Key Words: divalproex, valproic acid, valproate, divalproex sodium, elderly, neuropsychiatric disorders, agitation, Alzheimer's disease

Valproate Use in Neuropsychiatric Disorders in the Elderly

By Pierre N. Tariot, MD

ABSTRACT *~ The literature regarding the use of valproate in the elderly derives primarily from studies in patients with dementia who experience agitation. At this juncture, there are 5 case reports or case series in patients with mixed neuropsychiatric disorders and 18 in patients with dementia, while there are 3 placebo-controlled studies in patients with dementia. In the aggregate, the published reports point toward probable improvement in agitation in a substantial proportion of patients. The level of evidence is not sufficient to define clinical practice, however, which is also a limitation with some other commonly used therapies, nor is the behavioral target of persistent agitation recognized by the Food and Drug Administration. Basic and preclinical studies of mechanism of action suggest a possible effect of valproate on cellular survival which, in theory, could be beneficial in patients with Alzheimer's disease. This hypothesis will be addressed in a multicenter trial beginning in 2003.* Psychopharmacology Bulletin. *2003;37(Suppl 2): 116-128*

INTRODUCTION

Divalproex sodium has been shown to be effective in the treatment of acute manic episodes associated with bipolar disorder and is approved by the US Food and Drug Administration (FDA) for this indication.[1,2] The literature regarding the use of valproate in the elderly focuses chiefly on dementia. In fact, there are only open-label case studies regarding the use of divalproex sodium (and its other formulations) in the treatment of manic symptoms in elderly nondemented persons,[3-5] while there are numerous case descriptions and controlled studies of valproate for agitation and aggression associated with dementia. The emphasis of this report therefore will be the studies in dementia.

The lifetime risk of significant neuropsychiatric disturbances in Alzheimer's disease (AD), the most common cause of dementia, is greater than 90%.[6-8] The most prevalent forms of psychopathology include psychosis, agitation, generalized restlessness, and anxious/depressive features.[9] Among these, agitation is perhaps the

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most troublesome. The term typically refers to "inappropriate verbal, vocal, or motor activity unexplained by apparent needs or confusion".[10] Once agitation is present, it is highly likely to persist, suggesting that in fact agitation may reflect an underlying neuropathological substrate of the dementia.[11] The usual approach to treatment of agitation entails identification and reversal of physical, social, and environmental precipitants. Symptomatic pharmacotherapy is considered only when these steps fail. There are no uniformly accepted drug therapies for agitation in dementia, a circumstance highlighted by the fact that the US FDA has not approved any therapy for persistent agitation. Nonetheless, there is substantial evidence that agitation can, once present, respond to appropriate therapy, the literature for which has been reviewed comprehensively elsewhere.[12] Antipsychotics as a class are used most commonly, although the effect size is only in the neighborhood of 15% to 20%.[12] Further, antipsychotics have a variety of potential safety and tolerability concerns including anticholinergic toxicity, extrapyramidal side effects, tardive dyskinesia, cardiac and respiratory side effects, and metabolic side effects.[13] For these reasons, other classes of agents, including anticonvulsants, have been examined.

CLINICAL STUDIES OF VALPROATE IN THE ELDERLY:

The earliest placebo-controlled studies of anticonvulsants were conducted with carbamazepine.[14-17] In the aggregate, these indicated that efficacy for agitation was likely and that tolerability was generally good in the short run,[14-18] validating the concept that anticonvulsants might be helpful for agitation. Since carbamazepine has a high likelihood of safety and tolerability concerns with long-term use, and a high rate of drug-drug interactions, attention shifted to other agents that might be safer and better tolerated.

At this juncture, there are five case reports or case series addressing the efficacy of valproate for agitation associated with mixed neuropsychiatric syndromes other than dementia,[19-26] and 18 case reports or case series in patients with dementia addressing efficacy, safety, and tolerability.[27-45] Across these reports, there was wide variation in the daily dose (240-4000 mg/d) and plasma valproate levels (14 -107 mg/ml). In the aggregate, approximately two-thirds of patients showed clinically evident improvement in agitation, chiefly reported in descriptive terms. Side effects were consistent with Package Insert information.[12] These preliminary data suggested that valproate may be effective and safe for the treatment of agitation associated with dementia, and supported further studies. There are now three placebo-controlled trials that have been published, one of which was followed by open extension treatment.

The first randomized, placebo-controlled, parallel group study was exploratory in nature, intended to establish whether larger, confirmatory studies should be performed.[46] The specific goal was to establish appropriate dosing, clarify safety and tolerability issues, and assess effect size for purposes of planning a larger trial. The primary hypothesis was that administration of divalproex sodium would reduce agitated behavior measured with the agitation factor of the Brief Psychiatric Rating Scale (BPRS),[47] as well as with a global clinical scale. Secondary questions addressed other measures of behavior, safety, and tolerability.

Subjects with probable or possible AD, vascular dementia, or mixed dementia[47] were included who also met operational criteria for agitation; namely, sufficient to achieve BPRS scores ≥3 on items rating tension, hostility, uncooperativeness, or excitement over the prior two weeks. Subjects were required to be medically stable, and best efforts had to have been exhausted to deal with the behavior nonpharmacologically. The only permissible concomitant psychotropic was chloral hydrate, available on an as-needed basis.

Clinically optimal divalproex doses were determined by a nonblinded physician on the basis of written reports of adverse effects and changes in behavior and blinded laboratory data. The initial dose was 375 mg/d in divided doses, increased in 125 mg increments to the clinically optimal dose. The blinded treatment period was 6 weeks. The mean daily dose of divalproex sodium at termination was 826 (+/- 2.16) mg/d (range 375 mg/d-1,375 mg/d), with a mean plasma concentration of 45.4 +/- 14.9 mg/ml (range 22-85 mg/ml). There was no difference in the two groups in the rate of chloral hydrate use. Fifty-six subjects were randomized; the mean age of the patients was approximately 85 years; and 71% had probable or possible AD.

The BPRS agitation factor decreased 2.3 points (+/- 2.5) during placebo treatment and 3.6 points (+/- 2.5) during divalproex treatment (t -1.76, P=.08). Using a planned analysis of covariance (ANCOVA), there was a significant effect for treatment factoring baseline severity of dementia and duration of washout from prior psychotropic use (P=.05). Table 1 shows the distribution of Clinical Global Impression (CGI) of therapeutic effect. Sixty-eight percent of patients on divalproex were rated as improved, versus 52% in placebo group (P=.07). The 95% confidence interval for the difference in CGI of change scores for therapeutic effect was – 0.9 to 0.42, P=.06 by ANCOVA. There were no changes on any secondary measures of behavior, which included the Overt Aggression Scale48, and the Behavior Rating Scale for Dementia of the Consortium to Establish a Registry for Alzheimer's Disease;[49] or on the Physical Self-Maintenance Scale as a screen for daily functional status;[50] or the Mini Mental State Examination used to assess cognitive status.[51]

Table 2 summarizes the CGI of side effects. There were more side effects on active treatment than placebo (P=.03, Fisher's exact test), generally considered minor. Descriptively, the adverse events occurring more often on divalproex than placebo included sedation (39% versus 11%), gastrointestinal symptoms (25% versus 7%), postural instability (14% versus 4%), respiratory problems (18% versus 0%); these were upper respiratory infections occurring during the influenza season), and weakness (14% versus 0%). There were no changes in laboratory data that were considered clinically significant, with a decrease in mean platelet count as usually seen and no increase in ammonia levels.

The main conclusions from this study were that the average divalproex dose at termination of treatment was an appropriate target, because it was associated with only mild side effects and yielded a trend toward improvement in the BPRS agitation factor versus placebo, a finding that was statistically significant in the ANCOVA adjusting for covariates. There were similar trend-level improvements in global ratings of therapeutic effect in both unadjusted and adjusted analyses. The adverse experiences observed were generally consistent with published information regarding this agent. The data suggested, but did not prove, that this form of therapy could reduce agitation in some patients with dementia in the nursing home.

TABLE 1

CLINICAL GLOBAL IMPRESSION: THERAPEUTIC EFFECT

	PLACEBO	N(%)	VALPROATE	N(%)	Z	P
Marked Effect	3	(11)	11	(39)		
Moderate Effect	6	(22)	3	(11)		
Minimal Effect	5	(19)	5	(18)		
Unchanged/Worse	13	(48)			1.78	.07

Tariot PN. *Psychopharmacology Bulletin*. Vol. 37. Suppl. 2. 2003.

TABLE 2

CLINICAL GLOBAL IMPRESSION: SIDE EFFECTS

	PLACEBO	N(%)	VALPROATE	N(%)	Z	P
None	18	(67)	9	(32)		
Does not interfere	6	(22)	16	(57)		
Significant	2	(7)	2	(7)		
Outweighs Benefit	1	(4)	1	(4)		
					-2.14	.03

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These results were used to design a multicenter, placebo-controlled trial in patients with dementia conducted by the Alzheimer's Disease Cooperative Study (ADCS) in 153 nursing home residents with probable or possible AD who were agitated. The results are not available at this point.

An extension of the above double-blind clinical trial was recently reported.[52] Of the 56 participants in the blinded phase of the trial, 46 were treated for 6 weeks in an open fashion with clinically optimal doses of divalproex sodium, resulting in a mean daily dose of 851 mg/d, range 250-1500 mg/d. Three of these subjects did not complete the open extension. The mean BPRS agitation factor decreased by 3.1 (SD 4.2) versus baseline (P<.002); 86% of those completing the open phase were rated as improved on the CGI. These changes were mirrored by changes in other behavior rating scales. Sixty percent of subjects had no side effects, 33% had side effects that were rated as mild. There were no significant changes in laboratory values. The authors noted that the doses, levels, and tolerability seen in this 6-week open extension were similar to those found in the blinded phase of the study. The results confirmed and extended the results from the placebo-controlled phase of the trial, suggesting that divalproex may be beneficial for some patients with this clinical problem and that doses in this range were generally well tolerated in these patients.

A later multicenter trial examined whether divalproex sodium is effective for treatment of signs and symptoms of secondary mania in nursing home residents with dementia. This was a 6-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Patients met clinical criteria for probable or possible AD and/or vascular dementia,[53] and operational criteria for secondary mania, defined using the Bech-Rafaelsen Mania Scale (BRMS),[54] as well as six items on the BPRS.[47] Specifically, subjects were required to have a BRMS total score ≥15; a BPRS item score of ≥3 on at least two items assessing tension, grandiosity, hostility, suspiciousness, uncooperativeness, and excitement; and a BPRS total score ≥15.

Patients were treated with divalproex sodium or placebo twice daily for 6 weeks; the minimum target dose was 20 mg/kg/d after 10 days. This target dose and titration was based on published reports regarding dosing in elderly manic patients. Rescue medication included lorazepam, oxazepam, or chloral hydrate. A disproportionate number of dropouts was seen on active versus placebo treatment, resulting in premature suspension of the trial. One-hundred-seventy-three subjects were randomized; 54% of divalproex treated patients and 29% of placebo treated patients withdrew from the study prematurely (*P*=.001). A significantly greater proportion of divalproex sodium treated patients withdrew prematurely due to somnolence (10 versus 0). The median dosage of

divalproex sodium was 1000 mg/d, or 18 mg/kg/d at endpoint. Serum valproate levels ranged from 55.3 mg/ml to 68.9 mg/ml.

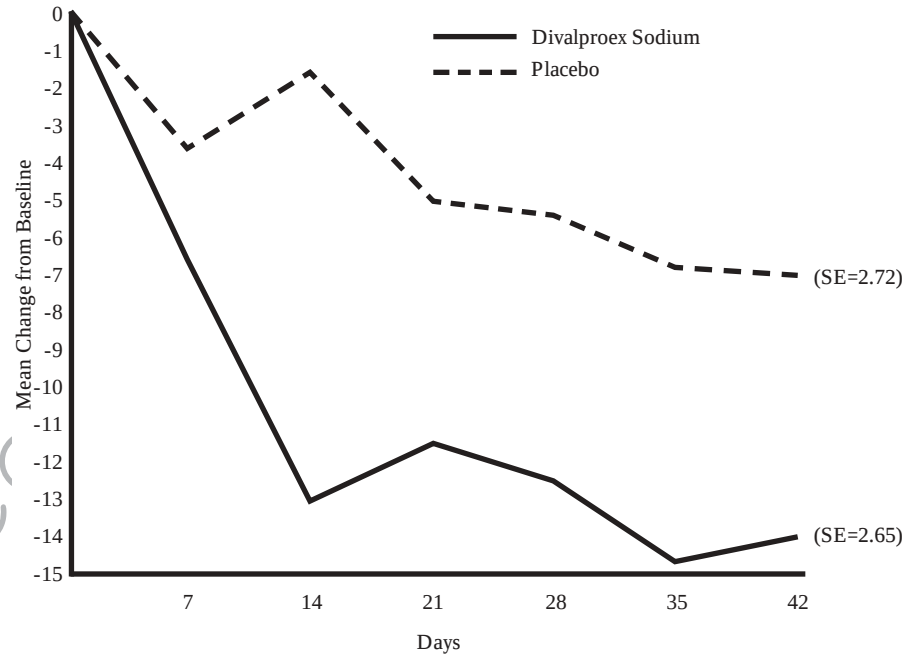
There was no difference between treatment groups in change in the primary outcome measure, the total BRMS score. The figure depicts the change in the total score of the 38-item Cohen-Mansfield Agitation Inventory (CMAI),[55] showing a statistically significant decrease from baseline in the active treatment group compared with the placebo group (P=.035). Last observaton carried forward (LOCF) analysis at each assessment indicated that this difference first occurred on day 14. There were no drug- placebo differences in BPRS scores; the CGI showed a small but statistically significant change in favor of placebo (.035).

Table 3 shows the adverse events reported by at least 5% of subjects in either treatment group. Somnolence was generally rated as mild-to-moderate. Thrombocytopenia was defined by investigator judgment or if it was a reason for early discontinuation. Platelet counts recovered on cessation of therapy for all subjects who experienced thrombocytopenia.

Although its premature termination limited the power of the study, several conclusions were possible. The original hypothesis, that manic

FIGURE

COHEN-MANSFIELD AGITATION INVENTOR TOTAL SCORE.



Significance derived from ANCOVA on LOCF data. *p<.05 vs. placebo.

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features in this population might respond selectively to mood stabilizing therapy, was not borne out. On the other hand, the signs and symptoms of agitation were significantly improved by divalproex sodium therapy as measured by the CMAI total score. It is perhaps worth emphasizing that this was not a study of actual manic episodes, but rather of manic symptoms in elderly patients with dementia. The difference in CGI favoring placebo probably reflected the higher number of discontinuations due to adverse events in the divalproex group (22%) compared with the placebo group (4%).

The target dose and/or titration rate were excessive for this population. The recommended starting dosage of divalproex sodium in younger patients with epilepsy is 15 mg/kg/d56. Of the 74 patients in this trial who reached a daily dosage of ≥15 mg/kg/d, 19% discontinued due to an adverse event. Somnolence was the major adverse event leading to discontinuation. This is a known side effect of divalproex sodium but was more prominent in this particular study. The reduction in platelet count was consistent with labeling information.

The authors concluded that divalproex sodium may in fact have a specific effect on agitation but not on manic symptoms in patients with dementia. The dose and titration schedule used in this study design led to intolerance manifested as somnolence in a substantial minority of patients. This information resulted in altered language in the package insert.

A single-center, randomized, placebo-controlled, double-blind crossover design study was reported by Sival et al.[57] Forty-two inpatients on a psychogeriatric short stay unit were included who met criteria for

TABLE 3

ADVERSE EVENTS REPORTED BY >=5% OF PATIENTS IN EITHER TREATMENT GROUP.

ADVERSE EVENT	DIVALPROEX SODIUM (N=87)	PLACEBO (N=85)
Any adverse event	72(83)*	53(62)
Somnolence	31(36)†	17(20)
Accidental injury	29(33)	21(25)
Anorexia	14(16)	6(7)
Infection	9(10)	10(12)
Urinary tract infection	9(10)	2(2)
Weight loss	8(9)	3(4)
Dehydration	7(8)	2(2)
Vomiting	6(7)	1(1)
Trombocytopenia	6(7)††	0(0)
Rash	5(6)	4(5)

*P=0.003
†P=0.027
††P=0.029

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dementia and operational criteria for aggressive behavior, a score ≥3 on at least one of the items of the Social Dysfunction and Aggression –9 scale (SDAS-9).[58] There was a 1-week baseline period, a 3-week treatment period, 1-week washout with placebo, and a 3-week treatment period. Patients were given sodium valproate at a fixed dose of 480 mg/d as an oral suspension. The primary outcome measures were scores on the SDAS-9 and CGI scale performed at the end of each treatment period. Sixty-seven patients entered the baseline period, 24 were excluded, 43 entered the treatment phase. One subject was excluded due to "protocol violation," and 3 dropped out. Results were presented without reference to treatment order.

The mean age was 80.4 years. Subjects were permitted to receive as-needed oxazepam, with the mean daily dose being 7.9 mg/d in the placebo group versus 6.5 mg/d in the active treatment group. Side effects were described as "rare". The mean plasma level of sodium valproate at the end of active treatment was 40.9 (SD=10.79) mg/ml. There were no drug-placebo difference in the measurements of aggressive behavior as measured by the SDAS-9 and CGI. Sodium valproate showed significant effects on restless, melancholic, and anxious behaviors with trends for improvement for dependent and suspicious behaviors. No other significant differences were found.

The authors noted the low doses of valproate used, the short treatment period, and the absence of statistical correction for multiple comparisons. The report lacks information about crossover effects. The authors concluded that some of the results were in agreement with effects of sodium valproate in studies of younger patients with affective or anxiety disorders,[59] while the findings regarding restlessness were consistent with the effects on agitation reported by others.[46,53]

SUMMARY OF CLINICAL STUDIES

In the aggregate, these studies provide a fairly strong signal for possible anti-agitation efficacy of valproate for agitation in at least some patients with dementia. There are substantial methodological differences among the placebo-controlled studies available which likely account at least in part for the modest differences in outcome. The data overall would not be sufficient to rigorously define clinical practice. The studies indicate that, in doses ranging from roughly 500 mg/d - 1000 mg/d (below 15 mg/kg/d), the medication is reasonably well tolerated. The most common side effects are sedation, gastrointestinal distress, and occasional thrombocytopenia, all consistent with labeling information. There are occasional reports of less frequent complications of valproate administration in the elderly, not seen in controlled trials, including reversible drug-induced parkinsonism with chronic use in patients with various

dementias, organic brain syndromes, and mental retardation.[60] There has also been a single case report of acute parkinsonism during valproate administration in a patient with dementia.[61] There is a single case report of valproate-induced hyperammonemia associated with mental status changes in an 88-year-old man with dementia.[62] This has been reported in other patient populations but there is only the single case report in dementia. To the extent that this has been examined in clinical trials, no instances of hyperammonemia were found.[46]

POSSIBLE MECHANISM OF ACTION OF VALPROATE

A variety of cellular mechanisms may contribute to valproate's clinically observable short-term effects in these patient populations. It has immediate modulatory effects on inhibitory and excitatory synaptic transmission. At low concentrations, valproate increases presynaptic g-aminobutyric acid (GABA) levels by enhancing its synthesis and inhibiting its degradation, and enhances GABA release, up- regulates postsynaptic GABA B receptors, and increases chloride-(GABA A) channel permeability.[63] Further, valproate appears to modulate glutamatergic N-methyl-D-aspartate (NMDA) receptor activation, possibly relevant in patients with AD.[64-66] Valproate also has widespread effects on other neurotransmitter systems, including serotonergic and noradrenergic systems.[67,68]

As the Figure demonstrates, the anti-agitation effect observed in the largest trial took two weeks to emerge, suggesting the possibility that time-dependent effects on intracellular signaling might be relevant. There are several potential neuroprotective mechanisms of action in valproate with possible special relevance to AD that have been reviewed recently.[69] Mark et al[70] were the first to propose that valproate treatment might reduce neuronal injury and the rate of disease progression in patients with AD. This has been supported by subsequent studies indicating that valproate, along with other anticonvulsants and mood stabilizers, has neuroprotective effects on a variety of model systems. The literature is quite complex, but can be reduced to suggest the possibility that valproate may achieve this effect via reduction of apoptosis through activation of bcl 2, blocking hyperphosphorylation of the microtubule-associated protein tau via inhibition of glycogen synthase kinase 3-beta, and promoting cell survival by activating a number of other protective cellular signaling pathways.

These intriguing effects on cellular signaling pathways were used as part of the rationale for an innovative clinical trial recently launched by the ADCS.[69] The trial poses the question of whether this form of therapy could delay, attenuate, or prevent the emergence of agitation in patients with AD who lack these features at baseline. This behavioral

prophylaxis design is by itself a novel approach to clinical trials and the design itself could be applied to future studies of agents being examined for their potential to exert prophylactic effects on emergent psychopathology in AD. The trial will be a 2-year, randomized, double-blind, placebo-controlled parallel-group study of divalproex sodium in low doses in 300 outpatients with probable AD of mild-moderate severity who have not been agitated or psychotic during their illness. The study will also address whether chronic valproate administration to patients with AD will attenuate clinical progression of illness as reflected by reduced functional and/or cognitive decline. The study design incorporates a collection of biological specimens to address putative mechanisms of action of valproate, as well as repeated static magnetic resonance imaging data.

The plan to address the neuroprotective potential of valproate is especially topical now in light of emerging data about the potential relevance of apoptosis and abnormal protein phosphorylation in AD. Recent papers report correlations between frontal lobe tangles and agitation in patients dying with AD.[71,72] This phenomenon in turn is relevant in light of new information about the striking co-occurrence of tau pathology and behavioral disturbance in frontal temporal dementias. The discovery of pathogenic tau mutations in at least some of these frontotemporal dementia patients provides a strong indication that tau pathology by itself can be a major cause of neurodegeneration and is linked to at least some forms of psychopathology.[73]

CONCLUSIONS

While valproate is primarily used for other indications in younger populations, the primary focus in the elderly has been on treatment of agitation in dementia. The preponderance of evidence thus far indicates a probable benefit on agitation in a substantial proportion of patients with dementia, not yet at a level of evidence to define clinical practice according to rigorous evidentiary criteria. On the other hand, there are in fact relatively few adequately defined treatments for persisting agitation in dementia (12), and none which have been recognized by the FDA. Interestingly, the available evidence suggest an effect size for valproate approximating that seen for antipsychotics (ie, about 15%). Recent basic and preclinical work suggests that valproate may have effects on cellular signaling pathways that could be beneficial in the long-term treatment of AD. These concepts have been combined in a novel clinical trial proposal that will address whether chronic valproate administration will delay emergence of agitation, slow cognitive or functional decline, or produce measurable changes in biochemical pathways that may lead to an improved understanding of the mechanism of action of this drug. ⌘

DISCLOSURE

Dr. Tariot has received grant and research support and limited honoraria for consultation from the Abbott Laboratories.

DISCLOSURE OF UNLABELED OR UNAPPROVED USES OF DRUGS

Please note that this review article contains discussions of unlabeled uses of FDA-approved pharmaceutical products. Please refer to the official prescribing information for approved indications, contraindications, and warnings.

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