Divalproex Sodium Versus Valproic Acid in Hospital Treatment of Psychotic Disorders

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Background: Approximately 50% of pharmacy prescriptions in the United States are filled with generic drugs, which have improved substantially in quality owing to increased governmental regulations. The remaining medicoeconomic question regards whether or not brand-name medications are worth the price. This study evaluates these questions for the brand-name mood stabilizer divalproex sodium and its generic counterpart, valproic acid.

Method: We conducted a retrospective chart review of all patients who had been taking divalproex and had been switched to valproic acid at 2 local mental health facilities in 1997. Data collected from the inpatient- and day-treatment charts for these 28 patients included dose, duration, side effects, and efficacy (determined using retrospective chart review and the Clinical Global Impressions scale [CGI]) of divalproex sodium compared with valproic acid treatment.

Results: t Tests for dependent samples revealed that valproic acid was administered at higher doses than divalproex sodium, but these treatments did not differ in efficacy on the basis of CGI scores. Fisher exact test analyses revealed a trend toward more nausea with valproic acid; also, the combination of nausea, abdominal discomfort, and diarrhea occurred more often in valproic acid–treated patients. There were no differences in the discontinuation of either medicine because of side effects, or in the use of medications to treat gastrointestinal side effects. Efficacy was similar for valproic acid and divalproex sodium. There was no single, significant side effect increase for valproic acid; however, when grouped together, gastrointestinal side effects were statistically significantly increased in valproic acid–treated patients. This appears clinically insignificant because of the lack of difference in drug discontinuation rate or gastrointestinal medication use.

Conclusion: Given these results and that valproic acid is much less expensive than divalproex sodium, valproic acid appears to be a satisfactory substitution for divalproex sodium in the treatment of frequently hospitalized psychotic patients.

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Choosing and tailoring cost-effective pharmacologic treatments for patients has been an area of interest for many years. When treating an individual for a specific condition, the clinician must choose a treatment that will improve the condition, achieving the best clinical outcome at the lowest cost. This approach is necessary to satisfy patients while minimizing the cost of health services. The advent of managed care has increased the emphasis on evaluating the economics of treatment options, which requires a better understanding of available treatment resources.

The use of generics instead of brand-name drugs has contributed to a decrease in medical spending.[1] This medicoeconomic issue has been extensively researched, especially in psychiatry. For example, the use of generic lithium as a treatment for bipolar disorder has saved $4 billion in the United States.[2]

The U.S. Food and Drug Administration (FDA) approved valproic acid in 1978 for the treatment of seizure disorder and approved divalproex sodium, its enteric-coated counterpart, in 1986 for the same indication. Few issues were raised in the use of these medications for seizure control; therefore, few studies were performed to compare them when the latter drug was introduced. These drugs had been studied in the past, and their anticonvulsant efficacies were equivalent. One study found valproic acid to be economically superior to divalproex sodium,[3] even when their differences in pharmacokinetic and side effect properties were considered.[4,5]

These differences have raised concerns about the use of valproic acid and divalproex sodium, since the costs of these drugs differ significantly. The cost of drugs is particularly important when treating psychiatric illnesses, which contribute significant and burdensome costs to most health care systems. As with other comparisons of generics and brand-name medications, whether 1 of these 2

mood-stabilizing drugs is more cost effective should be determined.

One recent review found that the side effects of valproic acid are so severe that the expense of divalproex sodium is warranted.[6] However, a review of the literature provided scarce data comparing valproic acid and divalproex sodium for cost-effectiveness. Therefore, this study was designed to investigate the impact of generic substitution of valproic acid for divalproex sodium at a local state psychiatric hospital and an outpatient continuing day program. The hospital switched from divalproex sodium to valproic acid to cut costs, hoping that valproic acid would be as effective as divalproex sodium. The hospital assumed that the incidence of side effects would be higher with valproic acid, but that these could be ameliorated with lower-cost gastrointestinal (GI) medications. Hypotheses included the following: (1) efficacy would be equivalent in patients who could tolerate therapeutic doses of either medication, (2) effective doses of valproic acid and divalproex sodium would be equal on a per-patient basis, (3) the noncompliance and dropout rates for valproic acid would be higher because of side effects, and (4) valproic acid–treated patients would have a higher concomitant use of GI medications. This study was designed to determine if this generic substitution was worthwhile and cost-effective.

METHOD

A local state psychiatric hospital, Hutchings Psychiatric Center (Syracuse, N.Y.), switched all inpatients who were taking the brand-name drug divalproex sodium to the generic valproic acid in 1997. In addition, intensively treated outpatients treated in the Cattaraugus County Continuing Day Treatment Program (Olean, N.Y.) were also switched. We performed a retrospective chart review of all of the patients who were involved in this switch. Data on dosage, frequency, blood drug levels, adverse effects, use of GI medications, diagnosis, and efficacy were collected. Efficacy was measured on the basis of relapse of symptoms, hospital admission recidivism, and Clinical Global Impressions scale (CGI) scores for each treatment by reviewing all chart notes during the study period. The CGI is a 7-point rating scale ranging from "very much worsened" to "very much improved" and relates to the clinical change of each patient.

Patients switching from divalproex sodium to valproic acid initially received valproic acid at the same dosage and dosing frequency as with divalproex sodium. Doses were usually divided for inpatients. The dosage of valproic acid was then adjusted for each patient on the basis of his or her response. Any use of medications to treat valproic acid–related side effects was noted.

Compliance was near 100%, since most patients were in inpatient wards and drug use was monitored. Blood levels and discontinuation rates were obtained through chart laboratory sheets and order sheets, yielding a statistical comparison between divalproex sodium and valproic acid treatment. Statistical analyses were performed on the collected data using standard software (StatSoft, Tulsa, Okla.). Dependent t tests and Fisher exact test analyses were run where appropriate.

Table 1. Demographics of Patients Switched From Divalproex Sodium to Valproic Acid (N = 28)

Variable	N	%
Gender		
Male	11	39.3
Female	17	60.7
DSM-IV diagnosis		
Schizophrenia		
Undifferentiated	5	17.9
Paranoid	4	14.3
Disorganized	2	7.1
Residual	1	3.6
Schizoaffective disorder	8	28.6
Bipolar disorder	5	17.9
Dementia not otherwise specified	1	3.6
Major depressive disorder	2	7.1

RESULTS

Charts of 28 patients were reviewed. Eleven (39%) were male and 17 (61%) were female. Table 1 shows patient demographics and DSM-IV diagnoses. Schizoaffective disorder was the most common diagnosis, followed by undifferentiated schizophrenia and bipolar disorder. Patient age ranged from 23 to 75 years (mean ± SD = 45.64 ± 13.37 years).

The mean ± SD dose of divalproex sodium before switching to valproic acid was 1205 ± 646 mg/day, and the mean dose of valproic acid after switching was 1554 ± 1021 mg/day; this difference was statistically significant (Table 2). Duration of treatment on divalproex sodium was 0.25 to 60 months (mean = 15.30 ± 15.79 months). Duration of valproic acid after the switch from divalproex sodium ranged from 0.30 to 12 months (mean = 7.21 ± 3.90 months). Blood divalproex sodium levels ranged from 32.0 to 107.0 mg/dL (mean = 68.39 ± 19.94 mg/dL). Blood valproic acid levels after the switch from divalproex sodium ranged from 16.0 to 95.0 mg/dL (mean = 64.36 ± 19.73 mg/dL). Olanzapine (N = 12), clonazepam (N = 7), and risperidone (N = 5) were the most commonly coprescribed standing medications in this population. Only 10 other standing nonpsychiatric prescriptions were given to these patients, and only 1 of these was a medication for GI problems.

CGI scores were similar for both groups: 2.75 ± 0.93 and 2.93 ± 1.05 for divalproex sodium and valproic acid, respectively, revealing insignificant clinical changes with the switch from divalproex sodium to valproic acid. Side effects were minimal when addressed separately. There

Table 2. Dosing and Efficacy of Divalproex Sodium Versus Valproic Acid (N = 28)[a]

Variable	Divalproex Sodium	Valproic Acid	t	df	p Value
Dose, mg/d mean ± SD[b]	1205 ± 646	1554 ± 1021	–2.07	27	.048
CGI score, mean ± SD	2.75 ± 0.93	2.93 ± 1.05	–1.04	27	.305
No. of discontinuations	5	5			1.000[c]
No. of GI medications prescribed	0	1			.500[c]

[a]Abbreviations: CGI = Clinical Global Impressions scale, GI = gastrointestinal.
[b]Significant difference between divalproex sodium and valproic acid.
[c]Fisher exact test p value.

Table 3. Side Effects of Divalproex Sodium and Valproic Acid (N = 28)[a]

Variable	Divalproex Sodium	Valproic Acid	Fisher Exact Test p Value
GI side effects			
Nausea	0	4	.0557
Abdominal discomfort	0	3	.1182
Diarrhea	0	1	.5000
Total GI side effects[b]	0	8	.0022
Sedation	2	0	.4909
Tremors	1	1	.7545
Weight gain	0	0	1.000
Hair loss	1	0	.5000

[a]Abbreviation: GI = gastrointestinal.
[b]Significant difference between divalproex sodium and valproic acid.

was a trend toward increased nausea in valproic acid patients. When all GI side effects were combined, however, there was a significant increase in side effects with valproic acid compared with divalproex sodium (Table 3). Five patients (18%) discontinued divalproex sodium treatment and 5 (18%) stopped valproic acid treatment (no significant difference; see Table 2). No differences were found between groups in concurrent use of GI medications such as antacids (see Table 2).

DISCUSSION

In many fields of medicine, including psychopharmacology, pressures exist to find the best drug for the lowest price. The use of generic drugs is increasing, and the high quality of many generic drugs has been documented. Many new psychopharmacologic agents are not yet available generically, but many of the common mood stabilizers are available as generics, including lithium, carbamazepine, and valproic acid. However, few published studies have compared the brand-name mood stabilizer divalproex sodium with its generic counterpart, valproic acid.[7–9] Most clinicians consider divalproex sodium to be the first-line treatment for bipolar disorder, but it is much more expensive than valproic acid. Similarly, divalproex sodium is becoming a first-line medication for use in impulsive and agitated patients, rather than as-needed neuroleptics.

At Hutchings Psychiatric Center in 1998, one hundred 250-mg tablets of divalproex sodium cost $67.00, whereas one hundred 250-mg tablets of valproic acid cost $6.00, a 121-fold difference. These data suggest that the cost of divalproex sodium ($1162.80 per patient per year) is not justified because valproic acid is as effective (at $133.20 per patient per year). In addition, the side effect profile of valproic acid in this patient sample was statistically worse in some instances, but the difference was clinically less significant in that discontinuations and GI medication use were similar for both drugs. The generic substitution of valproic acid for divalproex sodium appears clinically acceptable in this population of severely and chronically ill patients.

Significantly higher doses of valproic acid than those of divalproex sodium were required to achieve the same therapeutic response. Valproic acid is metabolized more rapidly than divalproex sodium, which could explain the need for higher doses. However, even at higher doses, treatment with valproic acid is still less expensive than with divalproex sodium because of the difference in price.

This study has some limitations. The sample size is small, and significant differences in clinical improvement and side effect rates may evolve with larger numbers of patients. As with all retrospective reviews, charting may have been incomplete; some mild side effects and clinical changes may have been omitted, which might have obscured differences in CGI scores and side effect ratings.

Blinding of chart reviewers was impossible because the medications were named frequently in the charts. Some patients may have been switched from divalproex sodium to valproic acid early in the treatment course, resulting in a lower efficacy rating for divalproex sodium. This does not seem to have occurred, given the average divalproex sodium treatment of 15 months. Fifteen months with therapeutic blood levels also constitutes a very thorough therapeutic trial. Additionally, many more side effects would be expected in the patients receiving higher doses of valproic acid later in the course of treatment, but this did not occur, showing reasonable tolerability of valproic acid. Noncompliance was not a problem with this population, since most patients were hospitalized. Because valproic acid usually requires multiple doses per day, and because a trend occurred toward increased GI side effects, compliance and effectiveness might be decreased in less severely ill outpatients. A larger sample size, prospective charting, better use of outcome measures and rating scales, and standardization of treatment regimens are improvements that could be instituted in another study, but were not possible because of the retrospective design of this study.

Despite these limitations, this study lends further input to the existing literature in determining the cost-effectiveness of treating patients with valproic acid or divalproex sodium. For example, the above findings replicate those of Sherr and Kelly's prospective study,[9] in which a similar therapeutic switch maintained efficacy with good tolerability. Similarly, we hypothesized that divalproex sodium and valproic acid would be equally effective and that valproic acid would have a higher rate of side effects. This hypothesis was partially correct: valproic acid and divalproex sodium appear to have equivalent efficacy in the treatment of hospitalized, chronically psychotic patients. Surprisingly, contrary to the literature, the side effect profile of valproic acid does not appear clinically significantly different since discontinuation rates in the 2 groups were similar. The results of this study suggest that valproic acid is an adequate generic or substitutive agent for the treatment of inpatient psychiatric patients: it costs less than divalproex sodium and produces a similar treatment outcome.

Drug names: carbamazepine (Tegretol and others), clonazepam (Klonopin and others), divalproex sodium (Depakote), lithium (Eskalith and others), olanzapine (Zyprexa), risperidone (Risperdal), valproic acid (Depakene and others).

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