A Pilot Study of Lithium Carbonate Plus Divalproex Sodium for the Continuation and Maintenance Treatment of Patients With Bipolar I Disorder

David A. Solomon, M.D., Christine E. Ryan, Ph.D., Gabor I. Keitner, M.D., Ivan W. Miller, Ph.D., M. Tracie Shea, Ph.D., Ali Kazim, M.D., and Martin B. Keller, M.D.

Background: This pilot study compared the efficacy of lithium plus divalproex sodium with the efficacy of lithium alone for the continuation and maintenance treatment of patients with bipolar I disorder.

Method: Twelve patients with bipolar I disorder as defined by the DSM-III-R were recruited and followed prospectively for up to 1 year. Each subject received lithium at serum levels of 0.8 to 1.0 mmol/L and a management/education session weekly or every 2 weeks. By random assignment, subjects received either divalproex sodium or placebo in conjunction with lithium. Divalproex sodium was adjusted to achieve a serum concentration of 50 to 125 μg/mL. Adjunctive medications were used on an as needed basis to treat psychosis, depression, and anxiety. The course of illness was monitored through use of the Longitudinal Interval Follow-up Examination.

Results: Subjects treated with the combination of lithium and divalproex were significantly less likely to suffer a relapse or recurrence ($p = .014$), but were significantly more likely to suffer at least one moderate or severe adverse side effect ($p = .041$). There was no significant difference between groups in the use of adjunctive medication.

Conclusion: These results provide preliminary evidence of the risks and benefits of combining lithium with divalproex sodium for the continuation and maintenance treatment of bipolar I disorder.

(J Clin Psychiatry 1997;58:95–99)

Received Feb. 5, 1996; accepted Nov. 18, 1996. From the Department of Psychiatry and Human Behavior, Brown University, Providence, R.I.

Supported by a Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression (Dr. Solomon) and a small grant from Abbott Laboratories (Drs. Solomon and Keller).

Reprint requests to: David A. Solomon, M.D., Mood Disorders Program, Rhode Island Hospital, 593 Eddy Street, Providence, RI 02903.

The natural course of bipolar I disorder is characterized by high rates of relapse and recurrence,[1] and lithium is often used to prevent these repeated episodes. Unfortunately, a large percentage of patients ultimately fail lithium prophylaxis. A review of controlled studies from the 1960s and 1970s found the mean failure rate for lithium was 33%,[2] and in a more recent study, the failure rate approached two thirds of patients.[3] In response, the National Institute of Mental Health Workshop on Treatment of Bipolar Disorder proposed clinical trials to test alternative treatments, including the combination of lithium and valproate.[4]

Controlled trials have demonstrated that valproate (in the form of divalproex sodium) is useful in the short-term treatment of acute mania.[5,6] While monotherapy with divalproex is effective in short-term trials, maintenance treatment may require more aggressive pharmacotherapy with a combination of drugs. The study of acute mania by Pope et al.[5] provides a good example. Of the 20 patients randomly assigned to divalproex, 9 responded with at least 50% improvement by the end of the 21-day study period. After completion of the study, the investigators continued to follow the responders. One patient discontinued divalproex because of side effects, 6 required the addition of neuroleptics or lithium to divalproex, and only 2 continued with divalproex monotherapy.

Although valproate has been successfully used for continuation and maintenance therapy as described in single case reports,[7] retrospective chart reviews,[8] and uncontrolled open trials,[9,10] the vast majority of the preliminary studies have used valproate in conjunction with other medications, such as lithium. Further, a randomized controlled trial comparing carbamazepine with lithium for the acute and longitudinal treatment of mania concluded that monotherapy with either drug was insufficient for the majority of patients.[11] For these reasons, polypharmacy is an approach that warrants further evaluation.

This report describes findings from a pilot study in which subjects with bipolar I disorder were randomly assigned to prophylactic treatment with lithium plus divalproex sodium or lithium plus placebo. Subjects were

subsequently followed for up to 1 year. The purpose of the study was to look for indications that the combination of lithium and divalproex can better control the course of illness in bipolar I disorder than lithium alone. It was hypothesized that the group treated with lithium plus divalproex would be less likely to suffer a relapse or recurrence, more likely to experience significant adverse side effects, and less likely to require treatment with adjunctive medication.

METHOD

Patients with bipolar I disorder, referred to a university-affiliated private psychiatric hospital for treatment of an episode of mania or major depression, were recruited as subjects. Eligible patients were interviewed with regard to past psychiatric history and treatment and received a physical examination, electrocardiograph, hematologic and serum chemistry studies, and urinalysis.

Inclusion criteria were (1) current episode of mania or major depression and diagnosis of bipolar I disorder, established with the Structured Clinical Interview for DSM-III-R[12]; (2) history of at least one prior mood episode in the previous 3 years; and (3) age 18 to 65 years. Exclusion criteria were as follows: (1) treatment of the acute (index) episode with valproate or carbamazepine; (2) current or past history of a medical illness that would contraindicate the use of lithium or divalproex sodium, including significant renal, liver, or cardiovascular disease; (3) current diagnosis of encephalopathy, mental retardation, or terminal illness; (4) presence of focal neurologic signs on physical examination; (5) history of seizure disorder or paroxysmal activity on electroencephalogram within the past 2 years; (6) structural brain damage from craniocerebral trauma, cerebrovascular disease, or demyelinating disease; and (7) female patients who were pregnant, lactating, or lacked adequate contraception if sexually active. All subjects provided written informed consent after receiving a complete description of the procedures and possible side effects.

After consent was obtained, responsibility for treatment was transferred to the study psychiatrist (D.A.S.). This marked intake into the study. Patients were seen frequently, with treatment directed at controlling the acute episode and establishing a therapeutic serum lithium level. When subjects began to show signs of improvement from the index episode, they were randomly assigned to receive the combination of lithium plus divalproex sodium or lithium plus placebo. Subjects were followed prospectively after randomization for up to 12 months. All subjects and the clinical interviewer conducting assessments were blinded to the treatment condition. The study psychiatrist prescribing the medication(s) was not blinded.

All subjects received lithium at a dose adjusted to achieve a serum concentration of 0.8 to 1.0 mmol/L.[13] Divalproex sodium was prescribed on a twice-per-day schedule, as was the placebo. The dose of divalproex sodium was adjusted to achieve a serum concentration of 50 to 125 μg/mL. Serum concentrations for both lithium and divalproex sodium consisted of trough levels drawn approximately 12 hours after the last oral dose. Other blood tests were periodically performed to measure function of the bone marrow, liver, kidney, and thyroid.

Neuroleptics prescribed during treatment of the index episode were tapered and discontinued whenever possible. However, neuroleptics were not forbidden, since they clearly have a role in the treatment of manic-depressive illness.[14] As such, they were prescribed on a short-term basis to forestall clinical deterioration. Similarly, antidepressants were used to treat major depression, and benzodiazepines were used to treat anxiety. Use of these adjunctive medications was recorded and treated as an outcome variable.

The psychiatrist met weekly with each subject for the first 6 months, and every 2 weeks thereafter. During this 15- to 30-minute session, the psychiatrist reviewed the subject's clinical status, adjusted the medication(s), managed side effects, and provided support, encouragement, and direct advice if necessary. The procedures used for this session were adapted from the Clinical Management-Imipramine/Placebo Administration Manual.[15] At each session, the patient was assessed for the presence of adverse side effects by using the Treatment Emergent Symptom Scale.[16]

A trained clinical interviewer, blinded to the use of divalproex sodium, assessed the course of illness for each subject with a modified version of the Longitudinal Interval Follow-up Evaluation (LIFE).[17] The LIFE is a precoded, semistructured instrument that measures the severity of psychopathology on a weekly basis, as well as the type and dose of all medication. Severity of psychopathology is quantified on a six-point scale called the psychiatric status rating (PSR). A PSR of 1 corresponds to no symptoms, and a PSR of 2 corresponds to one or two symptoms of a mild degree with no impairment of functioning. A PSR of 3 corresponds to moderate psychopathology considerably less than full criteria for a DSM-III-R disorder with no more than moderate impairment in functioning. A PSR of 4 denotes marked symptoms not meeting full criteria for a DSM-III-R disorder, with major impairment of functioning. A PSR of 5 indicates symptoms that meet full criteria for a DSM-III-R disorder, and a PSR of 6 indicates symptoms that meet full criteria for a DSM-III-R disorder along with psychosis or extreme impairment in functioning. The LIFE was administered at baseline and subsequently at 2-month intervals. At each interview, the rater assigned a PSR for each week, starting from the time of the last interview. To accomplish this, the rater first identified chronological anchor points, such as holidays, to assist the subject in remembering those times

Table 1. Sociodemographic and Clinical Characteristics of Sample

Patient	Age (y)	Sex	Marital Status	Socioeconomic Status[a]	Number of Mood Episodes, Lifetime	Past Treatment	
						Lithium	Divalproex
1	40	M	Married	5	3	No	No
2	36	M	Never married	4	6	No	No
3	31	F	Never married	3	2	Yes	No
4	65	M	Married	4	10	No	No
5	41	M	Married	3	51	No	No
6	39	F	Divorced	2	4	Yes	No
7	30	M	Married	2	3	Yes	No
8	39	M	Married	2	16	Yes	No
9	35	F	Never married	2	5	Yes	No
10	40	M	Married	1	10	No	No
11	38	F	Divorced	2	7	Yes	No
12	41	M	Widowed	4	30	Yes	No

[a]Hollingshead Redlich Two Factor Index for Social Position.[19]

when significant clinical improvement or deterioration occurred. Corroborative history from relatives and the medical record was obtained whenever possible.

All subjects entered the study while in a mood episode (PSR of 5 or 6) and were followed for changes in clinical status, as measured by the LIFE. *Partial remission* represented an improvement, such that the subject no longer met criteria for a mood episode, but continued to experience moderate to marked symptoms not meeting full criteria for a mood episode (PSR of 3 or 4). *Relapse* was a return of symptoms that met DSM-III-R criteria for a definite mood episode (PSR of 5 or 6) and occurred during a period of partial remission. *Recovery* was defined as at least 8 consecutive weeks of no symptoms or minimal symptoms (PSR of 1 or 2, respectively). *Recurrence* was the reappearance of the DSM-III-R disorder at full criteria (PSR of 5 or 6) and occurred only after the individual had first recovered from the preceding episode. Recurrence differed from relapse in that recurrence occurred during recovery, and thus signified a new mood episode.

Relapse or recurrence was treated as clinically indicated, including hospitalization. After stabilization, subjects were reassigned to their original treatment condition.

The two treatment groups were compared with respect to (1) the number of subjects who suffered from a relapse or a recurrence, (2) the number of subjects who suffered from one or more adverse side effects of moderate or severe intensity for a period of at least 4 weeks, and (3) the number of subjects treated with adjunctive medication (antipsychotic, antidepressant, or benzodiazepine) for a period of at least 4 weeks. These outcomes were analyzed by using the chi-square test of independence, with an adjustment made for small expected cell frequencies.[18]

RESULTS

Of the 12 subjects enrolled in the study, 5 were randomly assigned to treatment with lithium plus divalproex. Table 1 lists the sociodemographic characteristics and clinical history of the sample. Seven subjects had previously been treated with lithium; however, response or intolerance to previous trials with lithium was not systematically ascertained. None of the subjects had rapid-cycling bipolar disorder. Subjects assigned to lithium plus divalproex had a greater number of prior mood episodes, but the difference was not statistically significant (Wilcoxon rank sum $W = 42$, $p < .08$).

Table 2 shows the course of illness for each subject. Four of the 5 patients assigned to lithium plus divalproex entered the study with major depression at intake, and 5 of the 7 assigned to lithium plus placebo entered the study with mania at intake; the difference was not statistically significant ($\chi^2 = 2.8$, $df = 1$, $p < .10$). Each study patient achieved partial remission, and two thirds of the subjects did so within the first week after randomization. (Random assignment occurred when subjects began to show signs of improvement from the index episode.)

The mean ± SD length of participation in the study for subjects treated with divalproex sodium plus lithium was 43.8 ± 10.3 weeks; that for subjects treated with lithium alone was 42.9 ± 14.8 weeks. A total of 4 subjects withdrew from the study prior to completion. Two received lithium plus divalproex sodium, and both withdrew because of adverse side effects. The other 2 received lithium plus placebo and were suffering from a relapse at the time they withdrew.

Subjects treated with lithium plus placebo were significantly more likely to suffer from a relapse or recurrence, compared with subjects treated with lithium plus divalproex ($\chi^2 = 5.61$, $df = 1$, $p = .014$). Five of 7 study patients treated with lithium monotherapy relapsed or had a recurrence, compared with 0 of 5 treated with lithium plus divalproex. Relapse and recurrence occurred in 3 of the 4 women in the study, compared with 2 of the 8 men; the difference in sex was not significant ($\chi^2 = 2.51$, $df = 1$, N.S.).

Subjects treated with lithium plus divalproex were significantly more likely to suffer from at least one adverse side effect of moderate or severe intensity for a period of 4 or more weeks ($\chi^2 = 3.93$, $df = 1$, $p = .041$). All 5

Table 2. Course of Illness During Treatment Study*

Patient	Polarity at Intake	Randomized Treatment	Partial Remission From Index Episode (Wk From Randomization)	Recovery From Index Episode (Wk From Randomization)	No. of Relapses	No. of Recurrences	Adjunctive Medication[a]	Total Time in Study (Wk)
1	Depression	Divalproex	1	40	0	0	NL, AD	52
2	Mania	Placebo	1	38	1	1	NL, AD	52
3	Depression	Divalproex	1	Never	0	0	…	52
4	Mania	Divalproex	0[b]	0[b]	0	0	…	35
5	Depression	Divalproex	1	Never	0	0	AD	28
6	Depression	Placebo	1	Never	1	0	BZD	26
7	Mania	Placebo	…[c]	4	0	0	…	52
8	Depression	Placebo	1	27	0	0	AD	52
9	Mania	Placebo	6	10	0	1	NL, AD, BZD	52
10	Depression	Divalproex	1	10	0	0	AD	52
11	Mixed	Placebo	1	10	1	1	…	52
12	Mania	Placebo	11	Never	1	0	NL, BZD	14

*Abbreviations: AD = antidepressant, BZD = benzodiazepine, NL = neuroleptic.
[a]Used for at least 4 weeks.
[b]Subject 4 recovered after intake into the study, but prior to randomization.
[c]Subject 7 recovered abruptly in Week 4, with no intervening period of partial remission.

subjects treated with lithium plus divalproex suffered from at least one such side effect, compared with 3 of the 7 subjects receiving lithium plus placebo. The most common adverse effects of treatment with lithium plus divalproex were gastrointestinal distress, tremor, cognitive impairment, and alopecia.

Three of the 5 subjects receiving lithium plus divalproex were treated with an adjunctive medication for a period of 4 or more weeks, as were 5 of the 7 subjects receiving lithium plus placebo. There was no significant difference between the two groups in the use of adjunctive medication ($\chi^2 = 0.16$, df = 1, N.S.).

DISCUSSION

Subjects treated with the combination of lithium and divalproex sodium were significantly less likely to suffer a relapse or recurrence (p = .014). This finding is intriguing, particularly given that subjects assigned to combination therapy had a greater number of prior mood episodes, increasing their likelihood of further relapses and recurrences.[13,20] Lithium and valproate each appear to affect numerous neurotransmitters and second messenger systems, directly and indirectly. Some of these possible effects overlap (e.g., increased activity in gamma-aminobutyric acid, decreased dopaminergic function), but many do not.[21,22] The use of these two drug therapies together may enhance prophylaxis by combining different pharmacodynamic mechanisms.

Subjects receiving lithium plus divalproex were also significantly more likely to suffer at least one moderate or severe adverse side effect. Mood-stabilizing medication is often associated with adverse side effects, and polypharmacy may exacerbate the problem. The 2 subjects who withdrew because of adverse side effects were both receiving the combination of lithium plus divalproex. One issue to consider is whether it was necessary to use full doses or serum levels for each drug. It is possible that a lower serum level of one drug, or both drugs, may have helped patients better tolerate the combination of lithium and divalproex, with no change in efficacy.

Despite the absence of controlled trials, polypharmacy is common for patients with bipolar I disorder. The National Center for Health Statistics assessed over 38,000 outpatient visits to physicians and, as part of the analyses, examined prescriptions for psychotropic drugs.[23] They found that ambulatory patients with mania were four times more likely to be treated with multiple concurrent psychotropic medications than were outpatients with nonpsychiatric diagnoses. Furthermore, lithium was part of a polypharmacy regimen in over 70% of the visits in which it was prescribed, and of all psychotropic drugs, lithium was most likely to be used in combination with other psychotropic drugs. They concluded that the two best predictors of psychotropic polypharmacy were prescription of lithium and a diagnosis of mania.

No definitive conclusions regarding efficacy can be drawn from this pilot study. The methods were seriously limited by such factors as the small sample size, the use of adjunctive medications, and the nonblinded status of the research psychiatrist prescribing the randomized treatment and the adjunctive medications. The two treatment groups differed with regard to polarity at intake, such that 5 of the 7 patients randomly assigned to monotherapy were manic at study entry, whereas 4 of the 5 patients randomly assigned to combination therapy were depressed at study entry. Prior maintenance studies have found that response to treatment and the risk of relapse or recurrence is affected by the polarity of the index or most recent mood episode.[13,24] Further, the design of the study may have enriched the sample with lithium nonresponders. Despite these flaws, the findings are suggestive and support further investigation in a larger clinical trial.

Drug names: carbamazepine (Tegretol and others), divalproex sodium (Depakote).

REFERENCES

1. Zis AP, Goodwin FK. Major affective disorder as a recurrent illness: a critical review. Arch Gen Psychiatry 1979;36:835–839
2. Prien RF. Maintenance treatment of depressive and manic states. In: Georgotas A, Cancro R, eds. Depression and Mania. New York, NY: Elsevier Science; 1988:439–451
3. Maj M, Pirozzi R, Kemali D. Long-term outcome of lithium prophylaxis in bipolar patients [letter]. Arch Gen Psychiatry 1991;48:772
4. Prien RF, Potter WZ. NIMH Workshop Report on Treatment of Bipolar Disorder. Psychopharmacol Bull 1990;26:409–427
5. Pope HG Jr, McElroy SL, Keck PE Jr, et al. Valproate in the treatment of acute mania: a placebo-controlled study. Arch Gen Psychiatry 1991;48:62–68
6. Bowden CL, Brugger AM, Swann AC, et al. Efficacy of divalproex vs lithium and placebo in the treatment of mania. JAMA 1994;271:918–924
7. Sharma V, Persad E. Augmentation of valproate with lithium in a case of rapid cycling affective disorder. Can J Psychiatry 1992;37:584–585
8. McElroy SL, Keck PE Jr, Pope HG Jr, et al. Valproate in the treatment of rapid-cycling bipolar disorder. J Clin Psychopharmacol 1988;8:275–279
9. Lambert PA, Venaud G. Comparative study of valpromide vs lithium in treatment of affective disorders [French]. Nervure 1992;5:57–65
10. Calabrese JR, Woyshville MJ, Kimmel SE, et al. Predictors of valproate response in bipolar rapid cycling. J Clin Psychopharmacol 1993;13:280–283
11. Small JG, Klapper MH, Milstein V, et al. Carbamazepine compared with lithium in the treatment of mania. Arch Gen Psychiatry 1991;48:915–921
12. Spitzer RL, Williams JBW, Gibbon M, et al. Structured Clinical Interview for DSM-III-R, Patient Version (SCID-P). New York, NY: Biometric Research, New York State Psychiatric Institute; 1988
13. Gelenberg AJ, Kane JM, Keller MB, et al. Comparison of standard and low serum levels of lithium for maintenance treatment of bipolar disorder. N Engl J Med 1989;321:1489–1493
14. Kane JM. The role of neuroleptics in manic-depressive illness. J Clin Psychiatry 1988;49(11, suppl):12–13
15. Fawcett J, Epstein P, Fiester SJ, et al. Clinical Management-Imipramine/Placebo Administration Manual: NIMH Treatment of Depression Collaborative Research Program. Psychopharmacol Bull 1987;23:309–324
16. Guy W. ECDEU Assessment Manual for Psychopharmacology, Revised. Dept Health Human Services publication no. ADM 91-338. Rockville, Md: National Institute of Mental Health, Psychopharmacology Research Branch; 1991
17. Keller MB, Lavori PW, Friedman B, et al. The Longitudinal Interval Follow-up Evaluation: a comprehensive method for assessing outcome in prospective longitudinal studies. Arch Gen Psychiatry 1987;44:540–548
18. Berry KJ, Mielke PW Jr. R by c chi-square analyses with small expected cell frequencies. Educational Psychological Measurement 1986;46:169–173
19. Miller DC. Handbook of Research Design and Social Measurement. 4th ed. White Plains, NY: Longman; 1983
20. Consensus Development Panel. NIMH/NIH consensus development conference statement on mood disorders: pharmacologic prevention of recurrences. Am J Psychiatry 1985;142:469–476
21. Lenox RH, Manji HK. Lithium. In: Schatzberg AF, Nemeroff CB, eds. The American Psychiatric Press Textbook of Psychopharmacology. Washington, DC: American Psychiatric Press; 1995:303–349
22. McElroy SL, Keck PE Jr. Antiepileptic drugs. In: Schatzberg AF, Nemeroff CB, eds. The American Psychiatric Press Textbook of Psychopharmacology. Washington, DC: American Psychiatric Press; 1995:351–375
23. Nichol MB, Stimmel GL, Lange SC. Factors predicting the use of multiple psychotropic medications. J Clin Psychiatry 1995;56:60–66
24. Prien RF, Kupfer DJ, Mansky PA, et al. Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders: report of the NIMH collaborative study group comparing lithium carbonate, imipramine, and a lithium carbonate-imipramine combination. Arch Gen Psychiatry 1984;41:1096–1104