The Adverse Effect Profile and Efficacy of Divalproex Sodium Compared With Valproic Acid: A Pharmacoepidemiology Study

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Background: Divalproex sodium has been reported to be better tolerated than valproic acid. To our knowledge, no study has examined whether significant differences in the tolerability and efficacy exist between these preparations in psychiatric patients. The objective of the present study was to compare the tolerability and efficacy of divalproex sodium with those of valproic acid in psychiatric inpatients.

Method: Information gathered retrospectively from the medical records of 150 patients treated with divalproex sodium was compared with that of 150 patients treated with valproic acid. These medical records were photocopied, and any mention of divalproex sodium or valproic acid treatment was concealed. A series of demographic and clinical characteristics were compared.

Results: Patients treated with divalproex sodium compared with patients treated with valproic acid were less likely to have gastrointestinal side effects (14.7% vs. 28.7%, p = .003), specifically anorexia (6.0% vs. 14.7%, p = .012), nausea or vomiting (6.7% vs. 16.7%, p = .007), and dyspepsia (11.3% vs. 22.0%, p = .013). Divalproex sodium–treated patients compared with valproic acid–treated patients were less likely to have discontinued their medication because of side effects (4.0% vs. 12.7%, p = .0066). Twelve (63.2%) of 19 patients who discontinued valproic acid because of gastrointestinal side effects were subsequently treated with divalproex sodium, of whom only 2 continued to have gastrointestinal side effects. There were no differences in efficacy between the 2 drugs.

Conclusion: Divalproex sodium was better tolerated than valproic acid in inpatients with a variety of diagnoses and taking concomitant medications. Patients treated with divalproex sodium compared with patients treated with valproic acid were less likely to experience gastrointestinal side effects and to have discontinued their medication because of an adverse event.

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Valproic acid and its enteric-coated derivative, divalproex sodium, have been used extensively in a wide variety of seizure and psychiatric disorders.[1–5] In the field of psychiatry, divalproex sodium is indicated for the treatment of manic episodes associated with bipolar disorder.[6,7] Numerous open studies and 6 controlled trials have demonstrated that valproate is effective in the treatment of acute mania.[5–7] Valproate has been reported to be generally well tolerated. Side effects reported to occur with valproate treatment[8] include drowsiness[9] in 0.2% to 22.0% of cases, tremor[10] in 2% to 6% of cases, and hair loss or alopecia[11] in 3% to 12% of cases. Rare side effects associated with valproate therapy include pancreatitis[12,13] and an idiosyncratic irreversible hepatic failure[14–16] with a reported incidence of hepatic fatality of 0.20 per 10,000 during a 6-year period. Abnormal laboratory findings occurring secondary to valproate treatment include a dose-related asymptomatic elevation of liver enzymes of 2% to 44%,[4,16,17] thrombocytopenia in up to 10% of cases,[18,19] and leukopenia in approximately 0.02% of cases.[20]

However, the side effects most commonly reported to occur with valproate are gastrointestinal in origin, appearing in 3% to 22% of cases.[8,21] Also, increased appetite and weight gain have been reported to occur with valproate in 7% to 20% of cases.[2,22,23]

If a patient experiences gastrointestinal side effects with valproic acid, it has been suggested that the intake of food may be helpful in minimizing these side effects with-

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out a significant change in the volume of distribution, half-life, or elimination constant.[24] However, the intake of food has been reported to reduce the time to attain a peak serum concentration.[24] The effect of food on the absorption and gastrointestinal side effects occurring with the use of valproic acid has limited its use as a loading strategy in acute mania.[25,26] In addition, not all patients will have an improvement in their gastrointestinal side effects simply with the intake of food. Other strategies advocated for the management of gastrointestinal side effects include dose reduction, or if the patient is taking valproic acid, a switch to the enteric-coated form, divalproex sodium.[9] In one study, divalproex sodium was administered to 27 patients with a seizure disorder who had not tolerated valproic acid because of gastrointestinal symptoms.[27] In that study, 23 patients (85%) tolerated the change to divalproex sodium and continued therapy. In the same study, of 34 patients previously naive to valproate, divalproex sodium therapy was discontinued in only 4 patients (12%) because of gastrointestinal intolerance. The authors concluded that enteric-coated divalproex sodium tablets had fewer gastrointestinal side effects than valproic acid capsules.

While the use of divalproex sodium could possibly minimize the risk of gastrointestinal side effects and help with compliance, several hospital formularies have planned to eliminate divalproex sodium from their formularies for the less costly preparation valproic acid, arguing that there are no differences between these preparations and that significant cost savings would be achieved. To our knowledge, there has been no examination of whether there are any differences in the tolerability and efficacy of divalproex sodium compared with valproic acid in psychiatric patients.

The goal of this study was to determine if there are any differences in the safety and effectiveness of divalproex sodium compared with valproic acid in a psychiatric inpatient setting.

METHOD

We retrospectively identified all patients consecutively admitted to McLean Hospital (Belmont, Mass.) between May 1989 to May 1996, aged 18 years or older who were newly treated with divalproex sodium or valproic acid. During this 7-year period, of 37,290 patients admitted, 3648 patients (9.8%) (2115 female, 1533 male) received either divalproex sodium (N = 3260; 89.4%) or valproic acid (N = 388; 10.6%). The ratio of prescriptions of divalproex sodium to valproic acid was 8:1. From this list of 3648 patients, 150 patients treated with divalproex sodium were randomly chosen. For each patient selected for the divalproex sodium group, the next patient treated with valproic acid was selected for the valproic acid group, thus creating 2 groups. The start and stop dates (if applicable) of divalproex sodium and valproic acid were recorded. For patients discharged on treatment with divalproex sodium or valproic acid, the discharge date was considered as the stop date. The medical records of the patients treated with divalproex sodium were photocopied, and the patients' names and any mention of divalproex sodium treatment was concealed. The medical records for the patients treated with valproic acid underwent sham concealment of noncritical data, so that the medical records for the 2 groups were indistinguishable.

Another investigator (R.N.) collected the following information from the medical records (blind to whether the patient had been treated with divalproex sodium or valproic acid): age, gender, length of stay, age at onset, marital status, DSM-III-R/IV diagnosis (converted to DSM-IV for this report), history of alcohol abuse, presence of an active medical illness, current or past history of seizures, number of hospitalizations, history of intolerance or lack of response to lithium or carbamazepine, time to the first dose of divalproex sodium or valproic acid, length of treatment with divalproex sodium or valproic acid, mean dose of divalproex sodium or valproic acid (mg/day), and mean serum level of valproic acid (μg/mL). In addition, medical records were reviewed to obtain information regarding frequency of dosing of divalproex sodium or valproic acid, concomitant medications (including H_2 antagonists), and side effects, with a specific search for mention of gastrointestinal side effects (anorexia, nausea/vomiting, dyspepsia, diarrhea), rashes, hair loss, fatigue, headache, tremor, and increased appetite/weight gain. The frequency of dosing of divalproex sodium or valproic acid was classified as either occurring once a day (q.d.), twice a day (b.i.d.), 3 times a day (t.i.d.), or 4 times a day (q.i.d.). When the patient had more than one frequency, the frequency of dosing given for the majority of days was selected.

Laboratory tests collected from medical charts included aspartate aminotransferase levels, alanine aminotransferase levels, alkaline phosphatase (ALP) levels, lactate dehydrogenase (LDH) levels, total and direct bilirubin levels, white blood cell (WBC) count, and platelet count. The dates the patient had been exposed to the medications under study were supplied to the investigator reviewing the medical record. A determination was made a priori with regard to classifying the presence or absence of a side effect. A patient was rated as having had a side effect only if the patient had not had evidence of it prior to the initiation of divalproex sodium or valproic acid, or at the very least if they had previously had the side effect and that it clearly worsened with the initiation of the drug under study.

Efficacy of divalproex sodium or valproic acid was assessed according to a 4-point scale used in other studies.[28] High intraclass correlation coefficients were previously obtained with this scale in similar application ($\kappa = .80$).[29] Response was defined as follows: 0 = no response;

1 = minimal improvement, with slight reduction in symptoms and mild improvement in social or vocational functioning; 2 = moderate improvement, with significant but incomplete reduction in symptoms allowing clearly improved social or vocational functioning; and 3 = marked improvement, with virtual or complete remission of symptoms allowing return to premorbid social or vocational functioning. Response on this scale was determined by review of hospital records. The rater of response (C.A.Z.) was blind to diagnosis and whether the patients were taking divalproex sodium or valproic acid. For the purposes of this report, *responders* refers to patients displaying a moderate-to-marked response (score of 2 or 3) to treatment and *nonresponders* refers to patients displaying no-to-minimal response (score of 0 or 1) to treatment.

The above information was supplemented with detailed reviews of medical records of all inpatients by the Pharmacy and Therapeutics Committee as part of a continuous quality improvement program to monitor adverse drug reactions (ADRs) associated with new drugs introduced into the hospital formulary. In this program, a trained pharmacist investigator visited each inpatient psychiatric unit several times a week to solicit voluntary reports from personnel regarding possible ADRs. All ADRs were reviewed by the ADR continuous quality improvement team (consisting of a psychiatrist, nurse, internist, and pharmacist) for a final decision as to the likelihood that the ADR was related to the drug.

For statistical analyses, categorical variables were compared using the chi-square test or 2-tailed Fisher exact test when expected cell sizes were less than 5. Continuous variables were compared using the Wilcoxon rank sum test or unpaired t test as appropriate.

RESULTS

Table 1 presents the socioeconomic and clinical comparison of the groups treated with either divalproex sodium or valproic acid. The 2 groups were comparable in mean age, gender (divalproex sodium = 49.3% female; valproic acid = 56.7% female), marital status, length of stay, age at onset, alcohol abuse, concomitant medical illness, seizure history, number of hospitalizations, history of lack of response or intolerance to lithium or carbamazepine, time to first dose, mean dose of divalproex sodium or valproic acid, and mean serum level of valproic acid (Table 1). Similarly, there were no differences in the diagnoses of patients between the groups, the most common diagnoses being bipolar disorder (divalproex sodium = 58.0%; valproic acid = 49.3%) and schizoaffective disorder (divalproex sodium = 30.0%; valproic acid = 36.7%), or in the proportion of responders in both groups (70.7% vs. 65.3%, NS; divalproex sodium vs. valproic acid, respectively; see Table 1). Patients treated with divalproex sodium were more likely to have q.d. (12.7% vs. 2.0%, $\chi^2 = 13.0$, df = 1, p = .0004) and b.i.d. (79.3% vs. 22.7%, $\chi^2 = 96.4$, df = 1, p = .0001) dosing and less likely to have t.i.d. (8.0% vs. 51.3%, $\chi^2 = 67.5$, df = 1, p = .0001) and q.i.d. (0% vs. 24.0%, Fisher exact test, p = .0001) dosing than patients treated with valproic acid.

Table 1. Sociodemographic Characteristics of Patients Treated With Divalproex Sodium and Valproic Acid

Variable	Divalproex Sodium (N = 150)	Valproic Acid (N = 150)
Age (mean ± SD)	44 ± 17	42 ± 16
Gender, female, N (%)	74 (49.3)	85 (56.7)
Length of stay, d (mean ± SD)	23 ± 20	27 ± 21
Age at onset, y (mean ± SD)	25 ± 11	28 ± 16
Marital status, single, N (%)	130 (86.7)	126 (84.0)
Diagnosis, N (%)		
Bipolar disorder	87 (58.0)	74 (49.3)
Schizoaffective disorder	45 (30.0)	55 (36.7)
Major depression	9 (6.0)	15 (10.0)
Schizophrenia, other	9 (6.0)	6 (4.0)
Alcohol abuse, N (%)	50 (33.3)	39 (26.0)
Medical illness, N (%)	21 (14.0)	25 (16.7)
History of seizure, N (%)	6 (4.0)	10 (6.7)
Number of hospitalizations (mean ± SD)	9 ± 7	10 ± 7
Intolerant to lithium, N (%)	58 (38.7)	46 (30.7)
Lack of response to lithium, N (%)	60 (40.0)	66 (44.0)
Intolerant to carbamazepine, N (%)	46 (30.7)	43 (28.7)
Lack of response to carbamazepine, N (%)	30 (20.0)	39 (26.0)
Time to first dose of divalproex sodium or valproic acid, d (mean ± SD)	3 ± 2	4 ± 3
Length of treatment on divalproex sodium or valproic acid, d (mean ± SD)	17 ± 15	19 ± 14
Dose of divalproex sodium or valproic acid, mg/d (mean ± SD)	1185 ± 412	1272 ± 456
Serum level of valproic acid, µg/mL (mean ± SD)	61 ± 12	64 ± 18
Frequency of dosing, N (%)		
qd [a]	19 (12.7)	3 (2.0)
bid [b]	119 (79.3)	34 (22.7)
tid [c]	12 (8.0)	77 (51.3)
qid [d]	0 (0)	36 (24.0)
Moderate-to-marked response (score 2 or 3), N (%) [e]	106 (70.7)	98 (65.3)

[a] $\chi^2 = 13.0$, df = 1, p = .0004.
[b] $\chi^2 = 96.4$, df = 1, p = .0001.
[c] $\chi^2 = 67.5$, df = 1, p = .0001.
[d] Fisher exact test, p = .0001.
[e] Response: 0 = no response, 1 = minimal improvement, 2 = moderate improvement, 3 = marked improvement.

Adverse Events

Both groups were as likely to have at least one side effect (divalproex sodium = 22.0%; valproic acid = 29.3%, NS); however, patients treated with divalproex sodium were less likely compared with patients treated with valproic acid to have gastrointestinal side effects (14.7% vs. 28.7%, $\chi^2 = 8.6$, df = 1, p = .003), specifically anorexia (6.0% vs. 14.7%, $\chi^2 = 6.1$, df = 1, p = .012), nausea or vomiting (6.7% vs. 16.7%, $\chi^2 = 7.3$, df = 1, p = .007), and dyspepsia (11.3% vs. 22.0%, $\chi^2 = 6.1$, df = 1, p = .013)

Table 2. Adverse Events Associated With Divalproex Sodium and Valproic Acid*

	Divalproex Sodium (N = 150)		Valproic Acid (N = 150)	
Adverse Event	N	%	N	%
Gastrointestinal side effect[a]	22	14.7	43	28.7
Anorexia[b]	9	6.0	22	14.7
Nausea/vomiting[c]	10	6.7	25	16.7
Dyspepsia[d]	17	11.3	33	22.0
Diarrhea	6	4.0	8	5.3
Rashes	4	2.7	5	3.3
Hair loss	7	4.7	5	3.3
Fatigue	18	12.0	22	14.7
Headache	13	8.7	17	11.3
Tremor	24	16.0	27	18.0
Increased appetite/ weight gain	16	10.7	21	14.0
Any side effect	33	22.0	44	29.3
Discontinuation due to gastrointestinal side effect[e]	6	4.0	19	12.7

*Patients may have more than one side effect.
[a]$\chi^2 = 8.6$, df = 1, p = .003.
[b]$\chi^2 = 6.1$, df = 1, p = .012.
[c]$\chi^2 = 7.3$, df = 1, p = .007.
[d]$\chi^2 = 6.1$, df = 1, p = .013.
[e]$\chi^2 = 7.4$, df = 1, p = .0066.

Table 3. Concomitant Psychotropic Medications[a]

	Divalproex Sodium (N = 150)		Valproic Acid (N = 150)		
Medication	N	%	N	%	p Value
Antidepressants SSRIs	34	22.7	46	30.7	.117
Other antidepressants	10	6.7	13	8.7	.515
Antipsychotic drugs	77	51.3	67	44.7	.247
Benzodiazepines	61	40.7	72	48.0	.201
Carbamazepine	11	7.3	8	5.3	.477
Lithium salts	55	36.7	69	46.0	1.0
Other psychotropic medications	19	12.7	11	7.3	.123

[a]Abbreviation: SSRIs = selective serotonin reuptake inhibitors.

(Table 2). However, there were no significant differences in the rates of diarrhea (4.0% vs. 5.3%, $\chi^2 = 6.0$, df = 1, NS), rashes (2.7% vs. 3.3%, NS), hair loss (4.7% vs. 3.3%, NS), fatigue (12.0% vs. 14.7%, NS), headache (8.7% vs. 11.3%, NS), tremor (16.0% vs. 18.0%, NS), or increased appetite/weight gain (10.7% vs. 14.0%, NS) between both groups. Also, there were no differences in mean aspartate aminotransferase levels, alanine aminotransferase levels, ALP levels, total and direct bilirubin levels, WBC count, and platelet count between the 2 groups.

Patients treated with divalproex sodium were less likely compared with valproic acid–treated patients to have discontinued the medication because of gastrointestinal side effects (4.0% vs. 12.7%, $\chi^2 = 7.4$, df = 1, p = .0066; see Table 2). However, there were no differences in discontinuation rates due to lack of response in patients treated with divalproex sodium compared with patients treated with valproic acid (3.3% vs. 5.3%, NS).

Twelve (63.2%) of 19 patients who discontinued valproic acid because of gastrointestinal side effects were subsequently treated with divalproex sodium, of whom only 2 continued to have gastrointestinal side effects. Four patients treated with divalproex sodium were treated with valproic acid for an average of 4 days because of suspected noncompliance, after which all patients were continued with divalproex sodium.

There was also no difference in the use of concomitant psychotropic medications between patients treated with divalproex sodium and valproic acid (Table 3). Additionally, there were no differences between the groups in the rates of H_2 antagonists used (divalproex sodium = 8%, valproic acid = 13%, NS).

DISCUSSION

These data suggest that divalproex sodium was better tolerated than valproic acid in inpatients with a variety of diagnoses and taking concomitant medications. Methodological limitations may limit the generalizability of the present report. Data were collected retrospectively by reviewing medical records. As such, there is a possibility that adverse events were underreported. However, the rates of gastrointestinal side effects in the present study were within the range of 3% to 22% reported in other studies.[8,21] In addition, in cases of clinically important adverse effects, the data collected by chart review were compared with, and found congruent with, information gathered by extensive case reviews obtained by a continuous quality improvement program at the study site that involves the departments of psychiatry, medicine, nursing, and pharmacy at the study site.

In the present study, we found that patients treated with divalproex sodium compared with patients treated with valproic acid were less likely to experience gastrointestinal side effects (anorexia, nausea/vomiting, and dyspepsia). In addition, divalproex sodium–treated patients were less likely to have discontinued the medication because of an adverse event. Furthermore, of 12 patients who discontinued valproic acid because of gastrointestinal side effects and were subsequently treated with divalproex sodium, 83% (10/12) had no recurrence of the gastrointestinal side effects. Possible explanations for the differences in rates of gastrointestinal side effects between divalproex sodium and valproic acid groups include differences in dosage of divalproex sodium or valproic acid or differences in serum valproic acid levels, frequency of dosing, the use of concomitant medications that may in themselves cause gastrointestinal side effects (e.g., selective serotonin

reuptake inhibitors), or the use of H_2 antagonists, which may decrease gastrointestinal side effects (ranitidine, cimetidine, and famotidine).[30] However, we found no differences in these variables between the groups (see Table 1). Furthermore, divalproex sodium–treated patients were more likely to have once-daily and twice-daily dosing than valproic acid–treated patients. Minimizing the frequency of daily dosing has been suggested to help with the adherence to the treatment regimen.[31]

Another possible explanation for the differences between the 2 groups may be an institutional bias (e.g., cost or some other type of restriction); however, no restrictions exist for the prescribing of these medications at our institution. Selection of divalproex sodium and valproic acid was made by clinician's choice. A more likely explanation for these differences is that divalproex sodium is enteric coated and likely better tolerated on the gastric mucosa.[27] Valproic acid immediately releases into the stomach, and absorption occurs within minutes. As a result, the serum concentration levels have a rapid peak, which is associated with gastrointestinal irritation. In contrast, the enteric-coated presentation prevents the release of divalproex sodium until it reaches the small intestine, in turn leading to an apparent decrease in the initial gastrointestinal adverse effects.

In conclusion, divalproex sodium was as effective as, but better tolerated than, valproic acid in the treatment of a variety of inpatient psychiatric disorders.

Drug names: carbamazepine (Tegretol and others), cimetidine (Tagamet), divalproex sodium (Depakote), famotidine (Pepcid), ranitidine (Zantac), valproic acid (Depakene and others).

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