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Effect of Divalproex Combined with Olanzapine or Risperidone in Patients with an Acute Exacerbation of Schizophrenia

Daniel E Casey*[,1], David G Daniel[2,3], Adel A Wassef[4], Katherine A Tracy[5,6], Patricia Wozniak[5] and Kenneth W Sommerville[5]

[1]Portland VA Medical Center, Portland, OR, USA; [2]George Washington University, Washington, DC, USA; [3]Bioniche Development, Falls Church, VA, USA; [4]HCPC-University of Texas, Houston, TX, USA; [5]Abbott Laboratories, Abbott Park, IL, USA; [6]University of Illinois, Chicago, IL, USA

This double-blind, randomized, multicenter study investigated the use of divalproex with an antipsychotic agent in patients hospitalized for acute exacerbation of schizophrenia. Patients ($n = 249$) who met DSM-IV criteria for schizophrenia were randomly assigned to receive olanzapine monotherapy, risperidone monotherapy, divalproex plus olanzapine, or divalproex plus risperidone for 28 days. Divalproex was initiated at 15 mg/kg/day and titrated over 12 days to a maximum dosage of 30 mg/kg/day. Olanzapine and risperidone, were, respectively, initiated at 5 and 2 mg/day and were titrated over the first 6 days to respective target fixed daily dosages of 15 and 6 mg/day. Improvements from baseline were observed at all evaluation points throughout the 28-day treatment period in the two combination therapy and the two antipsychotic monotherapy groups, with statistically significant treatment differences favoring combination therapy as soon as day 3 for Positive and Negative Syndrome Scale (PANSS) total score, derived Brief Psychiatric Rating Scale (BPRSd) total score, as well as PANSS and BPRSd subscales. These findings were confirmed in *post hoc* repeated-measures analyses of variance in which treatment differences favoring combination therapy were observed for PANSS total ($p = 0.020$) and PANSS positive scale scores ($p = 0.002$). Both combination therapy and antipsychotic monotherapy were well tolerated. Treatment with divalproex in combination with an atypical antipsychotic agent resulted in earlier improvements in a range of psychotic symptoms among acutely hospitalized patients with schizophrenia. Further evaluation is warranted to confirm these findings.
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INTRODUCTION

In spite of a large armamentarium of agents available to treat schizophrenia, the treatment of patients with psychotic symptoms remains challenging. The pathophysiology of schizophrenia has long been believed to involve dopamine disturbances, with the effect of conventional antipsychotic agents on positive symptoms of schizophrenia (and inducing extrapyramidal side effects) conferred via inhibition of dopamine receptors (Seeman, 1987). Ongoing research of the biochemical basis of schizophrenia identified a role for serotonin, leading to the development of atypical antipsychotic compounds such as olanzapine and risperidone, which demonstrate both serotonin type 2 (5-HT_2) and dopamine receptor antagonism (Eli Lilly and Company, 2000; Janssen Pharmaceuticals, 1999). Recent attention has been given to the possible involvement of disturbances in γ-aminobutyric acid (GABA) systems as well. The putative involvement of GABA in the pathophysiology of schizophrenia is thought to involve inhibitory effects on dopamine systems. An agent such as divalproex may therefore be useful in schizophrenia via enhancement of GABAergic transmission across synapses, possibly via inhibition of dopaminergic activity in the mesolimbic system and stimulation of dopaminergic activity in the mesoprefrontocortical tract (Wassef *et al*, 1999).

Currently, divalproex is indicated for treatment of mania associated with bipolar disorder, treatment of absence and complex partial seizures, and prophylaxis of migraine. Divalproex is increasingly being used in combination with an antipsychotic in patients with psychotic disorders, with one report citing a near tripling in the percentage of schizophrenic patients being treated with valproate between 1994 and 1998 (Citrome *et al*, 2000). A limited number of studies, primarily open-label in design, support the clinical benefit of divalproex in psychotic disorders (Gundurewa *et*

*Correspondence. DE Casey, Associate Director of Research, VISN 20 MIRECC (Mental Illness Research, Education and Clinical Center), Portland VA Medical Center (P3MIRECC), 3710 SW US Veterans Hospital Road, Portland, OR 97201, USA. Tel: +1 503 220 8262 ext 56477, Fax: +1 503 273 5211, E-mail: daniel.casey@med.va.gov
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al, 1980; Moringo *et al*, 1989; Wassef *et al*, 1989, 2000; Chong *et al*, 1998). In a 21-day double-blind, randomized pilot study of hospitalized patients being treated for acute exacerbation of chronic schizophrenia, the addition of divalproex to haloperidol resulted in greater improvements from baseline on the Clinical Global Impression-Severity (CGI-S) scale ($p \leqslant 0.04$) and the Brief Psychiatric Rating Scale ($p \leqslant 0.007$) than observed with haloperidol monotherapy (Wassef *et al*, 2000). In other double-blind reports, little improvement to worsening of psychotic symptoms was observed in a few chronic schizophrenic patients after treatment with valproate (Ko *et al*, 1985; Dose *et al*, 1998; Hessinger *et al*, 1999). Larger, controlled studies were needed to clarify whether divalproex is of benefit for psychosis related to schizophrenia.

This is the first large-scale, randomized, double-blind study designed to examine the potential incremental benefit conferred by combining divalproex with a commonly used atypical antipsychotic agent (*vs* antipsychotic monotherapy) in patients hospitalized for acute psychosis associated with schizophrenia.

PATIENTS AND METHODS

Patients

Patients between 18 and 65 years of age who were hospitalized with an acute exacerbation of schizophrenia were enrolled. Patients with a current DSM-IV diagnosis of schizophrenia, as confirmed by a Structured Clinical Interview for DSM-IV (SCID) conducted during screening (First *et al*, 1999), were selected for inclusion on the basis of having (a) a Positive and Negative Syndrome Scale (PANSS) total score (Kay *et al*, 1987) of $\geqslant 60$ (based on a 1 to 7-point scale) at the time of screening, (b) scores totaling $\geqslant 8$ on any two of the four items from the psychosis cluster of the BPRS, derived from the PANSS (BPRSd) (Kay *et al*, 1987), that correspond to positive symptoms, that is, hallucinatory behavior, unusual thought content, conceptual disorganization, and suspiciousness, and (c) a total score of $\geqslant 6$ on either hostility and uncooperativeness or excitement and tension. The eligible patient must have had a positive response to treatment with antipsychotics within the 2 years prior to enrollment in this study.

Patients were excluded from the study if they had a current diagnosis of schizoaffective disorder, drug-induced psychosis, manic episode, or depressive episode, as were those who had current serious violent, homicidal, or suicidal ideation. Also excluded from the study were pregnant or lactating females and patients with clinically significant abnormal laboratory data, unstable medical conditions, or an underlying condition that would confound the interpretation of study results.

Study Design

The study was a randomized, double-blind, parallel-group, multicenter trial, consisting of a washout period and a 4-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 legally authorized representative before enrollment into the study.

After written informed consent was obtained, each patient who met entry criteria entered the washout period of the study, which lasted for at least 3 times the mean elimination half-life of the antipsychotic or psychotropic medication that the patient was taking. Patients were then randomized to one of four treatment groups: (a) olanzapine monotherapy (Zyprexa; Eli Lilly and Company), (b) risperidone monotherapy (Risperdal; Janssen Pharmaceuticals); (c) divalproex (Depakote delayed release tablets; Abbott Laboratories) plus olanzapine, or (d) divalproex plus risperidone. Concurrent use of any antipsychotic medication other than the study drugs was not allowed during the study.

Divalproex was initiated on day 1 at 15 mg/kg/day (administered twice daily) and was titrated to clinical response, as deemed appropriate by the investigator, over 12 days (not to exceed maximum dosage of 30 mg/kg/day). Olanzapine and risperidone were initiated at 5 and 2 mg/day, respectively (administered once daily); increased to 10 and 4 mg/day, respectively, on day 3; and increased to a target daily dosage of 15 and 6 mg/day, respectively, on day 6. Once these dosages were achieved, they were to be continued for the remainder of the study. The investigators were instructed to discontinue the participation of any patient who could not tolerate the fixed target dosages of olanzapine or risperidone.

Certain adjunctive medications were allowed as needed during the washout and treatment periods, although not within 8 h prior to efficacy ratings. Chloral hydrate (up to 2 g/day) or zolpidem tartrate (up to 10 mg/day) could be used for the control of insomnia. Lorazepam (up to 6 mg/day during the washout phase, up to 4 mg/day during weeks 1 and 2 of the treatment period, and up to 2 mg/day during week 3 of the treatment period) was permitted for control of severe agitation. The use of chloral hydrate, lorazepam, and zolpidem tartrate was prohibited during week 4. Propranolol HCl (according to the investigator's discretion) could be prescribed for akathisia, and benztropine mesylate (up to 4 mg/day) could be prescribed for control of extrapyramidal symptoms.

Patients were required to remain hospitalized for 28 days; however, leave from the hospital was allowed for up to 7 days, provided the patient completed the 2-week dosage titration phase and had a CGI-Improvement (CGI-I) score of 'much improved' after day 14. Patients on leave from the hospital were required to return to the study site for the regularly scheduled assessments, ratings, and procedures.

Clinical Evaluations

The protocol-defined psychiatric status of patients was evaluated using the PANSS total and subscales and the CGI scale (Guy 1976). The evaluations were conducted on days 1 (baseline), 3, 5, 7, 10, 14, 21, and 28. The PANSS was scored as the patient had appeared over the previous 48 h. The raters' proficiency had to meet pre-established criteria before the study commenced, and an interim assessment was conducted during the trial to assure the proficiency of the raters.

Safety Assessment

The data obtained to evaluate the safety of the study drugs included physical examinations, vital sign and body weight measurements, adverse events, and laboratory test results. Extrapyramidal side effects were assessed during the double-blind treatment period using a movement rating scale battery, including the Simpson–Angus Scale (SAS) (on days 1, 14, and 28) (Simpson and Angus, 1970), the Barnes Akathisia Scale (BAS) (on days 1, 14 and 28) (Barnes, 1989), and the Abnormal Involuntary Movement Scale (AIMS) (days 1 and 28) (Guy, 1976). Patients were monitored for adverse events between the time study drug was initiated and 30 days after the discontinuation of therapy, inclusive. Plasma concentrations of valproate were evaluated on day 28.

Statistical Analyses

The primary objective of this study was to evaluate the efficacy and safety of divalproex in the treatment of schizophrenia when combined with an atypical antipsychotic, with change from baseline to final evaluation on the PANSS total score being the primary efficacy end point.

All statistical tests were two-tailed, and p-values of 0.050, after rounding to three decimal places, were considered statistically significant. All analyses were performed with the SAS System (version 6.12; SAS Institute, Cary, NC).

The two antipsychotic monotherapy groups were combined, as were the two combination therapy groups, for comparisons of baseline characteristics and efficacy parameters. A target sample size of 120 patients each for the combined antipsychotic monotherapy group and the combined combination therapy group was selected to provide 80% power for an effect size of 0.362 and 90% power for an effect size of 0.418.

Efficacy analyses were performed on the intent-to-treat data set, which included all patients who received at least one dose of randomized study medication and had a PANSS total score recorded at baseline and at least once during treatment. To address missing evaluations, a 'last observation carried forward' analysis was performed. This technique was used to reduce bias caused by patients who prematurely discontinued for lack of efficacy.

Baseline comparability between the combination and antipsychotic monotherapy groups for demographic characteristics was assessed by one-way analysis of variance (ANOVA) with treatment group as the main effect for quantitative variables (age, weight) and by Fisher's exact test for qualitative variables (gender, race). For statistical testing, race was categorized as Caucasian and non-Caucasian. For psychiatric history variables, baseline comparability between treatment groups was assessed by the Wilcoxon rank sum test (age at first diagnosis), by the Cochran–Mantel–Haenszel test (lifetime number of hospitalizations, number of suicide attempts), and by Fisher's exact test (schizophrenia subtype). Baseline comparability among treatment groups for all efficacy and movement rating scale scores was assessed by two-way ANOVA with factors for treatment group and investigator. Treatment differences (combination therapy *vs* antipsychotic monotherapy) in the percentage of patients prematurely discontinuing from the study were assessed by Fisher's exact test both for overall and for each individual item.

Comparisons of the combination and monotherapy groups were made for mean trough total valproic acid plasma concentrations using a mixed effects model (with effects for treatment group, visit, treatment group by visit interaction, study center, age, and weight).

Treatment differences in the percentage of patients who were granted hospital leave and the percentage of patients using adjunctive medication were assessed by Fisher's exact test. Treatment differences in the number and percentage of days each medication was prescribed and in the average daily dose of each medication were evaluated by a one-way ANOVA.

Treatment differences in the mean change from baseline to each evaluation for the PANSS total score and subscales, BPRSd total score and subscales, the supplemental anger item from the PANSS, and the CGI-S score were assessed using a two-way ANOVA with factors for treatment and investigator. Because there were baseline differences for PANSS positive scale score and the PANSS individual item of delusions, an analysis of covariance (ANCOVA) with factors for treatment and investigator and with baseline as the covariate was performed. A *post hoc* repeated-measures ANOVA was also performed on observed cases data using PROC MIXED with fixed-effect factors for scheduled visit day, treatment, and investigator, and an AR(1) covariance structure. Treatment differences in the percentage of patients with at least a 20 and 30% improvement from baseline to final evaluation on the PANSS total score at each scheduled visit were assessed by the Cochran–Mantel–Haenszel test, with investigators as strata.

For change from baseline to final value on the PANSS total score, ANOVA was performed with factors for investigator, study drug (divalproex *vs* placebo), type of antipsychotic (olanzapine *vs* risperidone), and the interaction between study drug and antipsychotic. The test of interaction provided a test of the validity of combining treatment groups for the efficacy analyses.

Safety analyses were performed for all patients who received at least one dose of randomized study medication. Because of the differing safety profiles of olanzapine and risperidone, safety data for each antipsychotic monotherapy group were compared with those of the corresponding divalproex plus antipsychotic group. Fisher's exact test was used to assess treatment group differences in treatment-emergent adverse event incidence rates. Treatment differences in mean change from baseline to final evaluation for the movement rating scales (SAS, BAS, AIMS) were assessed by a two-way ANOVA with factors for treatment and investigator. Treatment differences in laboratory data and vital signs (including weight) for mean change from baseline to the final evaluation were assessed by one-way ANOVA.

RESULTS

A total of 249 patients were randomized at 29 investigative sites. Of these patients, 65 received olanzapine, 66 received divalproex plus olanzapine, 60 received risperidone, and 58 received divalproex plus risperidone. Of the 249 enrolled patients, 242 patients were included in the intent-to-treat

analyses of efficacy, with 4 excluded because they did not have an on-treatment PANSS score and 3 excluded because they were randomized at two sites (only their second randomization was excluded from the efficacy analyses).

The treatment groups were similar at baseline based on demography, schizophrenia subtype, age at first diagnosis, number of past hospitalizations, and the number of suicide attempts (Table 1). The mean age of the intent-to-treat study population was 38.8 years (range: 18–63 years). The majority were male (76%), and there was an equal distribution between Caucasians (46%) and blacks patients (49%). Most patients had a history of paranoid schizophrenia (82%); 56% were hospitalized six or more times for their schizophrenia, and 46% made at least one suicide attempt. At the time of their enrollment in the study, 214 patients (88%) were treated with one or more antipsychotics, including 78 patients (32%) with olanzapine and 81 patients (33%) with risperidone. The mean baseline PANSS score was 100 and 103 for patients in the antipsychotic monotherapy and combination therapy groups, respectively, with no significant difference between treatment groups.

A total of 83 (33%) patients prematurely discontinued their participation in the study, the most common reason being consent withdrawn (25 (20%) patients given antipsychotic monotherapy and 12 (10%) patients given combination therapy, $p \leqslant 0.05$). Seven patients (3 (2%) patients in the antipsychotic monotherapy group and 4 (3%) patients in the combination therapy group) discontinued their participation in the study because of treatment-emergent adverse events, as did 16 patients (6 (5%) and 10 (8%) patients in the respective treatment groups) for lack of

Table 1 Baseline Demographic and Clinical Characteristics of Intent-to-Treat Patients[a]

Characteristic	Antipsychotic monotherapy ($n = 120$)	Combination therapy ($n = 122$)
Gender, *n* (%)		
Female	29 (24%)	29 (24%)
Male	91 (76%)	93 (76%)
Race, *n* (%)		
Caucasian	54 (45%)	57 (47%)
Black	63 (53%)	56 (46%)
Other	3 (2%)	9 (7%)
Age (years)		
Mean ± SD	39.3 ± 10.5	38.3 ± 9.9
Range	18–60	19–63
Weight (lb)		
Mean ± SD	85.4 ± 18.5	86.2 ± 20.5
Range	54.5–138.8	50.3–149.2
Schizophrenia subtype		
Paranoid	97 (81%)	101 (83%)
Disorganized	8 (7%)	4 (3%)
Undifferentiated	15 (13%)	17 (14%)
Age at first diagnosis (years)		
Mean ± S.D.	25.0 ± 8.9	24.0 ± 7.8
Range	12–55	6–48
Lifetime number of hospitalizations		
Never	1 (<1%)	2 (2%)
1–5	55 (46%)	48 (39%)
6–10	28 (23%)	27 (22%)
>10	36 (30%)	45 (37%)
Number of suicide attempts		
0	63 (53%)	69 (57%)
1–5	53 (44%)	48 (39%)
>6	4 (3%)	5 (4%)
Mean PANSS Total score	100	103
Mean PANSS Positive Scale score	25.8	26.9
Mean PANSS Negative Scale score	25.2	26.0
Mean PANSS General Psychopathology Scale Score	49.1	50.1
Mean BPRSd Total Score	58.7	60.6
Mean CGI-S	4.8	4.8

[a]$p > 0.05$ for all comparisons, except PANSS Positive Scale score ($p = 0.04$).

Table 2 Mean (± SD) Daily Dose of Antipsychotic Agent by Study Day and Treatment Group

	Olanzapine		Divalproex/Olanzapine		Risperidone		Risperidone/Divalproex	
Study day	***n***	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean (SD)**	***n***	**Mean (SD)**
1–2	64	5.00 (0.00)	65	5.04 (0.31)	59	2.00 (0.00)	57	2.04 (0.26)
3–5	60	10.08 (057)	64	9.87 (0.95)	55	3.99 (0.20)	57	4.00 (0.18)
⩾6	57	14.98 (0.13)	62	14.90 (0.65)	51	5.99 (0.03)	55	5.99 (0.03)

efficacy. No statistically significant between-group differences were noted for overall premature discontinuation rates or premature discontinuation rates because of treatment-emergent adverse events or lack of efficacy.

The frequency with which patients left the hospital during the study was similar among the treatment groups. One-third of the patients (32% in the monotherapy group and 35% in the combination therapy group) had leave from the hospital during the study (mean hospital leave length of 4.2 and 4.9 days, respectively).

Dosing of Study Drugs and Adjunctive Medications

Most patients received the targeted therapeutic daily dosages of olanzapine (15 mg/day) and risperidone (6 mg/day) (Table 2). For olanzapine, 96% of patients in the monotherapy group and 95% of patients in the combination therapy group received the maximum dose by day 6. For risperidone, 94% of patients in the monotherapy group and 96% of patients in the combination therapy group received the maximum dose by day 6.

In the olanzapine and risperidone combination therapy groups, the mean modal daily dose of divalproex was 2364 mg (range: 500 –3500 mg) and 2259 mg (range: 1000 – 3500 mg), respectively, resulting in final (day 28) mean trough total valproic acid plasma levels of 98.2 ± 31.4 μg/ml with olanzapine ($n = 23$ samples) and 100.2 ± 22.1 μg/ml with risperidone ($n = 21$ samples) ($p =$ ns).

The use of adjunctive rescue medications (ie lorazepam, chloral hydrate, zolpidem, benztropine mesylate, and propranolol) during the study, including dosage (mg/day), number of days used, and percentage of patients using rescue medications, was similar among the treatment groups. Just over two-thirds (171/242) of the patients used at least one of these adjunctive medications during their participation in the study, including the use (at least one time) of lorazepam by 50% of patients (for a mean of 5.6 days) for agitation, propranolol by 8% of patients for akathisia, and benztropine mesylate by 19% of patients for extrapyramidal symptoms.

Efficacy Results

PANSS total scores decreased (improved) throughout the 28-day treatment period in both the combination therapy and antipsychotic monotherapy groups (Figure 1a). Statistically significant treatment differences in change from baseline PANSS total score favoring combination therapy were observed as early as the third treatment day and persisted through day 21 ($p \leqslant 0.05$ at days 3, 5, 14, and 21 and $p < 0.01$ at days 7 and 10). At day 28, the same trend ($p = 0.108$) was observed (mean change from baseline: −21.2, antipsychotic monotherapy and −25.1, combination). The change in effect size and variability over time are shown in Figure 2. *Post hoc* repeated-measures ANOVA of the change from baseline scores demonstrated a statistically significant treatment difference favoring combination

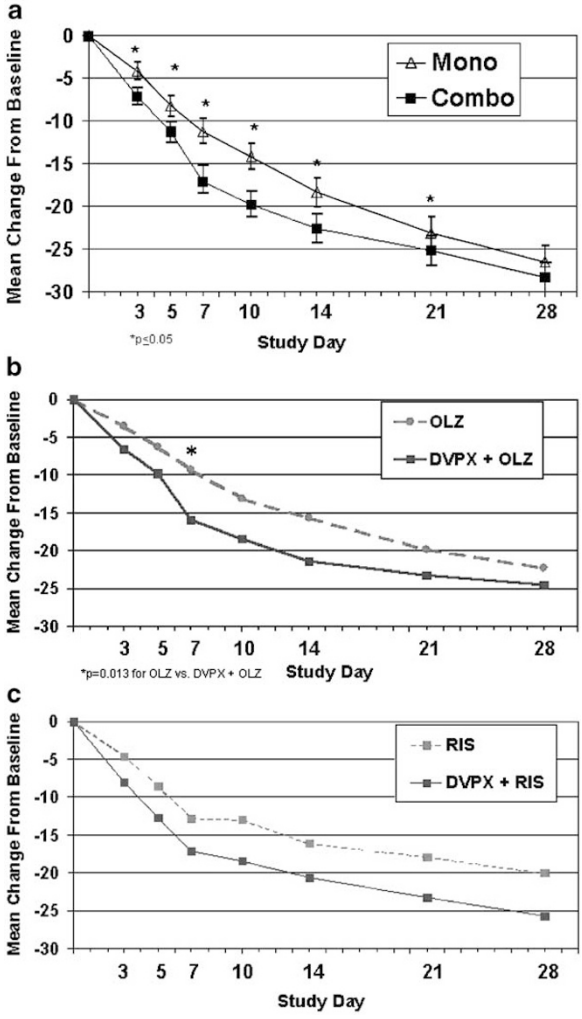

Figure 1 (a) Comparison of antipsychotic monotherapy (olanzapine or risperidone) *vs* combination therapy (divalproex plus olanzapine or risperidone) for mean change from baseline to each evaluation for PANSS total score. A statistically significant ($p \leqslant 0.05$) treatment effect in change from baseline PANSS total score favoring combination therapy was observed at days 3, 5, 7, 10, 14, and 21. (b) Comparison of olanzapine (OLZ) with and without divalproex (DVPX) for mean change from baseline to each evaluation for PANSS total score. * $p = 0.013$ for OLZ *vs* DVPX+OLZ. (c) Comparison of risperidone (RIS) with and without divalproex (DVPX) for mean change from baseline to each evaluation for PANSS total score.

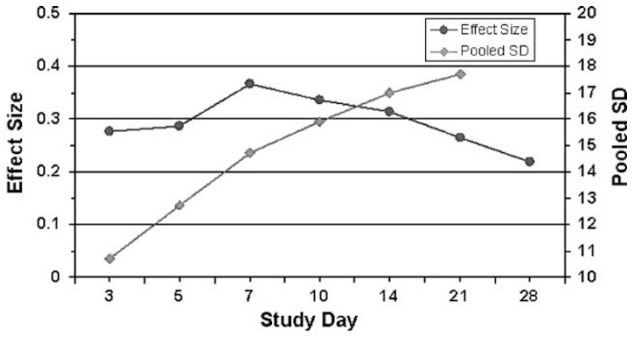

Figure 2 Changes in effect size and variability over time for PANSS total score. While a treatment difference was maintained throughout the study, the effect size decreased over the course of the study, most likely because of increased variability.

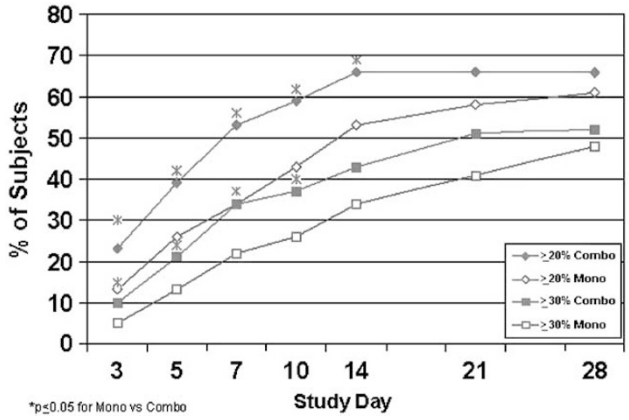

Figure 3 Percentage of patients with ⩾20 or ⩾30% improvement in PANSS total score. Clinical improvement, defined as a ⩾20 or ⩾30% reduction from baseline in PANSS total score, was consistently observed in a higher proportion of patients in the divalproex plus antipsychotic combination therapy group compared with the antipsychotic monotherapy group, with statistically significant ($p \leqslant 0.05$ for Mono *vs* Combo) treatment differences observed as early as the third treatment day.

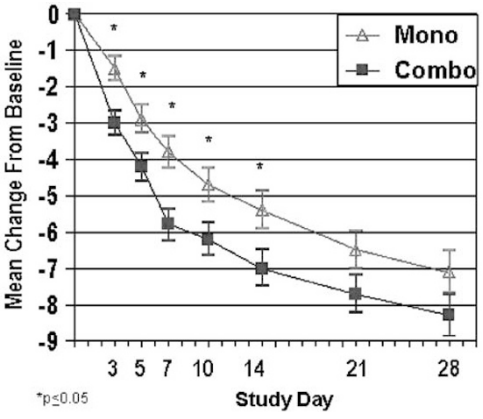

Figure 4 Mean change from baseline to each evaluation for PANSS positive scale score. Improvements favoring divalproex plus antipsychotic combination therapy were observed across all the evaluation points for mean PANSS positive scale score, with statistically significant ($p \leqslant 0.05$, ANCOVA) treatment differences observed on days 3, 5, 7,10, and 14.

therapy over antipsychotic monotherapy throughout the 28 days of the study for the PANSS total score ($p = 0.020$).

In the ANOVA model (which included factors for investigator; study drug, divalproex *vs* placebo; type of antipsychotic, olanzapine *vs* risperidone; and the interaction between study drug and type of antipsychotic), the interaction term was not statistically significant, indicating that the effect of divalproex on PANSS total scores was similar when added to either antipsychotic agent (Figures 1b and c) and supporting the validity of combining the two combination treatments and the two antipsychotic treatments for ANOVA analysis.

Clinical improvement, defined as a ⩾20 or ⩾30% reduction from baseline in PANSS total score, was consistently observed in a higher proportion of patients in the combination therapy group compared with the antipsychotic monotherapy group ($p \leqslant 0.05$ on days 3, 5, 7, and 10 for the ⩾20% and ⩾30% thresholds and on day 14 for ⩾20% only) (Figure 3). A 20% or greater improvement in PANSS total score was observed in 53% of patients in the combination group on day 7, but not until day 14 in the antipsychotic monotherapy group.

Improvements favoring combination therapy were also observed across all the evaluation points for mean PANSS positive scale score (Figure 4). An ANCOVA showed statistically significant treatment differences at days 3, 5, and 7. Improvements in the mean PANSS general psychopathology scale score ($p < 0.05$ at days 5, 7, 10, and 14) and the PANSS supplemental anger item ($p < 0.05$ at days 3 and 7) favoring combination therapy were also noted. The PANSS negative scale showed little treatment difference ($p < 0.05$ at day 10). *Post hoc* repeated-measures ANOVA demonstrated a statistically significant treatment difference favoring combination therapy over antipsychotic monotherapy throughout the 28 days of the study for the PANSS positive scale score ($p = 0.002$) and the PANSS supplemental anger item ($p = 0.02$), but not the PANSS negative scale score ($p = 0.167$). Furthermore, statistically significant treatment differences favoring the combination group over the antipsychotic monotherapy group were observed at three or more evaluation points for several PANSS individual items, including delusions (days 3, 7, 10, and 14 (ANCOVA)), excitement (days 3, 7, 10, and 14), difficulty in abstract thinking (days 5, 7, 10, and 28), unusual thought content (at all evaluation points), and lack of judgment and insight (days 5, 7, and 10). Statistically significant treatment differences for other PANSS items, such as grandiosity, either did not reach the level of statistical significance or did so at a minority (⩽2) of evaluation points during the study.

Results of the BPRSd total and subscale scores were consistent with those from the PANSS. Statistically significant treatment differences favoring the combination therapy group were noted at several evaluation points for BPRSd total (days 3, 5, 7, 10, and 14), positive symptoms (days 3, 5, and 7), and agitation (days 7 and 14) scores. At day 28, a numerical, but not a statistically significant, difference was also noted. A *post hoc* repeated-measures ANOVA demonstrated a statistically significant difference favoring combination therapy over antipsychotic monotherapy throughout the 28 days of the study for BPRSd total ($p = 0.027$), positive symptoms ($p = 0.022$), and agitation ($p = 0.023$) scores.

Statistically significant treatment differences were generally not observed for either CGI-S or CGI-I scores. For both combination and antipsychotic monotherapy, mean CGI-S scores decreased (improved) about one point from baseline at the end of the 28-day study, reflecting a change from 'markedly mentally ill' to 'moderately ill.'

Safety Results

Seven patients (3%) discontinued their participation in the study because of treatment-emergent adverse events. These included two patients each in the olanzapine group (because of abnormal liver function tests results and asthma), the divalproex plus olanzapine group (hyperglycemia and rash) and the divalproex plus risperidone group (dyspepsia and flank pain (muscle strain offered as a likely etiology for the latter)) and one patient in the risperidone group (somnolence and hypotension).

There were no treatment group differences for overall incidence of treatment-emergent adverse events (Table 3). Most adverse events were mild or moderate in severity. Across the treatment groups, the most commonly reported treatment-emergent adverse event was somnolence (29% of patients), followed by headache (20%), dyspepsia (18%), and weight gain (12%).

Seven patients reported a serious adverse event, all of which were judged by the investigators to be not related or probably not related to the study drug. All of the serious adverse events occurred after the termination of study drug, with the exception of one episode of chest pain, which began on day 21 (with associated ECG changes in a patient with coronary artery disease) and resolved the next day. The serious adverse events were psychosis (one patient each in the olanzapine, divalproex plus olanzapine, and divalproex plus risperidone groups); suicide attempt (one patient in the olanzapine group); lung carcinoma, chest pain (one patient in the divalproex plus olanzapine group); and schizophrenic reaction (one patient in the divalproex plus risperidone group).

In the analyses of movement rating scores (ie SAS, BAS, and AIMS), no statistically significant differences between the combination and the antipsychotic treatment groups were noted for the mean change from baseline to the final evaluation. Scores were generally low at baseline and showed little change during the study.

Increases from baseline to the final evaluation were observed across the treatment groups for body weight: +3.50 kg (+7.7 lb), +3.74 kg (+8.3 lb), +1.90 kg (+4.2 lb), and +3.40 kg (+7.5 lb) among patients in the olanzapine, divalproex plus olanzapine, risperidone, and divalproex plus risperidone groups, respectively (no difference between olanzapine *vs* divalproex plus olanzapine; $p<0.05$ for risperidone *vs* divalproex plus risperidone). There were no statistically significant treatment differences for the percentage of patients experiencing a weight gain of $\geqslant 7\%$ from baseline when each antipsychotic agent was compared with its respective combination treatment group (15 (23%) olanzapine, 16 (24%) divalproex plus olanzapine, 8 (13%) risperidone, and 15 (26%) divalproex plus risperidone).

When each pair of combination and antipsychotic monotherapy groups was compared for mean change from baseline to final value for hematology and clinical chemistry indices, several statistically significant and potentially clinically significant treatment differences were observed (Table 4). A decrease in the platelet count was observed in both combination therapy groups. In all, 6% of patients had a baseline platelet value that was either above or within the reference range, and a final value that was below the lower limit of the reference range ($<140\times10^9$/l for those 12 –59 years old and $<130\times10^9$/l for those $\geqslant 60$ years old); however, there were no associated adverse events of bleeding or bruising. Five patients in the olanzapine group and one patient in the divalproex plus risperidone group had at least one SGPT/ALT value measured during the study that was between three and five times the upper limit of the reference range; one patient in the olanzapine group had an SGPT/ALT value (220 IU/l) that was greater than five times the upper limit of normal. Although elevations in liver enzymes were noted in some patients, there were no reports of hepatitis, jaundice, or hepatic failure. For cholesterol, a mean increase from baseline was observed with antipsychotic monotherapy, whereas virtually no change from

Table 3 Treatment-Emergent Adverse Events Occurring in $\geqslant 10\%$ of Patients in any Treatment Group or that were Statistically Significantly Different between Groups

Event	Olanzapine ($n=65$)	Divalproex + Olanzapine ($n=66$)	Risperidone ($n=60$)	Divalproex + Risperidone ($n=58$)
Any adverse event	48 (74%)	53 (80%)	47 (78%)	52 (90%)
Somnolence	16 (25%)	25 (38%)	13 (22%)	17 (29%)
Headache	9 (14%)	10 (15%)	15 (25%)	16 (28%)
Dyspepsia	11 (17%)	9 (14%)	11 (18%)	14 (24%)
Weight gain	9 (14%)	9 (14%)	5 (8%)	6 (10%)
Pain	7 (11%)	7 (11%)	11 (18%)	4 (7%)
Constipation	5 (8%)	4 (6%)	12 (20%)	2 (3%)*
SGPT increased	5 (8%)	0 (0%)*	0 (0%)	1 (2%)
Nausea	5 (8%)	3 (5%)	9 (15%)	11 (19%)
Anxiety	3 (5%)	2 (3%)	7 (12%)	2 (3%)
Asthenia	3 (5%)	7 (11%)	4 (7%)	4 (7%)
Dizziness	3 (5%)	9 (14%)	7 (12%)	7 (12%)
Vomiting	3 (5%)	5 (8%)	8 (13%)	5 (9%)
Rhinitis	2 (3%)	2 (3%)	8 (13%)	1 (2%)*

*$p<0.05$ for olanzapine *vs* divalproex and olanzapine or risperidone *vs* divalproex and risperidone.

Table 4 Mean Change From Baseline to Final Evaluation for Laboratory Variables of Special Interest

Analyte	Olanzapine ($n=58$)	Divalproex + Olanzapine ($n=61$)	Risperidone ($n=56$)	Divalproex + Risperidone ($n=54$)
Platelets ($\times 10^9$/l)				
Baseline mean	261.26[a]	258.72	252.83[b]	257.65
Mean change to final	5.61	−48.49**	−13.74	−48.43**
Glucose (mg/dl)				
Baseline Mean	111.81	104.41	100.61	96.11
Mean change to final	6.40	9.89	3.79	9.39
SGOT/AST (IU/l)				
Baseline Mean	23.83	24.15	20.96	20.37
Mean change to final	6.88	−2.61**	1.39	−2.5
SGPT/ALT (IU/l)				
Baseline mean	27.07	27.80	19.98	22.56
Mean change to final	20.67	−4.02**	6.20	−5.39*
Cholesterol (mg/dl)				
Baseline mean	192.74	198.28	187.98	192.06
Mean change to final	26.62	0.87**	9.64	−13.44**

[a]$n=57$. [b]$n=53$. *$p<0.05$ for risperidone *vs* divalproex and risperidone; **$p<0.001$ for olanzapine *vs* divalproex and olanzapine or risperidone *vs* divalproex and risperidone.

baseline was observed with divalproex plus olanzapine and a small decrease from baseline was observed with divalproex plus risperidone.

DISCUSSION

This is the first large, multicenter, prospective, double-blind study examining the use of divalproex in combination with an antipsychotic agent in the treatment of schizophrenia. Based on the results from multiple, validated instruments for measuring efficacy of drugs in schizophrenia, divalproex consistently contributed to the treatment effects of the antipsychotic agents. Significant reductions in the severity of schizophrenia symptoms, as measured by PANSS and BPRSd total scores and PANSS and BPRSd positive scores, were observed beginning as early as the third treatment day, and further improvements were noted throughout the 28-day trial. These findings were consistent with those from *post hoc* repeated-measures ANOVA, in which a statistically significant treatment difference favoring combination therapy *vs* antipsychotic monotherapy over the 28 days of the study was observed for the PANSS and BPRSd total and positive scale scores. The improvements in the olanzapine and risperidone monotherapy PANSS total score observed in this study are consistent with those published by others who directly compared olanzapine and risperidone monotherapy for schizophrenia or schizoaffective disorders (Tran *et al*, 1997; Conley and Mahmoud, 2001). The baseline value and change from baseline for the CGI-S score with antipsychotic monotherapy in this study were also similar to those observed by others (Tran *et al*, 1997).

Importantly, the current study demonstrated that divalproex combination treatment improved core positive symptoms of psychosis, including individual symptoms such as delusions, unusual thought content, excitement, and difficulty in abstract thinking. Furthermore, when considering all of the efficacy measurements, the divalproex combination treatment group consistently showed numerically greater improvement compared with the monotherapy group.

Evidence for an acceleration of response with combination therapy is supported by the clinical improvement analyses. For instance, a 20% or greater improvement in the PANSS total score was observed by the seventh treatment day in 53% of patients in the combination group, compared with 34% of patients in the antipsychotic monotherapy group. Not until treatment day 14 did 53% of patients in the antipsychotic monotherapy group show at least 20% improvement in their PANSS total score. Early improvement in symptoms of psychosis is important in the acute management and stabilization of patients with schizophrenia. The findings from this trial have potential benefits related to patient safety and compliance and to earlier hospital discharge. The latter is suggested by Wassef *et al* (2001), who showed that early augmentation of haloperidol with divalproex in patients with schizophrenia led to not only significantly improved therapeutic outcomes (ie decreases in BPRS) but also a 45% decrease in length of hospitalization, as compared with haloperidol monotherapy (12.6 days *vs* 22.8 days, $p=0.002$). In contrast to the studies of Wassef *et al* (2000, 2001) and the report of Citrome *et al* (2000), which suggest the use of divalproex as an add-on agent to antipsychotic therapy, the current study initiated divalproex and the antipsychotic agent simultaneously. Such a change in methodology may, in part, account for the early detection of treatment differences.

No unexpected safety concerns were identified during the course of this study. Combination therapy was as well tolerated as antipsychotic monotherapy. Seven patients discontinued the study prematurely because of treatment-

emergent adverse events; premature discontinuation rates were similar among the treatment groups. Adverse events were generally mild or moderate in severity and were consistent with those commonly associated with the individual study drugs.

Mean weight gain was observed across the treatment groups, which was expected based on previous experience with conventional as well as atypical antipsychotic agents and mood stabilizers. Overall, the observed changes in laboratory values were expected. Based on the experience of this 4-week trial, transaminase (ie SGOT and SGPT) and total cholesterol levels tended to be elevated with antipsychotic monotherapy, but were unchanged or decreased in the combination therapy groups. Others have documented statistically significant reductions (*vs* control) in total cholesterol and low-density lipoprotein (LDL) cholesterol among patients treated with valproic acid (Heldenberg *et al*, 1983; Calandre *et al*, 1991; Franzoni *et al*, 1992; Eiris *et al*, 1995) Results from animal studies suggest that valproic acid modifies cholesterol metabolism by enhancing hepatic peroxisomal β-oxidation (Horie and Suga, 1985). The clinical significance of these findings merits further study. The observed dose-related reduction of platelet count with divalproex has been well documented (Gidal *et al*, 1994).

The mechanism whereby divalproex affects psychotic symptoms, as observed in this trial, is unknown. The benefits of combination therapy with divalproex and either olanzapine or risperidone seem unlikely to be attributable to a simple pharmacokinetic interaction. Studies have suggested that valproate may have little to no clinically significant effect on the plasma concentrations of antipsychotic agents, such as clozapine and risperidone (Facciola *et al*, 1999; Spina *et al*, 2000). Nor does the therapeutic effect observed in this trial appear to be the result of a nonspecific sedating effect of divalproex. The incidence of somnolence with divalproex plus antipsychotic combination therapy was similar to that with antipsychotic monotherapy, suggesting that the improvements resulting from the addition of divalproex were probably not from increased sedation. Furthermore, since schizoaffective patients were excluded from this study, improvements in psychotic symptoms did not appear to result from antimanic effects of divalproex.

The mechanism by which divalproex exerts therapeutic effects in epilepsy and the manic phase of bipolar disorder has not been established. Discussion, however, often centers on the early observation that divalproex elevates GABA levels in the central nervous system (Goden *et al*, 1969). The GABA system appears to be an appropriate area for speculation with respect to its apparent effects on symptoms of schizophrenia, as well.

A preliminary but growing body of literature suggests a role for GABA in the pathophysiology of schizophrenia. GABAergic interneurons exert both inhibitory and disinhibitory modulation of cortical and hippocampal circuits involving gating of sensory mechanisms, discriminative information processing, and other functions that are abnormal in schizophrenia (Benes and Berretta, 2001). An increasing body of post-mortem data is consistent with abnormalities in the GABA system in cortical and subcortical areas of relevance to schizophrenia. Recent examples include abnormalities of GABA synthesis and reuptake in the prefrontal cortex (Volk *et al*, 2001), and loss of GABAergic interneurons (Reynolds *et al*, 2001). Of specific relevance to the amelioration of symptoms of schizophrenia is the apparent role of GABA in modulating dopaminergic activity in the mesocortical and mesolimbic dopaminergic tracts (see Garbutt and van Kammen (1983), Preisendorfer *et al* (1987), and Wassef *et al* (1999) for a review).

Meltzer *et al* (2001) recently reported on valproate potentiation of atypical antipsychotic-induced dopamine release in the medial prefrontal cortex in rats. In theory, a modulatory influence of GABA on these circuits could augment the effects of an antipsychotic on both positive and negative (deficit) symptoms of schizophrenia. GABA is largely an inhibitory neurotransmitter that plays a key role via interneurons in modulating dopaminergic and other neurotransmitter activity within the cortico-striatal-thalamic pathway (Egan and Hyde, 1999). If abnormalities in the GABA system do play a role in the pathophysiology of schizophrenia, the apparent adjunctive utility of divalproex in combination with an antipsychotic may stem from its enhancement of GABA activity at the synapse secondary to inhibition of GABA transaminase. These findings lend additional support to the results of the current clinical trial and suggest that divalproex may have a unique mechanism of action in the treatment of schizophrenia.

Several elements may limit the interpretation of the data from this study. Firstly, although compelling treatment differences favoring divalproex combination therapy over monotherapy with an atypical antipsychotic agent were observed at all evaluation points, the treatment difference for mean change from baseline to day 28 in PANSS total scores did not reach the level of statistical significance. Although the reasons for this are not entirely clear, there are several potential contributing factors. While the mean treatment difference was maintained throughout the study, the effect size decreased over the course of the study, most likely because of increased variability (Figure 2). Regression to the mean (a possible natural improvement in symptoms) may have also contributed. Secondly, optimal dosing is critical to the interpretation of study results. The targeted dosages of both olanzapine and risperidone received by patients who participated in this study are consistent with those approved by the Food and Drug Administration (Eli Lilly and Company, 2000; Janssen Pharmaceuticals, 1999), with those used in recent direct comparisons of the atypical antipsychotic agents (Tran *et al*, 1997; Conley and Mahmoud, 2001), and in some large outcome studies (Kasper *et al*, 2001) but not others (Edgell *et al*, 2000).

This study specifically investigated divalproex combination treatment in patients with acute exacerbation of schizophrenia. Notably, patients with schizoaffective disorder, drug-induced psychosis, and manic or depressive disorder were excluded from this study in order to distinguish the mood-stabilizing effects of divalproex from its effects in psychosis. Extrapolation of the positive results of this study to the general population of patients with psychosis should be done with careful consideration.

Finally, the results of this trial must be interpreted in the context of an acute (28 day) treatment trial. Data regarding the use of divalproex plus antipsychotic combination therapy beyond 4 weeks are still lacking. It is unknown

whether the efficacy results observed in this study will be sustained, increased, or diminished over longer periods of follow-up. The adverse events associated with the use of divalproex plus antipsychotic combination treatment beyond the 4-week period of this study are also unknown. Future trials are warranted to investigate the safety and efficacy of long-term use of divalproex in combination with antipsychotic agents.

In summary, this study demonstrated that combination therapy with divalproex plus either olanzapine or risperidone improved PANSS total and positive scores compared with antipsychotic monotherapy. This enhanced response was seen as early as day 3 of treatment. Furthermore, over the 28-day course of this trial, combination therapy with divalproex was as well tolerated as antipsychotic monotherapy. Taken together, these findings suggest that combination treatment with divalproex plus an atypical antipsychotic agent may have advantages for patients with acute exacerbation of schizophrenia. Further studies are warranted to confirm the findings of this study.

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