Valproate in the Treatment of Behavioral Agitation of Dementia

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Behavioral agitation is common in patients with moderate to severe dementia, present in up to 90% of patients depending on how broadly it is defined.1-2 For example, in a chart review of 57 patients with Alzheimer’s disease, Reisberg et al reported that 33 (58%) patients had “significant behavioral symptomatology,” including delusions, nonspecific agitation, and diurnal rhythm disturbances.4 Among a community sample of 183 patients with dementia, Ryden reported that 65% were aggressive.8 Of 126 ambulatory patients with dementia (57 of whom had Alzheimer’s disease) attending a dementia research center, Swearer et al reported that 83% exhibited one or more of nine “troublesome and disruptive behaviors,” with 51% of patients displaying angry outbursts, 45% sleep disturbance, 32% paranoia, 22% hallucinations or delusions, and 21% assaultive or violent behavior.10 Evaluating 408 nursing home residents for 29 agitated behaviors, Cohen-Mansfield et al reported that 93% of residents manifested one or more agitated behaviors at least once a week, with residents exhibiting a mean of 9.3 (±8.6 SD) agitated behaviors at least once per week.12 The most frequently exhibited agitated behaviors were general restlessness, pacing, repetitive sentences, requests for attention, complaining, negativism, and cursing. Burns et al similarly reported that of 178 patients with Alzheimer’s disease, aggression was present in 20% of patients, wandering in 19%, urinary incontinence in 48%, and sexual disinhibition in 7%.14

Sometimes more so than cognitive decline, behavioral agitation in patients with dementia causes substantial distress in family members and caregivers.1,2 Behavioral agitation is a major factor in determining the use of more intensive and costly levels of treatment (e.g., residential treatment rather than outpatient treatment, and psychiatric hospitalization rather than residential treatment).1,2,17 In addition, untreated behavioral agitation in patients with dementia (especially those who are elderly) may be associated with increased morbidity and mortality (e.g., from hip fractures, head trauma, and other injuries). Behavioral agitation of dementia is, therefore, a significant public health problem that undoubtedly contributes to the enormous cost of treating dementia.

Despite the frequent occurrence of behavioral agitation in patients with dementia, it has no widely accepted operational definition. For example, Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV)14 defines agitation as “excessive motor activity associated with a feeling of inner tension” that is “usually nonproductive and repetitious and consists of such behaviors as pacing, fidgeting, wringing of the hands, pulling of clothes, and inability to sit still.” DSM-IV also describes a number of agitated behaviors as “associated features” of dementia. However, it does not provide a codable specifier for the presence or absence of behavioral agitation in dementia. Rather, it lists the specifier “With Behavioral Disturbance,” which cannot be coded and is
simply defined as “clinically significant behavioral disturbances (e.g., wandering).” Nonetheless, many studies have examined the phenomenology of behavioral agitation of dementia, with consistent findings.\textsuperscript{3,4,6,8-17,19-21} These studies indicate that dementia-related behavioral agitation is characterized by disturbances in several psychological and behavioral domains, including: changes in mood (e.g., irritability, depression, affective liability, and hostility); hyperactivity (e.g., restlessness, wandering, pacing); increased verbal or vocal behavior (e.g., babbling, screaming, cursing, repetitive sentences or requests for help); sleep and other diurnal rhythm disturbances; aggressive or violent behavior (e.g., hitting, biting, scratching, kicking); other inappropriate behaviors (e.g., hypersexual behavior, disrobing, urinary and fecal incontinence); and psychotic symptoms (especially paranoia and persecutory delusions).

Thus, behavioral agitation of dementia is probably best viewed as a syndrome with various psychological and behavioral symptoms, rather than a single behavioral dimension.\textsuperscript{12} Valproate is approved by the US Food and Drug Administration for the treatment of dementia-related behavioral agitation. Nonetheless, the treatment of dementia-related behavioral agitation usually includes psychotropic medications (in addition to psychosocial interventions).\textsuperscript{21,23,25,31} Antipsychotics and benzodiazepines are the most commonly used agents, but beta-blockers, lithium, carbamazepine, and serotoninergic drugs, among others, are also used. Most of these agents, however, are associated with modest efficacy at best or side effects or drug-drug interactions that are problematic for elderly or cognitively-impaired patients.\textsuperscript{21,23,27,32}

Several lines of evidence led us and others to hypothesize that valproate, a simple branched-chain carboxylic acid marketed for the treatment of epilepsy and mania,\textsuperscript{13,34} might be a useful treatment for dementia-related behavioral agitation.\textsuperscript{15,34} First, growing research has demonstrated that valproate is effective in a broad range of psychiatric conditions characterized by agitation, including mania, panic disorder, and alcohol and sedative-hypnotic withdrawal.\textsuperscript{13,34,39,40} Indeed, because of their phenomenologic similarities, it has been hypothesized that behavioral agitation of dementia might be a form of secondary mania (or mania due to a general medical condition).\textsuperscript{22,38} Second, preliminary animal\textsuperscript{41,42} and human\textsuperscript{33,39,43-46} data suggest that valproate may also have anti-aggression effects. As described above, dementia-related behavioral agitation often involves verbal and physical aggression. Third, deficits in \textit{y}-aminobutyric acid (GABA),\textsuperscript{37,46} serotonin (5-IT), its major metabolite 5-hydroxy-indoleacetic acid (5-HIAA), and various 5-IT receptors\textsuperscript{48-51} have been demonstrated in the brains of patients with Alzheimer's dementia. Valproate enhances central GABAergic neurotransmission by inhibiting GABA catabolism, stimulating GABA synthesis, and potentiating GABA's postsynaptic effects.\textsuperscript{33,34} It may also enhance serotonergic transmission.\textsuperscript{52} Fourth, valproate is associated with a relatively benign side effect profile and few drug-drug interactions, making it an attractive medication choice for elderly patients.\textsuperscript{33,34}

Based on this evidence, we treated 10 agitated elderly demented patients with valproate. As described in our earlier report, eight of the 10 patients displayed clinically meaningful and sustained reductions in agitated behavior with minimal side effects.\textsuperscript{38} In this paper, we review this and other published studies of valproate in the treatment of behavioral agitation of dementia. We also present preliminary guidelines for the use of this agent in this patient population.

**OVERVIEW OF STUDIES OF VALPROATE IN BEHAVIORAL AGITATION OF DEMENTIA**

To date, there are no controlled studies of valproate in the treatment of behavioral agitation of dementia. However, a growing number of case reports and open studies (Table) suggest that valproate may substantially reduce behavioral agitation without sedation or other deleterious cognitive or neurological side effects in some patients with dementia.\textsuperscript{55-58} Specifically, of 38 demented patients in these four reports, 21 (61%) displayed a moderate or marked reduction in agitation in response to valproate treatment. Only five (13%) of these 38 patients were reported to have side effects. Interestingly, in their study of 23 behaviorally disturbed patients, Sival et al. observed that physical aggression, verbal aggression, and restlessness were the types of behaviors responding best to valproate.\textsuperscript{56}

In brief, although preliminary, these studies suggest that valproate may be an effective, safe, and well tolerated agent for the treatment of dementia-related behavioral agitation. These studies also suggest that valproate's anti-agitation effects are often apparent within 1-3 weeks of treatment; that valproate may be effective as monotherapy and in patients whose agitation has failed to respond to (or has been worsened by) antipsychotics and benzodiazepines; and that some, but not all, patients who respond acutely continue to display reduced behavioral agitation over extended periods of time. Further, these studies suggest that valproate may be effective in a variety of types of dementia, including dementia of the Alzheimer's type, multifarct dementia, and the combination of the two. Finally, these studies also indicate that valproate may effectively reduce behavioral agitation in some elderly demented patients at doses and serum concentrations lower than those generally required for efficacy in epilepsy and mania (e.g., 125 mg/D to 750 mg/D and 15 mg/L to 50 mg/L versus 750 mg/D to 4,000 mg/D and 50 mg/L to 150 mg/L, respectively). However, some patients may respond only when the latter valproate doses and serum concentrations are used.
TABLE

Studies of Valproate in Behavioral Agitation (or Disturbance) of Dementia

<table>
<thead>
<tr>
<th>Study</th>
<th>Design (duration)</th>
<th>No. of patients (age in years; range)</th>
<th>Dementia diagnosis</th>
<th>VPA Dose (mg/D)</th>
<th>VPA Level (mg/L)</th>
<th>Response</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mellow et al., 1993</td>
<td>Open, prospective</td>
<td>4 (65-83) (1 to 3 mos)</td>
<td>AT</td>
<td>7500 - 2500</td>
<td>(45-93)</td>
<td>2 showed significant improvement; 1 transient improvement</td>
<td>None</td>
</tr>
<tr>
<td>Sival et al., 1994</td>
<td>Retrospective chart review (NR)</td>
<td>23</td>
<td>13 AT, 2 MI, 7 NOS, 1 pick</td>
<td>240 - 1200 (NR)</td>
<td>52% displayed partial (26%) or complete disappearance of disturbed behavior; all patients resistant to neuroleptics or benzodiazepines</td>
<td>Drowsiness in 2 patients; ataxia in 1 patient</td>
<td></td>
</tr>
<tr>
<td>Horne &amp; Lindley, 1995</td>
<td>Case report (NR)</td>
<td>1 (96)</td>
<td>AT</td>
<td>NR (62)</td>
<td>NR (62)</td>
<td>&quot;Gradual improvement&quot; in agitated screaming and cooperativeness; patient had worsened with combination of haloperidol and lorazepam</td>
<td>NR</td>
</tr>
<tr>
<td>Lott et al., 1995</td>
<td>Open, prospective (4-34 weeks)</td>
<td>10</td>
<td>5 AT, 71-94</td>
<td>375-750 (13-52)</td>
<td>8 (80%)</td>
<td>Mild sedation in 50% or greater reduction in agitation</td>
<td>Mild</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td></td>
<td></td>
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</tbody>
</table>

VPA = valproate; mos = months; AT = Alzheimer's type; MI = multi-infarct; NOS = not otherwise specified; NR = not recorded
Mean age for men = 79 years; mean age for women = 82 years
Mean ± SD VPA dose = 481.3±248.3 mg/D
Serum levels determined, but not reported, in six patients (four who responded and two who did not respond); serum levels in three of four who responded were "below the therapeutic range for epilepsy"

PRELIMINARY GUIDELINES FOR VALPROATE USE IN DEMENTED PATIENTS WITH BEHAVIORAL AGITATION

Our group presently considers valproate as a first-line treatment for most demented patients with behavioral agitation (once other potential medical causes for their agitation are excluded or corrected), particularly if the patient's agitation is marked by manic-like symptoms such as irritability, affective lability, hyperactivity, increased verbal or vocal activity, aggression, insomnia and other diurnal rhythm disturbances, and psychosis. Because side effects of valproate include benign hepatic transaminase elevations and thrombocytopenia, which are both reversible, and, extremely rarely, fatal hepatic failure, which occurs primarily in children and in patients on multiple antiepileptic drugs, leukopenia, and acute hemorrhagic pancreatitis, a medical history with special attention to hepatic, hematologic, and gastrointestinal abnormalities is performed prior to initiation of valproate. Also, baseline liver function and hematologic parameters should be obtained. Because valproate is a nonspecific inhibitor of hepatic metabolism and is highly protein bound, patients' concurrent medications should also be reviewed prior to valproate administration for potential drug-drug interactions.

Our group typically begins valproate treat-
ment with the enteric-coated divalproex sodium formulation (divalproex) to minimize gastrointestinal side-effects (e.g., nausea, dyspepsia, and diarrhea). For patients who have difficulty swallowing pills, divalproex sprinkle capsules (which can be pulled apart and sprinkled on food) may be used. To minimize gastrointestinal distress, sedation, and other neurological side effects, divalproex is usually begun at 125 mg/D to 250 mg/D (usually given as 125 mg q HS or bid), depending on the patient’s age, medical condition, concomitant medications, and severity of agitation. The divalproex dosage is then increased according to response and side effects, usually by 125 mg/D or 250 mg/D every several to 10 days. If gastrointestinal or neurological side effects occur, these can usually be managed by dosage reduction. Gastrointestinal distress can also be reduced by switching to the divalproex sodium sprinkle formulation or adding a histamineH receptor antagonist. For patients who fail to respond or respond partially, the valproate dosage may be increased, if tolerated, to achieve serum concentrations of 50 mg/L to 125 or 150 mg/L. Also, for partial responders, other “anti-agitation” agents (e.g., antipsychotics, lithium, or carbamazepine) may be carefully added to augment valproate’s anti-agitation effects.

If at the time valproate is to be started the patient is receiving other psychotropics (e.g., antipsychotics, benzodiazepines, lithium, or carbamazepine) that appear to have had some therapeutic effect, these agents may be continued, if the patient is not experiencing untoward side effects, and valproate added to the regimen, while carefully observing for side effects and potential drug interactions. If the patient responds well to the addition of valproate, concurrently administered psychotropics may be gradually withdrawn, one at a time, observing carefully for worsening of agitation, and thus, for possible beneficial synergistic effects.

For patients who display an acute response to valproate, the drug is continued as a prophylactic treatment—usually at the same dose and/or serum concentration required for acute efficacy. In many patients, the entire daily valproate dosage may be administered as one dose before sleep for convenience and to enhance compliance.

Regarding monitoring for adverse effects, clinical monitoring is more important than routine blood monitoring. However, because clinical experience with valproate in demented patients is not extensive, and because demented patients often cannot communicate side effects, we monitor liver function and hematologic indices at weekly to monthly intervals after initiation of valproate treatment for several months until all indices are stable. These parameters are then monitored every six to 24 months, and more importantly, whenever clinically indicated, while the patient remains on the drug. If hepatic transaminase elevations or thrombocytopenia are severe, valproate may be discontinued and restarted at a lower dose once abnormalities have resolved. Of note, because acute hemorrhagic pancreatitis is a rare but potentially fatal side effect of valproate, severe or persistent gastrointestinal distress or increased agitation (possibly due to abdominal pain) should be evaluated with a serum amylase test. If a patient develops valproate-induced pancreatitis, he or she should not be given the drug again, because re-exposure has been associated with re-induction of pancreatitis.35

CONCLUSION

Why might valproate have beneficial effects in dementia-related behavioral agitation? As noted earlier, GABA, the major inhibitory neurotransmitter within the central nervous system, is deficient in the brains of patients with dementia. Preliminary animal and human data indicate that GABA agonists, including valproate, have anxiolytic and anti-aggression effects in addition to anticonvulsant properties.41-46 Valproate might therefore reduce agitation in dementia by enhancing central GABAergic neurotransmission. Another possibility is that valproate reduces dementia-related behavioral agitation by enhancing serotonergic neurotransmission. As noted earlier, reduced concentrations of 5-HT, 5-HIAA, and various 5-HT receptors have been found in certain cortical regions of the brains of persons with Alzheimer’s disease. This possibility is supported by animal and human data showing that reduced serotonergic neurotransmission is associated with impulsive aggression.53

Yet another possible explanation is that dementia-associated behavioral agitation represents a form of secondary mania, or mania due to a general medical condition, and is responding to valproate’s antimanic or mood-stabilizing properties (which might also be related to the drug’s GABAergic or serotonergic effects).22,35,38,41 This conceptualization is supported by the phenomenological similarities between these two conditions, which include irritability, dysphoria, affective instability, hyperactivity, hypertalkativeness, verbal and physical aggression, insomnia, and other diurnal rhythm disturbances, and psychosis, and by the fact that many of the other medications used to treat dementia-related behavioral agitation (especially antipsychotics, lithium, and carbamazepine) also have antimanic or mood-stabilizing effects.

In sum, behavioral agitation of dementia is an enormous public health problem. The most commonly used medical treatments (e.g., antipsychotics, benzodiazepines, and other various psychotropic agents) are associated with limited efficacy or side effects and drug-drug interactions that are problematic for the elderly and cognitively impaired. Although controlled data are lacking, a growing number of open studies suggest that valproate may be an effective, well-tolerated, and safe treatment for some dement-
ed patients with behavioral agitation, including those patients who are unable to tolerate or respond inadequately to antipsychotics and benzodiazepines. In light of the magnitude of this problem and the lack of systematic data regarding its treatment, further studies of valproate in elderly patients with dementia-related behavioral agitation appear warranted. These should include double-blind, placebo-controlled studies of valproate, as well as controlled trials comparing the efficacy of valproate with more commonly used agents (e.g., antipsychotics). In addition, long-term studies should be done in community-based patients to determine whether early treatment of behavioral agitation has beneficial effects on the long-term course of dementia, including reducing time spent in long-term care facilities.

REFERENCES