Evaluation and Management of Aggressive Behavior in the Elderly Demented Patient

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Aggression is common in elderly patients with dementia and often leads to placement of these patients in long-term care facilities. Unfortunately, identification and evaluation of aggression is sometimes hindered by disagreement as to how aggression is distinguished from agitation. Aggression in elderly patients with dementia is best understood as a product of the interaction of neurobiological, cognitive, and environmental factors. Such a complex etiology calls for an approach to treatment that considers pharmacologic therapy as well as environmental manipulation; however, further research is needed to clarify the causes of aggression in elderly patients with dementia and thus allow the refinement of approaches to treatment. *(J Clin Psychiatry 1999;60[suppl 15]:45–49)*

Aggression—hostile action directed toward objects, others, or self[1]—is a common symptom of late-life dementia. A major determinant of placement in long-term care facilities, aggression can be verbal, physical, vocal, or sexual. Physical aggression, for example, is the most common behavioral precipitant for nursing home admission; the aggressive behavior of dementia patients often scares and exhausts caregivers, who in turn elect to give over charge of the patients to nursing homes. Moreover, verbal, physical, and sexual aggression all have been identified in nursing home patients with dementia.[1]

Coupled with the fact that noncognitive behavioral problems tend to increase in number as Alzheimer's disease progresses,[2] the prevalence of aggression in elderly patients with dementia calls for greater understanding of what aggression is, how it can best be identified, and how it can most effectively be treated. Aggression in elderly demented patients is not the product of any single cause; instead, it is a result of the interplay between neurobiological, cognitive, and environmental factors. Proper identification and management of aggression in elderly demented patients require a working knowledge of this interplay as well as a precise distinction between specifically aggressive behaviors and behaviors that fall under the broader category of agitation.

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IDENTIFYING AND EVALUATING AGGRESSION

One of the chief problems in identifying and measuring aggression in elderly patients—or any other patients—is that disagreement exists in the psychiatric community as to how aggression and agitation are defined and distinguished. Some researchers list aggression (hostile action directed at someone or something) as a subcategory of agitation (general physical or vocal disruption manifest in inappropriate verbal, vocal, or motor activities).[3] Others, however, try to make a more definite distinction between the two, listing them as separate types of behavior.

This confusion extends, not surprisingly, to rating scales. For example, the Neuropsychiatric Inventory (NPI),[4] an increasingly used instrument that provides a comprehensive assessment of psychopathology in dementia patients, lists many items under the heading "agitation/aggression"—slamming doors, throwing objects, attempting to hurt or hit others—usually associated with aggression, not agitation. On the contrary, the agitated behaviors pacing and fidgeting are listed not under "agitation/aggression" on the NPI but instead under "aberrant motor behavior." Wording difficulties are also found in the Brief Psychiatric Rating Scale (BPRS)[5]; however, the BPRS has been shown to be usable, reliable, and sensitive to change in the evaluation of aggression in elderly demented patients undergoing psychopharmacologic treatment.

CAUSES OF AGGRESSION IN ELDERLY PATIENTS WITH DEMENTIA

Although aggression is commonly found in patients with schizophrenia or other forms of dementia, such disruptive behavior does not always stem from psychiatric problems. Three types of factors—neurobiological, cogni-

tive, and environmental—can influence aggressive behavior. Because these types of factors do not exist in a vacuum but instead influence each other, a comprehension of aggression in elderly patients with dementia requires an understanding of the interplay of these types of factors as well as of the individual factor types themselves.

Neurobiological Factors

One way to refine the approach to treating a disorder is to understand that disorder's underlying neurobiology. Indeed, several neurobiological factors may contribute to aggressive behavior in elderly patients with dementia. In a postmortem study, Victoroff et al.[6] found that Alzheimer's disease patients with histories of interpersonal violence had significantly higher numbers of dopaminergic neurons in the substantia nigra pars compacta than did nonviolent patients with Alzheimer's disease. These high numbers of neurons denoted increased dopaminergic sensitivity and suggested that preservation of dopaminergic neurons may be a risk factor for physical aggression in Alzheimer's disease. Decreased cholinergic activity in the central nervous system (CNS) may also lower the threshold for aggression in elderly demented patients. Bodick et al.[7] reported that the selective muscarinic receptor agonist xanomeline can reduce disturbing behavioral symptoms in patients with Alzheimer's disease. Likewise, decreased CNS activity of serotonin may contribute to aggression in dementia. Reduced serotonergic activity can increase susceptibility to physically aggressive behavior in the context of irritability and impulsiveness[8]; patients with Alzheimer's disease have lowered levels of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in tissue and in spinal fluid.

Research has also explored the role of norepinephrine in mediating aggressive behavior in patients with dementia and has shown that increased CNS noradrenergic activity and increased sensitivity to released norepinephrine may contribute to agitation and aggression in patients with advanced Alzheimer's disease. Elderly patients with Alzheimer's disease, even though they experience substantial neuronal loss, have greater sensitivity to norepinephrine in the cerebrospinal fluid (CSF) than do healthy patients. Peskind et al.[9] found that, although normal elderly subjects and patients with Alzheimer's disease had similar elevation of CSF norepinephrine compared with younger subjects, the patients with Alzheimer's disease were more agitated and aggressive than the normal elderly subjects after receiving the α_2-adrenergic antagonist yohimbine, a drug that stimulates CNS noradrenergic activity by blocking α_2 receptors that mediate norepinephrine feedback of locus ceruleus neurons. Moreover, Raskind et al.[10] noted significantly higher plasma norepinephrine and 3-methoxy-4-hydroxyphenylglycol (MHPG) levels in patients with advanced Alzheimer's disease than in patients with moderate Alzheimer's disease or normal controls.

The high CSF levels of norepinephrine in patients with Alzheimer's disease suggest increased up-regulation of locus ceruleus neurons in these patients rather than decreased clearance of norepinephrine (decreased clearance would be accompanied by low levels of dihydroxyphenylglycol [DHPG]; low levels of DHPG are not seen in Alzheimer's disease patients). For example, my colleagues and I[11] found that compared with young persons, elderly persons, including those with Alzheimer's disease, had higher CSF concentrations of dopa, the precursor for norepinephrine and the indicator of activity of tyrosine hydroxylase, the major rate-limiting enzyme for norepinephrine synthesis. Our studies in postmortem brain tissue are consistent with these CSF findings; we found higher tyrosine hydroxylase messenger RNA (mRNA) expression per remaining neuron in the locus ceruleus of patients with advanced Alzheimer's disease than in elderly subjects cognitively intact prior to death.[11]

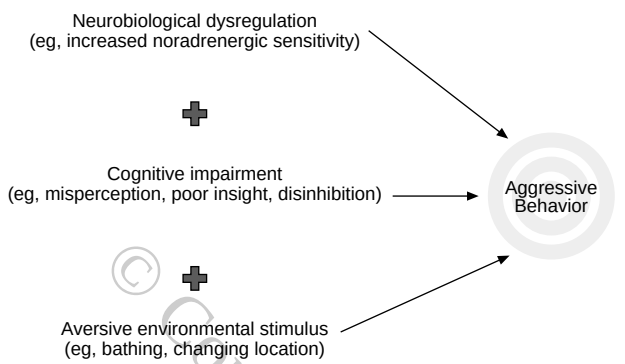
Cognitive and Environmental Factors

Although aggression is termed a noncognitive abnormal behavior in dementia, studies have demonstrated a possible relationship between cognitive function and aggression. Cohen-Mansfield and Werner,[3] in a study of elderly persons living in the community, found that increases in verbally and physically aggressive behaviors correlated significantly with low baseline levels of cognitive function; physical aggression was associated with baseline cognitive impairment as well. In another community-based study, Cohen-Mansfield and Werner[12] reported that cognitive impairment, along with poor relationship quality, is a chief predictor of physical aggression in elderly persons. Likewise, Ryden[13] found a significant relationship of aggression to degree of cognitive impairment in subjects with dementia who lived in the community.

Aversive environmental stimuli also can lead to aggressive behavior in elderly patients with dementia. These patients often see no need to maintain personal hygiene and respond aggressively to caregivers' attempts to encourage bathing, changing clothes, or moving from one place to another.

Clinicians should remember that neither neurobiological, cognitive, nor environmental factors alone precipitate aggression in elderly demented patients. Instead, aggression in this population is best understood as a result of the interaction of these 3 types of factors (Figure 1). Neurobiological dysregulation lowers the threshold for expression of aggression in Alzheimer's disease. This potential for aggression is increased by cognitive impairment, i.e., damage to brain structure hinders comprehension of one's environment, leading to misperceptions, poor insight, disinhibition, and poor memory. Aversive environmental factors, then, may be seen as only an immediate—not necessarily an ultimate—provocation of aggressive behavior in patients with dementia.

Figure 1. Additive Model of Aggression in Dementia



TREATMENT OF AGGRESSION IN ELDERLY DEMENTIA PATIENTS

Because aggression in elderly patients with dementia is the product of not one but multiple precipitants, treatment strategies should focus on improvement of cognition and control of patients' environment as well as on mediation of neurobiological disruption. Research to date has examined both pharmacologic and environmental approaches to treating aggression in this population, although our knowledge of the most effective treatments is far from complete.

Pharmacologic Approaches

Antipsychotics. Psychotic symptoms are similar to and may even be linked to agitated behaviors, including aggression. Thus, it is not surprising that antipsychotics have long been used to treat nonpsychotic and behavioral problems associated with dementia. However, studies have found that traditional antipsychotic medications are only modestly effective compared with placebo in treating noncognitive behavioral symptoms. For instance, a meta-analysis by Schneider et al.[14] showed that, although traditional antipsychotics were somewhat more effective than placebo in treating dementia patients with psychotic and/or disruptive problem behaviors, the improvements seen in these patients were substantially smaller than those seen in young schizophrenia patients without dementia. Likewise, in a study by Petrie et al.,[15] only 32% of patients receiving loxapine and 35% of patients receiving haloperidol (compared with 9% of patients receiving placebo) showed moderate or marked improvement of noncognitive behavioral symptoms.

Furthermore, even the benefits of traditional antipsychotic agents in treating behavioral problems can be negated by the adverse effects, including pseudoparkinsonian rigidity, tremor, and bradykinesia, that often accompany treatment with these medications. Devanand et al.,[16] for example, reported that extrapyramidal effects associated with treatment with traditional antipsychotics limited improvements in quality of life that had resulted from reductions in behavioral symptoms. The atypical antipsychotic medications, on the other hand, are much less likely to lead to adverse effects such as parkinsonism than are the traditional antipsychotics; however, only anecdotal information is available concerning the efficacy and tolerability of the atypical antipsychotics in the treatment of dementia patients with behavioral disturbances.

β-Blockers. β-Blockers have been reported anecdotally to treat aggression in elderly dementia patients. Shankle et al.[17] found that low doses (10–80 mg/day) of propranolol reduced aggressive behavior in patients with dementia; Shankle and colleagues warn, however, that higher doses of propranolol can lead to unwanted side effects.

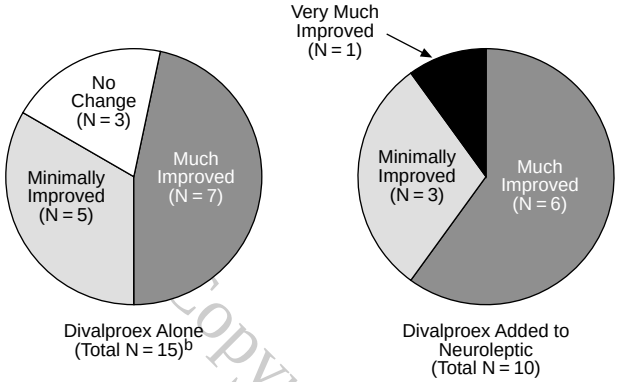
Antidepressants. Because aggressive patients with dementia tend to have reduced CNS serotonergic activity, the selective serotonin reuptake inhibitor (SSRI) antidepressants have been hypothesized to be helpful in treating these patients. Studies have not focused on the effects of SSRI therapy specifically on aggressive symptoms in elderly patients with dementia; however, SSRIs have been shown to reduce noncognitive behavioral symptoms in some patients with Alzheimer's disease. Nyth and Gottfries,[18] in a multicenter study, found citalopram to be more effective than placebo in improving behavioral symptoms in patients with Alzheimer's disease, although not in patients with vascular dementia. Furthermore, Olafsson et al.[19] found nonsignificant differences between fluvoxamine and placebo in improving noncognitive symptoms in elderly patients with dementia. The SSRIs, as a medication class, have a benign side effect profile and thus merit further study in the treatment of aggression in dementia.

Cholinergic drugs. Decreased CNS cholinergic activity is thought to contribute to the cognitive symptoms of Alzheimer's disease; thus, drugs that increase CNS cholinergic activity are used to treat these cognitive symptoms. Because cholinergic deficiency may also contribute to changes in behavior in patients with Alzheimer's disease,[20] cholinergic drugs may prove useful in combating behavioral as well as cognitive symptoms in dementia. The cholinesterase inhibitors tacrine and metrifonate and the experimental M_1-muscarinic cholinergic agonist xanomeline all have been shown to reduce noncognitive behavioral symptoms in Alzheimer's disease.[21]

Still, despite these findings and the fact that increases in aggressive behavior have been correlated with a decline in cognitive functioning,[3] further study of cholinergic drugs is needed before their role in treating aggression in elderly patients with dementia is defined.

Anticonvulsants. Studies have reported the effectiveness of anticonvulsants in treating aggressive behavior in elderly patients with dementia. Carbamazepine has been shown to effectively treat aggression associated with de-

Figure 2. Response of Patients With Dementia and Behavioral Disturbance to Treatment With Divalproex or Combination of Divalproex and Neuroleptics[a]



[a]Data from reference 23. Improvement rating based on results of a modified 7-point Clinical Global Impressions-Severity of Illness scale (CGI-S).
[b]Three patients with no change and 3 patients with minimal improvement with divalproex alone were later much improved when neuroleptic was added to divalproex; thus, 20 (80%) of 25 patients were either very much improved or much improved at discharge.

mentia. In a recent study by Tariot et al.,[22] 77% of patients receiving carbamazepine versus 21% of patients receiving placebo showed global improvement on the Clinical Global Impressions scale; improvement in patients receiving carbamazepine was attributed to reduced agitation and aggression.

Divalproex sodium, an anticonvulsant that enhances GABAergic neurotransmission and is used in the treatment of mania, was retrospectively shown to be effective both as monotherapy and in combination with neuroleptics in reducing noncognitive behavioral problems, including physical and verbal aggression, in older patients with dementia. For example, Narayan and Nelson,[23] in a chart review, found that 14 (56%) of elderly demented inpatients with behavioral problems responded to either divalproex sodium alone or to divalproex plus a neuroleptic (Figure 2). Similarly, a chart review by Kunik et al.[24] showed that divalproex sodium lessened physical aggression, as well as general psychiatric symptoms, overall agitation, and nonaggressive physical agitation, in 13 elderly inpatients with dementia accompanied by behavioral disturbances. Herrmann,[25] in an open study, found valproate to be beneficial in reducing behavioral disturbances associated with dementia, especially physical agitation and aggression.

Environmental Approaches

Clinicians should determine, before prescribing medications for the treatment of aggressive behaviors, that other causes such as medical illness or reaction to nonpsychotropic medications do not underlie the behaviors.[21] Modification of the caregiver's behavior may also alleviate patients' noncognitive behavioral problems. In general, regulation of environment is much more feasible for patients in an institution than for patients who live alone or with caregivers. Holmberg,[26] for example, found a 30% reduction of aggressive events in elderly nursing home patients with dementia on days when they went for group walks compared with days without walks. Furthermore, Verma et al.[27] describe several other environmental modifications, such as changing of roommates and isolating disruptive patients, that can help curtail disruptive behavior in inpatients.

CONCLUSION

Conclusive study is needed to confirm the effectiveness of pharmacologic and environmental strategies for treating aggression in elderly patients with dementia. Specifically, the postmortem studies of noradrenergic activity in Alzheimer's patients can perhaps provide a model for research on the other neurotransmitter systems in this patient group. Above all, however, a closer look is needed at the way neurobiological, cognitive, and environmental factors affect each other in producing aggressive behaviors.

Aggression in elderly patients with dementia is prevalent and thus merits further study. Refined definition of aggressive behaviors will lead to greater precision in identifying such behaviors, and increased understanding of the complex etiology of aggression in this patient population will yield a more informed approach to treatment. Controlled studies of drugs that appear promising in the treatment of aggression, such as anticonvulsants and SSRI antidepressants, are needed.

Drug names: carbamazepine (Tegretol and others), citalopram (Celexa), divalproex (Depakote), fluvoxamine (Luvox), haloperidol (Haldol and others), loxapine (Daxolin, Loxitane), propranolol (Inderal and others), tacrine (Cognex), yohimbine (Yocon and others).

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