A Pharmacokinetic and Clinical Evaluation of Switching Patients With Bipolar I Disorder From Delayed-Release to Extended-Release Divalproex

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Objective: To determine the optimal strategy for converting stable bipolar patients from twice-daily divalproex delayed release (DR) to once-daily divalproex extended release (ER).

Method: This prospective, open-label, crossover study compared 4 divalproex regimens in euthymic outpatients with bipolar I disorder (DSM-IV diagnosis confirmed by Mini-International Neuropsychiatric Interview). Serum valproic acid levels were collected 12, 16, 20, and 24 hours after the last bedtime dose of the following regimens: DR twice daily (DR b.i.d.) during week 1; total daily DR dose once daily (DR q.h.s.) during week 2; once-daily ER at equal daily DR dose (ER 1:1) during week 3; and once-daily ER with the dose increased by 500 mg (ER + 500) during week 4. Patients continued on ER + 500 for 4 additional weeks after the pharmacokinetic phase. Side effects and psychiatric symptoms were assessed at weeks 1 through 4, 6, and 8. Twenty-one patients were enrolled from July 2002 to July 2004.

Results: Of the regimens tested, DR q.h.s. produced the widest fluctuations in valproic acid levels, with the highest 12-hour (82 μg/mL) and lowest 24-hour (44 μg/mL) levels. The ER + 500 dose was the only regimen that maintained the mean minimum valproic acid concentration above 50 μg/mL. Each regimen was well tolerated, and no significant changes in psychometric indices were observed.

Conclusions: When converting stable bipolar patients from twice-daily divalproex DR to once-daily ER, we recommend increasing the total daily dose by 250 to 500 mg to ensure maintenance of therapeutic valproic acid levels.

(J Clin Psychiatry 2007;68:1546–1551)

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This study was supported by an investigator-initiated grant from Abbott Laboratories, Chicago, Ill. The authors acknowledge the support of VA Research and Development, Tuscaloosa VA Medical Center, Tuscaloosa, and the Department of Psychiatry and Behavioral Neurobiology, University of Alabama School of Medicine, Birmingham, Ala.

An interim analysis was presented at the 43rd annual New Clinical Drug Evaluation Unit meeting, May 28, 2003, Boca Raton, Fla.

The authors appreciate the technical nursing assistance of Sandra Ambrose, M.S.N., University of Alabama, Tuscaloosa, and Elizabeth Waldrop, R.N., Tuscaloosa VA Medical Center, as well as the editing support of Kaplan Communications, LLC, Fairfield, Conn.

Financial disclosure appears at the end of the article.

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Divalproex extended release (ER) was recently approved by the U.S. Food and Drug Administration for the treatment of adult mania associated with bipolar disorder. In a prospective, 21-day, 1:1, randomized, placebo-controlled study of treatment of mixed- or manic-episode bipolar I disorder,[1] improvement from baseline on the Mania Rating Scale (MRS) was significantly greater among patients treated with divalproex ER (N = 192) than among those treated with placebo (N = 185) at the first on-treatment rating assessment, day 5, and all subsequent ratings through day 21. Furthermore, a significantly greater proportion of patients treated with divalproex ER achieved at least a 50% improvement from baseline on the MRS (48% vs. 34%, $p < .05$).[1]

Divalproex delayed release (DR) and ER are 2 oral formulations of divalproex sodium. On the market since 1983, divalproex DR (also know as divalproex EC [enteric coated]) is an enteric coated tablet that has a delayed-release pharmacokinetic profile and requires multiple daily doses to maintain steady serum valproic acid levels. Released in 2002, divalproex ER is a sustained-release formulation that only requires once-daily administration. Divalproex ER may provide the advantages of more convenient once-daily dosing, reduced peak-related side effects, and improved patient adherence

to medication compared with the split-dose regimen of divalproex DR. Clinicians may be interested in switching their stable bipolar patients taking divalproex DR to the new ER formulation. Previous pharmacokinetic studies in healthy subjects show the bioavailability of ER is lower than that of DR, indicating a possible need to increase total daily dose when switching patients from DR to ER.[2] The current prospective, open-label, crossover study systematically evaluated serial valproic acid levels in euthymic bipolar I patients who were switched from divalproex DR to once-daily therapy with divalproex ER.

METHOD

The study was approved by the Institutional Review Board of the Tuscaloosa Veterans Affairs Medical Center (TVAMC) (Tuscaloosa, Ala.), where the study was performed. The study was conducted in accordance with the Declaration of Helsinki and its amendments. Twenty-one outpatients were enrolled from July 2002 to July 2004. After providing signed informed consent, patients received standard laboratory, medical, and psychiatric examinations. Entry criteria included a diagnosis of bipolar I disorder; age of 19 to 70 years; currently psychiatrically stable as defined by scores of less than 15 on the Young Mania Rating Scale (YMRS),[3] less than 15 on the 17-item Hamilton Rating Scale for Depression (HAM-D-17),[4] and less than or equal to 3 on the Clinical Global Impressions (CGI) scale[5]; stable general medical condition with no clinically significant abnormal laboratory values; and currently treated with divalproex DR. Exclusion criteria included a diagnosis of an active Axis I disorder of schizoaffective disorder, schizophrenia, or cognitive disorder; current treatment with lamotrigine; alcohol or substance dependence (except for nicotine or caffeine) in the previous month; woman of childbearing potential who was pregnant, breastfeeding, or planning to become pregnant; liver function tests more than twice the upper limit for the TVAMC laboratory reference range; and significant risk of suicide or violent behavior.

Assessments

DSM-IV diagnosis was confirmed using the Mini-International Neuropsychiatric Interview.[6] Symptom severity was rated at baseline and at follow-up clinic visits using the YMRS, HAM-D-17, and CGI. Adverse events were recorded during all follow-up visits.

Medication

From baseline, patients continued on their current regimen of divalproex DR and returned to the clinic 1 week later for pharmacokinetic evaluation. Nineteen of the 21 patients were on a twice-daily dosing regimen of divalproex DR, and 2 received their total dose at bedtime. Patients were allowed to remain on all other previously prescribed concomitant medications, provided dosing was stable and held constant during the study.

Patients returned weekly for 4 weeks for the collection of valproic acid serum samples at 12, 16, 20, and 24 hours following the last bedtime dose of that week's assigned regimen of divalproex.

For the first week, patients continued to take their current total dose of divalproex DR as a divided dose given twice daily (DR b.i.d.). The morning dose was given after the 12-hour serum collection. During week 2, patients were instructed to take the total daily dose of divalproex DR at bedtime (DR q.h.s.). During week 3, patients were switched to divalproex ER on a milligram for milligram basis and instructed to take the total daily dose of divalproex ER at bedtime (ER 1:1). During week 4, the dose of divalproex ER was increased by 500 mg, and the total daily dose was taken at bedtime (ER + 500). During weeks 5 through 8, patients continued taking ER + 500 at bedtime.

Patients returned to the clinic at weeks 6 and 8 for monitoring of clinical status using the YMRS, HAM-D-17, and CGI and for documentation of possible adverse effects.

Valproic Acid Levels

Valproic acid levels were quantified by a routine commercial laboratory immunoassay in the TVAMC laboratory using the Beckman Coulter Synchron LX 20 Pro system (Beckman Coulter Inc., Fullerton, Calif.). The Synchron valproic acid assay uses a competitive particle-enhanced turbidimetric immunoassay method. Interreliability and intrareliability quality control is confirmed by the TVAMC via proficiency testing using commercial products from the College of American Pathologists.

Statistical Methods

All parameters were analyzed for change over time and change from baseline using the general linear models procedure in Statistical Application Software, version 9.1 (SAS Institute Inc., Cary, N.C.). Post hoc comparisons were made using the least-squares means procedure. The same analysis applied to comparison of the valproic acid levels for the 4 dose groups over time. Any missing observations for symptom rating scales (YMRS, HAM-D-17, and CGI) were treated as last observation carried forward. All patient data were analyzed, including those for a patient who exited the study prior to week 4 and one who exited prior to week 8.

RESULTS

Twenty-one patients gave informed consent, met the entry criteria, and were enrolled. Twenty patients com-

Table 1. Patient Characteristics and Concomitant Medications at Baseline

Variable	Value (N = 21)
Male, N (%)	20 (95)
White, N (%)	17 (81)
Age, mean (SD), y	50 (8.9)
Other Axis I disorders, N (%)[a]	
Posttraumatic stress disorder	7 (33)
Substance use disorder (lifetime)	6 (29)
Panic disorder	3 (14)
Other anxiety disorder	2 (10)
Concomitant medications, N (%)[b]	
Clonazepam	4 (19)
Low-dose trazodone	3 (14)
Atypical antipsychotic	3 (14)
Sertraline	2 (10)
Carbamazepine	1 (5)
Nefazodone	1 (5)
Low-dose nortriptyline	1 (5)

[a]Six patients had > 2 Axis I disorders.
[b]Five patients were receiving > 2 psychotropic medications.

pleted the pharmacokinetic phase, and 19 completed the entire 8-week study. One patient was lost to follow-up prior to week 4, and 1 withdrew consent prior to week 8. Table 1 summarizes baseline patient characteristics.

Table 2 shows serum valproic acid levels over time for the 4 dosing regimens. There was a significant group effect ($p < .0001$) and time effect ($p < .0001$). As outlined in the Method section above, with DR b.i.d., patients took their morning dose immediately after the 12-hour laboratory collection, which explains the slight valproic acid peak at 16 hours. Valproic acid levels with DR b.i.d. were consistently numerically higher than levels with ER 1:1; however, they only reached a statistical trend difference at 16 hours ($p = .0569$). The 12-hour valproic acid level with DR b.i.d. was significantly lower than with ER + 500 ($p = .0389$) and DR q.h.s. ($p = .0145$).

As shown in Figure 1, DR q.h.s. produced the greatest variability in valproic acid concentration, with the highest mean 12-hour peak and lowest 24-hour trough level. The 12-hour level following DR q.h.s. was significantly higher than DR b.i.d. ($p = .0145$) and ER 1:1 ($p = .0015$) but not significantly different than ER + 500.

Divalproex ER 1:1 produced consistently lower valproic acid levels than DR b.i.d. (not significant) and significantly lower levels than ER + 500 at 12 hours ($p = .0048$) and 16 hours ($p = .0143$). Valproic acid levels were higher following ER + 500 than DR b.i.d. and ER 1:1 at 12 hours and ER 1:1 at 16 hours.

Samples for the 24-hour valproic acid level were collected immediately prior to the bedtime dose and thus represent the true trough levels for all groups. At 24 hours, the valproic acid level was significantly higher for ER + 500 compared with DR q.h.s. ($p = .0122$) but not significantly different from ER 1:1 ($p = .0735$) or DR b.i.d. ($p = .4469$).

Maximum valproic acid concentration (C_{max}) was significantly higher following DR q.h.s. ($p = .012$) and ER + 500 ($p = .0131$) compared with ER 1:1. Minimum valproic acid concentration (C_{min}) was significantly lower for DR b.i.d. ($p = .01$) and ER 1:1 ($p = .017$) compared with ER + 500. The mean percent differences between C_{max} and C_{min} were 36% ± 12% for DR b.i.d., 46% ± 13% for DR q.h.s., 27% ± 11% for ER 1:1, and 29% ± 11% for ER + 500.

Table 3 shows the results of the psychometric evaluations over time. There were no significant changes detected in YMRS, HAM-D-17, or CGI scores over the course of this 8-week study.

Overall, the conversion to ER was well tolerated. The incidence of adverse events was too small to analyze statistically. Mild to moderate insomnia was reported in 3 patients and was possibly related to ER, although hypersomnia was reported in 1 patient taking DR and in 1 patient taking ER. One patient relapsed with alcohol at week 7 (unrelated to study medication), and 1 patient stopped all medication and was subsequently hospitalized for depression exacerbated by psychosocial stressors (unrelated to study medication). One patient complained of mild dry mouth while taking DR. One patient complained of severe tremor while taking ER, and 2 patients reported increased appetite while taking ER. Only 2 patients elected to convert back to a DR regimen at the end of the study because of side effects: 1 for insomnia and 1 for tremor.

DISCUSSION

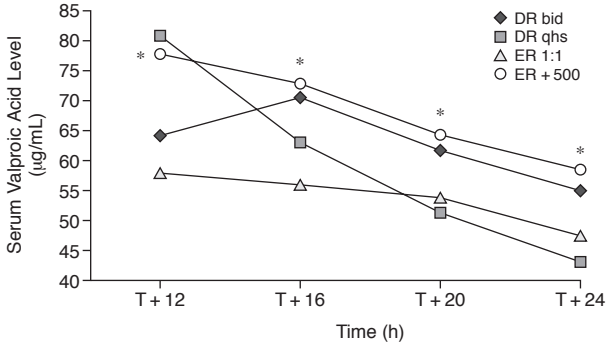
Our findings support the need to increase the total daily divalproex dose when converting well-controlled bipolar patients from DR to ER therapy, in order to provide equivalent valproic acid levels throughout a 24-hour period. Although the differences were not statistically significant, serum valproic acid levels with divalproex ER 1:1 were consistently lower than with the divalproex DR twice-daily regimen and fell to a lower 24-hour trough level (47 μg/mL vs. 55 μg/mL, respectively). Divalproex ER + 500 dosing was the only regimen that maintained an average minimum valproic acid concentration (C_{min}) above 50 μg/mL. Combining the total daily dose of DR into a single bedtime dose (DR q.h.s.) produced wide fluctuation in valproic acid levels, with the highest 12-hour level (82 μg/mL), lowest 24-hour level (44 μg/mL), and greatest percent difference between peak and trough levels (46%) of the regimens tested. Lower serum valproic acid concentrations in the ER 1:1 group, compared with both DR dosing groups, reflect the reduced bioavailability of ER at all timepoints. As reflected by stable YMRS, HAM-D-17, and CGI scores, conversion from DR to once-daily ER did not result in exacerbation of mania or depression.

Table 2. Mean (SD) Serum Valproic Acid Concentrations Over Time for the 4 Dosing Regimens

Regimen	Mean (SD) Daily Dose, mg/d	Mean (SD) Serum Valproic Acid Concentration, μg/mL					
		12 hr	16 hr	20 hr	24 hr	C_{max}	C_{min}
DR bid	1261.9 (464.2)	64.2 (22.9)[a]	70.6 (22.9)	61.8 (21.4)	54.9 (20.4)	76.1 (21.1)	49.7 (19.0)
DR qhs	1275.0 (472.3)	80.8 (24.9)[a]	63.0 (21.3)	51.2 (19.5)	43.1 (17.1)	79.8 (24.6)[a]	43.1 (17.1)
ER 1:1	1275.0 (472.3)	57.9 (17.3)[a]	55.9 (17.3)	53.6 (16.6)	47.5 (13.6)	62.5 (17.5)	44.1 (12.1)
ER + 500	1775.0 (472.3)	77.8 (21.1)[a]	72.7 (23.1)[a]	64.3 (21.4)[a]	58.4 (22.4)[a]	79.6 (21.3)[a]	57.4 (20.0)[a]

[a]$p < .05$; see text for details.
Abbreviations: C_{max} = maximum concentration; C_{min} = minimum concentration; DR bid = divalproex delayed release, twice daily; DR qhs = DR, total daily dose at bedtime; ER 1:1 = divalproex extended release, same total daily bedtime dose as DR qhs; ER + 500 = ER at the same total daily dose as DR plus 500 mg.

Figure 1. Mean Serum Valproic Acid Levels With 4 Divalproex Regimens



*$p < .05$; see text for details.
Abbreviations: DR bid = divalproex delayed release, twice daily; DR qhs = DR, total daily dose at bedtime; ER 1:1 = divalproex extended release, same total daily bedtime dose as DR qhs; ER + 500 = ER at the same total daily dose as DR plus 500 mg.

It is well established that the bioavailability of divalproex ER is lower than that of DR.[7] Dutta and Reed[2] analyzed pharmacokinetic data from 5 DR to ER conversion studies—3 comparing equal daily doses of DR and ER and 2 in which the ER dose was increased 8% to 20%. In the 3 equal-dose studies, the bioavailability of ER compared with DR (i.e., the ratio of areas under the curve [AUCs]) was approximately 0.89. However, in the 2 studies in which the ER dose was increased, the 2 regimens proved bioequivalent, with an AUC ratio of about 1.0.[2]

We compensated for the lower bioavailability of ER by increasing the daily dose by roughly 40% (500 mg). A 500-mg increase was the minimum possible increase at the time the study was conducted, as the 250-mg tablet was not yet in production. In addition, this increase would be the most likely scenario for a clinician prescribing DR or ER in 500-mg increments. Not surprisingly, the mean 12-hour serum valproic acid level for twice-daily DR was significantly lower than the 12-hour level for ER + 500. However, no other significant differences were detected. On the basis of these data, conversion from twice-daily DR to once-daily ER + 500 appears to be appropriate and well tolerated.

Overall, the conversion from DR to ER was well tolerated. These outcomes are consistent with the published findings of other DR to ER conversion studies. Stoner et al.[8] described 10 patients who had been hospitalized for mood or thought disorders and were stabilized on divalproex DR but had problematic rates of tremor, sedation, and gastrointestinal upset. Conversion to divalproex ER produced no change in mood, but significant reductions were noted in complaints of tremor ($p = .004$), sedation ($p = .02$), and gastrointestinal upset ($p = .045$).[8] Smith et al.[9] pooled data from 9 open-label DR to ER conversion studies involving 321 epilepsy and psychiatry patients. Divalproex ER was associated with superior tolerability, reduced incidence of adverse events, and significant improvements in tremor, weight gain, and gastrointestinal toxicity ($p < .001$). Conversion to ER also improved seizure control ($p = .02$) and psychiatric symptoms ($p = .003$). Three of the 9 trials ($N = 93$) recorded patient preference for therapy after conversion: 88% preferred ER, 11% had no preference, and 1% preferred DR ($p < .001$).[9]

Irrespective of therapeutic category, it is generally accepted that once-daily dosing yields higher rates of patient compliance than twice-daily dosing. Once-daily dosing of divalproex ER also allows more convenient monitoring of serum valproic acid levels for patients and physicians, in that patients taking ER can be monitored for serum valproic acid levels at any time of the day, not just in the morning before their first DR dose. In the current study, the differences between the peak and trough valproic acid levels for ER (27% ± 11% for ER and 29% ± 11% for ER + 500) were less than those for DR (36% ± 12% for DR b.i.d. and 46% ± 13% for DR q.h.s.).

Limitations of the current study include the small sample size and the lack of full 24-hour pharmacokinetic profiling (i.e., no levels drawn from 0 hours to 12 hours). No serum samples were collected between the evening dose and the morning DR dose, preventing an AUC analysis. However, other published pharmacokinetic studies have shown that once-daily ER at doses 8% to

Table 3. Psychometric Evaluations Over 8 Weeks (N = 20)[a]

	Study Week					
Rating Scale	0	2	3	4	6	8
YMRS score, mean (SD)	6.9 (4.5)	6.7 (4.1)	6.3 (5.0)	6.3 (4.0)	5.1 (4.8)	5.2 (3.7)[a]
HAM-D-17 score, mean (SD)	7.7 (5.1)	7.1 (6.4)	6.1 (4.7)	6.1 (5.3)	5.3 (4.9)	7.4 (4.6)[a]
CGI score, mean (SD)	2.8 (0.5)	2.8 (0.8)	2.7 (0.8)	2.8 (0.8)	2.4 (0.8)	2.7 (0.9)[a]

[a]No significant changes in rating scale scores were detected.
Abbreviations: CGI = Clinical Global Impressions scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, YMRS = Young Mania Rating Scale.

Table 4. Established Bioavailability of Divalproex ER Versus DR in Healthy Subjects When ER Dose is 8% to 20% Higher Than DR[a]

		Relative Bioavailability		
Population	Regimen	AUC_{24}	C_{max}	C_{min}
Healthy volunteers (N = 35)	ER 1000 and 1500 mg vs DR 875 and 1250 mg	1.059	0.882	1.173
Patients taking concomitant enzyme-inducing antiepileptic drugs (N = 64)	ER 1000–5000 mg vs DR 875–4250 mg	1.008	0.899	1.022

[a]Data from reference 7.
Abbreviations: AUC_{24} = 24-hour area under the curve, C_{max} = maximum concentration, C_{min} = minimum concentration, DR = divalproex delayed release, ER = divalproex extended release.

20% higher than total daily DR doses reduces fluctuation between peak and trough serum concentrations (Table 4),[7] thereby reducing the potential for trough-related breakthrough symptoms or peak-induced side effects.

A strength of the current study is the enrollment of patients from a general mental health outpatient clinic, which provides some generalizability to other settings. The generally low serum valproic acid levels (i.e., < 90 μg/mL) reported in this study reflect the low dosing for maintenance for these patients in a naturalistic outpatient clinical setting prior to study entrance. However, as shown by a recent analysis,[10] there is a linear relationship of valproic acid serum concentration to response to divalproex for acute mania. In a stratified analysis of 7 groups (N = 374) based on valproic acid levels, efficacy was significantly better for divalproex at a range of greater than or equal to 71.4 to 85 μg/mL compared with placebo, with the greatest effect size for the treatment of acute mania associated with valproic acid levels greater than 94 μg/mL. However, less is known about the minimal therapeutic level for maintenance treatment of euthymic bipolar patients, which may be lower than 94 μg/mL, as reflected by this clinical population under study. More systematic analysis of the maintenance treatment studies would need to be conducted to attempt a correlation between valproic acid levels and relapse.

In conclusion, when converting a stable bipolar patient from twice-daily divalproex DR to once-daily divalproex ER, we recommend that total daily dose be increased by 250 to 500 mg to ensure maintenance of therapeutic serum valproic acid level for the full 24 hours. A dose conversion table is available at http://www.pbm.va.gov/tig/DepakotTIG.pdf. While a 1:1 switch is practicable and some clinicians may prefer to initiate conversion with equal dosing, the clinician should remain mindful that the bioavailability of divalproex ER is approximately 89% that of DR, be alert for breakthrough symptoms, monitor for side effects, and individualize treatment as needed.

Drug names: carbamazepine (Carbatrol, Equetro, and others), clonazepam (Klonopin and others), divalproex (Depakote), lamotrigine (Lamictal and others), nortriptyline (Pamelor and others), sertraline (Zoloft and others).

Financial disclosure: Dr. Davis has served as a consultant to Cyberonics, Abbott, Shire, and Bristol-Myers Squibb; has received grant/research support from the Veterans Administration, National Institute of Mental Health, Abbott, Bristol-Myers Squibb, Eisai, Forest, Ortho-McNeil, Janssen, Shire, Southwestern Oncology Group, and AstraZeneca; has received speaking honoraria from Abbott, Cyberonics, Bristol-Myers Squibb, and Sanofi-Aventis; has served on the speakers or advisory boards of Abbott, Cyberonics, and Bristol-Myers Squibb; and is a stock shareholder of Pfizer. Dr. Li has received grant/research support from National Institutes of Health, Janssen, Eli Lilly, Bristol-Myers Squibb, and National Alliance for Research on Schizophrenia and Depression. Drs. Bartolucci, Williford, and Lowe report no other affiliations relevant to the subject of this article.

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