Rapid Titration of Mood Stabilizers Predicts Remission From Mixed or Pure Mania in Bipolar Patients

Joseph F. Goldberg, M.D.; Jessica L. Garno; Andrew C. Leon, Ph.D.; James H. Kocsis, M.D.; and Laura Portera, M.S.

Background: Recent investigations have suggested that the antimanic agents divalproex sodium and carbamazepine may each hasten hospital discharge and be especially beneficial in treating mixed-state mania. This study retrospectively compared the time to remission for pure versus mixed manic bipolar inpatients who were taking lithium, divalproex, or carbamazepine, or their combination, under naturalistic conditions.

Method: Records were reviewed for 120 bipolar inpatients from 1991 to 1995. Research DSM-III-R diagnoses of pure or mixed mania were assigned along standardized guidelines. Data were obtained on daily symptoms, medication doses, and blood levels. Weekly improvement was evaluated by Kaplan-Meier survival analysis of Clinical Global Impressions scale scores. Variables associated with "remission" versus "nonremission" were examined by logistic regression.

Results: Mixed mania (N = 70) was more common than pure mania (N = 50). No significant differences were observed in the time to remission for mixed or pure manic bipolar patients who took lithium compared with those who took divalproex or carbamazepine. In patients who remained symptomatic with lithium as a single-agent mood stabilizer despite therapeutic serum lithium levels, the addition of a second mood stabilizer led to rapid symptom improvement. Among all medication subgroups, the speed with which patients achieved therapeutic blood levels of any of these agents significantly affected the time to remission.

Conclusion: Mixed manic bipolar patients taking lithium, divalproex, or carbamazepine under naturalistic conditions remit at comparable rates. Those failing to respond to single-agent mood stabilizers often receive combinations of mood stabilizers. However, delays in optimizing a medication regimen may attenuate short-term outcome, regardless of the mood stabilizer selected. Rapid achievement of therapeutic blood levels of any antimanic agent appears to be strongly related to swift symptom remission.

(J Clin Psychiatry 1998;59:151–158)

Received Jan. 23, 1997; accepted Aug. 20, 1997. From the Payne Whitney Clinic, New York Hospital-Cornell University Medical College, New York, N.Y.

Supported by a small grant from Abbott Laboratories, Abbott Park, Ill., and by resources from a fund established in The New York Community Trust by DeWitt-Wallace.

Presented, in part, at the 51st annual meeting of the Society for Biological Psychiatry, May 4, 1996, New York, N.Y., and the 36th annual meeting of the New Clinical Drug Evaluation Unit (NCDEU), May 30, 1996, Boca Raton, Fla.

The authors thank Mark Frye, M.D., for helpful comments regarding the manuscript and Amy Kossoy for assistance with data collection.

Reprint requests to: Joseph F. Goldberg, M.D., Payne Whitney Clinic, New York Hospital, 525 East 68th Street, New York, NY 10021.

Complex presentations of mania, particularly mixed affective episodes, have been identified as important predictors of treatment response and longitudinal course in bipolar affective disorders. A number of follow-up studies have observed poor outcome and high relapse rates when depressive features arise during mania.[1,2] In contrast, patients with pure manic episodes appear more likely to recover and regain adequate levels of work and psychosocial functioning. Newer treatments for bipolar illness, particularly divalproex sodium and carbamazepine, may offer an advantage over lithium for some bipolar patients. However, it remains an open question whether these agents can preferentially hasten recovery from mixed or dysphoric mania. The current study examined patterns of medication use and the time course to symptom remission among bipolar patients hospitalized for mixed or pure manic episodes.

Lithium, divalproex, and carbamazepine all appear superior to placebo for a majority of bipolar patients.[3–5] To date, 2 randomized controlled trials have reported higher response rates with divalproex than with lithium when salient depression coincides with acute mania prior to treatment.[5–7] Bowden et al.,[5,8] however, have noted that because both lithium and divalproex are highly effective in treating mania, substantial statistical power would be needed to detect a difference between these 2 treatments. Nonetheless, a recent naturalistic chart review by Frye et al.[9] found a shortened length of hospital stay among mixed-state bipolar patients treated with divalproex alone or with carbamazepine plus lithium, compared with patients taking lithium alone. Similarly, in pharmacoeconomic analyses of cost and outcome in bipolar illness,

Keck et al.[10,11] found that acutely manic inpatients who underwent oral loading[12] with divalproex were discharged from the hospital an average of 4.1 days sooner than patients treated with lithium. Although hospital length of stay is, as Keck et al.[11] note, a "parameter with high uncertainty," their findings could suggest that the rapidity of divalproex dosing by oral loading (and its clinical tolerability) may contribute substantially to the differences observed with lithium in the time until discharge.

The present study was undertaken to broaden existing knowledge about factors that influence symptom remission, treatment, and immediate outcome in bipolar patients hospitalized for mixed or pure manic episodes. There is a compelling need for additional naturalistic data in this area, particularly in light of the observation by Bowden et al.[5] that a comparable and significant within-group effect size was seen for divalproex (1.01) or lithium (0.79) versus placebo (0.3) in data from the largest existing multicenter trial of these pharmacotherapies for bipolar illness. Elsewhere, Bowden[8] has noted that "the relatively small difference in effectiveness between 2 effective compounds such as divalproex and lithium precludes a reasonable likelihood of establishing a significant difference between the 2 with attainable size samples." Furthermore, it is possible that other preliminary studies with small sample sizes which report large differences in outcome between these treatments[9] could reflect either true differences or a type I error. It is also possible that the rapidity and tolerability with which clinicians are able to attain therapeutic serum levels of one mood stabilizer versus another may be at least as important for immediate outcome as other factors that may be intrinsic to lithium or divalproex.[10]

Clinical outcome measures in the present study were assessed in relation to differential treatment with lithium, divalproex, or carbamazepine under routine clinical conditions. The specific aims of this study were (1) to compare pure and mixed manic bipolar inpatients on the basis of the pharmacotherapies they received during hospitalization; and (2) to explore clinical predictors of "remission" during hospitalization using Kaplan-Meier survival analysis and a logistic regression analysis. We hypothesized, based on current literature, that mixed (but not pure) manic bipolar patients would remit sooner with an anticonvulsant mood stabilizer (i.e., divalproex or carbamazepine) than with lithium during naturalistic treatment.

METHOD

Patient Sample

Consecutive admissions to the Payne Whitney Clinic of New York Hospital from 1991 through 1995 were evaluated by 2 of us (J.F.G., J.L.G.) based on chart discharge diagnoses of bipolar I disorder. Screening a total of 206 records, raters used the DSM-III-R to confirm independently a diagnosis of bipolar I disorder. Patients were excluded from the study if their past psychiatric histories or symptoms while in the hospital suggested a prominent schizophrenic, schizoaffective, characterologic, substance-induced, or other organic etiology. In addition, patients had to have (1) received lithium and/or an anticonvulsant mood stabilizer during the index hospitalization and reached an adequate serum level (as defined below), and (2) had to have been hospitalized for at least 14 days. The criterion of excluding patients who were hospitalized for less than 14 days was used to maximize the likelihood of including only those patients who received a treatment of adequate duration. No patients underwent oral loading of divalproex. The majority of patients who were discharged from the hospital in fewer than 14 days did not meet standards of consistent treatment while in the hospital.

The patient population was representative of a general adult psychiatric inpatient service. Treatment with mood stabilizers and/or other medications occurred under ordinary (nonprotocol) clinical conditions as prescribed by the inpatient psychiatry staff. The research protocol was approved by the Committee on Human Rights for the New York Hospital–Cornell Medical Center.

A total of 120 patient records were included for subsequent analyses. At the time of admission, patients had a mean ± SD age of 40.3 ± 15.3 years, 71% were white, and 57% were female. Patients had a mean ± SD number of 3.8 ± 4.2 prior hospitalizations; 37% were first- or second-admission patients. Seventy percent were psychotic (i.e., had evidence of delusions or hallucinations) during their hospitalization. There were 70 patients (58%) in a mixed manic state and 50 (42%) in a pure manic state. The mixed and pure manic samples did not differ significantly in the preceding variables. However, the mixed patients were significantly more likely to have had a history of prior substance abuse compared with the pure manic patients ($\chi^2 = 8.7$, df = 1, $p < .01$); they also had higher baseline severity levels of psychopathology at admission based on Clinical Global Impressions (CGI)[13] Severity of Illness ratings ($t = 3.05$, df = 118, $p < .01$). These factors were controlled for in subsequent analyses.

The presence of depressive symptoms during the hospital course was rated using operational definitions for mixed mania as described in Table 1, based on criteria proposed by McElroy et al.[14] Patients who had 2 ("probable") or 3 ("definite") prominent depressive symptoms were classified as having a mixed manic episode. Only 2 of the 120 bipolar patients were observed to cycle from 1 discrete affective pole to another during their hospitalization ("cycling within the index presentation"[1]). Finally, patients who were admitted for more than 1 bipolar episode during the 5-year study period were included only once, during the longest of their hospitalizations. Only 7 of the 120 bipolar patients had been hospitalized twice and none 3 times at the Payne Whitney Clinic during this

Table 1. Operational Diagnostic Criteria for Dysphoric or Mixed Mania*

Full manic syndrome by DSM-III-R criteria
Simultaneously, ≥ 3 depressive symptoms ("definite") or 2 depressive symptoms ("probable") from among the following:
Depressed mood
Anhedonia
Appetite increase or decrease
Hypersomnia
Psychomotor retardation
Fatigue
Worthlessness/guilt
Helplessness/hopelessness
Suicidal ideation

*Adapted from McElroy et al.[14]

time period. For those 7 patients, no significant differences were observed in the mean durations of their 2 separate admissions. Therefore, the longer of their 2 hospitalizations was included to provide the greatest time period of observation during naturalistic treatment.

Clinical Assessments

Data were collected from patient records by systematic assessment in a number of major clinical areas. Ratings, made by the authors, were derived primarily from clinical admission and discharge summaries, daily physician progress notes, and nursing notes. In addition to demographic characteristics, information was obtained on the following: (1) manic, depressive, and psychotic symptoms throughout the index hospitalization; (2) prior treatments, hospitalizations, medical histories, and psychiatric diagnoses; (3) alcohol and other substance abuse prior to admission; and (4) daily medication use and serum medication levels obtained during the hospitalization. Attempts were made to identify patients noted to have histories of treatment noncompliance or of rapid cycling (as defined by 4 or more affective episodes per year), although such information was not systematically available. The retrospective analysis employed in the current study bears similarity to the design used by Frye et al.[9] In contrast to that methodology, however, the present study involved a larger sample size and symptom-based outcome measures, rather than a focus on discharge from the hospital as the primary index of remission.

Overall severity of psychopathology was rated from all narrative chart material at baseline (admission) and at weekly intervals thereafter using the CGI–Severity of Illness scale (CGI-S).[13] Similarly, weekly ratings of improvement from baseline were made using the CGI-Improvement scale (CGI-I),[13] an index ranging from 1 ("very much improved") to 7 ("significantly worse"). Interrater reliability was evaluated on the CGI-I, based on week-by-week recordings, with intraclass correlation coefficients ranging from .44 to .88 with a median of .71. Initial levels of symptom severity at baseline were rated using the 7-point CGI-S. "Remission" was defined by patients' achieving a CGI-I score of 2 ("much improved") for at least 1 week.

Table 2. Medication Use Among Mixed and Pure Manic Patients*

	Mixed Mania (N = 70)		Pure Mania (N = 50)	
Treatment Modalities[a]	N	%	N	%
Lithium alone (N = 65)	39	56	26	52
DVP and/or CBZ alone (N = 22)				
DVP alone	9	13	4	8
CBZ alone	4	6	3	6
DVP + CBZ	1	1	1	2
Combination class (N = 33)				
Lithium + DVP	7	10	5	10
Lithium + CBZ	10	14	10	20
Lithium + DVP + CBZ	0	0	1	2
Adjunctive neuroleptics and/or benzodiazepines	62	89	44	88
Adjunctive ECT	4	6	0	0

*Abbreviations: CBZ = carbamazepine, DVP = divalproex sodium, ECT = electroconvulsive therapy. Column percentages based on numbers of mixed or pure manic patients.
[a]Antidepressant medications were used in 6 patients taking lithium alone; none taking DVP alone; none taking CBZ alone; 2 taking lithium + DVP; 3 taking lithium + CBZ; 1 taking DVP + CBZ; none taking lithium + DVP + CBZ; and 16 taking neuroleptics and/or benzodiazepines.

Statistical Analyses

Mean differences between 2 independent groups were analyzed using 2-tailed t tests. Mean differences in a continuous variable between 3 or more independent groups were analyzed by 1-way analyses of variance (ANOVAs). Dichotomous outcome variables (e.g., remission versus nonremission) were compared by chi-square analyses. The time course to achieve remission across subdiagnostic or medication groups was analyzed using Kaplan-Meier survival curves with log-rank statistics. A logistic regression model was used to examine the association of clinical and demographic variables with remission, from which odds ratios (OR) and 95% confidence intervals (CI) are presented. The hypothesized explanatory variables are described in the Results section.

RESULTS

Pharmacotherapy During Hospitalization

Information on medication use during the hospitalization is presented in Table 2. Nearly all patients, regardless of bipolar subtype, were prescribed neuroleptics or benzodiazepines during the course of their hospitalization.

The mixed and pure manic patients were subdivided into 3 groups of prescribed mood stabilizers: (1) those who took lithium as the sole mood stabilizer; (2) those who took an anticonvulsant (divalproex or carbamazepine or their combination) as the sole type of mood stabilizer; and (3) those who took a combination of lithium with divalproex and/or carbamazepine ("combination class treatment"). In addition, 1 patient took lithium, divalproex, and carbamazepine and was included in the third (combination) medication group for the purposes of further analyses. There were no

Table 3. Antimanic Pharmacotherapy: Comparative Treatment Parameters

Medication Group	Mixed Mania (Mean ± SD)	Pure Mania (Mean ± SD)	t	df	p
Lithium alone					
Peak lithium dose (mg/d)	1512 ± 407	1638 ± 680	0.94	63	NS
Peak serum lithium level (μg/mL)	1.2 ± 0.2	1.3 ± 0.3	1.00	63	NS
Days of treatment	39 ± 31	26 ± 30	0.40	63	NS
DVP and/or CBZ					
Peak DVP dose (mg/d)	1560 ± 705	1813 ± 688	0.61	12	NS
Peak serum DVP level (μg/mL)	64.6 ± 12.8	84.7 ± 13.9	2.80	13	< .05
DVP days of treatment	32 ± 22	33 ± 7	0.09	13	NS
Peak CBZ dose (mg/d)	780 ± 110	1050 ± 443	1.33	7	NS
Peak serum CBZ level (μg/mL)	9.6 ± 1.7	10.8 ± 1.6	1.08	7	NS
CBZ days of treatment	23 ± 12	50 ± 27	1.96	7	NS
Lithium + DVP and/or CBZ					
Peak lithium dose (mg/d)	1597 ± 600	1625 ± 717	0.12	31	NS
Peak serum lithium level (μg/mL)	1.2 ± 0.4	1.1 ± 0.3	0.25	31	NS
Lithium days of treatment	34 ± 17	40 ± 29	0.64	31	NS
Peak DVP dose (mg/d)	1179 ± 494	1467 ± 1092	0.63	11	NS
Peak serum DVP level (μg/mL)	62.9 ± 11.5	60.2 ± 20.2	0.28	9	NS
DVP days of treatment	18 ± 10	33 ± 39	0.95	11	NS
Peak CBZ dose (mg/d)	700 ± 452	645 ± 175	0.37	19	NS
Peak serum CBZ level (μg/mL)	8.5 ± 2.9	8.2 ± 1.8	0.24	17	NS
CBZ days of treatment	25 ± 9	22 ± 13	0.54	19	NS

significant differences in the numbers of mixed versus pure manic patients who were represented among each of the 3 medication groups ($\chi^2 = 0.96$, df = 2, NS). There were also no significant differences among the 3 mood-stabilizer groups in the number of weeks in which concomitant neuroleptics were prescribed (F = 0.50, df = 2,117; NS) or concomitant benzodiazepines were prescribed (F = 0.51, df = 2,117; NS).

Data on the parameters of treatment with antimanic agents (lithium, divalproex, and carbamazepine) are presented for the mixed and pure bipolar patients in Table 3. As indicated in Table 3, the 2 bipolar patient groups did not differ significantly in their mean medication dosages, peak serum drug levels, or number of days of treatment with any of these 3 medications, with 1 exception: serum divalproex levels were significantly higher among the pure than the mixed bipolar patients. The duration of hospitalization did not differ between the 3 patient groups treated with lithium, carbamazepine and/or divalproex, or combination class treatment (F = 0.39, df = 2,117; NS). Minimum therapeutic serum levels adopted for the current study were as follows: lithium ≥ 0.8 mEq; divalproex ≥ 50 μg/mL; and carbamazepine ≥ 8 μg/mL. In general, mean dosages and serum levels for all patients tended to be in the higher range of therapeutic for lithium than for divalproex or carbamazepine.

Time Course to Remission

Figures 1 and 2 depict the Kaplan-Meier survival curves of remission (as defined by CGI-I scores) for the pure and mixed manic patients, respectively, stratified by the 3 major medication groups: (1) those taking lithium alone (baseline, N = 26 for pure mania; N = 39 for mixed); (2) those taking divalproex and/or carbamazepine alone (baseline, N = 8 for pure mania; N = 14 for mixed); and (3) those taking combination class mood stabilizers (i.e., lithium plus divalproex and/or carbamazepine) (baseline, N = 16 for pure mania; N = 17 for mixed mania). The baseline in these survival analyses was the time at which a therapeutic serum level was achieved for at least 1 antimanic agent (lithium, divalproex, or carbamazepine).

Pure Mania

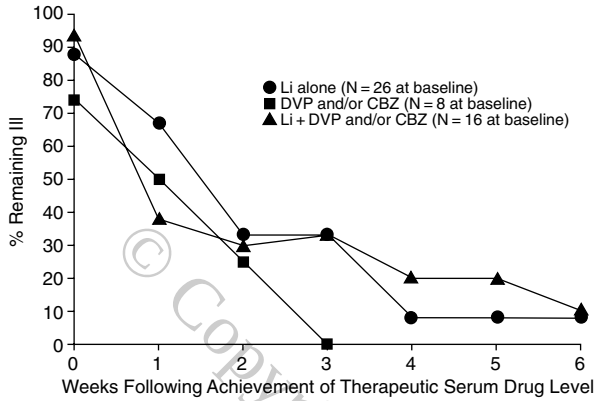
Among the pure manic patients, a marked improvement was evident for most patients in all 3 medication groups within 3 weeks after attaining a therapeutic serum drug level. The most dramatic rate of improvement was seen after 1 week among patients taking lithium combined with divalproex and/or carbamazepine. (The cumulative proportion of those remaining ill decreased in the first week from 94% to 38%.) However, there were no statistically significant differences between the 3 medication groups in their comparative time course to remission (log-rank statistic = 2.50, df = 2, NS).

The overall remission rate while in the hospital among pure manic patients, ignoring differential treatment period (i.e., length of hospital stay) and censorship in the survival analysis depicted in Figure 1, was separately calculated. One hundred percent (8/8 patients) of those taking only divalproex and/or carbamazepine achieved remission while in the hospital, as did 81% (13/16 patients) of those taking lithium plus divalproex and/or carbamazepine and 69% (18/26 patients) of those taking lithium alone.

Mixed Mania

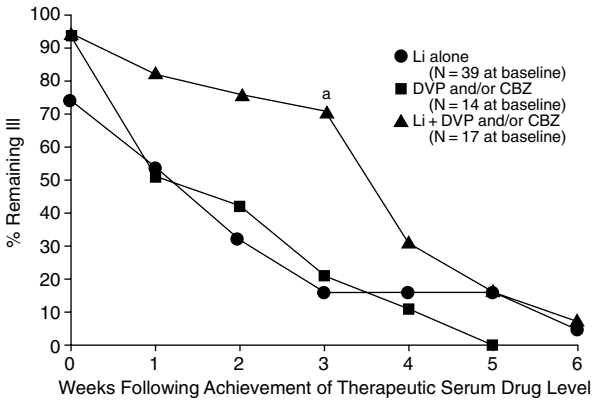
Among the mixed manic patients, after achieving a therapeutic serum drug level, those taking lithium plus divalproex and/or carbamazepine had a significantly slower

Figure 1. Pure Mania and CGI-Improvement: Proportions Remaining Ill After Achieving Therapeutic Serum Level of Mood Stabilizer*



*Abbreviation: Li = lithium. Baseline is the time at which a therapeutic serum level was achieved for at least 1 antimanic agent. No statistically significant differences in time course to remission were found between the 3 medication groups (log-rank statistic = 2.50, df = 2, NS).

Figure 2. Mixed Mania and CGI-Improvement: Proportions Remaining Ill After Achieving Therapeutic Serum Level of Mood Stabilizer*



*Baseline is the time at which a therapeutic serum level was achieved for at least 1 antimanic agent. Patients taking Li + DVP and/or CBZ had a significantly slower time course to remission compared with the other 2 medication groups (log-rank statistic = 6.54, df = 2, p < .04). [a]Indicates time point at which a significant difference (p < .05) was observed between lithium alone and lithium + DVP and/or CBZ.

time course to remission compared with those taking lithium alone or an anticonvulsant alone (log-rank statistic = 6.54, df = 2, p < .04). Comparisons of the overall remission rates while in the hospital, ignoring differential treatment period and censorship in the survival analysis depicted in Figure 2, reveal the following: 74% (29/39 patients) of those taking lithium alone achieved remission in the hospital, as did 79% (11/14 patients) of those taking only divalproex and/or carbamazepine and 82% (14/17 patients) of those taking lithium plus divalproex and/or carbamazepine.

Further examination of the mixed manic patients revealed no significant differences in the mean ± SD baseline CGI-S scores for those taking lithium plus divalproex and/or carbamazepine (5.5 ± 0.8) compared with those taking lithium alone (5.8 ± 1.0) or those taking divalproex and/or carbamazepine (6.2 ± 1.0) (F = 2.09, df = 2,67; NS). The mixed manic patients who were taking lithium plus divalproex and/or carbamazepine had nearly significantly more prior hospitalizations (mean ± SD = 4.4 ± 4.3) compared with the mixed patients taking lithium alone (2.4 ± 2.9) or divalproex and/or carbamazepine alone (5.0 ± 5.9) (F = 2.71, df = 2,67; p < .07).

Finally, although the mixed manic patients taking lithium plus divalproex and/or carbamazepine achieved remission at a slower rate than the other groups, they tended to attain a therapeutic serum level of at least 1 antimanic agent sooner than did the other groups; 67% of these combined class treatment patients (10 of 15 patients with complete data) had a therapeutic serum level within 1 week of admission, as did only 18% of those taking lithium alone (6 of 34 patients with complete data) and 27% of those taking divalproex and/or carbamazepine (3 of 11 patients with complete data) ($\chi^2 = 5.64$, df = 2, p < .08). Of note, for the majority of patients in the combined class group, the second class of antimanic drug was added after achievement of a therapeutic serum level of the first drug, which was often lithium. In other words, many of the combined class treatment patients at the time of admission had been taking only 1 mood stabilizer (usually lithium), remaining floridly symptomatic despite having a therapeutic serum level in the majority of instances. Nearly all of those "lithium-resistant" patients who attained therapeutic serum levels of the second class of antimanic drug achieved remission within 2 to 3 weeks.

Data on the presence or absence of rapid cycling (4 or more episodes per year) were available for 102 patients, and rapid cycling was clearly evident in only 3% (N = 3). Because of this small number, patterns of remission could not be systematically analyzed for the bipolar patients with rapid cycling versus those without rapid cycling.

Factors Associated With Remission

Because the mixed manic patients had a higher rate of prior hospitalizations compared with the pure manic patients, we separately compared rates of remission versus nonremission for first-admission versus readmission patients within each diagnostic subgroup. No significant differences were observed for the mixed manic patients ($\chi^2 = 0.33$, df = 1, NS) or the pure manic patients ($\chi^2 = 0.21$, df = 1, NS).

A logistic regression analysis was conducted to examine the strength of association of key demographic and clinical variables with remission. The following independent variables were screened for potential entry into the model: (1) sex, (2) number of years since the first affective episode, (3) CGI-S score at baseline, (4) the number

of weeks needed to achieve a therapeutic serum level with at least 1 antimanic medication (lithium, divalproex, or carbamazepine), (5) history of substance abuse, (6) presence of psychotic symptoms, (7) "mixed" versus "pure" manic subtype, (8) history of treatment with lithium prior to admission, (9) history of treatment with divalproex or carbamazepine prior to admission, and (10) medication class during the index hospitalization (lithium or divalproex/carbamazepine). These variables were chosen a priori based on clinical features previously found to be of clinical significance in the literature.

From among these 10 variables, the only one that emerged as a statistically significant predictor of remission was the number of weeks needed to achieve an adequate serum level of an antimanic pharmacotherapy. While controlling for each of the other variables in the regression model, the likelihood of remission was found to decline 27% for each week needed to attain a therapeutic serum level (OR = 0.73, 95% CI = 0.54 to 0.97).

We separately compared the mean number of days necessary to achieve a peak divalproex or carbamazepine serum level from the time either medication was begun. Complete data were available for 15 bipolar patients who received divalproex and 13 who received carbamazepine (either alone or in combination with lithium). Patients receiving divalproex achieved a therapeutic serum level 14.7 ± 12.0 days (mean ± SD) after having begun divalproex, while those receiving carbamazepine achieved a therapeutic serum level 9.8 ± 8.7 days after beginning carbamazepine. For the bipolar patients who took lithium (either alone or in combination with divalproex or carbamazepine), therapeutic serum lithium levels were obtained 11.9 ± 10 days after admission. In addition, no significant differences emerged by t tests between the mixed and pure manic patients when comparing the mean duration until therapeutic serum levels were achieved for each of these 3 agents.

DISCUSSION

The present findings, which are a compilation of data obtained during naturalistic treatment under ordinary clinical conditions in a single inpatient setting, suggest comparable effectiveness for lithium, divalproex, and carbamazepine in the acute treatment of mixed or pure mania. For both mixed and pure manic patients, we did not observe a significant difference in the relative time to remission during treatment with lithium, divalproex, carbamazepine, or their combination. These results contrast with several previous reports that have suggested a possible therapeutic advantage for anticonvulsant mood stabilizers, particularly divalproex, when prominent depression co-occurs with acute mania.[5–7,9] Indeed, recent Expert Consensus Guidelines for the treatment of bipolar disorder advocate the use of divalproex as the preferred agent over lithium for mixed mania.[15]

In this sample receiving pharmacotherapy under noncontrolled, nonrandomized conditions, the lack of superior improvement for the divalproex-treated mixed manic patients was unexpected and runs counter to other reports suggesting that the preferential use of divalproex over lithium in mixed manic patients may lead to shorter lengths of hospitalization.[9,10] Other preliminary studies, such as the one by Frye et al.,[9] have been limited by their use of retrospective designs, small sample sizes (only 5 patients received divalproex in their chart review), and outcome variables that are multideterminate (hospital discharge). The present study, while also limited by its retrospective design, involved a somewhat larger sample size and focused on symptom remission as an endpoint. This may more accurately reflect a patient's clinical status, particularly in an era when factors such as managed care reimbursement may, at least to some degree in the early 1990s, have influenced decisions regarding hospital discharge. Although the possibility exists that newer antimanic agents such as divalproex hold special promise for mixed/cycling bipolar patients, more definitive investigations are needed, using prospective, double-blind comparison trials, in order to demonstrate intrinsic superior efficacy.

Methodological factors, such as the use of retrospective designs, small sample sizes, and different outcome measures (clinical improvement vs. hospital discharge), may in part account for the seeming disparity between the present findings and those by Frye et al.[9] However, 2 other factors would appear important in explaining the current findings in relation to the broader literature. First, underdosing of divalproex among mixed manic patients in the present cohort may have led to a suboptimal treatment outcome. Although the mean peak serum divalproex concentrations for both the mixed and pure manic groups eventually fell within the reported therapeutic range of 45–125 μg/mL,[16] the peak levels observed during single-agent treatment were lower for the mixed manic patients (63 μg/mL) than for the pure manic patients (84.7 μg/mL).

Second, and perhaps even more importantly, therapeutic serum levels were rarely achieved before the first 2 weeks after beginning divalproex treatment in the current sample. By contrast, in the study by Frye et al.,[9] 3 of the 5 divalproex patients who had serum divalproex levels drawn were noted to achieve levels above 60 μg/mL within 10 days of admission, while 2 of these 3 had therapeutic serum levels at day 5. This time factor may be a central aspect of the therapeutic response observed with divalproex, or quite possibly any other mood stabilizer.

In the present study, no significant differences were observed once therapeutic serum levels were reached for any of the 3 mood stabilizers, even when controlling for baseline levels of severity. From one perspective, this finding might call into question the relative superiority of divalproex or carbamazepine over lithium (as opposed simply to their comparable effectiveness) in mixed mania.

However, from another perspective, the present data are compatible with those of Frye et al.[9] and others[10,11] in that they underscore the importance of rapid attainment of therapeutic serum levels of a mood stabilizer.

In this regard, divalproex may yet offer a relative advantage in that rapid therapeutic serum levels can be reached safely, along with a marked reduction in symptoms, within 5 days after oral loading, dosed at 20 mg/kg body weight.[12] None of the patients in the current sample underwent oral loading of divalproex, and thus the optimal benefits of divalproex may have been understated. The time window needed to obtain a therapeutic serum level of a mood stabilizer during acute mania may be of considerable prognostic importance. Consistent with this interpretation is the finding by McElroy et al.[17] that divalproex, when orally loaded, is comparable to haloperidol in the time to reduction in manic symptoms over a 1-week period. In the current naturalistic study, treatment for some patients may have been nonsystematically escalated, delayed, or tapered before therapeutic serum levels were achieved. Hence, the aggressiveness with which one undertakes a clinical trial of a mood stabilizer may be at least as important, if not more important, than the actual choice of antimanic agent.

A nomogram was developed by Cooper et al.[18,19] for rapidly predicting the lithium dose necessary to produce a therapeutic serum lithium level, measured 24 hours after a single test dose of 600 mg. A similar algorithm for predicting lithium dosages necessary to produce therapeutic serum levels has been described by Norman et al.[20] Current clinical practice often favors a relatively gradual titration of lithium dosing to achieve therapeutic serum levels, although few studies have systematically evaluated the efficacy and tolerability of approaches such as these.[21–23] Bowden[24] recently suggested beginning lithium at 15 mg/kg body weight and increasing the dosage every 3 to 4 days until achieving a serum lithium level of 1.2 to 1.4 μg/mL. The present findings may indicate that it is worthwhile for clinicians to reconsider such methods for rapid lithium loading in acute mania, when feasible. Further studies of rapid lithium dosing may also be of value in order to describe the tolerability of rapid loading strategies, potential side effects, and outcomes.

The findings of this study regarding treatment with a combination of 2 classes of mood stabilizers warrant further discussion. Among both the mixed and pure subgroups, a relatively high proportion of patients on combined regimens tended to remain significantly ill despite having reached a therapeutic serum level of at least 1 mood stabilizer. Interestingly, for a majority of these patients, improvement did not occur until after the achievement of a therapeutic serum level of the second mood stabilizer—following which most patients rapidly entered remission. In routine clinical practice, it is possible that when a bipolar patient remains symptomatic despite having a therapeutic serum level of an antimanic medication, there is little advantage in continuing this regimen without the addition of a second mood stabilizer, dosed to attain a therapeutic serum level. It remains an open question as to whether subsequent improvement may then arise because of the singular efficacy of the second agent or by virtue of synergy between the 2 medications. In the absence of controlled data in this area, drug discontinuation studies are needed to investigate these hypotheses. During the continuation and maintenance phases of treatment for bipolar disorder, Solomon et al.[25] recently found in an open pilot study that lithium plus divalproex was superior to lithium with placebo in preventing affective recurrences. It is currently unknown from controlled studies whether a similar treatment strategy would lead to more rapid resolution of an acute affective episode in bipolar illness.

The current study is limited by a number of factors, including the retrospective nature of its design, the derivation of patients from a single institution, the nonrandom assignment of treatment modalities, and the noncontrolled mechanisms by which patients received a given treatment at a given intensity. The present sample size, although adequate to detect large group differences, lacked adequate power (> .80) to detect small to moderate differences. However, the sample size in the current study is larger than that of the only other study,[9] using a similar design, which addresses questions about differential time to remission during naturalistic treatment with anticonvulsants or lithium.

In addition, the nonspecific effects of psychosocial treatments (e.g., psychoeducation, milieu therapy) and other interventions (e.g., benzodiazepines and neuroleptics, taken by nearly all patients) prevent one from drawing definitive conclusions about treatment efficacy in this study. However, these naturalistic data highlight patterns of treatment administration in a typical urban academic medical center, where clinical decisions to undertake a new pharmacotherapy or augment an existing regimen are influenced by numerous factors. These include the initial certainty of a bipolar diagnosis, comorbid conditions, side effects, patient compliance, dependability of outpatient follow-up, and interrupted or nonaggressive dosing toward therapeutic levels.

As is the case with other retrospective studies, decisions to prescribe a particular mood stabilizer are often guided by clinical parameters that could bias the results. As noted by Keller et al.,[26] naturalistic treatment is in itself a kind of outcome measure. For bipolar patients, the decision to prescribe one mood stabilizer over another often reflects an individual's clinical status: less severely ill patients may be those who are most likely to receive a well-established therapy such as lithium, while those who have failed standard treatments may be more likely to receive new or alternative pharmacotherapies. Among the mixed manic patients in the current study, treatment with

2 classes of mood stabilizers occurred more often for those who had multiple prior hospitalized episodes. Although baseline severity levels at admission were no greater among the combined medication group than the other groups, the combined group may have had a form of bipolar illness that is more chronic and treatment resistant.

What factors might alter the relative effectiveness of any mood stabilizer under ordinary treatment conditions? In the case of lithium, Goldberg et al.[27] outlined the profile of bipolar patients for whom ongoing treatment may show diminished efficacy. In addition to mixed states and rapid cycling, other key factors identified in the literature include the following: a cycling pattern of depression followed by mania and then recovery, psychotic symptoms, delaying the initiation of treatment until after the third affective episode, patterns of kindled episodes early in the longitudinal course of illness, and resistance to monotherapy. Other factors, such as substance abuse, comorbid psychopathology, poor social support, and abrupt lithium discontinuation, also mitigate against an optimal treatment outcome. Whereas anticonvulsants have been shown to augment a poor response to lithium maintenance,[28,29] some of these parameters could nonetheless detract from the best possible response not only to lithium, but to divalproex or carbamazepine as well. It may therefore be essential for future, prospective studies with larger sample sizes to identify and control for comorbidity and medication compliance issues in order to draw meaningful conclusions about the differential effectiveness of treatments under naturalistic conditions.

When the comparative efficacies of different pharmacotherapies for mixed mania are compared in randomized clinical trials, anticonvulsants such as divalproex may nonetheless prove to be superior to lithium. However, when 2 or more agents of established efficacy are compared against one another under nonrandomized, typical conditions—thus not excluding comorbidity and other "real world" phenomena—the relative effectiveness of each medication may not differ as markedly.

In summary, the time course to remission from both mixed mania and pure mania appears strongly influenced by the speed with which patients achieve a therapeutic serum level of an antimanic agent. Further controlled studies are therefore essential in order to affirm whether existing treatments for complex, severe forms of acute mania do, in fact, show relative superiorities after controlling for rates of initial titration.

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

REFERENCES

1. Keller MB, Lavori PW, Coryell W, et al. Differential outcome of pure manic, mixed/cycling, and pure depressive episodes in patients with bipolar illness. JAMA 1986;255:3138–3142
2. Keller MB, Lavori PW, Coryell W, et al. Bipolar I: a five-year prospective follow-up. J Nerv Ment Dis 1993;181:238–245
3. 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
4. Small JG, Klapper MH, Milstein V, et al. Carbamazepine compared with lithium in the treatment of mania. Arch Gen Psychiatry 1991;48:915–921
5. 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
6. Freeman TW, Clothier JL, Pazzaglia P, et al. A double-blind comparison of valproate and lithium in the treatment of acute mania. Am J Psychiatry 1992;149:108–111
7. Swann AC, Bowden CL, Morris D, et al. Depression during mania: treatment response to lithium or divalproex. Arch Gen Psychiatry 1997;54: 37–42
8. Bowden CL. Comparison of open versus blinded studies in bipolar disorder. In: Goldberg JF, Harrow M, eds. Bipolar Disorder: Clinical Course and Outcome. Washington, DC: American Psychiatric Association. In press
9. Frye MA, Altshuler LL, Szuba MP, et al. The relationship between antimanic agent for treatment of classic or dysphoric mania and length of hospital stay. J Clin Psychiatry 1996;57:17–21
10. Keck PE Jr, McElroy SL, Bennett JA. Health-economic implications of the onset of action of antimanic agents. J Clin Psychiatry 1996;57(suppl 13):13–18
11. Keck PE Jr, Nabulsi AA, Taylor JL, et al. A pharmacoeconomic model of divalproex vs lithium in the acute and prophylactic treatment of bipolar I disorder. J Clin Psychiatry 1996;57:213–222
12. Keck PE Jr, McElroy SL, Tugrul KC, et al. Valproate oral loading in the treatment of acute mania. J Clin Psychiatry 1993;54:305–308
13. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:217–222
14. McElroy SL, Keck PE Jr, Pope HG Jr, et al. Clinical and research implications of the diagnosis of dysphoric or mixed mania. Am J Psychiatry 1992; 149:1633–1644
15. The Expert Consensus Guideline Series: Treatment of Bipolar Disorder. J Clin Psychiatry 1996;57(suppl 12A)
16. Bowden CL, Janicak PG, Orsulak P, et al. Relation of serum valproate concentration to response in mania. Am J Psychiatry 1996;153:765–770
17. McElroy SL, Keck PE Jr, Stanton SP, et al. A randomized comparison of divalproex oral loading versus haloperidol in the initial treatment of acute psychotic mania. J Clin Psychiatry 1996;57:142–146
18. Cooper TB, Berner PE, Simpson GM. The 24-hour lithium level as a prognosticator of dosage requirements. Am J Psychiatry 1973;130:601–603
19. Cooper TB, Simpson GM. The 24-hour lithium level as a prognosticator of dosage requirements: a 2-year follow-up study. Am J Psychiatry 1976; 133:440–443
20. Norman KP, Cerrone KL, Reus VI. Renal lithium clearance as a rapid and accurate predictor of maintenance dose. Am J Psychiatry 1982;139: 1625–1626
21. Fava GA, Molnar G, Block B, et al. The lithium loading dose method in a clinical setting. Am J Psychiatry 1984;141:812–813
22. Moscovich DG, Shapira B, Lerer B, et al. Rapid lithiumization in acute mania patients. Hum Psychopharmacol 1992;7:343–345
23. Baker CB, Woods SW, Sernyak MJ. Cost-effectiveness of divalproex versus lithium [letter]. J Clin Psychiatry 1997;58:363
24. Bowden CL. Dosing strategies and time course of response to antimanic drugs. J Clin Psychiatry 1996;57(suppl 13):4–9
25. Solomon DA, Ryan CE, Keitner GI, et al. A pilot study of lithium carbonate plus divalproex sodium for the continuation and maintenance treatment of patients with bipolar I disorder. J Clin Psychiatry 1997;58:95–99
26. Keller MB, Lavori PW, Endicott J, et al. "Double depression": two-year follow-up. Am J Psychiatry 1983;140:689–694
27. Goldberg JF, Harrow M, Sands JR. Lithium and the longitudinal course of bipolar disorder. Psychiatr Ann 1996;26:651–658
28. Peselow ED, Fieve RR, Difiglia C, et al. Prophylactic efficacy of lithium carbonate in manic-depressive illness: the value of combination treatment. Br J Psychiatry 1994;164:208–214
29. Denicoff KD, Smith-Jackson EE, Bryan AL, et al. Valproate prophylaxis in a prospective clinical trial of refractory bipolar disorder. Am J Psychiatry 1997;154:1456–1458