Efficacy of Lithium vs. Valproate in the Treatment of Mania in the Elderly: A Retrospective Study

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Background: This retrospective study was conducted to assess the efficacy of lithium and valproate and associated serum levels in the treatment of mania in elderly patients.

Method: Records of 59 patients aged 55 years and older with minimal or no neurologic impairment, hospitalized for mania, and discharged on lithium (N = 30) or valproate (N = 29) therapy were reviewed. Data on mood stabilizer choice, serum levels, and type of mania were recorded. A clinician blinded to medications rated improvement in each case with Clinical Global Impressions (CGI) scores based on abstracted notes.

Results: Overall, the percentage of patients improved was significantly greater in the lithium group than in the valproate group (67% vs. 38%, $\chi^2 = 4.88$, p = .027). Patients taking lithium with serum levels ≥ 0.8 mmol/L were more improved at discharge than those outside this range (≥ 0.8, CGI 2.0 ± 0.6 vs. < 0.8, CGI 2.6 ± 0.8, t = 2.15, p = .043). Patients taking valproate with serum levels between 65–90 μg/mL were more improved at discharge than those outside this range (65–90, CGI 2.1 ± 0.6 vs. < 65, > 90, CGI 3.3 ± 0.8, t = 3.73, p = .002). When response rates among only patients with these "therapeutic" levels were assessed, they were similar for lithium (82%) and valproate (75%). The difference in efficacy between drugs was maintained in classic mania, but the 2 drug groups were similar when only mixed mania was analyzed (lithium 63% vs. valproate 67% improved).

Conclusion: Results suggest that lithium may be more efficacious than valproate overall, but response rates for the 2 drugs were similar when "therapeutic" serum levels were achieved. For lithium, levels similar to those reported for younger adults were associated with response. For valproate, a "therapeutic window" different from that in younger adults was found. While the retrospective and naturalistic design of this study has limitations, these data may help direct further studies and treatment of mania in the elderly.

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Mania is relatively common among elderly psychiatric patients.[1] The incidence of first admissions for mania increases with age,[2,3] and period prevalence rates among geropsychiatric inpatients are reported to be between 4.7% and 9.0%.[4–6] Actual rates may be higher, as this condition is often misdiagnosed in the elderly.[6] Despite these data, information on the efficacy of different treatment strategies in the elderly is limited. In a 1980 retrospective study, Himmelhoch et al.[7] reported that 69% of 81 elderly bipolar outpatients responded to lithium, but did not specify which phase of illness was being treated. Another study found valproate to be effective in 7 elderly patients with mania.[8] To our knowledge, there are no other published studies addressing the efficacy of pharmacotherapy in this population.

Younger adults with mania respond to acute treatment with both lithium and valproate.[9–11] Comparative studies of these 2 agents suggest equal efficacy for classic manic episodes[12,13] and a favorable response to valproate for mixed states.[13] Therapeutic serum levels have been reported for these drugs. Serum lithium levels of at least 0.8 mmol/L are associated with greater likelihood of response, while toxicity increases significantly above 1.2 to 1.4 mmol/L.[14] Serum valproate levels ≥ 45 μg/mL are more likely to result in improvement than lower levels, while levels > 100 μg/mL are associated with greater frequency of adverse effects but not with greater efficacy.[15] Data on therapeutic serum levels for the acute treatment of mania in elderly patients have not been published to our knowledge.

The goals of this study were to (1) assess whether lithium and valproate were efficacious in the treatment of elderly patients hospitalized for mania and (2) assess serum levels associated with therapeutic efficacy for this group.

METHOD

The University of California, Los Angeles, Neuropsychiatric Hospital was the site for this retrospective study. After procurement of human subjects' waiver, computerized screening found 144 unique patients aged 55 and older (196 admissions) hospitalized between January 1991 and December 1996 with a DSM-III-R or DSM-IV discharge diagnosis of a bipolar disorder in which the index episode was mania. Of these patients, those who were discharged on lithium or valproate as the single mood stabilizer were considered for the study. Patients were excluded from the study if there was (1) concurrent diagnosis of dementia, delirium, substance abuse disorders, or acute medical illness other than a simple urinary tract infection; (2) concurrent electroconvulsive therapy; (3) discharge to another acute inpatient facility or against medical advice, or readmission within 1 week following discharge; (4) medication refusal of > 25% of doses; (5) neuroimaging suggestive of structural abnormalities other than mild atrophy or ischemic disease; and (6) concomitant use of another mood stabilizer, e.g., carbamazepine or lithium/valproate combination. The final study group consisted of 59 patients on mood stabilizer monotherapy—30 treated with lithium and 29 treated with valproate. Inpatient records were reviewed for the following data: past psychiatric history, age at onset of mood disorder, use of antipsychotics and benzodiazepines, cognitive status, thyroid function, length of hospitalization, and serum levels of mood stabilizer. In addition, each case was classified as either a classic or mixed mania based on extensive review of clinician notes, which detailed admission mood symptomatology. Serum levels drawn within 3 days of discharge were considered "discharge" serum levels. Additional demographic and admission data are shown in Table 1.

Admission and progress notes were abstracted and given to one investigator (S.M.E.) who was blinded to medications used and their serum levels. The rater then made Clinical Global Impressions (CGI)[16] ratings for each patient on the day of admission, day 5, and day of discharge. A patient with a CGI score of 1 (very much improved) or 2 (much improved) was considered to be improved in dichotomous analyses.

Statistical analyses were performed using SAS software.[17] Comparisons of the medication groups on a number of descriptive characteristics were performed using t test (continuous variables) or chi-square analyses (frequencies) as appropriate. Regression analysis was used to determine relationships between serum levels and improvement to evaluate evidence for a therapeutic range for each drug, and between age, age at onset, and improvement. Response rates with respect to type of manic episode were also compared using chi-square analyses.

To evaluate possible differential rates of improvement across time, a factorial repeated measures logistic regression analysis was performed (SAS Proc CATMOD). Medication (lithium vs. valproate), time point (day 5 vs. discharge), and the interaction (testing whether the size of medication effects was constant from day 5 to discharge) were the design effects.

Table 1. Characteristics in 59 Elderly Inpatients With Mania Treated With Lithium or Valproate[a]

Variable	Lithium N = 30 (51)	Valproate N = 29 (49)	Total N = 59 (100)
Age (y)	69.4 ± 8.2	71.2 ± 8.2	70.3 ± 8.2
N (%) with mixed episodes	8 (27)	6 (21)	14 (24)
N (%) female	21 (70)	21 (72)	42 (71)
N (%) with psychotic features	20 (67)	19 (66)	39 (66)
Age at onset (y)[b]	46.4 ± 16.7	43.2 ± 17.8	44.8 ± 17.2
Number of past psychiatric hospitalizations[b]	4.1 ± 4.3	4.2 ± 6.8	4.2 ± 5.6
Number of past medical problems	1.9 ± 1.7	2.1 ± 1.5	2.0 ± 1.6
Admission Clinical Global Impressions score	5.1 ± 0.9	4.9 ± 0.8	5.0 ± 0.8
Admission Mini-Mental State Exam score[b]	25.2 ± 6.1	23.6 ± 6.1	24.4 ± 6.1
Admission thyroid-stimulating hormone (μU/mL)[b]	5.4 ± 13.6	5.9 ± 17.2	5.7 ± 15.4
Hospital day mood stabilizer started	1.5 ± 2.1	1.9 ± 2.5	1.7 ± 2.3
Number of medications at admission	2.6 ± 2.1	3.2 ± 2.0	2.9 ± 2.0
Number of psychotropics at admission	1.4 ± 1.2	1.1 ± 1.1	1.2 ± 1.1
N (%) treated with antipsychotics			
Day 5	18/29 (62)	17/28 (61)	35/57 (61)
Discharge	15/30 (50)	19/29 (66)	34/59 (58)
N (%) treated with benzodiazepines			
Day 5	9/29 (31)	12/28 (43)	21/57 (37)
Discharge	6/30 (20)	8/29 (28)	14/59 (24)
Length of hospitalization (d)	16.1 ± 9.9	15.4 ± 7.0	15.8 ± 8.5

[a]Values are mean ± SD or number of patients (%).
[b]Data not available on all patients.

RESULTS

There were no significant differences between lithium or valproate groups in age, gender composition, age at onset, number of prior hospitalizations, severity of index episode, percentages of patients with mixed episodes or psychosis, cognitive status, thyroid function, medical comorbidity, number of psychotropic and total medications at admission, or use of adjunctive antipsychotics or benzodiazepines (Table 1).

Improvement rates for lithium versus valproate are summarized in Table 2. Overall, more patients taking lithium than taking valproate were improved on day 5 and at discharge.

Table 2. Improvement Based on Mood Stabilizer, Serum Levels, and Type of Mania

Variable	Lithium N	Lithium %	Valproate N	Valproate %
All patients				
Day 5[a]	10/29	35	4/28	14
Discharge[b]	20/30	67	11/29	38
Type of manic episode				
Classic				
Day 5[c]	9/21	43	3/22	14
Discharge[d]	16/22	73	7/23	30
Mixed				
Day 5[c]	1/8	13	1/6	17
Discharge[d]	5/8	63	4/6	67

[a]Lithium vs. valproate, $\chi^2 = 3.14$, df = 1, p = .077.
[b]Lithium vs. valproate, $\chi^2 = 4.88$, df = 1, p = .027.
[c]Lithium classic vs. valproate classic, $\chi^2 = 4.56$, df = 1, p = .033.
[d]Lithium classic vs. valproate classic, $\chi^2 = 6.41$, df = 1, p = .011.

Figure 1. Relationship Between Improvement and Serum Lithium Levels at Discharge

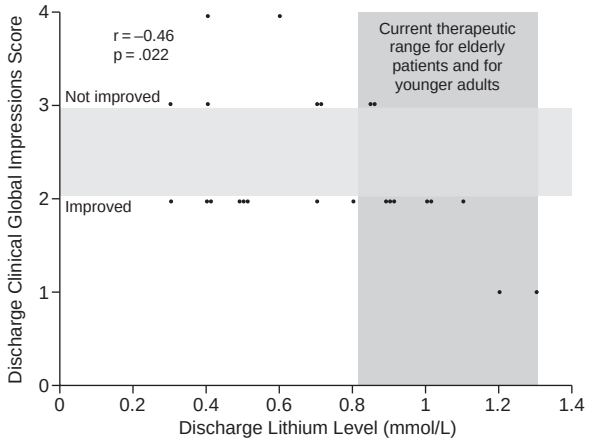


Figure 2. Relationship Between Improvement and Serum Valproate Levels at Discharge

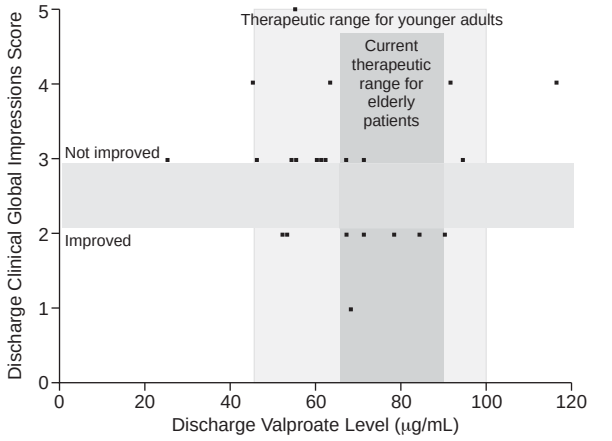
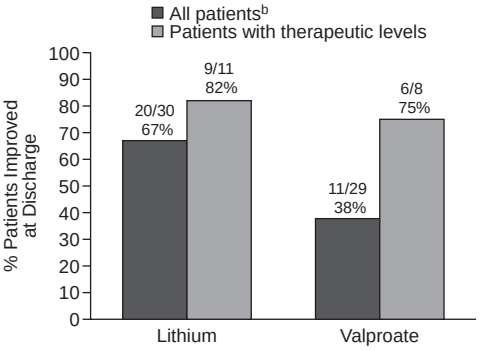


Figure 3. Percentage of All Patients and Patients With Therapeutic Levels[a] Improved at Discharge on Lithium vs. Valproate



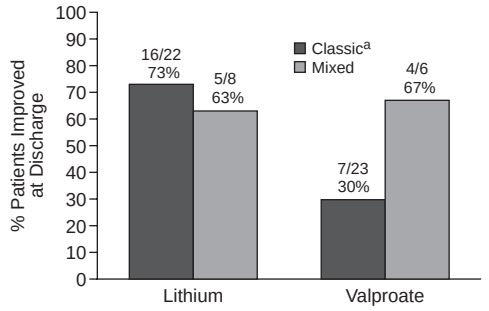
[a]Therapeutic serum levels: valproate 65–90 μg/mL; lithium ≥ 0.8 mmol/L.
[b]Lithium vs. valproate, $\chi^2 = 4.88$, df = 1, p = .027.

Relatively large and comparable percentages of patients had serum drug levels obtained at discharge: 24/30 (80%) for lithium and 23/29 (79%) for valproate. Significant relationships between serum levels and improvement emerged in both treatment groups. There was a significant correlation between lithium levels and degree of improvement (Figure 1). Levels ≥ 0.8 mmol/L (maximum, 1.3 mmol/L) were associated with significantly greater improvement than levels < 0.8 mmol/L at discharge (CGI 2.0 ± 0.6 vs. 2.6 ± 0.8, t = 2.15, p = .043, 2-tailed, unequal variances). Analysis of the valproate group using a more commonly accepted therapeutic range of 45–100 μg/mL did not distinguish responders from nonresponders. However, valproate levels between 65–90 μg/mL at discharge were associated with significantly greater improvement than those outside this range (CGI 2.1 ± 0.6 vs. 3.3 ± 0.8, t = 3.73, p =. 002, 2-tailed, unequal variances; Figure 2). Nine (82%) of the 11 elderly patients with valproate levels between 45–65 μg/mL were not improved. Thus, valproate levels between 65–90 μg/mL appeared to be the "therapeutic range" for antimanic efficacy in the elderly.

A greater proportion of patients on lithium than on valproate therapy had "therapeutic" levels at discharge, although this difference was not statistically significant (lithium ≥ 0.8 mmol/L, 11/24 [46%] vs. valproate 65–90 μg/mL, 8/23 [35%], $\chi^2 = 0.60$, df = 1, p = .55). Among patients with "therapeutic" levels at discharge, response rates were similar for lithium and valproate (Figure 3). "Therapeutic" serum levels early in the hospitalization, on day 5 (± 2 days), did not result in a greater improvement rate at discharge or shorter hospitalizations for either mood stabilizer.

No significant difference in age, age at onset, severity of episode, antipsychotic or benzodiazepine use, or length of hospitalization between those within versus outside

Figure 4. Percentage of Classic and Mixed Mania Patients Improved at Discharge on Lithium vs. Valproate



[a]Lithium vs. valproate, $\chi^2 = 6.41$, df = 1, p = .011.

"therapeutic range" for either medication group was found. Because of the potential interaction of age and age at onset with treatment response, age and age at onset were examined more closely. Pearson correlation analyses for each medication group and for all patients, with and without "therapeutic levels," yielded no statistically significant relationship ($p > .05$) between age or age at onset and discharge CGI scores. Only 12 patients had an onset of illness after age 55; among these patients, 3 of 6 improved in each medication group.

When treatment groups were compared based on mania type, superior efficacy of lithium over valproate (defined by percentage of patients with CGI = 1 or 2) was observed in the classic mania group on day 5 and at discharge (Table 2; Figure 4). Response rates for mixed mania were similar between the lithium and valproate groups at both time points.

The repeated measures logistic regression analysis yielded significant effects for time and medication. The highly significant time effect ($\chi^2 = 20.77$, df = 1, $p < .0001$) indicated that considerable improvement occurred in both medication groups from day 5 to discharge. The medication main effect ($\chi^2 = 6.36$, df = 1, p = .012) indicated that outcomes were better with lithium across both time points. The nonsignificant interaction ($\chi^2 = 0.53$, df = 1, $p > .4$) provided no evidence for more rapid improvement with one or the other drug.

DISCUSSION

Our study demonstrated that both lithium and valproate are efficacious antimanic agents in a group of elderly manic inpatients who are largely nonneurologically impaired and do not have a secondary mania, i.e., mania due to a medical or neurologic condition.[18] The results of this study indicate that, among all patients, the majority had a distinguishable improvement by discharge. The percentage of elderly patients receiving lithium who showed a marked response, 67%, is somewhat higher than the 49% reported in a large, placebo-controlled double-blind study of younger patients.[12] Compared to the results of the same study, in which 48% of those receiving valproate were markedly improved,[12] our results found that a lower proportion, 38%, of elderly patients receiving valproate were improved at discharge.

The overall difference in efficacy between lithium and valproate in this study of elderly patients deserves closer examination. One interesting observation was that more patients on lithium than on valproate therapy were within therapeutic range. For lithium, the therapeutic range among elderly patients in our study appears to be similar to that found in young adults (≥ 0.8 mmol/L).[14] For valproate, however, the low end of the range considered therapeutic for younger adults (45–100 μg/mL)[15] did not appear to be effective in elderly patients. Our group of elderly patients responded better to serum levels between 65–90 μg/mL. We found a less robust therapeutic response beyond 90 μg/mL, whereas in younger patients, toxicity (above 100 μg/mL) determined the upper range.[15] When patients with valproate levels between 65–90 μg/mL were compared to those with lithium levels ≥ 0.8 mmol/L, response rates for the 2 groups were similar, suggesting that there may be no significant difference in efficacy between drugs if appropriate drug serum levels are achieved in elderly patients. Among those patients with discharge serum levels, only a minority of patients—46% for lithium, 48% for valproate—were above the lower ends of these ranges. In a retrospective study, we can only infer from this finding that many elderly patients may not be able to tolerate doses required to achieve efficacy, due to neurotoxicity or other adverse effects, which may be one reason that clinicians did not prescribe higher doses in some patients. This inference, however, should be made with caution: previous case reports of neurotoxicity involved serum lithium levels ≥ 1.6 mmol/L, substantially higher than the levels in this study.[19] Future prospective studies will be able to study rates of neurotoxicity and adverse effects and their impact on serum drug levels and therapeutic response.

From a pharmacokinetic perspective, our findings on valproate levels are not intuitive. One might expect lower valproate levels to be therapeutic in the elderly. Valproate is highly bound to plasma protein, which decreases with age, making more pharmacologically active drug available. Factors that might account for this higher minimum therapeutic level and narrower therapeutic range in the elderly remain to be determined. The "therapeutic" level group included only 8 of 23 patients who had discharge serum valproate levels; a larger group and broader range of levels may have yielded different results. While our elderly patients showed little evidence of neurologic impairment, a representative group of elderly patients is likely to have more neurologic illness than a group of younger patients, which may account for the difference in

therapeutic levels for valproate. Similar to our findings, a series of 3 patients with organic brain syndromes and affective symptoms were reported to respond to valproate with serum levels in the range of 73 to 96 μg/mL.[20]

The roles of neurologic illness, age, and age at onset in treatment response are important issues in elderly patients. Himmelhoch et al.[7] reported that, among 25 elderly poor responders to lithium, 23 had neurologic illness. In the same study, however, age and later age at onset, both of which have been associated with more neurologic illness,[21–23] did not distinguish between good and poor response to lithium. Similarly, age and age at onset were not found to be related to treatment response in our study. Only a few patients had late-onset illness, and response rates among them were similar between treatment groups and to overall response rates, suggesting that late age at onset had little impact on our results. While the relatively healthy neurologic status of our patients reduces the probability that such a factor affected treatment response in this study, it does limit the generalizability of these results toward elderly patients with comorbid neurologic illness and mania. These factors, however, have yet to be examined prospectively as possible predictors of treatment response.

Differences in response to lithium versus valproate, irrespective of serum levels, emerged when classic and mixed mania subtypes were analyzed separately. The proportions of mania types in both medication groups were similar, suggesting that clinicians as a group did not appear to choose the antimanic agent based on type of manic episode. Whether prior medication response influenced current drug use is unclear, as this information was not systematically documented in physician notes. The overall superiority of lithium over valproate was maintained when only patients with classic mania were analyzed, which is consistent with studies on younger patients.[24–26] Several authors have suggested that valproate may be more effective than lithium in mixed episodes in younger patients.[27–29] Our study found the agents to be similarly effective in mixed episodes, although this analysis included a small number of patients.

In a naturalistic and retrospective study such as this one, methodological conditions were uncontrolled except by the treating clinicians, and therefore limit interpretation of the results. Choice of and response to a particular mood stabilizer may have been influenced or affected by prior medication response, data that could not be reliably collected in this study. As discussed above, many patients had subtherapeutic serum levels of mood stabilizer at discharge. Factors that may have restricted higher serum levels, and potentially better therapeutic response, include drug toxicity and intolerance to higher doses, which need further examination. Although this study included only patients who were able to tolerate a mood stabilizer, one cannot exclude drug intolerance and toxicity as factors in determining the final dose and treatment response.

Nonetheless, this study addressed previously unstudied questions in the elderly and examined comparison drugs in a relatively large group of patients. Our findings suggest that both lithium and valproate are efficacious in the acute treatment of manic symptoms in nonneurologically impaired elderly patients. Perhaps not consistent with current clinical trends in treatment of elderly patients, lithium may have an advantage in efficacy over valproate, at least in treating classic manic episodes. As in younger patients, certain serum levels may be associated with greater efficacy for each drug. From our data, lithium levels associated with therapeutic response are comparable among younger adults and the elderly (≥ 0.8 mmol/L), whereas the therapeutic range for valproate in the elderly is higher and narrower (65–90 μg/mL) than in younger adults. Because of the retrospective design of this study, these results serve not as definitive treatment guidelines, but, rather, offer clinicians practical data to consider when treating this population and researchers a starting point for further study.

Drug names: carbamazepine (Tegretol and others), divalproex sodium (Depakote and others), lithium (Eskalith and others), valproic acid (Depakene and others).

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