Treatment of Dementia With Behavioral Disturbance Using Divalproex or a Combination of Divalproex and a Neuroleptic

Meena Narayan, M.D., and J. Craig Nelson, M.D.

Background: Neuroleptics have been used extensively to treat noncognitive behavioral disturbances in dementia, although their efficacy is only moderate and side effects are prominent. This study aims to determine the efficacy and tolerability of the non-neuroleptic divalproex sodium in patients with dementia and behavioral problems.

Method: Charts of consecutive inpatients with dementia and behavioral problems according to DSM-IV were retrospectively reviewed. Patients treated with divalproex were analyzed for dosage, duration of divalproex treatment, levels, efficacy, side effects, and concurrent medications. Target behavioral symptoms were identified, and change was rated using a Clinical Global Impressions (CGI)-Severity of Illness scale. Patients who were much or very much improved were considered to be responders.

Results: Twenty-five patients (15 men and 10 women) with a mean ± SD age of 77 ± 7 years were identified. Fourteen (56%) of the 25 patients met our criteria for response after the addition of divalproex. Divalproex given alone was effective in 7 of 15 patients. Divalproex was added to an ongoing neuroleptic in 10 patients, and 7 patients responded. Patients received a mean final divalproex dose of 1650 mg/day with a mean blood level of 64 μg/mL. Divalproex was well tolerated in this population except for reversible sedation in 8 patients and transient worsening gait and confusion in 1 subject.

Conclusion: Divalproex appeared to be as effective as previously reported rates for neuroleptics in the treatment of behavioral disturbances in dementia. The combination of divalproex and a neuroleptic was effective in patients who had failed either agent administered independently.

(J Clin Psychiatry 1997;58:351–354)

Received June 24, 1996; accepted June 23, 1997. From the Department of Psychiatry, Yale University School of Medicine, New Haven, Conn.

Presented at the 2nd annual meeting of the American Society of Clinical Psychopharmacology, Feb. 16–18, 1996, Montego Bay, Jamaica.

Reprint requests to: J. Craig Nelson, M.D., Department of Psychiatry, Yale University School of Medicine, 20 York Street, EP-10-8-517, New Haven, CT 06504.

Five percent to 10% of Americans aged 65 years and older and as high as 47% of those aged 85 years and older suffer from dementia.[1] Alzheimer's disease and related dementias cost society an estimated $20 billion in direct costs and $38 billion in indirect costs each year.[2] In addition to cognitive disturbances that form the main cluster of symptoms, noncognitive behavioral problems are present in a high percentage of patients with dementia. Forty-two percent to 62% of residents in a nursing home study[3] and more than 50% of outpatients in a dementia clinic[4] had some form of behavioral disturbance. Some of the noncognitive behavioral problems that interfere with care of the patient include physical and verbal aggression, uncooperativeness, aimless wandering, noisiness, agitation, and increased nonpurposeful motor overactivity.[4] These behaviors contribute significantly to an increased burden on caregivers in the home and are a major reason for nursing home placement.

Antipsychotic drugs are widely prescribed to patients with dementia associated with disruptive behavior. In a survey of 55 rest homes, 39% of patients received antipsychotics.[5] The extensive use of neuroleptics for dementia with behavioral problems, however, is not a reflection of their efficacy, which, at best, is modest.[6,7] The meta-analysis by Schneider et al.[8] of seven placebo-controlled, parallel-group design studies of neuroleptic use in primary degenerative dementia or vascular dementia concluded that antipsychotic drugs are significantly more effective than placebo. However, the effect size was modest; 59% of patients with behavioral symptoms benefited from neuroleptic treatment compared to 41% who benefited from placebo. Furthermore, Devanand et al.[9] reported a significant decline in cognitive functions and an increase in extrapyramidal side effects in dementia patients during haloperidol treatment, although target behavioral problems improved.

In the last decade, the use of drugs other than neuroleptics for the management of behavioral disturbances has increased. Some of these drugs include trazodone, valproate, buspirone, β-blockers, and benzodiazepines.[10] Of the various drugs used, valproate is an effective antimanic, antiepileptic drug that is well tolerated in the elderly.[11,12] Valproate has been reported to be effective in reducing aggression and behavioral disturbance associated with primary psychiatric disorders other than dementia.[13,14] How-

ever, few studies evaluate the efficacy of valproate in the management of behavioral problems associated with dementia. Mellow et al.[15] used valproate to treat four patients with dementia and behavioral disturbance in an open-label study and found that two patients improved dramatically and one patient had a transient response. A second open-label study reported that 8 of 10 patients with dementia had a 50% decrease in the frequency of behavioral agitation.[16] Sival et al.,[17] in a retrospective review of 23 patients with dementia and behavioral problems admitted over 3 years to a hospital, found that at discharge disruptive behavior was completely abolished in 26% and decreased in 52% of valproate-treated patients. The present study aims to confirm the efficacy of divalproex sodium in a group of patients with dementia and behavioral problems.

METHOD

Charts of consecutive patients with a DSM-IV[18] diagnosis of dementia and behavioral disturbance who were admitted to the inpatient geriatric psychiatry unit at Yale New Haven Hospital during a 15-month period (January 1995 to March 1996) were reviewed retrospectively. Patients who displayed prominent target behavioral problems during the first 2–3 days in the hospital and who were treated with divalproex were selected. (Patients who were admitted because of behavioral problems, but did not display the behavioral problems in the hospital, were not included.) Patients with reversible causes of dementia or with delirium, major depression, bipolar disorder, schizophrenia, or delusional disorder were excluded. Patients with delusions or hallucinations persisting for 2 days or more were also excluded. A majority of patients had significant comorbid medical conditions including ischemic heart disease, cerebrovascular disease, and chronic obstructive pulmonary disease.

Intermittent use of a benzodiazepine was acceptable, but patients receiving lithium, buspirone, or carbamazepine were not included. In 9 of the 25 patients, divalproex was added to an ongoing neuroleptic (haloperidol, N = 5; risperidone, N = 2; thioridazine, N = 2) that had been ineffective. The neuroleptic dose was either held constant or reduced during the trial. Treatment was initiated with both haloperidol and divalproex in 1 patient. However, the neuroleptic was discontinued 3 days prior to discharge. The dosage, duration, and levels of divalproex, side effects, and concurrent medications were noted.

Charts of all patients were reviewed to determine the target symptoms for each patient. The individual symptoms were followed after the addition of divalproex, through nursing observations documented three times per day. Change in the frequency and intensity of individual symptoms was rated, and a global score was then determined for each patient. Patients were rated as unchanged, minimal, much, and very much improved or worse, using a modified seven-point Clinical Global Impressions (CGI)-Severity of Illness scale.[19] Very much (CGI score = 1) and much improvement (CGI score = 2) in symptoms were considered as a clinically meaningful response, while minimal improvement (CGI score = 3) and no change (CGI score = 4) were considered as a nonresponse.

RESULTS

During the 15-month period, 49 patients were admitted with dementia and behavioral problems. Twelve patients with delusions or hallucinations were treated with antipsychotic agents. In 5 patients, target behavioral symptoms were not observed in the hospital, although they received a diagnosis of dementia with behavioral disturbance based on the history obtained from the nursing home. Seven patients were continued on agents that had been started prior to admission, and the dose was optimized. The remaining 25 patients (15 men and 10 women) with nonpsychotic behavioral disturbance, observed in the hospital, were treated with divalproex and included in the sample (Table 1). The mean age of the patients was 77 years (range, 62–86). Twenty patients had severe dementia (Mini-Mental State Examination [MMSE] < 5), while 4 patients had moderately severe dementia (MMSE score = 15, 17, 17, and 21). One patient had a MMSE score of 19 at admission, but a second examination 2 days later revealed a score of 23. Diagnoses included Alzheimer's dementia (N = 16), vascular dementia (N = 5), dementia with parkinsonism (N = 2), dementia with amyotrophic lateral sclerosis (N = 1), and dementia NOS (N = 1). The most common target symptoms resulting in hospitalization were agitation, restlessness, physical aggression, and verbal aggression. Less frequent symptoms included uncooperativeness, decreased sleep, and noisiness.

Patients were started on 250 mg of divalproex, given as either b.i.d. or t.i.d. dosage. Dose was adjusted to achieve a blood level greater than 50 µg/mL. Above this level, dose was adjusted based on clinical need. The mean final dose achieved was 1650 mg/day (range, 250–4000) with a mean blood level of 64 µg/mL (range, 14–102).

Fourteen (56%) of the 25 patients met our response criterion. Of the 15 patients who received divalproex alone, 7 were much improved, 5 were minimally improved, and 3 were unchanged. Of the 10 patients also receiving neuroleptics, 1 was very much improved, 6 were much improved, and 3 were minimally improved after the addition of divalproex. No patient was rated as worse.

In 3 patients who were unchanged and 3 patients who were minimally improved on divalproex alone, neuroleptic was added and further behavioral ratings obtained. All 6 became much improved after the addition of a neuroleptic. Thus at discharge, 20 (80%) of the 25 patients had responded.

Table 1. Characteristics of Patients With Nonpsychotic Dementia and Behavioral Problems*

Patient	Dementia	Age (y)	Sex	MMSE Score	Divalproex Dose (mg)	Blood Level at Discharge (μg/mL)	CGI Score
1	Alzheimer's	62	M	< 5	3000	71	2
2	Alzheimer's	84	M	15	1250	53	2
3	Alzheimer's	75	M	< 5	1500	67	2
4	Alzheimer's	83	F	< 5	3750	88	2
5	Alzheimer's	79	M	17	4000	61	4
6	Alzheimer's	81	M	< 5	1250	69	3
7	Alzheimer's	73	M	< 5	2250	77	2
8	Alzheimer's	86	M	< 5	2500	89	2
9	Alzheimer's	80	F	< 5	750	49	2
10	Alzheimer's	81	F	< 5	750	54	1
11	Alzheimer's	77	F	< 5	1500	60	3
12	Alzheimer's	79	M	12	1500	80	4
13	Alzheimer's	70	M	< 5	1250	78	3
14	Alzheimer's	57	F	< 5	1500	49	2
15	Alzheimer's	85	F	< 5	1250	96	2
16	Alzheimer's	78	F	17	750	80	2
17	Parkinsonism	72	M	< 5	1500	49	3
18	Parkinsonism	80	M	< 5	250	14	2
19	Vascular	74	F	< 5	3000	102	3
20	Vascular	83	M	< 5	3000	51	3
21	Vascular	84	M	< 5	1000	35	2
22	Vascular	76	F	< 5	1000	56	4
23	Vascular	79	F	19/23	1500	90	3
24	Dementia NOS	78	M	< 5	500	40	3
25	Dementia and ALS	63	M	21	750	52	2
	Mean	77			1650	64	
	SD	7			1013	21	

*Abbreviations: ALS = amyotrophic lateral sclerosis, CGI = Clinical Global Impressions-Severity of Illness scale, MMSE = Mini-Mental State Examination.

Dose and blood level of divalproex were examined for each response category. The mean doses of divalproex for the very much improved, much improved, minimally improved, and the unchanged groups were 750 ± 54 mg/day, 1577 ± 1017 mg/day, 1688 ± 874 mg/day, and 2167 ± 1607 mg/day, respectively. Corresponding blood divalproex levels in the four response categories, however, were similar (54 μg/mL, 63 ± 24 μg/mL, 67 ± 22 μg/mL, and 66 ± 13 μg/mL).

Divalproex was well tolerated in this population except for sedation in 8 patients, and worsening gait and confusion in 1 subject. Six of the 8 patients with sedation improved with a decrease in divalproex dosage, while the 2 patients appeared to develop tolerance to the sedating side effects of the drug. Two of these 8 patients also developed swallowing difficulties during periods of sedation, which resulted in aspiration. However, the ability to swallow improved when these patients were more alert. With a reduction in the dosage of divalproex, these feeding problems resolved, along with a decrease in sedation.

DISCUSSION

In this study of 25 patients hospitalized because of behavioral disturbances associated with dementia, divalproex proved to be an effective agent, either used alone or in combination with a neuroleptic. The rate of response was modest in those receiving divalproex alone (47%). However, most patients in the study sample had failed several medication trials and had required hospitalization because of severe refractory behavioral disturbances that could not be managed in a nursing home setting. Our retrospective data do suggest that the combination of divalproex and a neuroleptic was particularly effective in this population. In patients who had failed a neuroleptic trial alone (N = 10) or divalproex alone (N = 6), and who received combined treatment with neuroleptic and divalproex, 13 of the 16 responded.

With respect to the relative efficacy of divalproex and neuroleptics, even if neuroleptics alone or the combination were somewhat more effective than divalproex, the lack of extrapyramidal side effects and tardive dyskinesia confers substantial advantage on the use of divalproex as a single agent. Further, in the present study, it was often possible to reduce the dose of and in one case discontinue the neuroleptic after divalproex was added without a worsening of the behavioral disturbance. The mean dose of haloperidol used in this study was 1.4 mg/day. Because the average length of inpatient stay was less than 2 weeks, discontinuation of the neuroleptic in all cases was not possible. With a longer drug trial, it is possible that the neuroleptic could have been discontinued and that divalproex would have been sufficient alone, as previous reports have described.[16,17]

Although the dose of divalproex used in this study (1650 ± 1013 mg/day) was substantially higher than two previous reports in patients with dementia and behavioral disturbances (481 ± 248 mg/day[17] and 525 ± 146 mg/day,[16] respectively), it was well tolerated in this population. The mean blood level achieved was 64 ± 21 μg/mL, which was similar to that reported by Mellow et al.[15] These levels appear to be within the reported range of levels in mania and epilepsy.[11,20] A therapeutic range for divalproex in dementia with behavioral problems could not be estimated from this study. The response of specific target symptoms to either divalproex or a combination of divalproex and neuroleptic could not be determined as global ratings of improvement were used.

The mechanism of action for divalproex is unclear. Lott et al.[16] have noted the similarity between the behavioral disturbance in dementia and the symptoms of mania and have proposed that valproate may exert therapeutic effects through its antimanic properties. Divalproex has many pharmacologic actions including its enhancing effects on central GABAergic and serotonergic neurotransmission.[21] However, it is unclear from this study which of these actions is most important in dementia. It does seem unlikely that sedation explains the efficacy of divalproex, as significant sedation was seen in only eight patients in this sample.

We excluded patients with persistent psychotic symptoms on the assumption that antipsychotics would be required. Raskind[10] suggested that antipsychotics may be most effective when the psychotic symptoms in patients with dementia resemble the signs and symptoms in schizophrenia. As a result, our findings apply to patients with dementia and behavioral disturbances without psychotic symptoms. The efficacy of divalproex alone or in combination with a neuroleptic in patients with psychotic symptoms is unknown.

Despite the methodological limitations of this retrospective study, divalproex appears to be effective in nonpsychotic patients with dementia and behavioral disturbances. Its efficacy appears to be comparable to reported rates for neuroleptics. Extrapyramidal symptoms were not observed with divalproex, and it was our impression that this drug was better tolerated than neuroleptics. Combining divalproex with a neuroleptic may enhance efficacy in patients refractory to either drug alone or may help to maintain efficacy while reducing the dose and side effects of the neuroleptic. Prospective, double-blind, placebo-controlled trials are required to further evaluate the efficacy of valproate with or without a neuroleptic in patients with dementia and behavioral disturbances.

Drug names: buspirone (BuSpar), carbamazepine (Tegretol and others), divalproex sodium (Depakote), haloperidol (Haldol and others), risperidone (Risperdal), thioridazine (Mellaril and others), trazodone (Desyrel and others).

REFERENCES

1. Bachman D, Wolf P, Linn P. Prevalence of dementia and probable senile dementia of the Alzheimer type in the Framingham study. Neurology 1992;42:115–119
2. Max W. The economic impact of Alzheimer's disease. Neurology 1993;43 (suppl 4):S6–S10
3. Zimmer J, Watson N, Treat A. Behavioral problems among patients at skilled nursing facilities. Am J Public Health 1984;74:1118–1120
4. Reisberg B, Borenstein J, Salob SP, et al. Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. J Clin Psychiatry 1987;48 (5, suppl):9–15
5. Avorn J, Dreyer P, Connelly M, et al. Use of psychoactive medication and the quality of care in rest homes. N Engl J Med 1989;320:227–232
6. Barnes R, Veith R, Okimoto J, et al. Efficacy of antipsychotic medications in behaviorally disturbed dementia patients. Am J Psychiatry 1982;139: 1170–1174
7. Petrie W, Ban T, Berney S, et al. Loxapine in psychogeriatrics: a placebo and standard-controlled clinical investigation. J Clin Psychopharmacol 1982;2:122–126
8. Schneider L, Pollock V, Lyness S. A metaanalysis of controlled trials of neuroleptic treatment in dementia. J Am Geriatr Soc 1990;38:553–563
9. Devanand D, Sackheim H, Brown R, et al. A pilot study of haloperidol treatment of psychosis and behavioral disturbance in Alzheimer's disease. Arch Neurol 1989;46:854–857
10. Raskind M. Treatment of Alzheimer's disease and other dementias. In: Schatzberg A, Nemeroff C, eds. Textbook of Psychopharmacology. Washington, DC: American Psychiatric Press; 1995:657–667
11. Bowden C, Brugger A, Swann A, et al. Efficacy of divalproex vs lithium and placebo in the treatment of mania. JAMA 1994;271:918–924
12. Puryear L, Kunik M, Workman R Jr. Tolerability of divalproex sodium in elderly psychiatric patients with mixed diagnosis. In: Abstracts of the 8th Annual Meeting of the American Association for Geriatric Psychiatry; Feb 17–20, 1995; Cancun, Mexico: 30
13. Mazure C, Druss B, Cellar J. Valproate treatment of older psychotic patients with organic mental syndromes and behavioral dyscontrol. J Am Geriatr Soc 1992;40:914–916
14. Sovner R. The use of valproate in the treatment of mentally retarded persons with typical and atypical bipolar disorders. J Clin Psychiatry 1989;50 (3, suppl):40–43
15. Mellow A, Solano-Lopez C, Davis S. Sodium valproate in the treatment of dementia. J Geriatr Psychiatry Neurol 1993;6:205–209
16. Lott A, McElroy S, Keys M. Valproate in the treatment of behavioral agitation in elderly patients with dementia. J Neuropsychiatry Clin Neurosci 1995;7:314–319
17. Sival R, Haffmans P, van Gent P, et al. The effect of sodium valproate on disturbed behavior in dementia. J Am Geriatr Soc 1994;42:906–907
18. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
19. Guy W. ECDEU Assessment Manual for Psychopharmacology, Revised. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976
20. Bourgeois B. Valproate: clinical use. In: Levy R, Dreifuss F, Mattson R, eds. Antiepileptic Drugs. 3rd ed. New York, NY: Raven Press; 1989: 633–642
21. Baf M, Subhash M, Lakshmana K, et al. Sodium valproate induced alterations in monoamine levels in different regions of the rat brain. Neurochem Int 1994;24(1):67–72