Valproate Prophylaxis in a Prospective Clinical Trial of Refractory Bipolar Disorder

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Objective: *The authors studied the efficacy of valproate plus lithium and of triple therapy with lithium, carbamazepine, and valproate in refractory bipolar illness.* *Method:* *The subjects were 24 bipolar outpatients who had completed an intended 3-year crossover study comparing lithium, carbamazepine, and their combination. Patients entered a 1-year phase of valproate plus lithium because of inadequate response or major side effects, and patients with inadequate responses were offered an additional year of treatment with all three mood-stabilizing drugs.* *Results:* *Six (33%) of the 18 evaluable patients had moderate to marked responses to valproate plus lithium; four of these six had not responded to any previous treatment condition. Three of seven patients responded to triple therapy, although only one response was marked.* *Conclusions:* *Some outpatients with bipolar disorder refractory to lithium and carbamazepine received clinically relevant prophylactic benefit from valproate when used with lithium or in triple therapy.*

(Am J Psychiatry 1997; 154:1456–1458)

Lithium is the drug of choice for the prophylaxis of bipolar disorder, but studies over the last decade (1, 2) suggest a generally poorer outcome than often assumed on the basis of the earlier studies by Baastrup and Schou (3) and others. Eleven partially controlled studies (4) suggest an approximately 63% rate of response to regimens involving carbamazepine prophylaxis. However, the fact that many patients do not respond and that tolerance to its psychotropic effects can develop (5) indicates that other treatment modalities are needed.

Although the efficacy of valproate for the treatment of acute mania has been demonstrated (6, 7), there is a lack of controlled data indicating the prophylactic efficacy of valproate for systematically evaluated nonresponders. However, some open studies (8–10) have shown that valproate may be effective for the prophylaxis of bipolar disorder.

Recently, we completed a randomized crossover study comparing a year of treatment with lithium or carbamazepine and a third year of the combination (11). The cumulative percentage of the evaluable patients who showed treatment responses (marked or moderate improvement) on the Clinical Global Impression scale (CGI) (12) was 50.0%. We were interested in assessing whether the use of valproate (plus lithium) would be efficacious for 24 patients who had inadequate responses. In addition, seven patients with a nonresponse or moderate response to valproate therapy were subsequently studied during a year of triple combination therapy with lithium, carbamazepine, and valproate.

METHOD

The subjects included in this study were 24 patients (bipolar I, N=16; bipolar II, N=8) from the original 52 patients with bipolar disorder (DSM-IV criteria) who were studied in a three-phase study comparing the therapeutic effects of an intended 1 year of lithium or carbamazepine, a crossover to the other drug in the second year, and treatment with the combination of both drugs in the third year (11). Oral and written informed consent was obtained. The patients ranged in age from 19 to 74 years (mean=40.7, SD=11.5) and included 11 women and 13 men. Most of the patients were employed: 11 worked full-time, eight worked part-time, two were students, two were retired, and one was receiving disability payments.

Of the 24 patients who entered the phase with valproate (divalproex sodium), three stopped taking it because of side effects (two had increased levels of liver transaminases, one had major gastrointestinal symptoms) and three were noncompliant with the medication regimen. Of the 18 evaluable patients, 17 were taking the combination of lithium and valproate and one was receiving valproate monotherapy (lithium was rejected for one patient because of major weight gain).

The patients entered the valproate-plus-lithium phase because of

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Additional support was provided by the Stanley Foundation.

The authors thank Kimberly Blake, Paula Jacob, Sharon Meglathery, Elizabeth Disney, Gabriele S. Leverich, Mark Jones, and the 3-West nursing staff for assistance in various phases of this work.

inadequate response (nonresponse or moderate response according to the CGI), major side effects from lithium and carbamazepine, or both. Seven patients with inadequate responses to valproate plus lithium entered a phase with three mood stabilizers: lithium, carbamazepine, and valproate. Although the patients knew they would take valproate during this study, they received disguised compounds and did not know whether they were receiving other mood stabilizers. Each phase lasted up to a year unless the patient was hospitalized, had several days of severe dysfunction, was unable to be stabilized after 4 months, or had treatment-limiting side effects. During the trial, undisguised adjuvant medications were used on a short-term basis for breakthrough episodes, as described elsewhere (11).

For each patient a retrospective life chart was completed, and a clinician created a prospective life chart by using the NIMH Life Chart Method (13). From the prospective life chart we were able to derive the percentage of time ill, average severity, and number of episodes. As previously described (11), ratings on the following instruments were determined monthly: Beck Depression Inventory, Hamilton Depression Rating Scale, and Young Mania Rating Scale. The CGI was used to assess the overall therapeutic effect of each treatment compared to the year before the patient began taking a mood-stabilizing medication or to the worst year during treatment with ineffective medications (if the illness had continued to progress despite treatment). Treatment response was defined as marked or moderate improvement according to the CGI scale, and nonresponse was defined as minimal change, no change, or worsening.

RESULTS

Of the 18 evaluable patients, six (33.3%) responded to valproate (one without lithium). Four of the six responders to valproate (all with lithium) had not responded to or had not tolerated any of the previous treatments, although only one of the four was rated as having a marked response. One patient who responded to valproate plus lithium subsequently experienced a manic relapse when the lithium dose was tapered. The comparison of efficacy for the 13 patients evaluable in all four treatment phases (ANOVA with repeated measures) showed a significant difference in the percentage of time patients were considered manic ($F=3.30$, df=3, 36, $p=0.04$), the average severity of mania ($F=3.68$, df=3, 36, $p=0.04$), and the number of manic episodes per year ($F=4.28$, df=3, 36, $p=0.02$). The post hoc Bonferroni t tests indicated that carbamazepine monotherapy was less effective than each of the other three treatment phases. No significant difference was found for any of the depression variables, including scores on the Beck inventory and the Hamilton depression scale. During the valproate phase 14 patients required acute antidepressant or antimanic adjunctive medication. There was no significant difference between the treatment phases in the use of adjunctive medication whether analyzed by the number of patients or by the percentage of time during which such medication was given.

When carbamazepine was added to the lithium-valproate combination for seven patients, three responded to treatment. Of these three patients, one had not responded to any previous treatment phase, one (with a marked response) had not responded to the lithium-carbamazepine treatment phases and had had only a moderate response to the valproate-lithium phase, and one had also had a moderate response to the lithium-valproate combination. Thus, a total of seven (38.9%) of the 18 evaluable patients had at least a moderate response to a treatment phase including valproate. However, the patient with a marked response to triple mood-stabilizer therapy began to show signs of loss of efficacy in the second and third years of continuation treatment, suggesting that tolerance (5) can occur even with regimens including three drugs in combination.

DISCUSSION

This study has some methodological flaws, including only a partially blind procedure, use of adjunctive medication, and lack of a parallel control group. However, this preliminary prospective clinical trial suggests that some bipolar patients preselected for inadequate response to lithium and carbamazepine received benefit when taking valproate (with or without lithium) or triple mood-stabilizer therapy.

The 18 evaluable patients included in this report are a subset of the original patients randomly assigned to 1 year of lithium or carbamazepine prophylaxis (11). The cumulative percentages of response were as follows: 33.3% of the patients taking lithium (14 of 42), 42.9% with carbamazepine (N=18), 50.0% with the lithium-carbamazepine combination (N=21), 59.5% with valproate plus lithium (N=25), and 61.9% with all three (N=26). Viewed from the opposite perspective, the data highlight the lack of a clinically meaningful response in almost 40% of bipolar outpatients given combination mood-stabilizer prophylaxis, even though adjunctive antimanic and antidepressant agents were used as necessary on a short-term basis. Clearly, new treatment options and algorithms are required and deserve systematic study in the long-term prophylaxis of patients with bipolar illness. On the other hand, in the last 2 years of an extended (5-year) prospective prophylactic study, combination treatments involving valproate achieved additional therapeutic success for some outpatients with otherwise refractory bipolar disorder.

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