Divalproex Sodium Versus Olanzapine in the Treatment of Acute Mania in Bipolar Disorder: Health-Related Quality of Life and Medical Cost Outcomes

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***Background*:** Divalproex sodium is a mood stabilizer used in the United States for the treatment of acute mania associated with bipolar disorder. Recently, olanzapine, an atypical antipsychotic, was approved for the treatment of acute mania. This study compares the clinical, health-related quality of life (HRQL), and economic outcomes of divalproex and olanzapine in the treatment of acute mania associated with bipolar disorder.

***Method*:** This 12-week, double-blind, double-dummy, randomized clinical trial included 120 subjects with DSM-IV bipolar disorder type I hospitalized for an acute manic episode recruited from 21 U.S. clinical centers. Subjects were randomly assigned to treatment with either divalproex or olanzapine and were followed in hospital for up to 21 days. If after 21 days clinical improvements (based on the Mania Rating Scale [MRS]) were not observed, subjects were discontinued. Subjects showing clinical improvement were treated for up to 12 weeks. HRQL was assessed using the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) after hospital discharge (baseline) and at 6 and 12 weeks. Medical resource use and costs were collected over the 12-week study.

***Results*:** A total of 120 subjects (N = 63 divalproex, N = 57 olanzapine) were randomized, and 78 (65%) were followed beyond 21 days. No statistically significant differences between the treatment groups for baseline-to-endpoint MRS or Q-LES-Q scores were observed. Total 12-week outpatient medical costs were significantly lower for the divalproex-treated group ($541) compared with the olanzapine-treated group ($1080) (p = .004). There was no significant difference in total medical costs between the 2 groups (divalproex = $13,703; olanzapine = $15,180; p = .88).

***Conclusion*:** Divalproex is associated with lower 12-week outpatient costs compared with olanzapine. Divalproex and olanzapine have similar short-term effects on clinical or HRQL outcomes in bipolar disorder subjects.

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Bipolar disorder is a disabling psychiatric disorder with 1-year prevalence rates of 1.2% to 1.3%.[1,2] The World Health Organization estimates that in 1990, bipolar disorder was the sixth most frequent reason for worldwide disability.[3] The natural history of bipolar disorder is characterized by patterns of stability and relapse[4] with impaired health-related quality of life (HRQL) even after symptomatic recovery.[5–8] Long-term prospective studies demonstrate that less than 50% of bipolar disorder subjects demonstrate a good response to treatment.[9,10]

Treatment with mood stabilizers can improve the symptoms of bipolar disorder. Guidelines for the pharmacologic management of acute mania and for maintenance treatment are available.[11] Lithium, divalproex sodium, and, more recently, the atypical antipsychotic olanzapine are approved for the treatment of acute mania. Lithium and divalproex have been extensively studied in clinical trials of treatment of acute mania[12–15] and for the maintenance treatment of bipolar disorder.[8,15,16] Olanzapine has

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been demonstrated to be more effective than placebo in treating acute mania.[17,18] A recent clinical trial found significant differences between olanzapine- and divalproex-treated acute mania subjects on Young Mania Rating Scale (YMRS) scores after 3 weeks (olanzapine change –13.4, divalproex change –10.4; p = .028).[19] Forty percent of divalproex-treated patients compared with 47% of olanzapine-treated subjects demonstrated a 50% reduction in YMRS scores (not significant).

In the United States, the economic burden of bipolar disorder has been estimated at $7 billion in direct medical costs and $38 billion in indirect costs.[20] Bipolar disorder patients have total medical costs that exceed those for patients with diabetes.[21] Revicki and colleagues[22] demonstrated that bipolar disorder subjects receiving mood stabilizer treatment have 12-month costs that are significantly lower than subjects not continuing mood stabilizer therapy.

Few pharmacoeconomic studies have examined the cost-effectiveness of treatments for acute mania or bipolar disorder. Keck et al.[23] developed a clinical decision analysis model to estimate the 1-year medical costs of treatment with divalproex or lithium. Divalproex was associated with lower total medical costs across all types of bipolar disorder subjects. A naturalistic randomized clinical trial demonstrated comparable clinical and HRQL outcomes for divalproex and lithium treatment over 12 months and $1700 lower annual total medical costs for divalproex compared with lithium.[22]

There are no pharmacoeconomic studies comparing divalproex and olanzapine for the treatment of bipolar disorder. An HRQL and economic evaluation was included as part of this randomized clinical trial comparing divalproex versus olanzapine in acutely manic bipolar disorder subjects.[24] Complete clinical efficacy and safety data for the divalproex and olanzapine treatment groups are reported separately in a companion article.[24] We measured HRQL, medical resource use, and costs over 12 weeks in subjects experiencing an acute manic episode requiring hospitalization.

METHOD

Design and Patient Sample

This was a 12-week, randomized, double-blind, double-dummy, parallel-group, multi-center clinical trial that compared divalproex versus olanzapine for the treatment of acute mania at 21 U.S. sites.[24] The clinical trial also included measures of HRQL and medical resource use and costs. Potential study subjects were screened, and eligible subjects were randomly assigned to either divalproex or olanzapine and followed for up to 12 weeks. Data were collected on all subjects for quality of life and pharmacoeconomic outcomes for up to 12 weeks, regardless of whether the subject discontinued the study treatment.

To be eligible for the clinical trial, subjects had to have a DSM-IV diagnosis of bipolar disorder type I (based on the Structured Clinical Interview for DSM-IV Axis I Disorders [SCID][25]) and a Mania Rating Scale (MRS) score ≥ 25 (based on the 10 Schedule for Affective Disorders and Schizophrenia [SADS][26] mania items and the item on insight), were between the ages of 18 and 65 years, and were hospitalized for an acute manic episode. Female subjects of childbearing age were eligible if they were using effective contraception. Subjects were excluded for pregnancy or intending to become pregnant, schizoaffective disorder, unstable medical condition, alcohol or substance dependence, history of intolerance or treatment failure after treatment with divalproex or olanzapine, depot psychoactive medications, or mood disorder secondary to a medical condition. Eligible subjects were screened within 3 days of randomization. Randomization occurred in a 1:1 ratio to divalproex or olanzapine. The research protocol was approved by the relevant institutional review boards from each study site. Prior to study participation and after complete description of the study, written informed consent was obtained from each subject.

Treatment Regimen

Subjects were randomly assigned to receive either divalproex or olanzapine. Divalproex was initiated at 20 mg/kg/day and could be increased by 500 mg/day on days 3 and 6 if clinically important symptoms of mania persisted. The maximum divalproex dose allowed was 20 mg/kg plus 1000 mg/day. Olanzapine treatment was initiated at 10 mg/day and could be increased by 5 mg/day on days 3 and 6 if mania symptoms persisted. The maximum allowed olanzapine dose was 20 mg/day. During the study, the dosage of divalproex or olanzapine could be lowered to improve tolerability. The mean maximum daily dose of divalproex was 2115 mg/day (range, 750 to 3250 mg/day), and the mean maximum daily dose of olanzapine was 14.7 mg/day (range, 5 to 25 mg/day). Lorazepam, chloral hydrate, benztropine mesylate, or zolpidem could be prescribed by the investigators as needed following protocol guidelines.

Clinical Outcomes

The MRS from the SADS Change Version[26] and the Hamilton Rating Scale for Depression (HAM-D)[27] were used to assess clinical symptoms. The MRS and HAM-D were assessed at 0 (randomization), 1, 2, 3, 4, 6, 8, and 12 weeks. Adverse events were monitored throughout the clinical study and are based on spontaneous reports by patients.

HRQL and Disability Days

HRQL, disability days, and medical resource use data were collected by telephone interviews at hospital discharge, 6 weeks, and 12 weeks. Information on age, gen-

der, and racial/ethnic group was also collected during the interview at hospital discharge.

HRQL outcomes were measured using the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q).[28] The Q-LES-Q was used to assess physical health, subjective feelings, leisure activities, social relationships, and medication and life satisfaction. The Q-LES-Q covers important domains of functioning and well-being in subjects with bipolar disorder.[7,29,30] The Q-LES-Q has good internal consistency, reliability, validity, and responsiveness in subjects with psychiatric disorders (depression, schizophrenia, bipolar disorder).[28,31]

A global measure of quality of life was contained in the subject outcome assessment. The global scale requested subjects to rate their current health on a scale from 0 (anchored as death) to 100 (anchored as complete health). Two questions on disability days, based on previously used items,[32] were also included in the interviews. Subjects were asked how many days over the previous month their usual activities had been restricted for more than one half day and how many days they had spent more than half the day in bed because of illness.

Medical Resource Use and Costs

The 6-week and 12-week follow-up interviews contained questions on the use of medical services. Data were collected on the number of outpatient psychiatric, physician, or clinic visits, home health service visits, emergency room visits, hospitalizations for psychiatric and other reasons, psychologist visits, and other mental health provider visits. For emergency room visits and hospitalizations, data were collected on reason and length of stay (for hospitalizations), and Uniform Billing Code of 1992 (UB-92) or other confirming data were collected from the hospital to verify reason for emergency room visit or hospitalization and to get detailed data on the length of stay and medical charges. Ninety-eight percent of the patient-reported emergency room visits and hospitalizations were confirmed by UB-92 and/or physician data. When disagreements between patient reports and hospital or clinician reports occurred (2%), the hospital or clinician records were used. The clinical investigators provided data on study medication doses, any change in doses, and all other psychotropic medications.

The economic perspective taken was that of the health care system; therefore, only direct medical costs were included in this study. We estimated hospital costs on the basis of inpatient and emergency room medical charges. Inpatient physician visits were estimated on the basis of the assumption of 1 initial visit on the day of admission and 1 subsequent visit per additional inpatient day. Charges for inpatient physician services were based on the Medicare Resource-Based Relative Value Scale for moderately complex visits.[33] For outpatient services, we based charges on moderately complex visits to a psychiatrist or other physician.[33] Mean hospital charges were adjusted to costs based on Health Care Financing Administration data.[34] We estimated costs per visit to nonphysician health care providers (e.g., home health care providers, counselors, therapists, psychologists) on the basis of costs reported in Revicki et al.[22]

Average wholesale medication costs for the study drugs and concomitant psychotropic medications were obtained from the *Drug Topics Red Book*.[35] These costs were estimated from data collected on relevant drugs, dosages, and duration of medication and included a pharmacy administration fee.

The primary endpoint for the economic analyses was total outpatient costs, which consist of emergency room visits; outpatient psychiatrist, physician, and other health provider visits; and medication costs. We estimated total medical costs, which include total outpatient costs plus hospital and physician costs for inpatient services.

Statistical Analysis

Baseline demographic, clinical, and HRQL variables were compared between treatment groups using chi-square tests for categorical variables and t tests for continuous variables. The statistical analyses were based on the initial random assignment, intent-to-treat principles, and last observation carried forward. Subjects who received at least 1 dose of study medication and who completed the interview at hospital discharge were included in the economic analysis. For the comparisons of HRQL endpoint data, subjects needed to have a baseline (i.e., hospital discharge) and at least 1 follow-up assessment.

Treatment differences in baseline to follow-up MRS and HAM-D assessments were evaluated using an analysis of covariance (ANCOVA) with treatment group and baseline score as a covariate. The Fisher exact test was used to compare frequency of treatment-related adverse events between treatment groups.

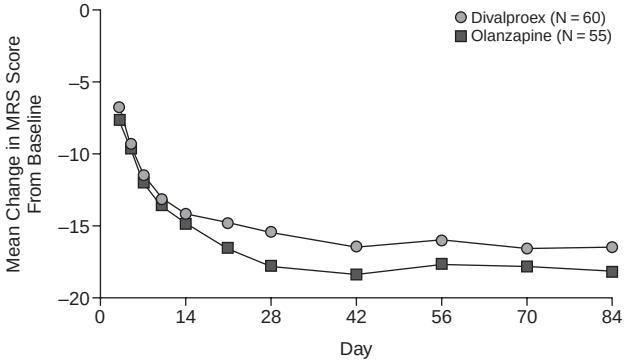
The 2 primary HRQL endpoints were the Q-LES-Q subjective feeling scores and number of restricted activity days. The remaining HRQL measures were considered secondary endpoints. Baseline to 6-week and baseline to 12-week HRQL endpoint scores were compared using ANCOVA models including treatment group and baseline HRQL score. Because weight gain is an adverse event associated with mood stabilizer treatment,[36] we completed an exploratory analysis of the relationship between weight gain and the HRQL outcomes. We used analysis of variance to compare mean HRQL scores between subjects reporting and not reporting weight gain as an adverse event. We correlated changes in weight and changes in HRQL to explore the impact of weight gain on HRQL. Wilcoxon rank-sum tests were used to compare between group differences on mean total outpatient costs, total medical costs, and disaggregated medical costs. A 2-tailed p value of .05 was used to assess statistical significance.

Table 1. Baseline Demographics, Clinical Characteristics, Quality of Life, and Other Patient Outcomes by Treatment Group[a]

Variable	Divalproex (N = 27)	Olanzapine (N = 25)
Age, y	38.6 (10.9)	37.3 (13.2)
Male, N (%)	13 (48.1)	10 (40.0)
Caucasian, N (%)	22 (81.5)	20 (80.0)
Mixed state, N (%)	15 (55.6)	13 (52.0)
Rapid cyclers, N (%)	9 (33.3)	8 (32.0)
MRS score	30.8 (4.4)	31.9 (4.8)
HAM-D total score	16.5 (8.1)	14.4 (8.4)
Days of hospitalization during acute phase	14.6 (9.8)	13.9 (11.1)
Q-LES-Q scales		
Physical health	67.3 (15.8)	71.1 (14.4)
Subjective feelings	73.7 (12.2)	74.4 (12.6)
Leisure time activities	43.8 (10.2)	43.2 (9.0)
Social relationships	68.6 (16.9)	66.8 (15.8)
General activities	71.0 (13.2)	72.1 (14.3)
Medication	3.3 (1.3)	3.7 (1.1)
Overall life satisfaction	3.6 (1.1)	3.8 (1.0)
Global quality of life	62.8 (18.4)	71.1 (18.8)

[a]Values shown as mean (SD) unless otherwise noted. No statistically significant differences in baseline variables were found between the 2 treatment groups.
Abbreviations: HAM-D = Hamilton Rating Scale for Depression, MRS = Mania Rating Scale, Q-LES-Q = Quality of Life, Enjoyment, and Satisfaction Questionnaire.

Figure 1. Mean Change in Mania Rating Scale (MRS) Score From Baseline to Each Evaluation With Baseline as a Covariate[a]



[a]Differences between divalproex and olanzapine were not statistically significant at any timepoint.

RESULTS

Of the 120 bipolar disorder subjects randomly assigned to treatment with divalproex or olanzapine, 78 (65%) were followed for more than 21 days. Sixty-three (81%) of these 78 subjects completed the baseline HRQL interviews at hospital discharge. There were no significant differences in demographic or baseline clinical variables between the total study sample and the subsample of subjects included in the HRQL and economic analyses. Twenty-seven of the divalproex and 25 of the olanzapine treatment group provided at least 1 follow-up assessment (83% of all subjects with a baseline HRQL assessment). There were no differences between the 2 treatment groups on demographic, clinical, or HRQL variables at hospital discharge (Table 1). There were no differences in duration of follow-up between the 2 groups (divalproex mean = 10.2 weeks, SD = 3.1; olanzapine mean = 11.2 weeks, SD = 2.4; p = .208).

Clinical Outcomes

No statistically significant differences between divalproex and olanzapine treatment were observed in changes from baseline to week 3 in MRS scores or for any other between-group comparisons over the 12-week study (p > .05) (Figure 1). Changes from baseline to week 3 in MRS scores were –14.9 (baseline mean = 30.8) for the divalproex group and –16.6 (baseline mean = 32.3) for the olanzapine group (p = .368). No statistically significant differences were seen in HAM-D scores after 3 weeks of treatment or at any of the other follow-up assessments (p > .05, data not shown).

Adverse events occurring in a greater percentage of olanzapine-treated than divalproex-treated patients include somnolence (47% versus 29%), weight gain (25% versus 10%), rhinitis (14% versus 3%), edema (14% versus 0%), and slurred speech (7% versus 0%) (all comparisons p < .05). No adverse events occurred significantly more frequently in the divalproex-treated group compared with the olanzapine-treated group.

HRQL Outcomes

The baseline to week 6 and baseline to week 12 change scores by treatment group for the Q-LES-Q subscales and other HRQL measures are summarized in Table 2. There were no statistically significant differences between the divalproex- and olanzapine-treated groups at week 6 or week 12.

There were no statistically significant differences between the groups on mean number of restricted activity days (p = .78) or bed disability days (p = .38). The divalproex group reported a mean of 4.1 (SD = 7.5) restricted activity days and the olanzapine group reported a mean of 3.5 (SD = 5.1) restricted activity days over the 12-week follow-up. The divalproex group reported a mean of 1.6 (SD = 4.5) bed days and the olanzapine group reported a mean of 3.3 (SD = 7.4) bed days over the 12-week follow-up.

Medical Cost Outcomes

Mean ± SD total outpatient costs (Table 3) for the 12-week follow-up period were significantly lower for the divalproex group relative to the olanzapine group ($541 ± $327 and $1080 ± $638, respectively; p = .004). The difference in total outpatient costs between the 2 groups was mainly attributable to differences in study

Table 2. Changes From Baseline to 6 and 12 Weeks in Health-Related Quality of Life Outcomes

	Baseline to Week 6			Baseline to Week 12		
Score	Divalproex	Olanzapine	p Value[a]	Divalproex	Olanzapine	p Value[a]
Physical health[b]	–2.7	–7.1	.35	–3.1	–10.4	.11
Subjective feelings[b]	–2.4	–2.1	.95	–4.4	–4.7	.95
Leisure time activities[b]	3.1	1.8	.75	–0.1	0.4	.89
Social relationships[b]	2.0	–0.5	.65	–4.3	–1.8	.63
General activities[b]	–4.4	–4.3	.98	–4.6	–4.8	.97
Medication satisfaction[c]	–0.4	–0.8	.46	–0.2	–0.6	.43
Overall life satisfaction[c]	–0.4	–0.6	.77	–0.6	–0.5	.96
Global quality of life[b]	–0.8	–10.5	.30	–2.4	–9.0	.45

[a]Two-tailed p value from analysis of variance model.
[b]Scores range from 0 to 100, with higher scores indicating better health status.
[c]Scores range from 1 to 6, with higher scores indicating greater satisfaction.

Table 3. Comparison of Mean (SD) Medical Costs (in US $) by Treatment Group

Costs	Divalproex	Olanzapine	p Value[a]
Total outpatient	541 (327)	1,080 (638)	.004
Emergency room	60 (157)	23 (87)	.40
Physician	73 (101)	79 (144)	.84
Other professional	28 (52)	18 (31)	.74
Study drug	358 (279)	924 (622)	.002
Other drugs[b]	22 (31)	16 (34)	.20
Inpatient	13,162 (8693)	14,442 (16,594)	.73
Total medical costs	13,703 (8708)	15,180 (16,780)	.88

[a]Two-tailed p value from Wilcoxon rank-sum test.
[b]Other drugs included lorazepam, zolpidem, chloral hydrate, and benztropine mesylate.

Table 4. Changes From Baseline to 6 Weeks in Health-Related Quality of Life Outcomes by Weight Gain as an Adverse Event

	Change From Baseline, Mean		
Variable	Weight Gain	No Weight Gain	p Value
Physical health[a]	–13.6	–1.0	.01
Subjective feelings[a]	–8.8	0.4	.08
Leisure time activities[a]	–4.4	5.0	.03
Social relationships[a]	–2.3	2.0	.48
General activities[a]	–11.4	–0.8	.03
Medication satisfaction[b]	–1.0	–0.4	.23
Overall life satisfaction[b]	–1.2	–0.2	.06
Global quality of life[a]	–6.6	–5.3	.90

[a]Scores range from 0 to 100, with higher scores indicating better health status.
[b]Scores range from 1 to 6, with higher scores indicating greater satisfaction.

Table 5. Correlation Between Change in Weight and Change in Health-Related Quality of Life at 6 Weeks

Variable	Change in Weight, r
Physical health	–0.41*
Subjective feelings	–0.40*
Leisure time activities	–0.31
Social relationships	–0.21
General activities	–0.39*
Medication satisfaction	–0.36*
Overall life satisfaction	–0.43*
Global quality of life	–0.10

*$p < .05$.

medication costs, $358 ± $279 for the divalproex group versus $924 ± $622 for the olanzapine group ($p = .002$). There were no significant differences in total medical costs between the divalproex and olanzapine groups ($p = .88$).

HRQL and Weight Gain

As a secondary analysis, we compared Q-LES-Q scores for subjects reporting weight gain as an adverse event (N = 13) versus subjects not reporting weight gain as an adverse event (N = 36) (Table 4). Subjects reporting weight gain as an adverse event had significantly lower 6-week change scores for the physical (–13.6), leisure activities (–4.4), and general activities (–11.4) domains when compared with subjects not reporting a weight gain as an adverse event (–1.0, 5.0, –0.8, respectively; $p < .05$). These differences were no longer apparent at 12 weeks of follow-up.

Changes from baseline to week 6 in weight and in HRQL were correlated (Table 5). The largest correlations were observed for life satisfaction ($r = –0.43$), physical health ($r = –0.41$), subjective feelings ($r = –0.40$), general activities ($r = –0.39$), and satisfaction with medications ($r = –0.36$).

DISCUSSION

This randomized clinical trial compared divalproex and olanzapine for the treatment of acute mania and followed subjects with bipolar disorder over 12 weeks. It showed an advantage for divalproex over olanzapine for outpatient costs and no difference for clinical symptom and HRQL outcomes. Although only 43% of the randomized study subjects completed the HRQL and economic components, there were no significant demographic or clinical differences between those subjects in the pharmacoeconomic subsample and the complete study sample. The average follow-up was 10 to 11 weeks in the pharmacoeconomic part of the clinical trial.

We found no significant differences between the treatment groups on any of the HRQL measures over the

12-week study. Post hoc estimates of statistical power to detect significant HRQL differences were 20%. However, the HRQL results were consistent with the absence of statistically significant differences in the MRS and HAM-D scores for the divalproex-treated and olanzapine-treated groups. No differences were seen in restricted activity days or bed disability days between the olanzapine and divalproex groups.

The divalproex-treated group had significantly lower total outpatient costs compared with the olanzapine-treated group. The 12-week total outpatient costs were $541 for the divalproex-treated group and $1080 for the olanzapine-treated group. Most of this cost difference was attributable to the considerably higher medication costs for the olanzapine group ($924 versus $358). Total medical costs were $1477 lower in the divalproex group, but this difference was not statistically significant.

In this clinical trial, olanzapine-treated subjects experienced greater weight gain compared with divalproex-treated subjects (8.8 vs. 5.5 pounds, $p < .05$) and more olanzapine-treated patients reported weight gain as an adverse event (25% vs. 10%, $p < .05$).[24] We found that weight gain among subjects with bipolar disorder was associated with decrements in functioning and well-being. Subjects reporting weight gain as an adverse event also reported significantly worse physical well-being and fewer leisure-related activities and general activities than those with no adverse event of weight gain. Changes in body weight were associated with impairment in physical functioning, psychological well-being, and leisure activities. Subject ratings of satisfaction with medication therapy were also associated with an adverse event of weight gain.

Several limitations must be considered when interpreting the findings of this study. First, not all study subjects were included in the pharmacoeconomic evaluation. However, there were no differences between the treatment groups in the proportion of subjects included in the economic analysis or in the duration of follow-up, nor were there substantial differences between the groups in reasons for discontinuation. Second, subjects were recruited during an inpatient admission, and, therefore, these results may not be generalizable to bipolar disorder subjects experiencing an acute manic episode not requiring hospitalization. Third, HRQL and the medical resource data were collected using telephone interviews, and the quality of the patient-reported data may differ from clinic interviews. We have demonstrated that reliable and valid HRQL and other outcome data can be collected from bipolar disorder subjects using trained telephone interviewers.[22,29] These economic results are based on small sample size and only 12 weeks of follow-up. Clearly, this small sample size limits statistical power. Given the need for long-term maintenance therapy for bipolar disorder subjects, these findings need to be confirmed in studies with longer follow-up. Finally, the cost-effectiveness analysis was conducted within the artificial setting of a clinical trial, with multiple protocol-related visits and close monitoring of subjects, and this setting might minimize differences between treatments in medical costs.[37]

Given the comparable clinical and HRQL outcomes between the 2 groups, the significant savings in total outpatient costs for divalproex is meaningful for the clinical management of bipolar disorder and for the mental health care system. These economic findings need to be confirmed in larger prospective, naturalistic studies comparing divalproex and olanzapine with clinical, HRQL, and economic endpoints and a longer follow-up period. On the basis of this study, divalproex had significantly lower outpatient costs in the short-term treatment of manic episodes in subjects with bipolar disorder.

Drug names: benztropine (Cogentin and others), divalproex sodium (Depakote), lorazepam (Ativan and others), olanzapine (Zyprexa), zolpidem (Ambien).

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