Safety and Efficacy of Switching Psychiatric Patients from a Delayed-Release to an Extended-Release Formulation of Divalproex Sodium

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Abstract: This study evaluated the safety and efficacy of divalproex sodium extended-release (ER) when patients were switched from therapy with divalproex sodium delayed-release (DR) to divalproex sodium ER. This open-label, 7-day study included 55 patients with bipolar disorder, major depression, schizophrenia, schizoaffective disorder, Alzheimer's disease, dementia, or intermittent explosive disorder. Baseline plasma valproate concentrations were determined, and patients received their usual morning dose of divalproex sodium DR. At 9:00 p.m. the same day, they received divalproex sodium ER at a dose equal to their total daily dose of divalproex sodium DR. Valproate concentrations were monitored, and efficacy was measured with the Positive and Negative Syndrome Scale (PANSS). Side effects were assessed using the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale. Valproate concentrations for 52 patients remained within the therapeutic range. Inpatient PANSS scores significantly improved from baseline to final evaluation on all subscales. For the combined inpatient and outpatient populations, a small but statistically significant improvement from baseline to final evaluation was seen for positive, general, and total PANSS subscale scores. At study's end, patients reported a significant decrease in the number and severity of adverse events; 54 of 55 patients elected to continue therapy with once-daily divalproex sodium ER. This study suggests that divalproex sodium ER is at least as effective as the DR formulation for treating patients with psychiatric illness and may be better tolerated. The ER formulation offers the advantage of once-daily dosing, which may help improve compliance.

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Medication noncompliance among patients with medical illnesses has been reported to range from 15% to 85%.[1] Psychiatric patients, in particular, are frequently noncompliant with medications. In a study of patients with bipolar disorder, Keck and associates reported a noncompliance rate of up to 64%.[2] In addition, noncompliance is the most frequent cause of relapse for this patient population.[3] Although many factors are associated with medication noncompliance, it is thought that physicians can help promote compliance by prescribing medications that require a minimal number of doses per day. In a study of headache patients by Mulleners and associates, compliance increased as the number of medication doses decreased. Compliance among these patients was 80% when patients had the convenience of once-daily dosing, as compared with 60% for twice-daily and 54% for three-times-daily dosing.[4]

Divalproex sodium delayed-release (DR) has been used for many years and has been shown to be effective in the treatment of acute mania associated with bipolar disorder.[5,6] The time to peak plasma concentration (T_{max}) occurs within 3 to 4 hours after the DR tablet is taken, and the functional half-life ($t_{1/2}$) is relatively short at 8 to 17 hours.[7] These pharmacokinetic parameters require that divalproex sodium DR be administered in a twice-daily dosing regimen. The United States Food and Drug Administration (FDA) recently approved an extended-release (ER) formulation of divalproex sodium, with a current indication of migraine prevention. This once-daily dosing formulation offers 10% to 20% less fluctuation in valproate plasma concentrations than divalproex sodium DR delivered twice daily, with maximum plasma concentrations (C_{max}) occurring 7 to 14 hours after ER dosing.[8] In addition to the advantage of once-daily dosing, the steadier valproate plasma concentrations may offer more effective mood stabilization and a reduction in the occurrence of adverse events.

If efficacy of once-daily dosing with divalproex sodium ER is equal to or better than that provided by the multiple-dose formulation, compliance may be improved. Moreover, compliance may be further enhanced if a lower

incidence of adverse events is associated with divalproex sodium ER. The present study was designed to evaluate the safety and efficacy of divalproex sodium ER when patients were switched from treatment with the divalproex sodium DR formulation to that with the ER formulation.

MATERIALS AND METHODS

This open-label, 7-day study included 55 patients with a DSM-IV diagnosis of bipolar disorder, major depression, schizophrenia, schizoaffective disorder, Alzheimer's disease, dementia, or intermittent explosive disorder (Table 1). All subjects were consecutive patients of the first author and were receiving divalproex sodium DR prior to entering the study. No patients were excluded from the study for any reason. Forty-one subjects (75%) were outpatients and 14 (25%) were inpatients, hospitalized for acute symptoms. All patients were previously undergoing therapy with a stabilized (i.e., unchanging) dosage of divalproex sodium DR.

On day 1, baseline plasma valproate concentrations were determined, after which patients received their usual morning dose of divalproex sodium DR. At 9:00 p.m. on the same day, they received divalproex sodium ER at a dose equal to their total daily dose of divalproex sodium DR. On days 2 through 7, patients received the same evening dose of divalproex sodium ER, equal to the total daily dose of divalproex sodium DR. On days 3, 5, and 7, plasma valproate concentrations were assessed 10 to 12 hours after the last dosing. The use of concomitant medications was recorded, and the doses of these medications remained constant during the study.

TABLE 1. Patient demographics (N=55)

Mean age, years (range)	42.0 (14–85)
Gender, n (%)	
Male	27 (49)
Female	28 (51)
Race, n (%)	
White	47 (85)
Black	4 (7)
Hispanic	2 (4)
Asian	2 (4)
Diagnosis (DSM-IV), n (%)	
Bipolar disorder*	20 (36)
Major depression†	15 (27)
Schizophrenia	9 (16)
Schizoaffective disorder	6 (11)
Other‡	5 (10)
Concomitant medications, n (%)§	
No medications	21 (38)
Any medications	34 (62)
Antipsychotics	22 (40)
Antidepressants	26 (47)
Anxiolytics	1 (2)
Anticholinergics	1 (2)
Other¶	12 (22)

*Included bipolar disorder type I–manic (n=5), bipolar disorder type I–depressed (n=4), bipolar disorder type I–mixed (n=8), and bipolar disorder type II (n=3).

†Divalproex was use as a mood stabilizer to treat depression and irritability in these patients.

‡Included Alzheimer disease, dementia, intermittent explosive disorder.

§Some patients were taking >1 concomitant medication.

¶Included levothyroxine (5%), disulfiram (4%), gabapentin (2%), donepezil (2%), atorvastatin (2%), estrogen (4%), celecoxib (2%), pindolol (2%).

Because plasma valproate concentrations were determined at trough while patients were receiving the DR formulation and at the midpoint of the dosing interval (and therefore possibly close to peak concentration) while patients were receiving the ER formulation, a subset analysis was performed. Fifteen patients were reanalyzed for trough plasma valproate concentrations (i.e., at 23 hours post-dose) while receiving the ER formulation.

Efficacy was assessed with the Positive and Negative Syndrome Scale (PANSS) on day 1 (baseline) and day 7. This scale assesses the positive symptoms (e.g., hallucinations and delusions) and the negative symptoms (e.g., blunted affect and passive social withdrawal) of psychiatric illness. The PANSS evaluates 30 symptoms that are rated on a 7-point scale ranging from absent (1) to extreme (7). The assessment yields separate scores for positive symptoms, negative symptoms, and general psychopathology.

Adverse events were assessed with the Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale developed by the Subcommittee of the Scandinavian Society for Psychopharmacology.[9] The UKU scale systematically assesses 45 adverse events by degree in four categories, including psychic, neurologic, autonomic, and "other." Included in the "other" category are skin reactions, weight gain or loss, headache, endocrinologic changes, physical or psychological dependence, and changes in sexual function and desire. Patients were asked about the presence and severity of each of the symptoms before being switched to the ER formulation and again at the final evaluation on day 7. Severity was rated with the standardized UKU scoring system: none (0), mild (1), moderate (2), or severe (3). The sum of the severity scores for the 45 items was used to yield a severity-adjusted side effect score.

Paired Student *t*-tests were used to analyze the statistical significance of changes from baseline in both PANSS and UKU scores. After day 7, divalproex sodium ER dosing could be adjusted by the physician on the basis of clinical response and total valproate concentrations. Values of $p < 0.05$ were considered statistically significant.

Study objectives were explained to the patients, and each patient signed an informed consent before participating in the study. This study was carried out in accordance with the Declaration of Helsinki.

RESULTS

All 55 patients were switched from divalproex sodium DR to divalproex sodium ER. Table 1 presents demographic data, including diagnoses and concomitant medications taken during the study. Of the 55 patients studied, 27 were men and 28 were women. The patients had been undergoing treatment with divalproex sodium DR at a stabilized dosage for periods ranging from 2 days to >4 years (mean dosage, 1,827 mg/d [range, 500–5000 mg/d]). Thirty-four patients (62%) were taking at least one concomitant medication, 18 of whom were taking multiple drugs; 21 patients (38%) were not taking concomitant medications.

The mean baseline valproate plasma concentration (± standard deviation [SD]) for all patients was 81.5 μg/mL (±20.4), which increased to 87.4 μg/mL (±21.3), 88.7 μg/mL (±24.1), and 88.5 μg/mL (±23.2) on days 3, 5, and 7, respectively (Table 2). When analyzing inpatient and outpatient populations separately, we noted that valproate concentrations were similar in both groups at baseline and on days 3, 5, and 7 (Table 2). Overall, valproate plasma concentrations increased in 32 patients and decreased in 23 patients in comparison with baseline.

With three exceptions, plasma valproate concentrations remained within the therapeutic range (i.e., 50–125 μg/mL). In the first two cases, patients had elevated plasma valproate concentrations while receiving the ER formulation; one outpatient had an increase from 59.0 μg/mL at baseline to 157.1 μg/mL on day 5, and the other had an increase from 90 μg/mL at baseline to 144.5 μg/mL on day 7. Neither patient developed symptoms of toxicity. Divalproex sodium dosages were decreased from 2,000 mg/d to 1,000 mg/d for the outpatient (day 5), and from 1,000 mg/d to 500 mg/d (day 7) for the hospitalized patient. On day 14, plasma valproate concentrations for both patients returned to the therapeutic range of 50 to 125 μg/mL.

In the third case, involving an outpatient, the plasma valproate concentration decreased from 77.5 μg/mL at baseline to 42.6 μg/mL on day 7. Although the patient's PANSS scores had improved slightly, the dosage was increased from 1,000 to 2,000 mg/d. On day 14, the patient's plasma valproate concentration was within the therapeutic range of 50 to 125 μg/mL.

In addition, four patients (one inpatient and three outpatients) had plasma valproate concentrations in the range of 41 to 49 μg/mL at baseline; however, after the transition to divalproex sodium ER, plasma valproate concentrations in all four patients increased so that they were within the therapeutic range. PANSS total scores improved slightly for two patients and were unchanged for the other two patients.

For the subset of 15 patients whose plasma valproate concentrations were reanalyzed at 23 hours post-dose while receiving the ER formulation, the mean plasma valproate concentration was 79.1 μg/mL (±17.62). In comparison, mean plasma valproate concentrations for this subset were 82.1 μg/mL (±12.8) at baseline (i.e., while they were receiving the DR formulation) and 88.7 μg/mL (±13.45) at 11 hours (i.e., while they were receiving the ER formulation).

When the inpatient and outpatient groups were analyzed separately, inpatient PANSS scores significantly improved from baseline to the final evaluation on all subscales. Baseline scores for the positive, negative, general psychopathology, and total PANSS subscales for the inpatient population were 24.6 (±5.1), 20.6 (±4.3), 50.9 (±4.6), and 96.1 (±12.1), respectively. By the final evaluation, these scores were statistically significantly improved, with a mean change of −4.3 (±4.3; $p = 0.0024$) for the positive scale, −1.4 (±1.9; $p = 0.0151$) for the negative scale, −7.2 (±5.2; $p = 0.0002$) for the general psychopathology scale, and −12.9 (±9.9; $p = 0.0003$) for the total PANSS score. For the outpatient population, baseline scores for the positive, negative, general psychopathology, and total PANSS scores were 15.4 (±5.8), 13.5 (±4.0), 34.1 (±9.4), and 63.2 (±16.9), respectively. At the final evaluation, mean changes in scores for these patients were −0.5 (±3.3) for the positive scale, 0.1 (±2.3) for the negative scale, −0.8

TABLE 2. Changes in plasma valproate concentrations

	All patients (N=55)		Hospitalized patients (n=14)		Outpatients (n=41)	
	Mean concentration ± SD	Mean change ± SD	Mean concentration ± SD	Mean change ± SD	Mean concentration ± SD	Mean change ± SD
Baseline	81.5 ± 20.4	–	81.5 ± 15.0	–	81.5 ± 3.4	–
Day 3	87.4 ± 21.3	5.9 ± 19.8	88.3 ± 19.7	6.8 ± 19.6	87.1 ± 3.4	5.6 ± 20.1
Day 5	88.7 ± 24.1	7.2 ± 23.8	90.7 ± 22.6	9.2 ± 26.9	88.0 ± 3.9	6.6 ± 23.0
Day 7	88.5 ± 23.2	7.0 ± 26.7	94.3 ± 22.4	12.7 ± 27.0	86.5 ± 3.6	5.0 ± 26.6

SD=standard deviation. All plasma valproate concentrations are given in μg/mL.

(±5.0) for the general psychopathology scale, and −1.2 (±9.9) for the total PANSS, but these changes were not statistically significant.

When combining inpatient and outpatient populations, we observed a small but statistically significant improvement in mean total PANSS score from the baseline (71.5 ± 21.4) to the final evaluation (mean change, −4.3 ± 11.1; $p = 0.0065$). Overall, PANSS scores decreased for 35 patients, were unchanged for 14 patients, and increased for 6 patients. Statistically significant improvement from baseline in the positive subscale (baseline, 17.8 ± 6.9; mean change, −1.5 ± 3.9; $p = 0.0073$) and general psychopathology subscale (baseline, 38.4 ± 11.1; mean change, −2.5 ± 5.7; $p = 0.0025$) was evident. For the negative subscale of the PANSS, slight improvement was noted (baseline, 15.3 ± 5.1; mean change, −0.3 ± 2.3) but was not statistically significant.

Patients reported a significant decrease in both the number and the severity of adverse events ($p < 0.0001$) after 7 days of divalproex sodium ER treatment. The mean number of symptoms per patient decreased from 7.7 (± 4.3) at baseline to 6.2 (±3.8) on day 7, and the overall severity score decreased from 12.5 (±8.7) to 9.7 (±7.3). Table 3 shows common adverse events reported by patients. The adverse events present at baseline may have been symptoms of the psychiatric illness, side effects from concomitant medications, or side effects from divalproex sodium DR.

TABLE 3. Adverse events from baseline to final evaluation occurring in ≥10% of all patients*

Side effect	Baseline (DR) (%)	Final (ER) (%)
Poor concentration	80	72
Tension	65	62
Depression	50	45
Increased fatigue	44	34
Weight gain	42	38
Failing memory	38	29
Reduced duration of sleep	36	33
Diminished sexual desire	33	27
Emotional indifference	33	29
Sedation	29	16
Amenorrhea	27	27
Increased duration of sleep	22	13
Diarrhea	14	14
Dizziness	14	14
Orgastic dysfunction	14	11
Tension headache	14	11
Visual disturbances	13	11
Erectile dysfunction	11	11
Increased dream activity	11	5
Increased salivation	11	9
Increased sexual desire	11	14
Increased sweating	11	9
Tremor	11	13

*Adverse events were rated using Udvalg for Kliniske Undersogelser (UKU) Side Effect Rating Scale[9]

At the end of the study, 54 of the 55 patients elected to continue treatment with divalproex sodium ER. One patient elected to return to the DR formulation because she preferred twice-daily dosing.

DISCUSSION

In this study, all 55 patients with psychiatric disorders were successfully switched from divalproex sodium DR to the ER formulation. No patients experienced mental status deterioration when the switch was performed. Clinical response was achieved at plasma valproate concentrations of 50 to 125 μg/mL in most patients. With three exceptions, all patients' plasma valproate concentrations remained therapeutic during the switch. Of the three patients who required dosing adjustment, it was necessary to reduce the dose for two patients and increase it for one. Also, four patients had plasma valproate concentrations in the range of 41 to 49 μg/mL at baseline; however, in all four the concentrations became therapeutic after the switch to divalproex sodium ER. Overall, similar plasma valproate concentrations were found between the inpatient and outpatient groups.

When analyzing the inpatient and outpatient groups individually, we noted that inpatients had clinically and statistically significant improvement in all PANSS subscale scores, as well as the PANSS total score, whereas there was no significant change in scores for the outpatient group. The difference in clinical response between the inpatient and outpatient groups was of particular interest, especially in view of the much smaller number of inpatients than outpatients. Plasma valproate concentrations could not have played a role, as they were similar between the groups.

The difference may be explained by the fact that those who were hospitalized had been more acutely ill at baseline, whereas those who were receiving treatment on an outpatient basis were generally more stable. Hence, PANSS scores were initially higher for the acutely ill inpatients than for the outpatient group; improvement at final evaluation (lower PANSS score) was therefore greater in the inpatient group. Another possible explanation for the greater improvement noted in the inpatient group is that the inpatients may have been more compliant.

Because of these factors, the improvement seen in inpatient PANSS scores is presumably not a function of which divalproex formulation the patients were receiving; that is, these subjects' scores would likely have shown improvement if they had continued therapy with the DR formulation. However, the fact that switching to the ER formulation did not result in PANSS score deterioration for these patients is notable.

In the combined inpatient and outpatient populations, a small but statistically significant improvement from baseline to final evaluation was seen in positive, general, and total PANSS subscale scores. However, this difference appears to stem mainly from changes in inpatient PANSS scores, which were higher at baseline than outpatient PANSS scores, therefore allowing more room for improvement during the study period. Some improvement may also be attributable to the pharmacokinetic properties of the divalproex sodium ER formulation; ER tablets given once daily have been shown to produce 10% to 20% less fluctuation in plasma valproate concentrations than DR tablets given twice daily.[8] This reduction in peaks and troughs may help provide better mood stabilization for patients.

After the switch from divalproex sodium DR to ER, statistically significant decreases were noted in both the number and severity of adverse events reported by patients. The decrease in adverse events may be due to the pharmacokinetic properties of the divalproex sodium ER formulation. Steadier drug concentrations may minimize the adverse events and risk of toxicity associated with elevated peak concentrations. However, one must not discount the possibility that decreased reports of adverse events after the switch to the ER formulation could be linked to improvement in features of the patients' underlying illness.

In this study, we found that our strategy for switching patients from the DR to the ER formulation of divalproex sodium was both safe and effective. Before a psychiatric patient receives divalproex sodium ER, he or she should start treatment with divalproex sodium DR to rapidly establish the appropriate therapeutic dose. Rapid loading of the divalproex sodium DR at 20–30 mg/kg per day is advisable in cases of acute mania or for inpatients for whom rapid response to divalproex sodium is important in order to bring valproate plasma concentrations to a therapeutic level as quickly as possible.[10, 11] Once a therapeutic plasma valproate concentration is established, patients can be switched easily to divalproex sodium ER. Blood sampling should continue during the transition in order to determine whether a dosage change is needed for a particular patient.

Notably, over half of the patients in this study (58%) had an increase in valproate plasma concentrations when they were switched from divalproex sodium DR to ER. This contradicts published data showing that the ER tablet has an average bioavailability of 81% to 89% relative to that of divalproex sodium DR given twice daily.[8] However, because valproate concentrations were measured at 10 to 12 hours post-dose, these measurements reflected trough concentrations while patients were receiving the DR formulation and midpoint (i.e., possibly close to peak) concentrations while patients were receiving the ER formulation. A subset analysis of ER trough concentrations for 15 patients revealed a mean plasma valproate concentration of 79.1 μg/mL (±17.62), as compared with the subset's mean baseline DR trough measurement (82.1 μg/mL [±12.8]) and 11-hour ER measurement (i.e., close to peak) of 88.7 μg/mL (±13.45).

This subset analysis indicated a minimal decrease in plasma valproate concentrations when patients were switched from the DR to the ER formulation, with mean trough plasma valproate concentrations for the ER formulation being 96.3% relative, to mean trough plasma valproate concentrations for the DR formulation. It is important to note that although a 1:1 DR to ER dosage switch was performed successfully in this small sample of patients, divalproex sodium DR and ER are not bioequivalent, and caution should be exercised in the application of such a strategy, whether it be for psychiatric patients or others, such as epilepsy or headache patients.

Fewer adverse events associated with divalproex sodium ER may also be attributed to its bioavailability. In addition to potentially steadier drug concentrations that may minimize adverse events, the fact that the ER formulation has a lower bioavailability than the DR formulation may also explain why patients in this study generally experienced fewer adverse effects after the switch.

This open-label study suggests that divalproex sodium ER is at least as effective as the DR formulation for treating patients with psychiatric illness and may be better tolerated. In addition, the once-daily dosing regimen of divalproex sodium ER may help improve compliance in this patient population. An important limitation of this study was its open-label design. Additionally, it should be noted that at the time of this study, a 250-mg dose of the ER formulation was not commercially available. Double-blind, controlled studies are warranted to further investigate the use of divalproex sodium ER for psychiatric patients.

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