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Divalproex ER Combined with Olanzapine or Risperidone for Treatment of Acute Exacerbations of Schizophrenia

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The objective of this study was to evaluate the efficacy and safety of divalproex sodium extended release (divalproex ER) *vs* placebo in combination with olanzapine or risperidone for the treatment of acute exacerbations of schizophrenia. In this 12-week, randomized, double-blind, parallel-group, multi-center trial, a total of 402 patients were randomized and treated; 103 received olanzapine/placebo, 99 received olanzapine/divalproex ER, 101 received risperidone/placebo, and 99 received risperidone/divalproex ER. Divalproex ER was initiated on day 1 at 20 mg/kg per day q AM and was titrated to clinical effect on days 3, 7, and 10, not to exceed a maximum dosage of 35 mg/kg per day. Olanzapine and risperidone were initiated at 5 and 2 mg/day q PM, respectively, increased to 10 and 4 mg/day on day 3, and increased to fixed target doses of 15 and 6 mg/day on day 6. No significant treatment difference was demonstrated between the combination therapy and antipsychotic monotherapy groups on the primary efficacy variable of the mean change from baseline to day 14 last observation carried forward on the Positive and Negative Syndrome Scale (PANSS) total score, although antipsychotic monotherapy did demonstrate superiority to combination therapy on the PANSS Negative subscale at several time points. Combination therapy also failed to show an advantage over antipsychotic monotherapy at day 84 on the PANSS total score. Most adverse events observed in the study were mild to moderate in severity, and the overall number of adverse events did not differ significantly between the combination therapy groups and their corresponding antipsychotic monotherapy group.
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INTRODUCTION

Schizophrenia is a severe, debilitating, and chronic mental disorder characterized by positive (hallucinations, delusions) and negative (withdrawal, apathy, anhedonia) symptoms. The conventional antipsychotic drugs used to treat schizophrenia are believed to produce their effects through blockade of the dopamine type 2-receptor and are effective in treating positive symptoms but are associated with extrapyramidal side effects (EPS). The second generation antipsychotic drugs (such as risperidone and olanzapine) cause fewer EPS, and have shown promise in reducing the negative symptoms of schizophrenia, possibly due to their inhibition of serotonin type-2 receptor activity (Möller, 2003). In spite of these advances, the treatment of schizophrenia remains suboptimal; the disorder usually follows a chronic relapsing course, and the side effects of current therapies are of concern (Meltzer, 1999).

Although the monoamines (especially dopamine) have been the major focus of research in the pathophysiology of schizophrenia for many years, evidence also indicates abnormalities in other neurotransmitter systems, including the GABAergic system (Benes, 2000; Lewis *et al*, 2005). Studies have demonstrated a loss of inhibitory GABAergic neurons in the brains of schizophrenic patients. These findings produced speculation that drugs that enhance GABAergic activity may provide benefit in the treatment of schizophrenia (Benes, 2000; Berle and Spigset, 2005; Lewis *et al*, 2005).

Divalproex sodium (divalproex hereafter) has putative GABA agonism via multiple mechanisms (reviewed by Wassef *et al*, 2003) and potentiates antipsychotic-induced dopamine release in the prefrontal cortex of rats (Melzer *et al*, 2001). A number of small, open-label studies support the clinical benefit of divalproex in combination with conventional antipsychotic medications for the treatment of psychotic symptoms (Gunderewa *et al*, 1980; Moringo *et al*,

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1989; Wassef *et al*, 1989, 2000; Chong *et al*, 1998). Recently, a large, double-blind, multi-center trial demonstrated improvement in psychotic symptoms for divalproex *vs* placebo when given in combination with olanzapine or risperidone for the treatment of acute exacerbations of schizophrenia. Improvement with divalproex was seen as early as day 3 and continued to day 21 (Casey *et al*, 2003).

The objective of this study was to evaluate the effects of divalproex sodium extended release (divalproex ER hereafter) in combination with olanzapine or risperidone *vs* antipsychotic monotherapy with olanzapine or risperidone for the treatment of schizophrenia over a 12-week period.

METHODS

Patients

Hospitalized patients between the ages of 18 and 65 years with an acute exacerbation of schizophrenia were enrolled. Patients with a current DSM-IV-TR diagnosis of schizophrenia, as confirmed by a Structured Clinical Interview for DSM-IV-TR (SCID; First *et al*, 2002) were selected for inclusion on the basis of having (1) a Positive and Negative Syndrome Scale (PANSS; Kay *et al*, 1987) total score $\geqslant 70$ (based on a 1–7-point scale for each measure), (2) a score totaling $\geqslant 8$ on any two of the four items from the psychosis cluster of the Brief Psychiatric Rating Scale-derived (BPRSd), and (3) a total score $\geqslant 6$ on either hostility and uncooperativeness or excitement and tension items from the BPRSd. For inclusion, a patient must have had, in the investigator's opinion, a positive response to treatment with antipsychotics within the previous 2 years.

Patients were excluded from the study if they had a current diagnosis of schizoaffective disorder, drug-induced psychosis, manic episode, or major depressive episode, as were those who had serious violent, homicidal, or suicidal ideation, or had more than three psychiatric hospitalizations in the previous 6 months or more than 8 weeks of psychiatric hospitalization in the previous 12 months.

Study Design

The study was a randomized, double-blind, parallel-group, multi-center trial, consisting of a 1- to 5-day screening/washout period and a 12-week double-blind treatment period. The protocol was approved by the institutional review board of each participating study site. Written informed consent was obtained from each patient or the patient's authorized representative before enrollment in the study.

Patients were randomized to one of four treatment groups: (1) olanzapine/placebo, (2) risperidone/placebo, (3) olanzapine/divalproex ER, or (4) risperidone/divalproex ER. Divalproex ER was initiated on day 1 at 20 mg/kg per day q AM and was titrated to clinical effect on days 3, 7, and 10, not to exceed a maximum dosage of 35 mg/kg per day. Olanzapine and risperidone were initiated at 5 and 2 mg/day q PM respectively, increased to 10 and 4 mg/day on day 3, and increased to fixed target doses of 15 and 6 mg/day on day 6. Once these doses were achieved, they were continued for the remainder of the study.

Lorazepam, propranolol hydrochloride, and benztropine mesylate could be used as adjunctive medications, but were not to be used prophylactically. Lorazepam (up to 6 mg/day during screening, up to 4 mg/day on days 1–7 of the treatment period, and up to 2 mg/day from day 8 until hospital discharge) could be prescribed for severe agitation and for control of insomnia, but not within 8 h before efficacy ratings. Propranolol hydrochloride (according to the investigator's discretion) could be prescribed for severe or intolerable akathisia. Benztropine mesylate (up to 4 mg/day throughout the study) could be prescribed for severe or intolerable akathisia, EPS, or dystonia.

The double-blind treatment period consisted of a 14-day acute phase followed by a 10-week stabilization phase. Patients were required to remain hospitalized for a minimum of 14 days during the Acute Phase of the study and could be discharged (per investigator discretion) anytime after day 14. Once discharged, patients were seen as outpatients for the remainder of the study and were required to return to the study site for regularly scheduled assessments.

Clinical Evaluations

The psychiatric status of patients was evaluated using the PANSS total and subscales, and the Clinician's Global Impression (CGI) Severity and Improvement scales (Guy, 1976). The evaluations were conducted on days 1 (baseline), 3, 5, 7, 10, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, and 84. The PANSS was scored based on the previous 48 h symptoms. The BPRSd was administered as a secondary efficacy measure.

All raters received extensive training on rating the PANSS and other key scales, including initial training sessions in which raters were required to rate scales and score within 1.5 standard deviations of the mean of all raters. At approximately midstudy, raters attended refresher training sessions, during which rater scores demonstrated good reliability. Only individuals who successfully completed a rater-training program were permitted to administer and score the rating scales. If at all possible, the same rater performed all ratings for a given subject throughout the study.

Safety Assessment

Safety assessments included a physical examination, vital sign monitoring, body weight measurement, adverse event collection, and laboratory tests. EPS side effects were evaluated during the double-blind treatment period using the Simpson–Angus Scale (SAS; Simpson and Angus, 1970), the Barnes Akathisia Scale (BAS; Barnes, 1989), and the Abnormal Involuntary Movement Scale (AIMS; Guy, 1976).

Statistical Analysis

All statistical tests were two tailed with a significance level of 0.05. The primary treatment comparison for demographic and baseline characteristics and for efficacy endpoints was combination therapy *vs* antipsychotic monotherapy. The combination therapy group consisted of patients from the olanzapine/divalproex ER and risper-

idone/divalproex ER groups, and the monotherapy group consisted of patients from the olanzapine/placebo and risperidone/placebo treatment groups. Comparability of treatment groups was assessed by a one-way analysis of variance (ANOVA) for age and weight and by a Wilcoxon rank sum test for age at first diagnosis of schizophrenia. Treatment group differences for lifetime number of hospitalizations and number of suicide attempts (collected as 0, 1–5, 6–10, 11–15, 16–20, and >20) were assessed with the Cochran–Mantel–Haenszel test. Fisher's exact test was used to assess treatment differences in gender and race and in reason for discontinuation of study drug.

All efficacy analyses were performed on the intent-to-treat (ITT) dataset, defined as all randomized patients who received study medication and who were rated on the PANSS total at baseline and at least once while receiving treatment. The primary efficacy variable was the change from baseline to the day 14 evaluation using the last observation carried forward (LOCF) for the PANSS total score. The day 14 evaluation point was chosen because it was thought that the 2-week acute stabilization period would be the most clinically relevant, and that this period would also be the most controlled environment in which to test for efficacy given the potential for variations in compliance and environmental factors after discharge. In addition, the day 14 evaluation point was also within the time period in which apparent efficacy was demonstrated in the previous Casey *et al* (2003) study, thus allowing possible comparison of efficacy between the two studies. Treatment group differences for the primary efficacy variable were assessed by a two-way ANOVA with factors for treatment group and study center. Based on the results of Casey *et al* (2003), the planned sample size of 200 subjects each in the antipsychotic monotherapy and combination therapy groups had 80% power to detect a treatment difference of 5.1 with a pooled standard deviation of 18.2 (standardized effect size = 0.28) and a Type I error rate of 0.05 for a two-tailed test.

Supportive efficacy endpoints included change from baseline to each scheduled visit (using LOCF) for the PANSS total, positive, and negative scores, the BPRS total score derived from the PANSS, and CGI severity and improvement scores. All secondary endpoints except the CGI Improvement score were assessed as described for the primary efficacy endpoint. For the CGI Improvement score, the primary treatment comparison was assessed by Cochran–Mantel–Haenszel with study centers as strata.

All randomized patients who received at least one dose of study medication were evaluated for safety. The primary treatment comparison for safety data was each individual combination therapy group *vs* its corresponding antipsychotic monotherapy group (ie olanzapine/divalproex ER *vs* olanzapine/placebo and risperidone/divalproex ER *vs* risperidone/placebo). Adverse events were coded using the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) Version V dictionary. Treatment-emergent adverse events were those events that began or worsened in severity on or after the first day of dosing. Treatment differences in the percentage of patients reporting each treatment-emergent adverse event were assessed by Fisher's exact test. Treatment group differences in laboratory data were analyzed by a one-way ANOVA with treatment as the main effect. The primary analysis was the change from baseline (last determination obtained on or before day 1 of dosing) to the final evaluation for each variable.

RESULTS

A total of 402 patients were randomized for treatment: 103 received olanzapine/placebo, 99 received olanzapine/divalproex ER, 101 received risperidone/placebo, and 99 received risperidone/divalproex ER. 251 patients (62%) discontinued study drug. Reasons for premature discontinuations were adverse event (12% monotherapy, 16% combination therapy), withdrew consent (21% monotherapy, 17% combination therapy), lost to follow-up (5% monotherapy, 7% combination therapy), noncompliance (7% monotherapy, 9% combination therapy), ineffectiveness (19% monotherapy, 14% combination therapy), and other (12% monotherapy, 8% combination therapy); subjects may have reported more than one reason for premature discontinuations, but were counted only once in the total. No significant treatment differences were noted for overall discontinuation rate or discontinuation rate by specific reason. Overall, the majority of subjects who prematurely discontinued did so during the first 4 weeks of treatment (37%; 147/402). A total of 43, 46, 32, and 30 patients in the olanzapine/placebo, olanzapine/divalproex ER, risperidone/placebo, and risperidone/divalproex ER groups, respectively, completed the study.

Baseline demographic and clinical characteristics are listed in Table 1. The treatment groups did not differ in demographics, schizophrenia subtype, age at first diagnosis, or number of suicide attempts. Most patients (86%) had a diagnosis of paranoid schizophrenia, with more than six lifetime hospitalizations (55%), and at least one suicide attempt (51%). The mean baseline PANSS total score was 99.1 for the antipsychotic monotherapy group and 98.3 for the combination therapy group.

Efficacy Results

Efficacy results are summarized in Figure 1 and Table 2. The primary efficacy variable, mean change from baseline to day 14 LOCF in PANSS total score, did not demonstrate a significant treatment difference between the combination therapy group and the monotherapy group ($p = 0.307$). Similarly, there was no treatment difference on the PANSS total at day 84 ($p = 0.229$). No statistically significant differences were found between treatment groups on the PANSS positive subscale at day 14 ($p = 0.473$) or day 84 ($p = 0.623$), or the PANSS general psychopathology subscale at day 14 ($p = 0.603$) or day 84 ($p = 0.355$). Results of the PANSS negative subscale demonstrated a numerical advantage of antipsychotic monotherapy over combination therapy ($p = 0.085$) at day 14, and showed a significant treatment difference favoring antipsychotic monotherapy *vs* combination therapy on days 3, 5, 7, 10, 42, 49, 63, 77, and 84.

Change from baseline on the BPRSd was not significantly different for combination therapy *vs* antipsychotic monotherapy at day 14 ($p = 0.457$) or at day 84 ($p = 0.364$). The CGI severity and improvement scores also failed to show a

Table 1 Demographic Characteristics (Intent-to-Treat Dataset)

Demographic characteristic	Antipsychotic monotherapy	Combination therapy
Gender	(*N* = 198)	(*N* = 195)
Female	42 (21%)	47 (24%)
Male	156 (79%)	148 (76%)
Race	(*N* = 198)	(*N* = 195)
White	83 (42%)	93 (48%)
Black	104 (53%)	95 (49%)
Other	11 (5%)	7 (3%)
Age (years)	(*N* = 198)	(*N* = 195)
Mean (SD)	39.9 (10.49)	40.1 (10.54)
Range	18–64	18–65
Weight (kg)	(*N* = 198)	(*N* = 195)
Mean (SD)	87.4 (20.66)	87.5 (19.98)
Range	53.1–149.7	53.5–148.8
Schizophrenic subtype	(*N* = 198)	(*N* = 195)
Paranoid type	172 (87%)	166 (85%)
Disorganized type	9 (5%)	7 (4%)
Catatonic type	0 (0%)	1 (< 1%)
Undifferentiated type	17 (9%)	21 (11%)
Age (years) at first diagnosis	(*N* = 195)	(*N* = 194)
Mean (SD)	23.8 (8.1)	24.6 (8.5)
Median	22.0	22.0
Lifetime number of hospitalizations	(*N* = 198)	(*N* = 194)
0	3 (2%)	3 (2%)
1–5	76 (38%)	91 (47%)
6–10	52 (26%)	39 (20%)
> 10	67 (34%)	61 (31%)
Number of suicide attempts	(*N* = 198)	(*N* = 195)
0	108 (55%)	85 (44%)
1–5	80 (40%)	99 (51%)
⩾6	10 (5%)	11 (6%)

statistically significant difference between antipsychotic monotherapy and combination therapy at days 14 or 84.

The use of adjunctive rescue medications (ie lorazepam, propranolol hydrochloride, and benztropine mesylate) during the study, including dosage (mg/day), number of days used, and percentage of patients using rescue medications, was similar between the antipsychotic monotherapy and combination therapy groups. Lorazepam was used by 65% of patients on antipsychotic monotherapy for an average of 6.2 days, and by 59% of patients on combination therapy for an average of 6.4 days. The mean daily lorazepam dose was 1.5 mg in both groups. Only 16% of patients used either propranolol hydrochloride or benztropine mesylate.

Safety Results

The mean modal daily divalproex ER dose was 2828 mg in the olanzapine/divalproex ER group and 2712 mg in the risperidone/divalproex ER group. From weeks 2 through 12, the mean daily dose of olanzapine was 15 mg/day, and the mean daily dose of risperidone was 6 mg/day. According to pill counts, 82% of subjects were compliant at least 70% of the time. Valproate serum levels for observed cases are presented in Figure 2 and suggest a meaningful drop off in compliance following the inpatient phase of the study. The overall incidence of treatment-emergent adverse events was 83% in the olanzapine/placebo group, 88% in the olanzapine/divalproex ER group, 79% in the risperidone/placebo group, and 84% in the risperidone/divalproex ER group, with no significant differences between a specific combination therapy group and its corresponding antipsychotic monotherapy group. Most of the adverse events observed during the study were mild or moderate in severity. The incidence of constipation was significantly higher for risperidone compared to risperidone/divalproex ER (8 *vs* 1%; $p = 0.035$). Conversely, the incidence of somnolence (45 *vs* 19%; $p < 0.001$), weight gain (22 *vs* 10%; $p = 0.021$), and urinary incontinence (5 *vs* 0%; $p = 0.028$) was significantly higher for risperidone/divalproex ER *vs* risperidone monotherapy. The incidence of dry mouth was significantly higher in the olanzapine group compared to the olanzapine/divalproex ER group (13 *vs* 4%; $p = 0.041$), but the incidence of back pain was significantly higher in the olanzapine/divalproex ER group compared to the olanzapine monotherapy group (5 *vs* 0%; $p = 0.027$). One patient in the risperidone/divalproex ER group died on day 24 due to an accidental opioid overdose, which was considered not related to study drug by the investigator.

Laboratory assessments showed a significant decrease from baseline in platelet counts in each combination therapy group when compared to its respective monotherapy group. The mean serum level of LDL cholesterol was statistically significantly decreased from baseline in the antipsychotic combination therapy group *vs* the antipsychotic monotherapy group ($p = 0.004$). A similar decrease in LDL cholesterol level was seen when risperidone/divalproex ER was compared with risperidone monotherapy ($p = 0.036$) and when olanzapine/divalproex ER was compared with olanzapine monotherapy ($p = 0.056$). Table 3 presents the safety parameters by drug groups.

DISCUSSION

In this study, the addition of divalproex ER to olanzapine or risperidone did not enhance efficacy at either the primary endpoint of 14 days or in the extended 12-week treatment period. These results contrast somewhat with other reports of adjunctive or combination therapy using valproate in psychotic populations (eg Wassef *et al*, 1989, 2000) and with the findings from a similarly designed study of divalproex combination therapy with risperidone or olanzapine (Casey *et al*, 2003), in which improvement with divalproex was

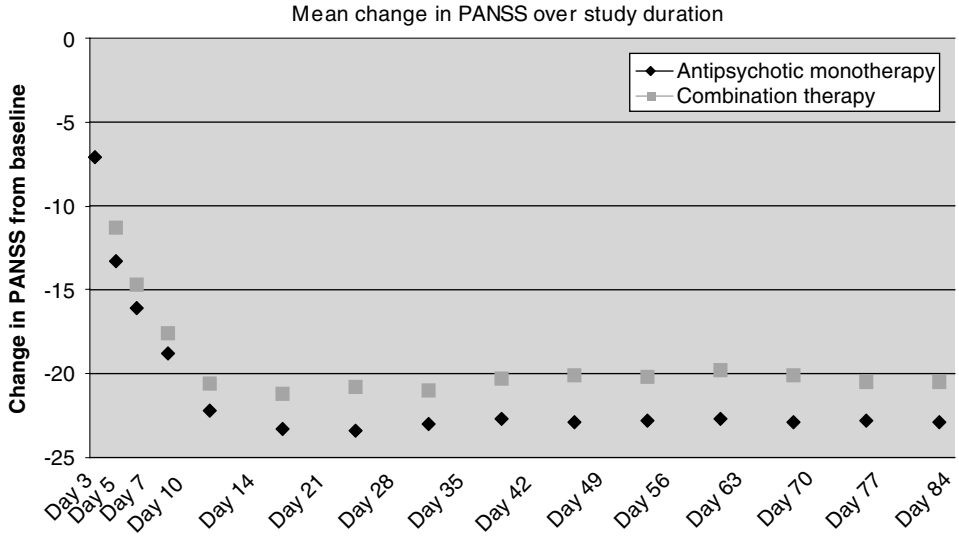

Figure 1 Change from baseline for the PANSS total LOCF. There were no significant differences between DVPX ER/antipsychotic combination therapy and antipsychotic monotherapy at any time point.

demonstrated as early as day 3 and which continued to day 21, but which failed to reach its primary efficacy endpoint of PANSS change score from baseline to week 4. In this study, mean negative symptom scores on the PANSS Negative subscales improved from baseline in both groups, but more so in the monotherapy group. However, statistically significant treatment differences in negative symptoms favoring antipsychotic monotherapy *vs* combination therapy were not seen in the earlier Casey *et al* (2003) study. It is possible that the effects of combination therapy on negative symptoms in this study were partially masked by sedative effects. For example, in this study, the incidence of somnolence was higher for the risperidone/divalproex ER *vs* risperidone monotherapy group (45 *vs* 19%; $p < 0.001$).

Overall, the basis for the different outcomes in these two similar studies is unclear. A comparison between the Casey *et al* (2003) study and this study suggests similar patient characteristics at enrollment. The duration of this study was 12 weeks, compared to 4 weeks for the previous study, and the primary endpoint in this study was 14 days, compared to the 28-day primary endpoint in Casey *et al* (2003). Although the primary efficacy measure was the same in both studies, different supportive efficacy measures were used in this study. Another difference was that the Casey *et al* (2003) study utilized divalproex BID whereas this study utilized divalproex ER administered QD. To account for differences in bioavailability between formulations, this study used a more rapid titration schedule than Casey *et al* (2003). By day 14, dosing was comparable in the two studies, as were serum valproate concentrations (in μg/ml, OLZ + DVPX, mean (SD): 91.2 (33.04) (this study) *vs* 97.2 (28.47) (Casey *et al*, 2003); RISP + DVPX, mean (SD): 105.5 (27.26) (this study) *vs* 102.5 (24.15) (Casey *et al*, 2003); all DVPX, mean (SD): 97.9 (31.20) (this study) *vs* 99.7 (26.53) (Casey *et al*, 2003)).

Another difference between the two studies is the serum valproate levels of subjects in the later time points of the studies. Final day mean trough levels of valproate at day 28 in the Casey *et al* (2003) study were 98.2 and 100.2 μg/ml in combination with risperidone and olanzapine, respectively, compared to levels in the 65–80 μg/ml range at the later time points in this study. The decrease in serum valproate levels over time in this study may be due to a reduction in compliance during the outpatient portion of the study. As the therapeutic range for adjunctive divalproex in the treatment of schizophrenic symptoms is not well delineated, it is unclear if the serum valproate levels achieved after day 14 in this study should be adequate to treat the symptoms of schizophrenia; however, in a previously reported 4-week open-label study (Citrome *et al*, 2004), thirty schizophrenic subjects were converted from divalproex DR to ER, and the 12-h post-dose trough plasma levels were 80.1 ± 20.4 and 73.1 ± 24.2 μg/ml (mean ± SD), respectively. In this previously reported study, psychopathology as measured on the total BPRS improved slightly ($p = 0.0322$), indicating that plasma levels of valproate in the vicinity of 73.1 μg/ml may have some therapeutic effect in schizophrenia. This suggests that the serum valproate levels achieved in the later stages of this study could be clinically relevant in the treatment of schizophrenia.

In addition, another key distinction between the two studies that is likely related to the differences in serum valproate levels discussed above is that in the Casey *et al* (2003) study, the subjects spent the study duration in an inpatient setting, whereas in this study, subjects could be discharged after 14 days of treatment. The length of time in the hospital very likely correlates with improved compliance, in contrast to an unsupervised outpatient setting. In Figure 1, the early reduction in psychotic symptoms in this study parallels the time course and degree of improvement that has been seen in several second-generation antipsychotic trials done primarily with inpatients (Casey *et al*, 2003). However, from days 14–84 there was virtually no change in response to 10 more weeks of treatment. This is highly unusual for antipsychotic trials in schizophrenia (Sherwood *et al*, 2006). Furthermore, the drop-off in serum valproate levels seen after day 14 (Figure 2) is consistent with decreased compliance as subjects left the inpatient

Table 2 Baseline and Mean Change from Baseline to Days 14 and 84 LOCF for Efficacy Variables (Intent-to-Treat Dataset)

Efficacy variable	Antipsychotic monotherapy mean (SE) $N = 198$	Combination therapy mean (SE) $N = 195$[a]	*p*-values
PANSS total			
Baseline	99.1 (1.00)	98.3 (1.03)	0.491
Day 14	−22.2 (1.33)	−20.6 (1.37)	0.307
Day 84	−22.9 (1.59)	−20.5 (1.64)	0.229
PANSS positive			
Baseline	26.7 (0.33)	26.7 (0.34)	0.989
Day 14	−7.3 (0.42)	−6.9 (0.43)	0.473
Day 84	−7.5 (0.50)	−7.2 (0.52)	0.623
PANSS negative			
Baseline	24.4 (0.40)	23.8 (0.41)	0.169
Day 14	−4.8 (0.40)	−3.9 (0.41)	0.085
Day 84	−4.9 (0.44)	−3.9 (0.45)	0.045
PANSS general psychopathology			
Baseline	47.9 (0.54)	47.8 (0.56)	0.811
Day 14	−10.2 (0.71)	−9.7 (0.73)	0.603
Day 84	−10.5 (0.84)	−9.5 (0.87)	0.355
BPRSd			
Baseline	58.1 (0.57)	58.1 (0.59)	0.976
Day 14	−13.9 (0.82)	−13.2 (0.84)	0.457
Day 84	−14.3 (0.97)	−13.2 (1.00)	0.364
CGI severity			
Baseline	5.0 (0.05)	5.0 (0.5)	0.633
Day 14	−1.0 (0.07)	−1.1 (0.07)	0.872
Day 84	−1.2 (0.08)	−1.1 (0.08)	0.725
CGI improvement			
Day 14	2.6 (0.08)	2.7 (0.08)	0.362
Day 84	2.7 (0.10)	2.7 (0.09)	0.720

[a]$N = 194$ for CGI severity.

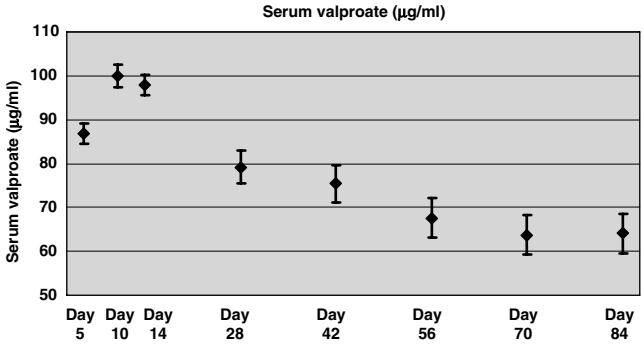

Figure 2 Serum trough valproate levels (µg/ml) mean and SE by Study Day for observed cases. The drop in serum levels on day 14 (after the inpatient phase) suggests decreased compliance in the outpatient phase of the study.

setting. Additionally, the percent of patients completing this study was lower than usual for antipsychotic trials, and was likely influenced by the lengthy period of time that many patients spent as outpatients, during which many extraneous variables may have influenced their participation and/or compliance in the study.

An examination of the efficacy results from the current trial and the similarly designed Casey *et al* (2003) study suggests that the combination therapies led to similar improvements through day 14 (the primary endpoint in this study). Figure 3 illustrates the change from baseline on PANSS total at day 14 for antipsychotic monotherapy and combination therapy for both studies. The striking difference between the studies is the change from baseline for the antipsychotic monotherapy groups. In fact, the difference in change scores for antipsychotic monotherapy across studies is larger than the within-study change scores between the antipsychotic monotherapy and combination therapy groups that led to a statistically significant result in Casey *et al* (2003). Likewise, the responder rates (20% improvement) across studies show that the most profound difference from one study to the next was in the antipsychotic monotherapy group. The combination therapy responder rates at day 14 were similar between the Casey *et al* (2003) study and this study (66 and 65%, respectively); however, the rate of responders in the antipsychotic monotherapy group was 53% in Casey *et al* (2003) *vs* 71% in this study. Taken together, these data suggest the possibility of a greater placebo response in this study, which may have diminished the apparent efficacy of the combination treatment when compared against the monotherapy treatment.

This study did not raise new safety concerns; the addition of divalproex ER to olanzapine or risperidone was associated with known adverse events such as somnolence, weight gain, and decreased platelet count. Consistent with a number of other previous studies across a variety of illnesses (Swann *et al*, 2001; Jafari *et al*, 2002; Beydoun *et al*, 2002; Bowden *et al*, 2006), divalproex ER lowered serum total and LDL cholesterol. This study extended previous findings showing that divalproex mitigates the increase in total cholesterol associated with olanzapine and risperidone (Jafari *et al*, 2003), an effect that remained robust through 12 weeks of combination therapy. Although not statistically significant, it is noteworthy that divalproex ER appeared to lower serum HDL cholesterol in the combination treatment group compared to the antipsychotic monotherapy group.

In conclusion, the lack of a significant efficacy benefit from adding divalproex ER to risperidone or olanzapine in this study contrasts with previous reports of efficacy for valproate combination therapy. Considering the potential for increased safety risks associated with combination treatment and the conflicting data regarding its efficacy, the use of antipsychotic/divalproex ER combination treatment for the treatment of schizophrenia is not strongly supported. Indeed, further studies are required to clarify the

Table 3 Mean Change from Baseline to Final Evaluation for Safety Parameters of Special Interest

Measure	OLZ[a]	OLZ+DVPX[a]	RISP[a]	RISP+DVPX[a]
Platelet count (× 10^9/L)				
Baseline	255.06	248.14	252.23	254.94
Change (SD)	−3.32 (49.15)	−42.34 (45.32)[b]	−3.02 (39.16)	−55.43 (65.24)[b]
SGOT/AST (IU/L)				
Baseline	21.69	20.56	20.62	21.34
Change (SD)	3.88 (14.08)	5.14 (16.48)	1.82 (16.13)	0.96 (12.36)
SGPT/ALT (IU/L)				
Baseline	23.58	21.73	19.88	22.73
Change (SD)	7.73 (28.77)	7.74 (29.95)	4.78 (29.33)	−1.13 (20.18)
Glucose				
Baseline	98.39	98.21	97.90	97.58
Change (SD)	5.17 (29.27)	10.48 (47.00)	6.77 (26.90)	5.04 (39.03)
Triglycerides				
Baseline	172.55	184.54	155.50	155.39
Change (SD)	9.38 (95.02)	16.27 (158.01)	−12.18 (92.47)	14.87 (154.24)
Total cholesterol				
Baseline	198.36	189.06	190.68	193.00
Change (SD)	7.00 (35.71)	5.36 (34.72)	1.32 (33.99)	−5.49 (40.09)
HDL cholesterol				
Baseline	46.79	47.15	48.02	47.00
Change (SD)	−1.79 (10.63)	−2.43 (10.03)	−1.02 (7.86)	−0.96 (9.79)
LDL cholesterol				
Baseline	117.82	108.83	110.66	114.64
Change (SD)	8.02 (32.03)	−0.40 (24.28)[c]	3.68 (28.33)	−5.41 (32.36)[b]
Wt (kg)				
Baseline	88.1	86.7	86.6	89.0
Change (SD)	2.8 (4.38)	4.5 (4.65)[b]	2.0 (3.76)	3.3 (4.54)[b]

[a]Sample sizes range from 94 to 101 for OLZ, 87–99 for OLZ+DVPX, 95–101 for RISP, and from 92 to 99 for RISP+DVPX.
[b]Comparison with monotherapy significant at $p<0.05$.
[c]Comparison with monotherapy $p=0.056$.

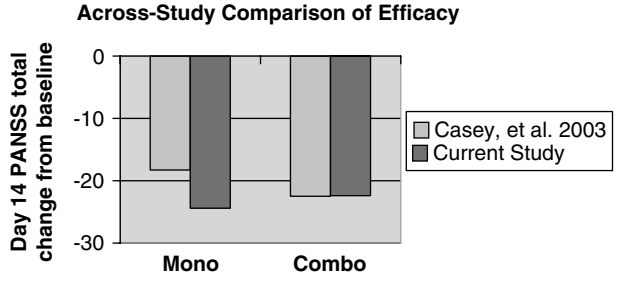

Figure 3 Across-study comparison of efficacy at day 14. The combination therapy groups across the two studies (this study and Casey *et al*, 2003) had identical PANSS total changes at day 14, however, the monotherapy group showed greater improvement in this study.

conflicting efficacy results reported to date and to better define the risk/benefit ratio of adding divalproex ER to olanzapine or risperidone in the treatment of acute schizophrenia.

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