

Pharmacoeconomic and Health Outcome Comparison of Lithium and Divalproex in a VA Geriatric Nursing Home Population: Influence of Drug-Related Morbidity on Total Cost of Treatment

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Abstract

Objective: Clinicians use mood stabilizers for treating agitation in older patients, but limited information is available regarding side effects and costs in clinical practice. Total costs of treatment were assessed for a subset of geriatric patients receiving either lithium carbonate or divalproex sodium for agitation.

Study Design: Retrospective cohort examination of the medical records of 72 patients, 55 years of age or older, in a Veterans Administration long-term, skilled nursing care facility, with a diagnosis of dementia or bipolar affective disorder or both.

Patients and Methods: Patients treated with lithium or divalproex during the previous 4 years (1994–1997) were evaluated. Quantitative information was collected and compared regarding routine care, including cost of treatment and laboratory monitoring; and occurrence of adverse events and associated diagnostic and treatment measurements.

Results: Routine care costs for the 2 groups were similar. The lower annual acquisition cost per patient-year for lithium (\$15 vs \$339 for divalproex) was offset by higher laboratory monitoring costs associated with its administration (\$278 vs \$53 for divalproex). Examining the adverse events showed that the lithium group had more medication-related adverse events (32 total) than the divalproex group

(10 total) and more severe occurrences, including 6 cases requiring medical intensive care unit (MICU) hospitalization. The total mean cost of treating drug-related mild-to-moderate morbidity was \$3472 for lithium and \$672 for divalproex. An additional cost per admission of \$12,910 (\$77,462 for all 6 cases) increased total morbidity-related expenditures in the lithium group to \$80,934.

Conclusions: Treating geriatric patients with lithium requires careful monitoring because of side effects. Staffing and resource limitations of a skilled nursing care facility may compromise optimal lithium monitoring in elderly patients. The collected data indicated that divalproex does not result in as many as or as severe adverse events and is, therefore, a safer treatment. The use of lithium was not only more expensive (on average \$2875 more per patient) than treatment with divalproex but, more importantly, it was associated with poorer patient outcomes.

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Persons over 65 years of age are the fastest growing population segment. Currently, this age group comprises 34 million Americans and will climb to more than 50 million in the next 25 years. Of the geriatric population, approximately 2 million reside in long-term care settings (ie, nursing homes). To place this in perspective, less than 1 million persons of any age are treated in acute, inpatient settings each year in the United States. Of the geriatric nursing home patients, approximately 1.5 million have dementia and many of these have a concomitant mood disorder (usually unipolar or bipolar depression).¹ Agitation is a significant behavioral

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problem occurring in 60-80% of geriatric patients^{1,2} with DSM-IV diagnosis of dementia and/or mood disorder.³ Treating this effectively will be one of the biggest challenges facing clinicians. Geriatric patients with agitation, with or without concomitant bipolar affective disorder, are often treated with lithium carbonate or divalproex sodium, 2 drugs that have demonstrated effectiveness in bipolar affective disorder.⁴⁻⁶ These are the only drugs that are approved by the US Food and Drug Administration for use in the United States as monotherapy of mania in patients with bipolar affective disorder. Some refractory patients have responded to combination therapy with both drugs.⁹ Lithium and divalproex are widely used and generally accepted as the primary choices for the 1.8 million people in the United States currently receiving treatment for bipolar affective disorder. Although formerly considered the best choice, lithium is not presently used as widely as it once was. Recent literature has demonstrated divalproex as superior to lithium in treating rapid cyclers and mixed states (accounting for 40-60% of all episodes) and equally efficacious in classic mania. Common problems such as cognitive dulling, renal dysfunction, and dehydration associated with lithium limit its usefulness in the geriatric population. Divalproex is better tolerated and leads to greater compliance and shorter hospital stays.⁸⁻¹³ Over a 3-year period, divalproex use had risen from 23% to 60%, and lithium use declined from 71% to less than 40%.¹¹ In long term follow-up studies, response to lithium is less than 50%, and of patients initially treated with lithium, only 30% remain on this treatment at the end of 2 years, mainly due to intolerability of side effects.^{10,11} It is becoming clear that by examining outcomes in clinical settings, tolerability of medications is an important factor for compliance and long-term treatment success.^{9-11, 14, 15}

Divalproex is an effective treatment for the behavioral disturbances associated with dementia in geriatric patients, and for uncontrolled aggressive behavior associated with other psychiatric disorders.¹⁶⁻²¹ Lithium is also used to control behavioral disturbances but has not been evaluated as extensively. In addition, its use in elderly patients can lead to serious sequelae, including dehydration, confusion, and delirium.^{19,21,22} At present, only limited information is available comparing the side effects and costs of these drugs in clinical practice.

Early published cost comparisons of the use of psychotropic medications often focused narrowly on

the issue of medication cost. Although pharmacologic treatment cost is an important component of the overall cost of therapy, it is usually not the most significant cost factor over the long term, especially among geriatric patients who require hospitalization and/or skilled nursing care. Many other factors, including the costs of acute hospitalization, supportive laboratory tests, and associated health services required to manage medication-related adverse events, should be considered when assessing the overall economic impact and patient outcome of psychotropic therapy.

The selection of appropriate pharmacotherapy not only contributes to psychiatric improvement but ideally results in a minimal incidence of side effects and related morbidity. A number of side effects associated with lithium have been described, including deficits in cognitive and motor functions, gastrointestinal upset, weight gain, dermatologic problems, lethargy, excessive urination, and thirst.²³ For the elderly patient population in particular, an inherent risk exists for dehydration and fluid imbalances resulting from reductions in intake of both solid foods and liquids. When treating these patients with lithium, there is an increased propensity for these risk factors and the subsequent health risks that follow.²⁴⁻²⁶ During our routine assessments of agitated geriatric patients residing in a long-term, skilled nursing care facility, observations were made suggesting that patients who were treated with lithium experienced a greater degree of drug-related morbidity than those treated with divalproex. Consequently, we decided to investigate the factors that could assist in determining whether lithium or divalproex would best serve as first-line therapy for patients based on both pharmacoeconomic and health outcomes. No previous studies have directly compared pharmacoeconomic outcomes following the use of these drugs in a population with increased susceptibility to adverse side effects, such as residents of a long-term, skilled nursing care facility.

This study was designed to examine the relevant costs associated with the use of lithium and divalproex as pharmacologic therapy for geriatric patients with agitation and a diagnosis of dementia, with or without concurrent bipolar affective disorder. Since this study was not intended to assess the efficacy of divalproex or lithium in controlling agitation in the elderly population, patients taking concomitant neuroleptics or benzodiazepines were not excluded. Health outcomes were noted informally as occurrences of adverse events.

... METHODS ...

This was a retrospective examination of the medical records of a cohort of elderly patients, aged 55 years or older, residing at a long-term, skilled nursing care facility located at the Veterans Administration (VA) Medical Center, Long Beach, California. The patients had been treated with either lithium or divalproex during the previous 4 years (1994–1997) for agitation with a diagnosis of dementia (DSM-IV-290) and behavioral disturbances with or without concurrent bipolar affective disorder (DSM-IV-296).³

Seventy-two patients were identified in the divalproex and lithium treatment groups, and none were excluded from the analysis. Divalproex and lithium were administered orally to 44 and 28 patients at average doses of 750 and 600 mg/d, respectively. Although none of the patients in the divalproex group were switched to lithium during the 4-year period, 15 patients in the lithium group were subsequently changed to divalproex after experiencing a lithium-related adverse event. These patients were switched to divalproex from an average lithium dose of 300 mg twice daily. Divalproex was titrated gradually, starting at an oral dose of 125 mg twice daily and increased as needed up to 2000 mg/d for behavioral control. Data collected for switched patients included only the costs incurred while they were undergoing lithium treatment.

Quantitative information regarding the costs of medical treatment and morbidity for these patients was collected systematically. For each patient, costs were estimated for the entire stay at the facility and separated into 2 categories: (1) routine care, including bed space and general nursing care at the skilled nursing facility, overhead, medication (divalproex or lithium), and routine treatment-related laboratory monitoring; and (2) adverse events associated with lithium or divalproex use, including additional laboratory monitoring, intravenous fluids, further treatment interventions, and medical intensive care unit (MICU) costs. Adverse events were deemed mild-to-moderate or severe (ie, requiring MICU hospitalization). Only those services that were confirmed to be due to drug treatment

were included. Costs of medical treatment for each patient were standardized using figures available for October 1997. Information regarding cost of stay, pharmacotherapy, and laboratory charges was obtained from the fiscal office, pharmacy, and medical laboratory, respectively. These data permitted the average overall cost of treatment to be determined.

In addition, the incidence of the following adverse events was evaluated based on the chart review: hepatotoxicity, thrombocytopenia, leukocytosis, renal insufficiency, hypothyroidism, drug toxicity (increased serum levels), and/or dehydration, as these are the most common adverse effects of divalproex and lithium.^{9, 10, 13, 25-27} Acute hospitalizations in the MICU were also evaluated, and only those attributed to drug toxicity were included in the analysis of costs due to adverse events. The average and total costs for a 1-week admission to the MICU were calculated for the following components: MICU hospitalization, electrocardiogram monitoring, intravenous rehydration, laboratory tests, and emergency measures to treat drug toxicity.

... RESULTS ...

Seventy-two patients were assessed. At the inception of the study period, 28 patients were treated

Table 1. Routine Initial Treatment Costs* Associated with Lithium Carbonate or Divalproex Sodium Treatment

Cost Component	Lithium Carbonate (US\$, n = 28)	Divalproex Sodium (US\$, n = 44)
Skilled care facility [†]	102,200	102,200
Pharmacologic therapy	15	339
Associated laboratory tests	278 [‡]	53 [§]
Total costs	102,493	102,592

*Mean overall costs per patient per year excluding costs associated with adverse events.

[†]Long-term, skilled nursing care facility cost: \$190 per day plus \$90 per day in overhead per patient, for a total cost of \$280 per day.

[‡]Lithium level, on average 7 times per year; complete blood cell count (CBC), on average 9 times per year; sodium, potassium, blood urea nitrogen, creatinine, chloride, carbon dioxide, glucose (Panel 7), on average 8 times per year; and thyrotropin, thyroxine, triiodothyronine, on average 2 times per year.

[§]Divalproex level and CBC, on average 3 times per year; aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyltransferase, on average 4 times per year.

Table 2. Occurrences of Morbidity Related to Initial Drug Therapy

Morbidity	Lithium Carbonate (n = 28)	Divalproex Sodium (n = 44)
Toxicity and/or dehydration*	19	3
MICU hospitalizations	6	0
Leukocytosis [†]	7	0
Thrombocytopenia [†]	0	4
Hepatotoxicity [†]	0	3
Total occurrences	32	10

MICU = medical intensive care unit.

*As evidenced by an increased serum level over therapeutic levels (lithium, 0.6 to 1.2 mEq/L; divalproex, 50 to 120 µg/mL) and/or clinical signs or symptoms.

[†]Indicated by abnormal values on serum test results.

with lithium (26 men and 2 women; mean age, 67 years) and 44 were treated with divalproex (41 men and 3 women; mean age, 71 years). All patients were prescribed either lithium or divalproex by their personal physicians before entering the skilled nursing care facility. Patients with dementia and agitation with and without bipolar affective disorder were present in both treatment groups.

Cost Assessments

As shown in Table 1, the mean overall routine costs (excluding the costs due to adverse events) of maintaining a patient in this long-term, skilled nursing care facility were essentially identical for treatment with either lithium (\$102,493; 600 mg/d average dose) or divalproex (\$102,592; 750 mg/d average dose), although the component costs differed. The annual mean acquisition cost of divalproex (\$339) was higher than that of lithium (\$15); however, the difference was largely offset by the higher annual cost of laboratory tests associated with lithium therapy (\$278 vs \$53).

The most common adverse events are presented in Table 2. Toxicity related to elevated drug levels and/or dehydration was the most common event reported in the lithium group (19 patients); thrombocytopenia was the most common event in the divalproex group (4 patients). Total adverse event occurrences were 3 times higher in the lithium group (32) than in the divalproex group (10). Leukocytosis is also very common in patients treated with lithium.²⁷ Although it is usually not clinically relevant, a laboratory finding of leukocytosis requires increased blood monitoring to rule out infection, with a resulting increase in associated costs. As shown in Table 3, the additional costs associated with the mild-to-moderate adverse events were \$3472

Table 3. Costs Associated with Mild-to-Moderate Morbidity* Related to Drug Therapy

Morbidity	Lithium Carbonate (US\$; n = 28)	Divalproex Sodium (US\$; n = 44)
Toxicity and/or dehydration	3236 [†]	368 [‡]
Leukocytosis	166 [§]	0
Thrombocytopenia	0	172 [¶]
Hepatotoxicity	0	123 ^{¶¶}
Rehydration with intravenous fluids	71 ^{**}	9 ^{**}
Total costs	3472	672

CBC = complete blood cell count; TSH = thyrotropin.

*Not including admission to the medical intensive care unit.

[†]Nineteen patients requiring additional lithium level, CBC, TSH, and Panel 7.

[‡]Three patients requiring additional divalproex level, CBC, liver function tests, and Panel 7.

[§]Seven patients requiring additional CBC and urinalysis.

[¶]Four patients requiring additional CBC and divalproex level; each case resolved.

^{¶¶}Three patients requiring additional liver function tests and 1 requiring hepatitis panel; each case resolved without additional intervention.

^{**}Fifteen patients requiring normal saline with potassium chloride (54% of the lithium-treated group).

^{**}Two patients requiring normal saline with potassium chloride (5% of the divalproex-treated group).

in the lithium group and \$672 in the divalproex group, a difference of \$2800. All of the divalproex-related adverse events listed in Table 2 resolved spontaneously without additional treatment. Costs related to thrombocytopenia and hepatotoxicity in divalproex-treated patients are those associated with increased laboratory monitoring.

None of the divalproex-treated patients required MICU hospitalization. In contrast, 6 (21%) of the 28 patients in the lithium group with an adverse event required MICU admission. All 6 patients had lithium toxicity, and reducing the serum lithium level enabled each patient to be discharged. These 6 MICU admissions increased the cost of treatment for the lithium group by \$12,910 per patient, resulting in a total severe morbidity cost of \$77,462 for this group. In contrast, there were no severe morbidity costs incurred in the divalproex-treated group (Table 4).

Overall, in this 4-year study, the total mean costs of drug treatment-related morbidity were \$2890 per patient with lithium and \$15 per patient with divalproex, yielding an increase in cost per patient of \$2875 with lithium (Table 5).

... DISCUSSION ...

The findings of this study indicate that patient outcomes, as measured by fewer and less severe occurrences of adverse events, were much better in the divalproex group. In addition, it was determined that this VA institution expended an additional \$80,262 (ie, \$2875 per patient) treating geriatric patients with agitation and a diagnosis of dementia and/or bipolar affective disorder using lithium rather than divalproex.

Although the annual acquisition cost of lithium 600 mg daily (\$15) was lower than that of divalproex

Table 4. Total Costs Associated with Severe Morbidity as Determined by the Need for MICU Hospitalization (average toxic lithium level, 2.1 mEq/L)

Cost Component	Lithium Carbonate (US\$; n = 28)	Divalproex Sodium (US\$; n = 44)
MICU (1-week admission)	12,299*	0
ECG monitoring	240	0
Intravenous fluid rehydration	31 [†]	0
Laboratory tests	327 [‡]	0
Emergency measures for toxicity	13 [§]	0
Cost per patient	12,910	0
Total costs	77,462 [¶]	0

MICU = medical intensive care unit; ECG = electrocardiogram.

*MICU hospitalization for 1 week at \$1171 per day plus overhead costs of \$586 per day, for a total cost of \$1757 per patient per day.

[†]Intravenous fluid rehydration with 23 bags of normal saline plus 20-mEq potassium chloride per week.

[‡]Lithium level on average 6 times per week; complete blood cell count with differential on average 9 times per week; Panel 7, on average 14 times per week; urinalysis, on average 4 times per week.

[§]Gastric lavage and activated charcoal intervention.

^{||}Per 1 MICU hospitalization.

[¶]Total for all 6 MICU hospitalizations.

Table 5. Differences in Morbidity or Adverse Event-Related Costs Associated with Lithium Carbonate Versus Divalproex Sodium Treatment

	Lithium Carbonate (US\$; n = 28)	Divalproex Sodium (US\$; n = 44)
Cost associated with mild-to-moderate morbidity*	3472	672
Cost associated with MICU stays [†] (severe morbidity)	77,462	0
Total cost [‡]	80,934	672
Total cost per patient [§]	2890	15

MICU = medical intensive care unit.

*Total costs associated with mild-to-moderate morbidity (see Table 3).

[†]Total MICU costs for all 6 patients (see Table 4).

[‡]Difference in total cost between lithium and divalproex groups: \$80,261.63.

[§]Difference in total cost per patient: \$2875.22.

750 mg daily (\$339), the difference was offset by the higher cost of laboratory testing required to monitor the safety of lithium therapy. Mean annual laboratory test costs for the lithium group were approximately \$278 compared with \$53 for the divalproex group. The use of laboratory tests varied somewhat, with most patients in the divalproex group being tested an average of 4 times per year, and patients treated with lithium being tested approximately 7 to 12 times per year, depending on their overall status. Frequent monitoring of lithium levels is indicated in patient populations at increased risk for side effects associated with toxicity because small changes in serum levels can have a substantial impact on a patient's health. Some authors have proposed monitoring as frequently as every 2 months in at-risk situations.²⁸⁻³⁵ The average lithium level in patients not requiring MICU hospitalization was 1.4 mEq/L (which is above the therapeutic range) despite frequent monitoring. This demonstrates the difficulty of achieving stable therapeutic levels of lithium in this patient population.

The additional costs associated with drug-related side effects should be included in an assessment of the total cost of therapy, along with the initial routine costs of treatment. One of the major limitations to lithium therapy is the high incidence of adverse events and cognitive deficits that occurs within the therapeutic serum concentration range (0.6 to 1.2 mEq/L),^{12,35-39} as well as in the toxic range.^{26,36} Six patients had average toxic serum lithium levels of 2.1 mEq/L (range, 1.4 to 3.9 mEq/L) and required MICU hospitalization. This has important implications for the elderly population as they are particularly sensitive to adverse events. Maintaining non-toxic serum lithium levels in the elderly is a clinical challenge, and sequelae of toxicity, including dehydration, weakness, dizziness, hypothyroidism, diarrhea, renal dysfunction, and deterioration of cognitive function and neurotoxicity, are not uncommon. Even patients with therapeutic lithium levels experience a wide range of adverse side effects, including neuropsychologic impairments that gradually reduce the patient's quality of life,⁴⁰⁻⁴² overall cognitive dulling, decreased concentration, and impairment of reading and thinking skills.^{35,36,38,42-44} Toxicity and dehydration, resulting from lack of adequate food and water or from diarrhea, are of particular concern in the elderly patient population. Therefore, the practical application of lithium use in a geriatric, long-term care setting is not very clear. Staffing and resource limitations have the potential to make lithium monitoring difficult or impossible.

In contrast, divalproex is generally well tolerated, with hepatic and hematologic toxicity, sedation, ataxia, dizziness, and gastrointestinal disturbances infrequently observed.^{9-11,13,14,24,41}

In this study, the additional costs incurred by the management of morbidity associated with the side effects of lithium treatment contributed substantially to the overall cost burden. By comparison, the morbidity in the divalproex group was mild or moderate in severity, generally self-limiting, and only infrequently required dose reductions. Therefore, divalproex appears to be a superior alternative to lithium, based on these findings. The low incidence of morbidity observed in patients treated with divalproex is in agreement with previously published reports, including those on geriatric patients.^{16,19,21,41} Some patients with bipolar affective disorder who experienced cognitive and functional deficits during lithium treatment have had their deficits ameliorated when therapy was switched either fully or partially to divalproex.⁴⁰

The cumulative morbidity-associated costs (excluding baseline long-term, skilled nursing care facility costs) were \$672 for the divalproex group and \$80,934 (MICU and non-MICU costs) for the lithium group. Had the 28 patients treated with lithium been treated with divalproex, a total savings of \$80,262, or \$2875 per patient, may have been realized by this VA medical center.

We did not formally measure changes in quality-of-life factors associated with divalproex therapy, but these less easily measured variables should be factored into the overall assessment of drug selection. Several studies⁴⁵⁻⁴⁷ demonstrating the effectiveness of divalproex for the reduction of behavioral agitation and aggression in patients with and without dementia have examined quality-of-life outcomes. Our informal observations of patients indicated that the cognitive abilities of the divalproex group, compared with those treated with lithium, were improved and patients reported feeling better. Patients treated with divalproex experienced fewer side effects and were not prone to serious morbidity that could result in extended MICU stays. These findings indicate both positive health outcomes and overall cost savings for patients treated with divalproex. Divalproex was well tolerated and efficacious in this patient population during the entire 4-year retrospective chart review. Moreover, our informal assessment has shown that these effects continued after the completion of the retrospective analysis. Of the 28 patients originally treated with lithium, 15 were subsequently switched to divalproex treatment

secondarily to adverse events. There were no changes made in the 44 original divalproex-treated patients at follow-up.

There is an inherent bias associated with the site at which this analysis was conducted. The patient population at a VA nursing home is predominantly male, as were the patients included in this study. Therefore, the results may not reflect those that would occur in a population with a higher proportion of women. In addition, the VA purchases medications at costs lower than those incurred in the private sector; this may influence the cost of initial therapy. A double-blind, prospective pharmaco-economic study incorporating quality-of-life variables would provide additional objective criteria for comparing divalproex and lithium therapy in the elderly.

...CONCLUSIONS ...

The results of this pharmaco-economic analysis indicate that, although drug acquisition cost is more expensive for patients treated with divalproex than for those treated with lithium, these costs are more than offset by the increased costs associated with adverse events in the lithium group. In this geriatric population, the use of lithium was not only costlier (\$2875 more per patient) than divalproex but, more importantly, it was associated with poorer outcomes, including severe morbidity requiring MICU hospitalization. Thus, divalproex was a more appropriate first-line therapy for geriatric patients with agitation.

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