The Safety and Early Efficacy of Oral-Loaded Divalproex Versus Standard-Titration Divalproex, Lithium, Olanzapine, and Placebo in the Treatment of Acute Mania Associated With Bipolar Disorder

Robert M. A. Hirschfeld, M.D.; Jeffrey D. Baker, Ph.D.; Patricia Wozniak, Ph.D.; Katherine Tracy, M.D., Ph.D.; and Kenneth W. Sommerville, M.D.

Background: Previous studies have examined the safety and tolerability of oral-loaded divalproex sodium in the treatment of acute mania, but not the early efficacy of this dosing strategy. The purpose of this study was to evaluate the early efficacy of oral-loaded divalproex.

Method: In this pooled analysis, 348 subjects from 3 randomized, double-blind, parallel-group, active- or placebo-controlled studies were used to compare the efficacy, safety, and tolerability of oral-loaded divalproex with standard-titration divalproex, lithium, olanzapine, or placebo. Subjects were inpatients diagnosed with acute mania associated with bipolar I disorder (DSM-III-R or -IV and SADS-Change Version). Patients were administered oral-loaded divalproex (20 or 30 mg/kg/day on days 1 and 2 followed by 20 mg/kg/day, and increased at physician's discretion), standard-titration divalproex initiated at 250 mg t.i.d. and titrated to 40–150 μg/mL, lithium (300 mg t.i.d. initial dose) titrated to 0.4 to 1.5 mEq/L, olanzapine (10 mg q.d. initial dose) up to 20 mg/day, or placebo.

Results: The results demonstrate an early efficacy advantage for oral-loaded divalproex compared to standard-titration divalproex at days 5, 7/8, and 10. Efficacy was improved over lithium on day 7/8. There were no efficacy differences between divalproex loading and olanzapine. Divalproex loading showed greater efficacy than placebo at all time points. Divalproex loading was as well tolerated or better tolerated than the other active treatments as measured by adverse events and changes in laboratory parameters.

Conclusion: These results suggest the oral loading of divalproex leads to a more rapid antimanic effect when compared with standard-titration divalproex, lithium, or placebo and is better tolerated than olanzapine and as well tolerated as lithium or standard-titration divalproex.

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Corresponding author and reprints: Robert M. A. Hirschfeld, M.D., Department of Psychiatry and Behavioral Sciences, 1.302 Rebecca Sealy, 301 University Blvd., Galveston, TX 77555-0188 (e-mail: rohirsch@utmb.edu).

The first goal clinically in the treatment of a patient with acute mania is stabilization as rapidly and safely as possible. Rapid and safe stabilization may also have financial implications because it may reduce hospital costs by enabling earlier discharge. Theoretically, one way to achieve this goal is to increase initial doses of antimanic medications.

There is a single report of an open study in which lithium was rapidly loaded.[1] Several studies[2–5] have examined the safety and efficacy of an oral ("rapid") loading strategy for divalproex to accelerate the time to attain therapeutic serum levels (50 μg/mL or higher).[6] In an open-label trial,[4] divalproex oral loading (20 mg/kg/day) produced therapeutic serum levels (≥ 50 μg/mL) in all patients within 24 hours. Oral-loaded divalproex was well tolerated and most of the patients showed significant improvement in manic symptoms (Mania Rating Scale [MRS] change from baseline) by day 5. The greatest percent change on the MRS for responders occurred in the first 3 days of treatment. An oral-loading strategy of 30 mg/kg/day was examined in a small preliminary retrospective chart review.[7] The 30-mg/kg loading dose was reasonably well tolerated in the 9 subjects examined. In a randomized, double-blind study,[2] oral-loaded divalproex (30 mg/kg/day on days 1 and 2, followed by 20 mg/kg/day on days 3–10) was compared with standard-titration divalproex or lithium. The oral-loaded patients achieved thera-

peutic serum levels more quickly than the standard-titration group. Eighty-four percent of loaded patients and 30% of standard-titration patients achieved therapeutic serum levels of divalproex by day 3. The 3 groups (oral-loaded divalproex, standard-titration divalproex, and lithium) did not statistically differ on the number and types of adverse events. The study was not statistically powered to directly compare the early efficacy of oral-loaded versus standard-titration divalproex or lithium.

Oral-loaded divalproex (20 mg/kg/day) was compared with olanzapine for the treatment of acute mania associated with bipolar disorder.[8] The 2 treatments did not significantly differ on MRS change from baseline at any time point. An open-label, randomized study[5] comparing divalproex oral loading (20 mg/kg/day) with haloperidol in hospitalized acutely manic patients found comparable rates and degrees of improvement. Again, the highest rate of improvement was found to occur within the first 3 days of treatment. Oral-loaded divalproex has also been shown to be well tolerated when combined with other treatments such as antipsychotics or benzodiazepines.[3,9]

In the studies described above, oral loading has been shown to be a well-tolerated strategy for accelerating therapeutic serum levels of divalproex. Although several studies have demonstrated the safety and tolerability of oral-loaded divalproex (monotherapy and in combination with neuroleptics), no adequately powered study has been conducted to evaluate whether there is an early efficacy advantage over standard-titration divalproex. The present report combines data from 3 previously reported studies to examine the safety, tolerability, and early efficacy of oral-loaded divalproex (20 or 30 mg/kg/day) compared with standard-titration divalproex, lithium, olanzapine, and placebo.

PATIENTS AND METHODS

This report pooled 358 participants (348 of whom were included in efficacy analyses) in 3 randomized, double-blind, parallel-group, active- or placebo-controlled studies.[2,8,11] The methodological characteristics of the previous studies are summarized in Table 1. The pooled data set allowed comparison of oral-loaded divalproex patients (N = 80) versus standard-titration divalproex (N = 87), lithium (N = 54), olanzapine (N = 55), and placebo (N = 72) in the treatment of acute mania associated with bipolar disorder. Subjects were inpatients diagnosed with an acute manic episode associated with bipolar disorder according to DSM-III-R or DSM-IV diagnostic criteria and the Schedule for Affective Disorders and Schizophrenia-Change Version (SADS-C).[10] A minimum score of 14 (based on scores starting at 0) on the MRS[2,8,11] with at least 4 items with a score of 2 or more was required for inclusion. Details regarding the inclusion and exclusion criteria are reported in the previous publications.[2,8,11]

Table 1. Methodological Characteristics of Pooled Studies of the Treatment of Acute Mania Associated With Bipolar Disorder

Study	Treatments	No. of Subjects (ITT)	Outcome Measures
Bowden et al (1994)[11]	Divalproex ST	67	MRS, BIS, and MSS at days 5, 10
	Lithium	35	
	Placebo	72	
Hirschfeld et al (1999)[2]	Divalproex ST	20	MRS, BIS, and MSS at days 2–6, 8, 10
	Divalproex load	20	
	Lithium	19	
Zajecka et al (2002)[8]	Divalproex load	60	MRS, BIS, and MSS at days 3, 5, 7, 10
	Olanzapine	55	

Abbreviations: BIS = Behavior and Ideation Scale, divalproex ST = divalproex sodium standard titration, MRS = Mania Rating Scale, MSS = Manic Syndrome Scale.

Each study consisted of a washout/screening period (1–3 days[2,8] or the longer of 3 days or 5 half-lives[11]) followed by at least 10 days of treatment. Divalproex oral loading was administered at 30 mg/kg/day on days 1 and 2 and followed by 20 mg/kg/day on subsequent days[2] or 20 mg/kg/day on days 1 and 2 with allowed increases of 500 mg/day on days 3 and 6 and a maximum of 20 mg/kg/day plus 1000 mg.[8] Standard-titration divalproex was initiated at 250 t.i.d. on days 1 and 2 with gradual increases on subsequent days to serum levels of 40–150 μg/mL. Lithium was initiated at 300 mg t.i.d. on days 1 and 2 and titrated to 0.4–1.5 mEq/L. Olanzapine was initiated at 10 mg/day on days 1 and 2 and titrated at the discretion of the investigator to a maximum dose of 20 mg/day. The use of adjunctive medications is reported in the respective previous publications[2,8,11] and was comparable across the 3 studies.

All 3 studies utilized change from baseline on the MRS,[12] as assessed by the SADS-C,[10] and the 2 subscales of the MRS, the Manic Syndrome Scale (MSS) and the Behavior and Ideation Scale (BIS), to evaluate efficacy. For the purpose of the present analysis, these scales were compared across treatments on days 3, 5, 7/8, and 10.

Safety evaluation included adverse events, laboratory values, and weight gain. Serum levels of divalproex were evaluated for the oral-loaded and standard-titration groups at day 3.

Statistical Analyses

All statistical tests were 2-tailed, and p values of .050 or less were considered statistically significant. Analyses of baseline characteristics and efficacy endpoints were performed on the intent-to-treat dataset, which included all patients who received at least 1 dose of study drug and had a baseline and at least 1 on-treatment MRS evaluation. For efficacy analyses, a last-observation-carried-forward (LOCF) analysis was used. For all analyses, pairwise comparisons were performed for divalproex oral loading versus each of the other treatments.

Baseline comparability among treatment groups was assessed by Fisher exact test for qualitative variables

Table 2. Characteristics of 348 Patients With Acute Mania Associated With Bipolar I Disorder

Characteristic	Divalproex Load (N = 80)	Divalproex Standard Titration (N = 87)	Lithium (N = 54)	Olanzapine (N = 55)	Placebo (N = 72)
Gender, N (%)					
Female	35 (44)	40 (46)	17 (31)	26 (47)	31 (43)
Male	45 (56)	47 (54)	37 (68)	29 (53)	41 (57)
Race, N (%)					
White	59 (74)	59 (68)	36 (67)	39 (71)	51 (71)
Nonwhite	21 (26)	28 (32)	18 (33)	16 (29)	21 (29)
Age, y					
Mean	38.5	38.8	36.8	38.0	38.8
Minimum–maximum	18–65	18–65	19–59	18–61	22–60
Weight, lb[a]					
Mean	184.5	173.0	168.7	183.5	180.6
Minimum–maximum	110–417	102–369	92–270	122–341	96–319
Mania type, %					
Mixed	43	30	22	45	0
Rapid cycling	24	10	17	27	0
Mean baseline score					
MRS	29.3	27.2*	26.9*	31.7*	28.0
MSS	14.9	13.8	13.7	16.3*	13.9
BIS	12.5	11.0*	11.1*	13.6*	11.6

[a]N = 86 for divalproex standard titration; N = 69 for placebo.
*Significantly differs from divalproex load at $p < .05$.
Abbreviations: BIS = Behavior and Ideation Scale, MRS = Mania Rating Scale, MSS = Manic Syndrome Scale.

(gender, race, diagnosis of mixed mania, diagnosis of rapid cycling) and by 1-way analysis of variance (ANOVA) for quantitative variables (age, weight).

Treatment differences in change from baseline to each evaluation through day 10 for MRS, MSS, and BIS were assessed by 1-way ANOVA. Baseline was the last evaluation on or before the first day of dosing. When treatment differences were statistically significant at baseline, an analysis of covariance was also conducted with baseline as a covariate. A 1-way ANOVA was used to compare 2 groups of divalproex-loaded subjects on change from baseline to each evaluation for MRS, MSS, and BIS: those who achieved a serum valproate level of 80 μg/mL or more by day 3 and those who did not. A 1-way ANOVA was also conducted on mean change from baseline to final visit on MRS, comparing divalproex-loaded subjects with serum valproate levels of 80 μg/mL or more at day 3 with each of the other treatment groups.

Safety analyses were performed for all patients who received at least 1 dose of randomized study drug. Fisher exact test was used to assess treatment group differences in the incidence of treatment adverse events during the first 10 days of each study. Treatment differences in change from baseline to final evaluation for laboratory parameters were assessed by 1-way ANOVA.

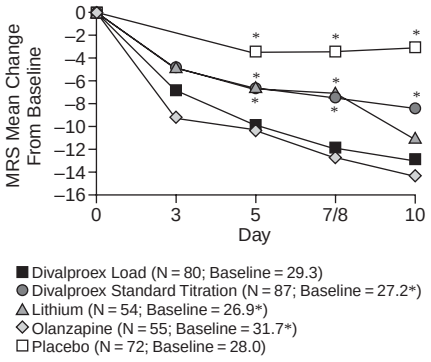
RESULTS

There were no differences at baseline between the groups on patient demographics (Table 2). MRS baseline differences were found between divalproex oral loading and standard-titration divalproex, lithium, and olanzapine. Analyses of covariance (ANCOVAs) with baseline as a covariant were used for these comparisons. The ANCOVA comparing MRS change from baseline for divalproex oral loading versus standard-titration divalproex showed significant statistical differences favoring divalproex oral loading at day 5 ($p = .017$), day 7/8 ($p = .003$), and day 10 ($p = .009$). Divalproex loading showed statistically greater improvement than lithium at day 7/8 ($p = .008$). Oral-loaded divalproex showed greater improvement than placebo at days 5, 7/8, and 10 ($p \leq .001$). The ANCOVA revealed that oral-loaded divalproex and olanzapine did not differ at any time point. Figure 1 illustrates the mean changes from MRS baseline for each treatment group.

There were no baseline differences between oral-loaded divalproex and the other treatment groups, except olanzapine ($p = .020$) on the MSS. The 1-way ANOVA revealed that oral-loaded divalproex was superior to standard-titration divalproex on the MSS change from baseline at day 5 ($p = .038$), day 7/8 ($p = .003$), and day 10 ($p = .003$). Oral-loaded divalproex was superior to lithium at day 5 ($p = .011$) and day 7/8 ($p = .001$). There were no significant differences on MSS change from baseline between oral-loaded divalproex and olanzapine at any timepoint. Oral-loaded divalproex was superior to placebo at days 5, 7/8, and 10 ($p < .001$). Figure 2 illustrates mean changes from baseline on the MSS for each treatment group.

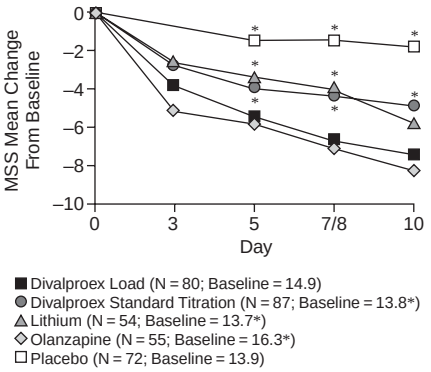
On the BIS, there were baseline differences from divalproex loading for divalproex standard titration, lithium, olanzapine, and placebo (Figure 3). The ANCOVA showed that divalproex loading showed statistically sig-

Figure 1. Mean Change From Baseline for Mania Rating Scale (last observation carried forward)[a]



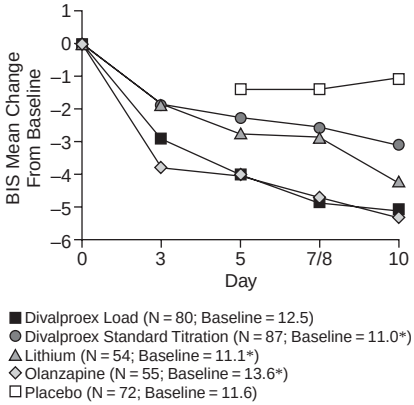
[a]Day 3 sample sizes: divalproex standard titration, N = 20; lithium, N = 19; placebo, N = 0.
*p < .05 versus divalproex load.

Figure 2. Mean Change from Baseline on the Manic Syndrome Scale (last observation carried forward)[a]



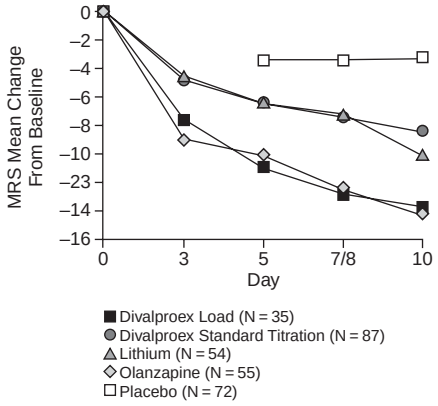
[a]Day 3 sample sizes: divalproex standard titration, N = 20; lithium, N = 19; placebo, N = 0.
*p < .05 versus divalproex load.

Figure 3. Mean Change From Baseline on Behavior and Ideation Scale (last observation carried forward)[a]



[a]Day 3 sample sizes: divalproex standard titration, N = 20; lithium, N = 19; placebo, N = 0.
*p < .05 versus divalproex load.

Figure 4. Change in Mania Rating Scale From Baseline: Divalproex-Load Patients Who Achieved ≥ 80 μg/mL



nificant improvement over standard-titration divalproex at days 5 (p = .022), 7/8 (p = .004), and 10 (p = .027). ANCOVAs found that oral-loaded divalproex showed significantly greater improvement than lithium at day 7/8 (p = .024), and no differences in efficacy were found between oral-loaded divalproex and olanzapine on the Behavior and Ideation Scale. Divalproex oral load showed significantly greater improvement than placebo at days 5, 7/8, and 10 (p < .001).

In order to evaluate the results for patients who attained higher serum levels, we compared those with serum divalproex levels of 80 μg/mL or higher with orally loaded patients who did not achieve that serum level on the MRS, MSS, and BIS. Those who achieved the 80-μg/mL level showed significantly greater improvement on the MRS at days 3 (p = .046) and 5 (p = .038) and the BIS at day 5 (p = .023). Figure 4 shows the results for divalproex-loaded subjects who achieved at least 80 μg/mL versus all other treatment groups.

Significant adverse events are summarized in Table 3. The frequency of adverse events was compared between divalproex loading and all other groups. There were very few differences between oral-loaded divalproex and standard-titration divalproex, with half of the adverse events being reported more often by those given standard titration. Divalproex loading was associated with significantly fewer adverse events of weight gain (p = .002), rhinitis (p = .026), speech problems (p = .026), dry mouth (p = .028), and edema (p = .026) when compared with olanzapine.

Laboratory parameters showed that both divalproex groups had significantly reduced platelet counts com-

Table 3. Treatment-Emergent Adverse Events With > 10% Incidence or Statistical Significance

	Divalproex Load (N = 83)		Divalproex Standard Titration (N = 89)		Lithium (N = 55)		Olanzapine (N = 57)		Placebo (N = 74)	
Adverse Event	N	%	N	%	N	%	N	%	N	%
Any adverse event	58	70	63	71	39	71	51	89*	49	66
Somnolence	17	20	10	11	8	15	19	33	8	11
Constipation	11	13	7	8	5	9	7	12	3	4
Nausea	11	13	15	17	12	22	3	5	9	12
Dyspepsia	10	12	8	9	6	11	7	12	5	7
Headache	10	12	12	13	17	31*	10	18	17	23
Vomiting	8	10	7	8	6	11	3	5	2	3
Dry mouth	5	6	0	0*	2	4	11	19*	1	1
Increased appetite	5	6	0	0*	2	4	3	5	1	1
Diarrhea	4	5	5	6	3	5	8	14	9	12
Weight gain	3	4	0	0	1	2	12	21*	0	0
Dizziness	3	4	11	12*	2	4	4	7	4	5
Pain	2	2	10	11*	1	2	4	7	9	12*
Edema	0	0	1	1	1	2	4	7*	0	0
Back pain	0	0	6	7*	0	0	0	0	3	4
Fever	0	0	0	0	4	7*	1	2	2	3
Speech disorder	0	0	0	0	0	0	4	7*	0	0
Rhinitis	0	0	1	1	0	0	4	7*	0	0

*Significantly differs from divalproex load at $p < .05$.

Table 4. Laboratory Parameters: Mean Change From Baseline to Final Evaluation

Parameter	Divalproex Load	Divalproex Standard Titration	Lithium	Olanzapine	Placebo
Platelet count ($\times 10^9$/L)					
Mean change from baseline	–47.87	–68.50	8.86*	0.78*	–19.22*
Final N	60	62	36	41	55
Glucose (mg/dL)					
Mean change from baseline	4.02	–9.29	–6.36	10.45	–1.18
Final N	64	69	33	42	55
SGOT/AST (IU/L)					
Mean change from baseline	–1.53	–1.77	–1.72	–0.71	–0.70
Final N	64	69	36	42	54
SGPT/ALT (IU/L)					
Mean change from baseline	–5.35	–0.77	2.60	3.88*	0.33
Final N	62	59	35	42	55
Total cholesterol (mg/dL)					
Mean change from baseline	–2.59	–11.32	–6.23	13.29*	3.02
Final N	58	62	31	42	55

*Significantly differs from divalproex load at $p < .05$.
Abbreviations: SGOT/AST = serum glutamic-oxaloacetic transaminase/aspartate aminotransferase, SGPT/ALT = serum glutamic-pyruvic transaminase/alanine aminotransferase.

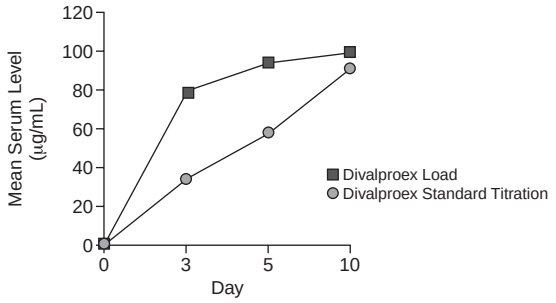
pared with the other groups (Table 4). No clinically significant thrombocytopenia occurred with any individual subject. Serum glutamic-pyruvic transaminase (SGPT) and cholesterol increased significantly with olanzapine compared to divalproex loading. Serum assays by day for divalproex load and divalproex standard titration are illustrated in Figure 5.

DISCUSSION

The results of this pooled analysis of 3 randomized, double-blind, placebo- or active-controlled studies demonstrated an early efficacy advantage for divalproex oral loading compared with standard-titration divalproex and lithium. Although several previous studies have demonstrated the safety and tolerability of the oral-loading strategy for divalproex, this is the first report statistically powered to evaluate the early efficacy advantage for oral-loaded versus standard-titration divalproex. The early antimanic effect in this analysis was not associated with increased adverse events.

This analysis also showed an early efficacy advantage for oral-loaded divalproex over lithium. Previous studies have shown an acute efficacy advantage for divalproex over lithium only when depressive symptoms are a significant component of the acute mania.[11,13,14] With its high degree of tolerability, the oral-loading strategy for divalproex offers a means to an efficacy advantage in early antimanic effects over conventionally dosed lithium. Oral-loaded divalproex was associated with fewer head-

Figure 5. Mean Serum Levels (μg/mL) for Divalproex Load and Divalproex Standard Titration[a]



[a]Divalproex load: day 3, N = 76; day 5, N = 69; day 10, N = 54. Divalproex standard titration: day 3, N = 67; day 5, N = 76; day 10, N = 73.

ache symptoms than lithium. No adverse event was higher in the divalproex oral-loaded group versus lithium. This result suggests that the increased early efficacy associated with the oral-loading strategy for divalproex does not come with increased risks for safety and side effects.

No efficacy differences were observed between oral-loaded divalproex and olanzapine at any timepoint. There were significant differences in adverse events between these 2 treatment groups. Divalproex loading was associated with less reported weight gain compared with the olanzapine group (4% for divalproex load versus 21% for olanzapine showed weight gain in the first 10 days of treatment). Olanzapine was also associated with significantly greater reports of dry mouth, rhinitis, and speech disorder.

The present report is limited to analysis of acute treatment effects. No conclusions can be drawn regarding the efficacy advantage of divalproex loading versus standard-titration divalproex and lithium beyond the 10 treatment days presented here. In fact, the intention of rapid oral loading is to achieve more rapid onset of efficacy but not necessarily to increase efficacy. The present report also encompasses the limitations of any pooled analysis in that it comprises different populations studied at nonparallel times.

In summary, oral-loaded divalproex is an effective strategy for achieving accelerated therapeutic serum levels of divalproex that leads to an early efficacy advantage over standard-titration divalproex, lithium, or placebo. Consistent with previous findings, oral-loaded divalproex is well tolerated and is associated with significantly less headache than lithium and significantly less weight gain than olanzapine. Finally, the early efficacy advantage of oral-loaded divalproex over standard-titration divalproex and lithium may result in earlier patient discharge and cost savings.

Drug names: divalproex (Depakote), haloperidol (Haldol and others), olanzapine (Zyprexa).

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