A Double-Blind, Randomized, Placebo-Controlled Study of Quetiapine as Adjunctive Treatment for Adolescent Mania

MELISSA P. DELBELLO, M.D., MICHAEL L. SCHWIERS, M.S., H. LEE ROSENBERG, B.S., AND STEPHEN M. STRAKOWSKI, M.D.

ABSTRACT

Objectives: This randomized, double-blind, placebo-controlled study examined the efficacy and tolerability of quetiapine in combination with divalproex (DVP) for acute mania in adolescents with bipolar disorder. It was hypothesized that DVP in combination with quetiapine would be more effective than DVP alone for treating mania associated with adolescent bipolar disorder. Furthermore, it was hypothesized that quetiapine would be well tolerated. **Method:** Thirty manic or mixed bipolar I adolescents (12–18 years) received an initial DVP dose of 20 mg/kg and were randomly assigned to 6 weeks of combination therapy with quetiapine, which was titrated to 450 mg/day ($n = 15$) or placebo ($n = 15$). Primary efficacy measures were change from baseline to endpoint in Young Mania Rating Scale (YMRS) score and YMRS response rate. Safety and tolerability were assessed weekly. **Results:** The DVP + quetiapine group demonstrated a statistically significantly greater reduction in YMRS scores from baseline to endpoint than the DVP + placebo group ($F_{1,27} = 5.04$, $p = .03$). Moreover, YMRS response rate was significantly greater in the DVP + quetiapine group than in the DVP + placebo group (87% versus 53%; Fisher exact test, $p = .05$). No significant group differences from baseline to endpoint in safety measures were noted. Sedation, rated as mild or moderate, was significantly more common in the DVP + quetiapine group than in the DVP + placebo group. **Conclusions:** The findings of this study indicate that quetiapine in combination with DVP is more effective for the treatment of adolescent bipolar mania than DVP alone. In addition, the results suggest that quetiapine is well tolerated when used in combination with DVP for the treatment of mania. *J. Am. Acad. Child Adolesc. Psychiatry*, 2002, 41(10):1216–1223. **Key Words:** mania, bipolar disorder, quetiapine, adolescent.

Although the onset of bipolar disorder typically occurs during adolescence (Lish et al., 1994), only one parallel-group, placebo-controlled study of adolescents or children with bipolar disorder has been published. Specifically, Geller and colleagues (1998) evaluated the efficacy of lithium in a 6-week, placebo-controlled study of 25 adolescents with bipolar disorder and concurrent substance use disorders. They found that lithium was more effective than placebo for reducing global psychopathology scores, but, nonetheless, nearly half of the patients did not respond to lithium (Geller et al., 1998). This rate of lithium response is similar to that observed in adults (McElroy and Keck, 2000).

In contrast to adults with bipolar disorder, children and adolescents with this illness are more likely to present with rapid cycling or in a mixed state (Geller et al., 2000), suggesting that anticonvulsants may be more effective than lithium therapy (Swann et al., 1997). However, open-label treatment studies have found that many children and adolescents with bipolar disorder do not respond to divalproex (DVP) (Kowatch et al., 2000; West et al., 1995). For example, Kowatch and colleagues (2000) assessed the comparative effectiveness of lithium, divalproex sodium, and carbamazepine for the treatment of mania and hypomania in children and adolescents with bipolar disorder, types I and II. In this 6-week, open-

Accepted May 10, 2002.

From the Bipolar and Psychotic Disorders Research Program, Department of Psychiatry, University of Cincinnati College of Medicine, Cincinnati. *Presented in part at the 4th International Conference on Bipolar Disorder, Pittsburgh, June 14, 2001.*

This study was supported by a grant from AstraZeneca Pharmaceuticals. The authors gratefully acknowledge the assistance of the following research staff: Angela Hudephol, Shawna Willhoit, Michelle Sellers, Vidya Sheshadri, M.D., and Kathi Montefiore, R.Ph. In addition, they appreciate the support and efforts of the Cincinnati Children's Hospital Medical Center Adolescent Medical Psychiatric Unit attending, nursing, social work, and administrative staff.

Correspondence to Dr. DelBello, Department of Psychiatry, University of Cincinnati College of Medicine, 231 Bethesda Avenue, P.O. Box 670559, Cincinnati, OH 45267-0559; e-mail: delbelmp@email.uc.edu.

0890-8567/02/4110–1216©2002 by the American Academy of Child and Adolescent Psychiatry.

DOI: 10.1097/01.CHI.0000024837.94814.41

label, randomized study, they found that although DVP demonstrated the largest response rate of the three treatments, 47% of the patients failed to respond to this therapy (Kowatch et al., 2000).

Together, these data suggest that alternative pharmacological options for the treatment of pediatric mania are needed. Controlled investigations of atypical antipsychotics suggest that they are efficacious for the treatment of mania in adults (Segal et al., 1998; Tohen et al., 1999, 2000), and several case series suggest that these agents are also effective for the treatment of mania in children and adolescents (Chang and Ketter, 2000; Frazier et al., 1999; Soutullo et al., 1999). Thus the addition of an atypical antipsychotic to a mood stabilizer may decrease manic symptoms and improve response rates. Indeed, Tohen and colleagues (2002) recently compared the efficacy of combined therapy with olanzapine and either DVP or lithium to DVP or lithium monotherapy for the treatment of acute mania in adults and found that the response rate was significantly higher in the combination group (68 versus 45%).

Quetiapine fumarate is an atypical antipsychotic agent with a unique receptor binding profile. Quetiapine has a high affinity for histaminergic H1 and α_1-adrenergic neuroreceptors. In addition, quetiapine exhibits affinity for brain serotonin 5-HT_2 and 5-HT_{1A} and dopamine D_1 and D_2 receptors and has higher selectivity for 5-HT_2 relative to D_2 receptors (Dev and Raniwalla, 2000; Jones et al., 2001). Several case reports suggest that quetiapine is effective and well tolerated for the treatment of mania in adults (Dunayevich and Strakowski, 2000; Ghaemi and Katzow, 1999; Zarate et al., 2000), affective psychosis in adolescents (McConville et al., 2000; Padla, 2001), and refractory bipolar disorder in children (Catapano-Friedman, 2001; Schaller and Behar, 1999). Furthermore, studies of patients with schizophrenia indicate that quetiapine does not differ from placebo in rates of extrapyramidal symptoms (EPS) or prolactin elevation (Kasper and Muller-Spahn, 2000).

With these considerations in mind, the aim of this double-blind, placebo-controlled augmentation study was to investigate the efficacy and tolerability of quetiapine as an adjunct to DVP for the treatment of acute mania in hospitalized bipolar adolescents. To our knowledge, this is the first parallel-group, placebo-controlled study to compare mood stabilizer monotherapy with the combination of mood stabilizer plus an antipsychotic in adolescents with acute mania. Furthermore, this is the first controlled investigation of an atypical antipsychotic for the treatment of pediatric bipolar disorder and the first controlled study of quetiapine for the treatment of bipolar disorder. We hypothesized that the combination of quetiapine and DVP would be more efficacious for the treatment of adolescent mania than DVP alone, and that quetiapine would be well tolerated as an adjunctive agent in this population.

METHOD

Bipolar adolescents who were hospitalized for a manic or mixed episode were recruited from consecutive inpatient admissions to the Adolescent Psychiatric Unit at Cincinnati Children's Hospital Medical Center from May 2000 through May 2001. Patients were included in the study if they were 12–18 years old, met *DSM-IV* criteria for bipolar I disorder currently mixed or manic, and had a Young Mania Rating Scale (YMRS) (Fristad et al., 1992; Young et al., 1978) score of ≥20. Patients were excluded if (1) they were pregnant; (2) their manic symptoms were secondary to substance intoxication or withdrawal; (3) they had a substance use disorder within the prior 3 months; (4) they had a diagnosis of mental retardation (IQ < 70); (5) they had an unstable medical or neurological disorder, cataracts, or clinically significant baseline laboratory abnormalities; or (6) they had a history of hypersensitivity, intolerance, or nonresponse to quetiapine or valproate. Nonresponse to valproate was defined as a 1-week trial with at least one therapeutic blood level of ≥80 mg/L during the index mood episode without improvement in manic symptoms as determined by the subjects' and primary caregivers' reports. Patients were also excluded if they had been treated with a depot neuroleptic within 3 months, an antidepressant or antipsychotic within a week (fluoxetine within a month), or a benzodiazepine or psychostimulant within 72 hours. Patients previously treated with lithium, valproate, or carbamazepine were required to have serum concentrations of <0.3 mEq/L, 30 mg/L, and 3 mg/L, respectively, before receiving quetiapine or valproate in this trial, to ensure that these medications were adequately "washed out." Patients were also excluded if they had been treated with other antiepileptic agents within 72 hours. Fifty potential study candidates were initially identified. However, 20 patients did not meet study inclusion and exclusion criteria because they had either congenital cataracts (n = 3), a history of intolerance or poor response to DVP (n = 2), a substance use disorder (n = 3), or a primary psychiatric diagnosis other than bipolar disorder (n = 12). Therefore, 30 bipolar patients were randomized into this study (Fig. 1).

This study was approved by the University of Cincinnati and the Children's Hospital Medical Center institutional review boards. Adolescent subjects provided written assent and their parents or legal guardians provided written informed consent for study participation and publication after study procedures were fully explained.

Diagnostic interviews were performed with the Washington University in St. Louis Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS) (Geller et al., 2001) by trained raters (M.P.D., H.L.R.) with established diagnostic reliability (κ = 0.94) (DelBello et al., 2001). Adolescent subjects and their primary caregivers were interviewed separately. Primary caregiver and child responses were combined to ascertain diagnoses. Teachers and another primary caregiver were interviewed if there was a discrepancy between the primary caregiver's and the adolescent's responses. All diagnoses were reviewed in a conference attended by the WASH-U-KSADS interviewer and at least one child and adolescent psychiatrist from which a consensus diagnosis was made.

Demographic information was obtained by interviewing the adolescent and his or her primary caregivers. The Self-Rated Tanner Scale was used to assess the stage of adolescent sexual development (Morris and Udry, 1980).

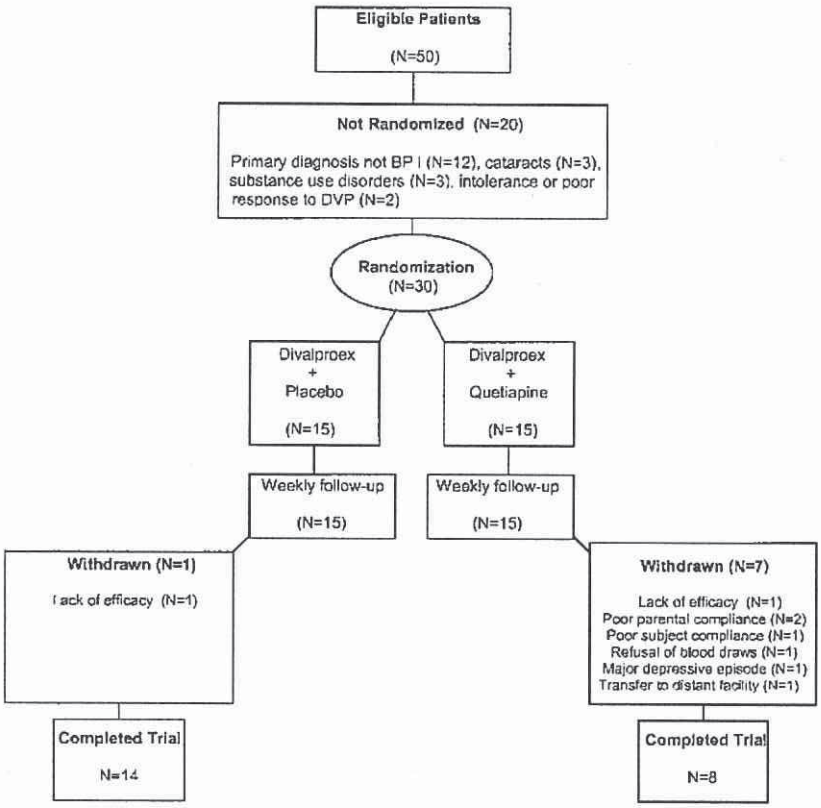

Fig. 1 Diagram of subject flow by treatment group. BP I = bipolar I disorder; DVP = divalproex.

Efficacy and Safety Measures

The primary efficacy measure was the YMRS (Fristad et al., 1992; Young et al., 1978). Secondary efficacy measures included the Positive and Negative Syndrome Scale-Positive subscale (PANSS-P) and the Children's Depression Rating Scale (CDRS) to assess the severity of psychotic (Kay et al., 1989) and depressive symptoms (Poznanski et al., 1979, 1983), respectively. Overall level of functioning was assessed at baseline and endpoint with Children's Global Assessment Scale (CGAS) scores (Shaffer et al., 1983). A child and adolescent psychiatrist with previously established reliability for each rating scale (M.P.D.) completed all ratings by interviewing the subject and his or her primary caregiver (intraclass correlation coefficient ≥ 0.9).

EPS were assessed with the Simpson-Angus (Simpson and Angus, 1970), Barnes Akathisia (Barnes, 1989), and Abnormal Involuntary Movement Scales (Guy, 1976). Laboratory tests obtained included a complete blood cell count (CBC) with differential and prolactin, thyroid-stimulating hormone (TSH), and valproic acid levels. In addition, liver function tests (LFTs), including alanine aminotransferase, aspartate aminotransferase, and total bilirubin, were obtained. Vital signs obtained included weight and orthostatic blood pressure and pulse. Electrocardiograms (ECGs) were monitored throughout the study. In addition, physical and slit-lamp ocular examinations were performed on each subject at baseline and endpoint. Adverse events were assessed when ratings were obtained by asking the adolescents and their primary caregivers open-ended questions about potential side effects.

Study Protocol

This study was a 6-week, randomized, parallel-group, double-blind, placebo-controlled investigation of DVP monotherapy versus the combination of DVP plus quetiapine. After meeting all inclusion and exclusion criteria, subjects were randomly assigned to receive either placebo or adjunctive quetiapine. Randomization, which was assigned by investigational pharmacists, was stratified by sex and the presence of psychosis using a random number generator. All inpatient and research staff were blind to subject treatment group.

All subjects received an initial DVP dose of 20 mg/kg per day on day 0, which was adjusted to achieve a therapeutic serum level of 80–130 mg/dL. On day 0, subjects were also randomly assigned to receive placebo or an initial quetiapine dose of 25 mg b.i.d., which was titrated to a maximum of 150 mg t.i.d. by day 7. A maximum of 2 mg of lorazepam per day was permitted during the first 14 days of the study.

Compliance was measured by pill count at each visit and by assessing valproic acid serum levels, which were collected 10 to 14 hours after the last DVP dose on days 3, 7, 14, 21, and 42 (or termination from the study). In addition, each subject was asked to keep a medication log to encourage compliance and identify missed doses. Subjects were discontinued from the study if they missed more than 2 consecutive days of study medication or more than six doses during any 7-day period.

Efficacy and safety ratings were performed at baseline, days 3 and 7, and then weekly until day 42 or termination from the study. Vital signs were monitored at each visit. Serum prolactin levels, LFTs, TSH,

and CBC were assessed at baseline and day 42 or termination. In addition, LFTs and CBC were also assessed at days 7 and 21. ECGs were performed at baseline and days 7, 21, and 42 or termination.

Inpatient attending physicians (not associated with the study) discharged study participants from the inpatient psychiatry unit when they determined that the subjects were clinically stable. All subsequent visits were performed in an outpatient setting. The majority of patients were discharged 7 to 14 days after admission (93%). There was no statistically significant group difference in length of hospitalization.

Statistical Analysis

Prior to study initiation, sample size estimates were calculated by assuming a directional hypothesis (i.e., that the combination therapy would be better than monotherapy) and a medium to large effect size, with 80% power and $\alpha = .05$ (Stevens, 1990).

Statistical analyses were performed with the Statistical Analysis System for the PC (SAS Institute, Cary, NC, 1999). Clinical and demographic variables were identified as potential covariates using t tests or Fisher exact tests and a liberal p value of .2 for differences between groups.

With the data from the intent-to-treat samples ($n = 15$/group), t tests were used to calculate differences from baseline to endpoint for each efficacy measure within each treatment group. Primary efficacy measures were change from baseline to endpoint in YMRS and YMRS response. Response was defined as a ≥50% reduction in YMRS score from baseline to endpoint. Analysis of covariance (ANCOVA) was used to compare group differences in endpoint YMRS score after controlling for baseline values. The effect size for each treatment group was calculated by using the mean change and standard deviation from baseline to endpoint in YMRS scores (Cohen, 1988). Group differences in YMRS response rates were compared by using a one-tailed Fisher exact test. Secondary efficacy measures were change from baseline to endpoint in CGAS, CDRS, and PANSS-P scores. ANCOVAs were used to compare group differences in endpoint CGAS, CDRS, and PANSS-P scores after controlling for baseline values.

In addition, likelihood-based mixed-model repeated-measures ANCOVAs (*proc mixed*) were conducted to evaluate group-by-day differences in YMRS, CDRS, and PANSS-P scores, with control for baseline scores. This analysis uses all available data and was selected to avoid biases that might be introduced with last observation carried forward or completer analyses. As a follow-up analysis, least-squares means were calculated at each time point for each rating instrument to determine on which days statistically significant group differences occurred.

Group differences in rates of side effects were assessed with two-tailed Fisher exact tests. ANCOVAs were used to compare endpoint laboratory measures between groups after controlling for baseline values. Other analyses were performed as necessary.

RESULTS

Baseline Comparisons of Patient Characteristics

Twenty-two (73%) of the 30 randomized subjects completed the 6-week protocol. One patient in each group discontinued prematurely (at day 14 in both cases) because of lack of efficacy for acute mania symptoms. The six remaining noncompleters were all in the DVP + quetiapine group. The reasons for these patients' premature termination included refusal to participate in blood draws ($n = 1$, day 7), parental treatment noncompliance ($n = 2$, days 28 and 35), adolescent treatment noncompliance ($n = 1$, day 28), transfer to a distant residential treatment facility ($n = 1$, day 28), and developing a major depressive episode after mania resolution ($n = 1$, day 21). No subjects in either group discontinued from the study because of medication side effects (Fig. 1).

There were no significant group differences in age, sex, race, socioeconomic status, Tanner stage, baseline CGAS, YMRS, CDRS, or PANSS-P scores or rates of mixed episodes, psychosis, and attention-deficit/hyperactivity disorder (Table 1). Age at onset of bipolar disorder was defined as the age at which a *DSM-IV* mood episode initially occurred and was determined with the WASH-U-KSADS. Subjects in the DVP + quetiapine group had a younger age at onset of bipolar disorder compared with those in the DVP + placebo group (Table 1; $p = .01$). Mean valproic acid level was 102 mg/dL in the DVP + placebo group and 104 mg/dL in the DVP + quetiapine group. By day 3, 97% (29/30) of the subjects reached a therapeutic valproic acid level (mean ± SD = 113 ± 20 mg/dL) and by day 7, 100% had reached a therapeutic valproic acid level (114 ± 26 mg/dL). Mean dosage of quetiapine was 432 mg/day in the DVP + quetiapine group. One subject in the DVP + quetiapine group was not titrated to the maximum dose of 450 mg/day because of excessive sedation and was treated with 250 mg/day.

Primary Efficacy Measures

Analyses within each treatment group revealed a statistically significant reduction from baseline to endpoint

TABLE 1
Demographic and Clinical Characteristics of Bipolar Adolescents by Treatment Group

Variable	DVP + Placebo ($n = 15$)		DVP + Quetiapine ($n = 15$)	
Sex, *n* (%), female	7	(47)	7	(47)
Age, mean (SD), yr	14.5	(2)	14.1	(2)
Race, *n* (%), Caucasian	13	(87)	12	(80)
Tanner stage, mean (SD)	3.9	(1.3)	3.3	(1.1)
SES, mean (SD)[a]	3.6	(1.9)	3.0	(1.5)
Age onset bipolar disorder, mean (SD), yr[b]	11	(3)	8	(3)
Mixed episode, *n* (%)	13	(87)	10	(67)
Psychosis, *n* (%)	7	(47)	7	(47)
ADHD, *n* (%)	8	(53)	10	(67)

Note: DVP = divalproex; SES = socioeconomic status; ADHD = attention-deficit/hyperactivity disorder.

[a] Range = 1–7, rating of 3 = parental yearly income of $20,000–$35,000.

[b] Significant difference between groups: $t_{28} = 2.75$, $p = .01$.

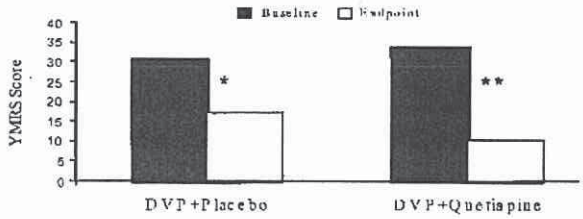

Fig. 2 Manic adolescents in the divalproex (DVP) + quetiapine group (n = 15) had a greater reduction in Young Mania Rating Scale (YMRS) scores from baseline to endpoint compared with those in the DVP + placebo group (n = 15); analysis of covariance: $F_{1,27} = 5.04$, $p = .03$. $^{*}p = .002$; $^{**}p < .0001$.

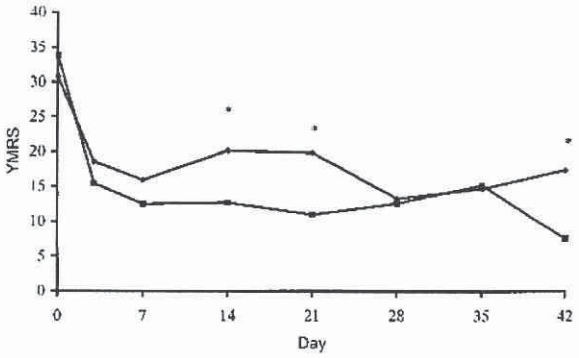

Fig. 3 Manic adolescents in the divalproex + quetiapine group (squares; n = 15) had a statistically significantly greater reduction in Young Mania Rating Scale (YMRS) scores over time than those in the DVP + placebo group (diamonds; n = 15); analysis of covariance: $F_{1,27} = 8.3$, $p < .01$. $^{*}p < .01$.

in YMRS score (Fig. 2). However, the DVP + quetiapine group demonstrated a significantly greater reduction in YMRS score from baseline to endpoint than the DVP + placebo group ($F_{1,27} = 5.04$, $p = .03$) (Fig. 2).

The YMRS response rate was significantly greater in the DVP + quetiapine group than in the DVP + placebo group (87% versus 53%; Fisher exact test, $p = .05$). YMRS responders did not differ from nonresponders in length of time in the study (mean length of time in the study was 5.3 and 5.1 weeks, respectively, $p = .7$).

Secondary Efficacy Measures

Within each treatment group, CDRS (DVP + placebo, $t = 4.7$, $p = .0004$ and DVP + quetiapine, $t = 3.0$, $p = .01$), PANSS-P (DVP + placebo, $t = 3.9$, $p = .002$ and DVP + quetiapine, $t = 3.1$, $p = .009$), and CGAS (DVP + placebo, $t = 8.6$, $p < .0001$ and DVP + quetiapine, $t = 11.0$, $p < .0001$) scores were significantly reduced from baseline to endpoint. However, there were no significant differences between groups in change from baseline to endpoint in CDRS ($F_{1,27} = 0.0$, $p = 1.0$), PANSS-P ($F_{1,27} = 0.1$, $p = .8$), and CGAS ($F_{1,27} = 1.5$, $p = .2$) scores.

Response Over Time

Subjects in the DVP + quetiapine group demonstrated an overall greater reduction over time in YMRS scores than did subjects in the DVP + placebo group ($F_{1,27} = 8.3$, $p < .01$) (Fig. 3). Specifically, statistically significant group differences were found on days 14, 21, and 42 ($p = .009$, $p = .005$, $p = .01$, respectively). No statistically significant group differences were found for change in CDRS ($F_{1,27} = 0.1$, $p = .7$) or PANSS-P ($F_{1,27} = 0.5$, $p = .4$) scores over time.

Lorazepam Use

Three subjects in the DVP + placebo group and two subjects in the DVP + quetiapine group required lorazepam during the first 14 days of the study. Four of the subjects required only one dose of lorazepam (0.5–1 mg) and one subject required three doses (total dose = 1.5 mg). There was no significant group difference in amount of lorazepam used ($p = .6$).

Tolerability and Side Effects

There were no significant group differences in change from baseline to endpoint in QTc interval, TSH, white blood cell count, hematocrit, platelet count, prolactin level, weight, EPS ratings, or LFTs (Table 2). In addition, there were no subjects who had an abnormally elevated prolactin level at endpoint. No subjects had orthostatic hypotension during this study. No subjects developed cataracts or a serious adverse event during this study.

The most common side effects in both treatment groups were sedation, nausea, headache, and gastrointestinal irritation (Table 3). Sedation was significantly more common in the DVP + quetiapine group than in the DVP + placebo group (Fisher exact test, $p = .03$). However, within the DVP + quetiapine group, there was no significant difference in rate of sedation between responders and nonresponders (Fisher exact test, $p = .4$). All side effects were rated as mild to moderate by the subjects and their caregivers.

DISCUSSION

The results of this study indicate that quetiapine in combination with DVP is more effective at reducing manic symptoms associated with bipolar disorder than DVP monotherapy. Furthermore, the results suggest that quetiapine is well tolerated when used in combination with

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.