# 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 novel 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.* Biol Psychiatry 2000;48: 539–557 © *2000 Society of Biological Psychiatry*

**Key Words:** Bipolar mania, mood stabilizers, atypical antipsychotics, novel antiepileptics

## Pharmacologic Treatments for Acute Mania

The knowledge base regarding the medical treatment of acute bipolar mania is rapidly expanding. Information about agents with established antimanic efficacy is increasing, and more agents with putative antimanic properties are being identified.

In this article we first review research supporting the efficacy of the established antimanic agents lithium, valproate, and carbamazepine and standard antipsychotics in the short-term treatment of acute bipolar mania. Because 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.

From the Biological Psychiatry Program, Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati, Ohio.

Address reprint requests to Susan L. McElroy, M.D., University of Cincinnati College of Medicine, Biological Psychiatry Program (ML559), 231 Bethesda Avenue, Cincinnati OH 45267.

Received February 4, 2000; revised June 7, 2000; accepted June 7, 2000.

## 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 acute treatment of mania) employed a parallel design (Bowden et al 1994); the four earlier studies were crossover trials of varying duration. Crossover studies are vulnerable to carryover and period effects, potential contamination of blindness, and abrupt treatment discontinuation effects (which may artificially lower placebo response rates via rebound recurrence of symptoms; Calabrese and Rapport 1999; Keck et al 2000b; Stallone et al 1974). Second, two studies utilized nonrandom assignment to lithium or a placebo (Goodwin et al 1969; Stokes et al 1971). Third, 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



0006-3223/00/$20.00

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

| Study | Design | *N* | Duration (days) | Outcome |
|---|---|---|---|---|
| Schou et al 1954 | Random, crossover[a] | 38[b] | "Usually" 14 for Li and PBO | 14 (37%) positive effect,[c]<br>18 (47%) possible effect,<br>6 (16%) negative effect |
| Maggs 1963 | Random, crossover, ABA vs. BAB | 28 | 14 for Li and PBO | Li superior to PBO for 18 patients who completed entire 6-week study |
| Goodwin et al 1969 | Nonrandom, crossover | 12 | ND | 9 (75%) response to Li,[c]<br>3 (25%) worse with Li |
| Stokes et al 1971 | Nonrandom, crossover | 28 | 7–10 for Li and PBO | 42 (75%) 56 response to Li,[d]<br>17 (41%) 42 response to PBO[d] |
| Bowden et al 1994 | Random, parallel-group, VPA comparison | Li 35,<br>PBO 73,<br>VPA 68 | 21 | 17 (49%) 35 response to Li ($p = .025$),<br>18 (25%) response to PBO,<br>33 (48% response to VPA ($p = .004$) |
| Overall monotherapy response[e] | | 85 | | 58 (68%) response to Li |

Li, lithium; PBO, placebo; ND, not documented; VPA, valproate.
[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

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

| Study | Design | *N* | Duration (days) | Outcome |
|---|---|---|---|---|
| Johnson et al 1968 | Random, parallel-group | Li 18<br>CPZ 11 | 21–28 | 14 (78%) response to Li,<br>4 (36%) response to CPZ |
| Platman 1970 | Random, parallel-group | Li 13<br>CPZ 10 | 21 | Li superior to CPZ after 3 weeks (ns) |
| Spring et al 1970 | Random, parallel-group, crossover of nonresponders | Li 7<br>CPZ 5 | 21 | 6 (86%) rsponse to Li,<br>3 (60%) response to CPZ (ns) |
| Johnson et al 1971 | Random, parallel-group | Li 13<br>CPZ 8 | 21 | 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 |
| Prien et al 1972 | Random, parallel-group | Mildly active 130<br>Highly active 125 | 21 | 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 |
| Shopsin et al 1975 | Random, parallel-group | Li 10<br>CPZ 10<br>HAL 10 | 21 | 7 (70%) response to Li,<br>1 (10%) response to CPZ,<br>2 (20%) response to HAL |
| Takahashi et al 1975 | Random, parallel-group | Li 37<br>CPZ 34 | 35 | 25 (68%) response to Li,<br>17 (50%) response to CPZ ($p = .05$) |
| Garfinkel et al 1980 | Random, parallel-group | Li + PBO 7<br>HAL + PBO 7<br>Li + HAL 7 | 21 | HAL + PBO = HAL + Li; both superior to Li + PBO in improving global clinical ratings on days 8, 15, and 22 |
| Segal et al 1998 | Random, parallel-group, HAL comparison | Li 15<br>HAL 15 | 28 | Li = HAL in decreasing manic symptoms |

Li, lithium; CPZ, chlorpromazine; BPRS, Brief Psychiatric Rating Scale; CGI, Clinical Global Impression; HAL, haloperidol; TRAM, Treatment Response Assessment Method; PBO, placebo.

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

Table 3. Double-Blind, Controlled Studies of Valproate in Acute Bipolar Mania

| Study | Design | *N* | Duration (days) | Outcome |
|---|---|---|---|---|
| Placebo controlled | | | | |
| Emrich et al 1981 | Random crossover, ABA | 5 | Variable | 4 (80%) marked response, 1 (20%) no response |
| Brennan et al 1984 | Random crossover, ABA | 8 | 14 | 6 (75%) marked response, 2 (25%) no response |
| Pope et al 1991 | Random, parallel-group, Li comparison | VPA 17<br>PBO 19 | 21 | 9 (53%) response to VPA, 2 (10%) response to PBO |
| Bowden et al 1994 | Random, parallel-group, Li comparison | VPA 68<br>PBO 73<br>Li 35 | 21 | 33 (48%) response to VPA ($p = .004$), 18 (25%) response to PBO, 17 (49%) response to Li ($p = .025$) |
| Müller-Oerlinghausen et al 2000 | Random, parallel-group, add-on to antipsychotic | VPA 69<br>PBO 67 | 21 | 48 (70%) response to VPA, 31 (46%) response to PBO ($p = .005$) |
| Lithium controlled | | | | |
| Freeman et al 1992 | Random, parallel-group | VPA 14<br>Li 13 | 21 | 9 (63%) response to VPA, 12 (92%) response to Li (ns) |
| Overall monotherapy response | | VPA 112<br>PBO 92<br>Li 48 | | 61 (54%) response to VPA, 20 (22%) response to PBO, 29 (60%) response to Li |

ABA, placebo/valproate/placebo; VPA, valproate; PBO, placebo; Li, lithium.

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 episodes 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

DOCKET ALARM

# Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

## Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

## Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

## Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

**LAW FIRMS**
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

**FINANCIAL INSTITUTIONS**
Litigation and bankruptcy checks for companies and debtors.

**E-DISCOVERY AND LEGAL VENDORS**
Sync your system to PACER to automate legal marketing.