD YMRS scores at the beginning of all three treatment phases (4.4 ± 4.1 for gabapentin, 5.5 ± 4.6 for lamotrigine, and 6.1 ± 4.8 for the placebo), reflecting minimal or subclinical manic symptomatology, along with its crossover design and small sample size.

Table 6. Double-Blind, Controlled Studies of Novel Antiepileptic Drugs in Acute Bipolar Mania

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Duration (days)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo controlled</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emrich et al 1985</td>
<td>Random, crossover</td>
<td>OXC  6</td>
<td>Variable</td>
<td>4 (67%) response to OXC</td>
</tr>
<tr>
<td>Frye et al, in press</td>
<td>Random, crossover</td>
<td>GBP  25</td>
<td>42</td>
<td>5 (20%) response to GBP, 11 (44%) response to LAM, 8 (32%) response to PBO (ns)</td>
</tr>
<tr>
<td>Anand et al 1999</td>
<td>Random, parallel-group, add-on to Li in some patients</td>
<td>LAM 25</td>
<td>56</td>
<td>5 (63%) response to LAM, 4 (50%) response to PBO (ns)</td>
</tr>
<tr>
<td>Pande et al, in press</td>
<td>Random, parallel-group, add-on to Li and/or VPA</td>
<td>PBO  25</td>
<td>70</td>
<td>YMRS decreased 6.5 on GBP, YMRS decreased 9.7 on PBO (p = .03), 37% response to GBP, 47% response to PBO (ns)</td>
</tr>
<tr>
<td>Lithium controlled</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ichim et al 2000</td>
<td>Random, parallel-group</td>
<td>LAM 15</td>
<td>28</td>
<td>8 (53%) response to LAM, 9 (60%) response to Li (ns)</td>
</tr>
<tr>
<td>Antipsychotic controlled</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Müller and Stoll 1984</td>
<td>Random, parallel-group</td>
<td>OXC  10</td>
<td>14</td>
<td>Mean decrease in mania scores by 55% in both OXC and HAL groups (ns)</td>
</tr>
</tbody>
</table>

OXC, oxcarbazepine; GBP, gabapentin; LAM, lamotrigine; PBO, placebo; Li, lithium; VPA, valproate; YMRS, Young Mania Rating Scale; HAL, haloperidol.
Despite these negative controlled trials, many open reports have described bipolar patients with acute manic and mixed episodes responding favorably to gabapentin—both as monotherapy (Stanton et al 1997) and in combination with other agents (Altshuler et al 1999; McElroy et al 1997; Schaffer and Schaffer 1997). Moreover, gabapentin’s anxiolytic properties may prove useful in the treatment of bipolar disorder accompanied by anxiety symptoms or disorders. Gabapentin has been demonstrated to have anxiolytic effects in various animal models predictive of anxiolysis (Singh et al 1996) and to decrease ratings of anxiety and depression in patients with epilepsy (Dimond et al 1996; Harden and Pick 1996). Also, one double-blind, controlled study has shown the drug to be superior to a placebo in the treatment of social phobia (Pande et al 1999), and another has shown it superior to a placebo in severe panic disorder (Pande et al 2000).

**Lamotrigine**

Lamotrigine is a novel antiepileptic drug that blocks voltage-sensitive sodium channels, thereby secondarily inhibiting the release of excitatory neurotransmitters, particularly glutamate and aspartate (Garnett and Pellock 1995; Rho and Sankar 1999). Three controlled studies, all methodologically limited, have evaluated lamotrigine in bipolar patients with acute manic symptoms (Table 6).

In the first (Frye et al, in press, discussed above), 13 bipolar I and 15 bipolar II patients were evaluated in a double-blind, randomized, crossover series of three 6-week monotherapy trials of lamotrigine, gabapentin, and a placebo. Lamotrigine was titrated to clinical efficacy, side effects, or a maximum daily dose of 500 mg. The CGI-BP response rate for manic symptoms did not differ among the three treatment groups: 44% for lamotrigine, 20% for gabapentin, and 32% for the placebo. As noted earlier, methodological limitations of this study were the extremely low mean YMRS score at the beginning of each treatment phase, the crossover design, and the small number of subjects.

In the second study (Anand et al 1999) 16 outpatients with mania, hypomania, or mixed states who were inadequately responsive to or unable to tolerate lithium and who had a YMRS score greater than 12 were randomized to receive lamotrigine (N = 8) or a placebo (N = 8) for 8 weeks. Study medication was either added to ongoing lithium therapy in inadequately responsive patients or administered alone to intolerant patients. Lamotrigine was begun at 12.5 mg/day and titrated to a maximum dose of 200 mg/day. There were no significant differences between the lamotrigine- and placebo-treated groups on changes in YMRS scores and in rates of response (defined as a 50% or greater decrease in YMRS scores from baseline to week 8), which were five (63%) of eight for lamotrigine and four (50%) of eight for the placebo. Limitations of this study included the small sample size and high placebo response rate.

In the third study (Ichim et al 2000) 30 inpatients with DSM-IV bipolar disorder, currently manic, were randomly assigned in double-blind fashion to receive lamotrigine (N = 15) or lithium (N = 15) for 4 weeks. Lamotrigine was administered at 25 mg/day for the first week, 50 mg/day for the second week, and 100 mg/day for the last 2 weeks. Lithium was given at 400 mg twice daily throughout the study, and the mean plasma lithium level was 0.7 mmol/L. Both lamotrigine- and lithium-treated patients showed significant and comparable improvement on the MRS, BPRS, CGI severity scale, CGI improvement scale, and GAF. Also, with response defined as a 50% or greater reduction in MRS scores, lamotrigine and lithium were associated with similar response rates: eight (53%) of 15 for lamotrigine and nine (60%) of 15 for lithium. The two groups did not differ in use of adjunctive lorazepam (mean daily dose of 2.7 mg in both groups). Limitations of this study included lack of a placebo comparison group, small sample size (and thus inadequate power to detect potential efficacy differences), and use of relatively low plasma lithium levels.

Open studies have suggested that lamotrigine may have acute antimanic and subsequent mood-stabilizing properties. For example, in one report (Calabrese et al 1999a) 75 patients received an open-label, prospective, 48-week trial of lamotrigine—either as adjunctive treatment (N = 60) or as monotherapy (N = 15). Of the 31 patients who received lamotrigine while manic, hypomanic, or mixed, the mean ± SD baseline SADS-C MRS score decreased from 20.9 ± 7.6 to 5.4 ± 4.8. Eighty-four percent of patients exhibited moderate (3%) or marked (81%) improvement. Of the 40 depressed patients who received lamotrigine, 68% showed moderate (20%) or marked (48%) improvement. When patients with and without rapid cycling were compared, improvement in depressive symptomatology was equivalent for patients presenting in a depressive episode (47.6% vs. 47.4%, respectively; Bowden et al 1999). By contrast, among patients beginning lamotrigine in a manic, mixed, or hypomanic episode, rapid cyclers displayed less improvement in manic symptomatology (57.6%) than nonrapid cyclers (90.5%; p = .01).

Of note, our group and others (Sporn and Sachs 1997) have witnessed hypomania and mania associated with lamotrigine treatment of bipolar depression. Indeed, consistent with observations that agents that induce manic symptoms may have antidepressant properties (Sri-surapanont et al 1995), one double-blind, controlled trial (Calabrese et al 1999b) has shown that lamotrigine mono-
therapy is superior to a placebo in the short-term treatment of bipolar I depression.

**Oxcarbazepine**

Soon to be available in the United States, oxcarbazepine, the 10-keto analogue of carbamazepine, has been studied in two controlled monotherapy trials in acute bipolar mania (Table 6). In the first (Müller and Stoll 1984), 20 patients were randomized to oxcarbazepine (N = 10; 900–1200 mg/day) or haloperidol (N = 10; 15–20 mg/day) for 14 days. Both groups showed a mean decrease of 55% on the Bech–Rafaelson Mania Rating Scale (MRS). In the second study (Emrich et al 1985), a double-blind, placebo-controlled, crossover (ABA) trial, four of six patients displayed a 50% or greater decrease in Inpatient Multidimensional Psychiatric Scale scores with oxcarbazepine treatment.

**Tiagabine**

Tiagabine is a selective GABA reuptake inhibitor approved by the FDA for the treatment of partial seizures. Although there are no controlled trials of tiagabine in the treatment of acute bipolar mania, there are isolated case reports of successful tiagabine augmentation of refractory bipolar I rapid cycling (Schaffer and Schaffer 1999). In these cases, tiagabine was used in outpatients in small doses, ranging from 1 to 4 mg/day; however, tiagabine has also been reported to be ineffective in a 2-week, open-label trial in eight hospitalized patients with acute bipolar mania (Grunze et al 1999b). In this trial, two patients received tiagabine as monotherapy and six received the drug as add-on therapy to previously inadequate mood-stabilizing medications. Also, high doses of tiagabine were rapidly achieved—specifically, 20 to 40 mg/day within 4 days. After 2 weeks of treatment, none of the eight patients displayed a response, with the mean Bech–Rafaelson MRS score in all eight patients decreasing from 28.9 to 27.

**Topiramate**

Topiramate (a sulfamate-substituted monosaccharide) is a structurally and pharmacologically novel antiepileptic drug with several possible mechanisms of action, including blockade of voltage-gated sodium channels, antagonism of the kainate/AMPA subtype of glutamate receptor, enhancement of GABA activity at the GABA_A receptor via interaction with a nonbenzodiazepine receptor site, and carbonic anhydrase inhibition (Ben-Menachem 1995; Meldrum 1996). Moreover, it has been associated with anorexia and weight loss in patients with epilepsy, in contrast to the appetite stimulation and weight gain of many mood stabilizers and antipsychotics (Norton et al 1997; Rosenfeld et al 1997).

There are no published controlled trials of topiramate in the treatment of acute bipolar mania. Preliminary open studies, however, suggest the drug may have antimanic as well as beneficial weight loss properties in some patients. In a 28-day open-label, prospective trial of topiramate monotherapy titrated to a mean (range) dose of 614 mg/day (50–1300 mg/day) in 11 hospitalized bipolar patients with severe treatment-resistant acute mania, three (27%) patients displayed an apparent response to the drug, defined as a ≥50% decrease in baseline total YMRS scores at end point (Calabrese et al 1998). Two other subjects showed 25–49% improvement on the YMRS. In another open-label trial of topiramate given as monotherapy or adjunctive therapy in 44 patients with rapid-cycling bipolar disorder (Marcotte 1998) 52% were described as displaying moderate or marked improvement after a mean duration of treatment of 16 weeks with a mean (range) dosage of 200 (25–400) mg/day. In a third open-label study (Kusumakar et al 1999) topiramate was added to existing medication regimens in 19 female outpatients with rapid-cycling bipolar disorder and psychotropic-induced weight gain. Ten patients displayed significant improvement in mood and five experienced a weight loss of more than 5%. In a fourth open-label study (Chengappa et al 1999) 20 patients with bipolar (N = 18) or schizoaffective (N = 2) disorder with manic, hypomanic, mixed, or rapid-cycling symptoms received adjunctive topiramate from 100 to 300 mg/day. By 5 weeks, 12 (60%) of the patients were responders, defined as a ≥50% reduction in YMRS score and a CGI-BP rating of much or very much improved. In addition, all patients lost weight, losing a mean of 9.4 lb by 5 weeks. Body mass index (BMI) was also significantly reduced. In a fifth open-label study (McElroy et al 2000) response of 54 bipolar outpatients who had been treated with adjunctive topiramate for at least 2 weeks was evaluated with the CGI-BP, the YMRS, and the Inventory for Depressive Symptoms (IDS). Patients’ weights and BMIs were also assessed. Of the 54 patients, 30 had manic, mixed, or cycling symptoms, 11 had depressed symptoms, and 13 were relatively euthymic at the time topiramate was begun. Patients who had been initially treated for manic symptoms displayed significant reductions in CGI-BP mania, YMRS, and IDS scores after 4 weeks, after 10 weeks, and at the last evaluation compared with baseline (mean ± SD duration of treatment = 239 ± 180 days). Those patients who were initially depressed or treated while euthymic showed no significant changes. Patients as a group displayed significant decreases in weight and BMI from topiramate initiation to week 4, to week 10, and to the last evaluation (mean ± SD duration of treatment = 214 ± 170 days).

These preliminary observations suggesting that topira-
mate may have antimanic and anticycling effects in some bipolar patients and may be associated with appetite suppression and weight loss that is viewed as beneficial by patient and clinician need further study in controlled trials.

**Zonisamide**

Zonisamide, a sulfonamide derivative antiepileptic commercially available in Japan since 1989, has a broad spectrum of antiepileptic activity and several potential mechanisms of action. The latter include blockade of voltage-sensitive sodium channels and T-type calcium currents, modulation of GABAergic and dopaminergic systems, and free-radical scavenging (Oommen and Mathews 1999). Kanba et al (1994) evaluated the open-label addition of zonisamide (100–600 mg/day) to other psychotropics in 15 acutely manic bipolar patients. Eighty percent of the patients showed at least moderate global improvement; 33% showed marked global improvement.

**Conclusions and Future Research**

Major advances have been made in the pharmacologic treatment of acute bipolar mania. Moreover, the relative amount of double-blind, placebo-controlled data supporting the efficacy of various agents in acute mania is changing (Table 7). Evidence from two randomized, double-blind, placebo-controlled, parallel-group monotherapy trials supports the efficacy of valproate and olanzapine in the short-term treatment of acute mania. One randomized, double-blind, placebo-controlled, parallel-group study and two randomized, placebo-controlled, crossover trials support the efficacy of lithium. One randomized, double-blind, placebo-controlled, parallel-
cluded. In addition, patients usually cannot have active comorbid alcohol or drug dependence or a history of head trauma or neurologic illness antedating their bipolar disorder. Moreover, these trials are usually only 2 to 4 weeks in duration and, thus, do not assess efficacy in the continuation or maintenance treatment of acute mania. Finally, such trials do not establish whether an antimanic agent also has antidepressant or long-term mood-stabilizing properties.

Nevertheless, the randomized, double-blind, placebo-controlled, parallel-group trial in acute bipolar mania remains the gold standard to determine whether a drug has antimanic properties. Moreover, proving that a drug is efficacious in acute bipolar mania has classically been the first step in determining whether a drug is a mood stabilizer. Indeed, although the precise definition of a mood stabilizer continues to be debated, every drug that is classified as such, to our knowledge, is clearly efficacious in acute bipolar mania.

Numerous treatment guidelines for acute bipolar mania have recently been published. Some have recommended lithium (alone, with a benzodiazepine, and/or with an antipsychotic) as the preferred first-line treatment for most patients (Bauer et al 1999). By contrast, others have recommended choosing from among lithium, valproate, and/or carbamazepine (with or without a benzodiazepine and/or an antipsychotic) as first-line agents—depending upon patient features and preference (i.e., lithium or valproate for pure mania, and valproate or carbamazepine for mixed mania or mania associated with rapid cycling or comorbid substance abuse; American Psychiatric Association Practice Guideline for the Treatment of Patients with Bipolar Disorder 1994; Kusumakar et al 1997; Rush et al 1999; Sachs et al 2000). Yet other guidelines include monotherapy with standard antipsychotics as appropriate first-line therapy for acute bipolar mania (Licht 1998).

The research reviewed here suggests that a number of agents have established efficacy in acute bipolar mania and, thus, should be considered as viable first-line antimanic medications (Table 7). These include lithium, valproate, olanzapine, standard antipsychotics, and carbamazepine. Available adequately done comparison trials suggest that some of these agents may be equally effective in the short-term (i.e., 3 weeks) treatment of acute bipolar mania (Bowden et al 1994; Prien et al 1972; Small et al 1991). Preliminary controlled data suggest that some of these agents may be more effective when used in combination than when used alone (Desai et al 1987; Müller-Oerlinghausen et al 2000; Sachs and Risperidone Bipolar Study Group 1999). Moreover, preliminary data suggest that whereas lithium is particularly effective in pure mania, valproate and olanzapine may also be effective in mania associated with depressive features or rapid cycling.

Thus, the research reviewed here would support evidence-based and flexible guidelines for the treatment of acute bipolar mania in which the choice of an agent was based on the depth of scientific evidence supporting its antimanic efficacy, as well as the characteristics of the particular patient (manic episode subtype, prior course of illness, psychiatric and medical comorbidities, family history, and medication preference), rather than guidelines that preferentially recommend lithium be first-line therapy or that certain specific treatment algorithms be followed.

In sum, many patients will respond to the established agents discussed here—either as monotherapy or in various combinations. Some patients, however, will respond poorly to all available agents, including the novel and untested drugs reviewed. Thus, the need for studies of alternative strategies of existing agents as well as of alternative agents remains. These strategies should include, for example, controlled comparisons of combinations of agents with a single agent, as well as controlled comparisons of novel agents with a placebo. As the therapeutic profiles of existing antimanic agents are more clearly delineated and new antimanic agents are found, treatment paradigms for acute mania should remain evidence based and flexible, so that they represent cutting edge advances in psychiatric medicine and can be tailored to the specific needs of individual patients.

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