Role of Cholinesterase Inhibitors in Managing Behavioral Problems in Alzheimer's Disease

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Alzheimer's disease is characterized by progressive cognitive and functional decline and the emergence of behavioral disturbances. Behavioral symptoms, in particular, cause great distress to caregivers, creating an emotional and financial burden that often prompts the caregiver to place the patient in a nursing facility. The clinical deterioration in Alzheimer's disease is, in part, a result of deficits involving several neurochemical pathways. The cholinergic system, which is the most consistently and dramatically affected neurotransmitter system in Alzheimer's disease, has been strongly implicated in the emergence of neuropsychiatric symptoms. This article reviews evidence suggesting that, in addition to effects on cognition and function, the cholinesterase inhibitors benefit the behavioral symptoms of Alzheimer's disease. Pharmacologic and nonpharmacologic treatment strategies for the management of behavioral symptoms are discussed.

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Alzheimer's disease (AD) is the most common cause of dementia in the elderly, with a prevalence that doubles every 5 years after the age of 60.[1] According to the National Institutes of Health, an estimated 8.5 million Americans will develop AD by the year 2030.[2] The disease may span several decades if the preclinical period is included.[3]

Significant clinical features of AD include progressive loss of memory, intellect, and autonomy.[4] Although cognition and functional abilities decline steadily in AD, the behavioral disturbances that occur as the disease progresses are often the most challenging aspect of caring for patients with AD. The behavioral disturbances, which cause considerable caregiver stress and burden, are a primary reason health care professionals are asked to intervene.[5,6] Moreover, behavioral disturbances often play a major role in the decisions to place patients in nursing homes.[5,6] Indeed, immediate precipitants of nursing home placement include agitation, aggression, increased nighttime wakefulness, and depression.[7–10]

Behavioral symptoms such as apathy and depression[4] may appear early in the disease course and can lead patients with AD to isolate themselves and withdraw from activities they once found enjoyable. More prevalent during the middle to late phases of AD, behavioral disturbances may range from repetitive verbalizations, agitation, and wandering to verbal and physical aggression[4] and eventually occur in up to 90% of demented individuals.[11,12] Behavioral disturbances also contribute significantly to the increased financial burden, particularly by necessitating nursing home placement, since institutionalization represents the single largest cost component of AD care.[13]

DATA SOURCES AND STUDY SELECTION

A PubMed literature search was conducted for publications from January 1970 to July 2003 on commonly prescribed cholinesterase (ChE) inhibitors, using the keywords *Alzheimer's disease*, *donepezil*, *galantamine*, and *rivastigmine* and the limits "English language" and "randomized, controlled trials." By systematic review, the list was further narrowed to double-blind studies of single ChE inhibitors with behavior- or neuropsychiatric-specific scales as the primary or secondary outcome measure. If measures of behavior or psychiatric symptoms were not used in trials of a particular ChE inhibitor, studies including a global function scale were included.

In all, 59 articles were retrieved. Of those studies, 5[15,16,30,35,37] met the additional inclusion criteria; one[16] of those 5 used a global function measure rather than a neuropsychiatric-specific scale. The small number of studies that assess the impact of ChE inhibitors on behavior or neuropsychiatric symptoms suggests a deficiency in the medical literature. Pivotal trials of ChE inhibitors have focused on the cognitive and functional deficits resulting from AD.[14–16] However, more recent clinical practice recommendations reflect increased recognition of the need to treat behavioral symptoms when caring for patients with

Table 1. Cholinergic Involvement in the Behavioral Disturbances of Alzheimer's Disease (AD)

Study	Finding
Longo[26]	Anticholinergic drugs induce AD-like behaviors (delusions, visual hallucinations, agitation, and amnesia) in healthy individuals.
Drachman and Leavitt[27]	Scopolamine, a muscarinic-receptor antagonist, induces amnesia in young, healthy subjects that may be reversed with cholinesterase (ChE) inhibitor therapy.
Sunderland et al[28]	Behavioral symptoms are exacerbated in patients with AD receiving anticholinergic drugs.
Minger et al[29]	Brain regions found to be associated with behavioral disturbances (eg, frontal and temporal regions) show a cholinergic deficiency.
Tariot et al,[15] Feldman et al,[30] and Morris et al[31]	Behavioral symptoms are ameliorated in patients with AD receiving ChE inhibitors.
Bodick et al[32]	Cholinergic replacement therapy with xanomeline and other cholinomimetics results in dramatic and favorable effects on disturbing behaviors in AD.
Tariot et al[37]	Behavioral symptoms improved in nursing home patients with AD receiving ChE inhibitors.

dementia.[17,18] Given the benefits patients with AD receive from ChE inhibitor therapy, long-term placebo-controlled trials to further define the impact of this class of drug on behavioral symptoms may not be considered ethical. Nevertheless, studies using reliable and validated measures of the behavioral symptoms associated with AD, such as the Neuropsychiatric Inventory (NPI) and the Behavioral Pathology in Alzheimer's Disease Rating Scale,[19] are warranted because alleviating these symptoms may increase the quality of life for both patient and caregiver.

CAREGIVER BURDEN

Caregiver burden increases as patients lose functional abilities and increasingly experience neuropsychiatric disturbances. Although functional decline necessitates greater levels of assistance,[4] behavioral symptoms can be particularly distressing for caregivers.[20] Behavioral disturbances are associated with caregiver depression,[21] psychological morbidity,[22] and distress.[23] Because behavioral problems have a profound impact on caregivers, physicians must remain alert to signs of depression and other distress-related illness in caregivers of patients with AD. Treatments that reduce neuropsychiatric disturbances may lead to decreased caregiver stress and burden.

CHOLINESTERASE INHIBITORS AND BEHAVIORAL SYMPTOMS OF ALZHEIMER'S DISEASE

The cholinergic system, which is the most consistently and dramatically affected neurotransmitter system in AD, has long been known to play a major role in the cognitive abnormalities of AD.[24] The cholinergic system has also been strongly implicated in the emergence of neuropsychiatric symptoms.[25] Evidence supporting a role for the cholinergic system in the behavioral disturbances of AD is presented in Table 1.

Various strategies have been investigated to attempt to increase cholinergic function in AD, but the use of ChE inhibitors has been the most clinically successful. There are currently 4 ChE inhibitors approved by the U.S. Food and Drug Administration for the symptomatic treatment of mild-to-moderate AD. Tacrine was the first ChE inhibitor to be approved in 1993; donepezil hydrochloride was approved in 1996; rivastigmine tartrate, in 2000; and galantamine hydrobromide, in 2001. Because of side effects associated with tacrine, including hepatotoxicity and the inconvenience of 4-times-daily dosing, it is rarely prescribed. Of the commonly prescribed ChE inhibitors, donepezil has been on the market the longest, and more published clinical trials exist for donepezil than for the newer drugs. Studies of donepezil represent the majority of data available on this drug class.

Although clinical trials have demonstrated benefits of ChE inhibitor therapy on cognition, global function, and activities of daily living, its effects on behavior have only recently been elucidated (Table 2). In an open-label study,[33] behaviors most responsive to therapeutic doses of tacrine were anxiety, apathy, hallucinations, disinhibition, and aberrant motor behavior. A follow-up study[34] showed significant reductions in apathy and disinhibition; however, as discussed previously, tacrine's use is limited by its side effects.

Donepezil therapy has been shown to improve behavioral symptoms in patients with moderate to severe AD.[30,35] The NPI, a 12-item, caregiver-rated instrument used to evaluate behavioral and neuropsychiatric symptoms such as delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy, disinhibition, irritability, aberrant motor behavior, nighttime behavior, and appetite/eating disorder was used in a 24-week, randomized, double-blind study of donepezil that enrolled patients with significant behavioral and neuropsychiatric symptoms.[30] NPI scores were improved with donepezil treatment versus placebo throughout the study; treatment differences were significant at weeks 4 and 24 ($p < .05$); treatment benefits were sustained through study end point. Statistically significant differences favoring donepezil over placebo were reported for the symptoms of anxiety, apathy/indifference, and depression/dysphoria.[35] Of note, because many patients were taking psychotropic drugs

Table 2. Cholinesterase Inhibitor Efficacy in Ameliorating Behavioral Disturbances in Alzheimer's Disease (AD)[a]

ChE Inhibitor	Evidence	Measure
Tacrine	Patients given therapeutic doses of tacrine showed improvements in behavior.[33] Anxiety, apathy, hallucinations, disinhibition, and aberrant motor behavior were the most responsive symptoms.	NPI
Tacrine	A follow-up study showed significant reductions in apathy and disinhibition.[34]	NPI
Donepezil	Donepezil significantly improved behavioral symptoms compared with placebo in a 24-week study.[30] Significant between-group differences were found for anxiety, apathy, and depression/dysphoria.[30,35]	NPI
Donepezil	Donepezil treatment of a subpopulation of patients with moderate AD resulted in improved scores throughout the study, with significant benefits at weeks 4 and 24.[36]	NPI
Donepezil	Donepezil improved agitation/aggression significantly over placebo in a 24-week, double-blind study of patients in nursing homes.[37]	NPI-nursing home version
Galantamine	Galantamine-treated patients (16 and 24 mg/d) maintained behavioral symptoms near baseline in a 5-month, randomized, placebo-controlled study.[15]	NPI
Rivastigmine	Beneficial effects on global functioning were reported, which included measures of behavior, cognition, and ADL.[16]	CIBIC-plus[a]
Metrifonate	Drug-placebo differences favoring metrifonate ($p < .05$) were reported in patients with mild to moderate AD in a 26-week study.[31]	NPI

[a]No specific neuropsychiatric outcomes addressed.
Abbreviations: ADL = activities of daily living, CIBIC-plus = Clinician's Interview-Based Impression of Change plus caregiver input, NPI = Neuropsychiatric Inventory.

at baseline, these differences are likely to be conservative. These findings reinforce the concept that cholinergic deficiencies play a significant role in some of the neuropsychiatric manifestations of AD.

Patients with AD residing in nursing homes are generally older and have more severe symptoms than patients residing in the community, including higher rates of behavioral disturbances.[38] A 24-week, double-blind study examined the safety and efficacy of donepezil in patients with AD residing in nursing homes.[37] Patients in this study were in general 12 years older and had more severe AD—as shown by lower Mini-Mental State Examination (MMSE) scores—than patients enrolled in previous outpatient trials with donepezil. Agitation/aggression was the most frequent behavioral symptom at baseline in this study, occurring in 64% of all patients. Donepezil significantly improved agitation/aggression versus placebo, as measured by the NPI-nursing home version. In another study of donepezil in AD patients with moderate disease, improvement in NPI scores was seen at 4 and 24 weeks.[36]

Galantamine has shown efficacy in treating behavioral disturbances associated with mild to moderate AD. In a 5-month, randomized, placebo-controlled trial, galantamine-treated patients (16 and 24 mg/day) maintained behavioral symptoms near baseline, while placebo-treated patients declined by 2 points on the NPI.[15] Both the 16- and 24-mg/day treatment groups had significantly better NPI total scores at 5 months than the placebo group ($p < .05$).

Rivastigmine has been shown to improve global functioning in AD, as measured by the Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC-plus).[16] While the CIBIC-plus is an overall measure incorporating assessment of cognition, activities of daily living, general function, and behavior, it does not provide a specific evaluation of behavior as would an instrument specifically designed to measure neuropsychiatric disturbances.[16] Thus, the behavioral benefits of rivastigmine treatment, on the basis of this study, should be carefully considered. In a 26-week, open-label study of 173 nursing home patients with moderate to severe AD, 59% of patients showed improvement on the NPI-nursing home version.[39] However, findings from this pilot study need to be confirmed in a placebo-controlled, double-blind clinical trial.

Although not approved for the treatment of AD, metrifonate is a ChE inhibitor that appears to exert beneficial effects on behavioral symptoms. In a 26-week, double-blind study of metrifonate treatment in patients with mild to moderate AD, the NPI was used to measure behavioral outcomes.[31] Metrifonate treatment was associated with significantly less decline in neuropsychiatric disturbances compared with placebo ($p < .05$).[31]

A recent meta-analysis of clinical studies assessing neuropsychiatric outcomes with the NPI in patients with mild to moderate AD reported modest benefits of the ChE inhibitors tacrine, donepezil, galantamine, and metrifonate for behavioral symptoms.[40] However, interpretation of these results is limited by the low incidence of behavioral problems and the use of psychoactive medications in this patient cohort. Nonetheless, in light of the modest benefits observed, it was proposed that ChE inhibitors be considered for the management of the neuropsychiatric symptoms in AD. Indeed, in a study of patients with moderate to severe AD and a high incidence of behavioral disturbances, donepezil treatment was demonstrated to significantly improve behavior ($p < .001$ at study end point).[35]

The above clinical trial data support the potential benefits of ChE inhibitors in treating neuropsychiatric symptoms. ChE inhibitors represent an increasingly important and recognized aspect of treatment in managing neuropsychiatric disturbances in patients with AD. The following case history highlights the benefits of a ChE inhibitor for behavioral disturbances in AD.

Case History

Ms. A, an 84-year-old divorced woman, was taken to a memory disorder clinic by her daughter for an evaluation. Symptoms of cognitive impairment had developed gradually over the previous few years and had become more evident within the past year. Her initial symptoms included a marked decrease in appetite with associated weight loss and increasing forgetfulness of recent events. She had shown symptoms of apathy during the prior 6 months, a behavior that her family found discouraging and troubling.

On examination at the memory disorder clinic, Ms. A was awake, alert, attentive, and pleasant. She scored 8/30 on the MMSE, on which she recalled none of the 3 words. Her speech was fluent with normal prosody and no paraphasic errors. Visuospatial function was markedly impaired. The results of the patient's neurologic examination were normal except for mild bradykinesia and rigidity in the upper extremities and mild vibration loss at both distal lower extremities. Her gait was normal. A magnetic resonance imaging scan revealed mild atrophy most prominent in the frontoparietal region, as well as mild changes in the periventricular white matter. There was no evidence of infarct or subdural hematoma. Her mother had died at age 78 with some memory problems, but there was no other known family history of dementia.

Ms. A was started on donepezil at 5 mg/day. Her other medications included aspirin, 81 mg/day; megestrol, 40 mg p.o. b.i.d.; metoclopramide, t.i.d. (for years); meclizine, p.r.n.; a multivitamin; and vitamin E, 400 IU/day. It was recommended that she increase her vitamin E to 1000 IU b.i.d. and discontinue the metoclopramide. Ms. A returned to the clinic after 1 month of donepezil treatment, and her dose was escalated to 10 mg/day of donepezil.

After 6 months of 10 mg/day of donepezil, Ms. A's MMSE score was 12/30. Her behavior continued to improve, with no depressive symptoms and increased socialization with family members. After 1 year of donepezil, Ms. A's MMSE score had improved to 14/30, and her cognitive and behavioral condition was relatively stable.

In patients with AD, successful treatment is most often seen as stabilization or slowed decline in cognition, function, and behavioral symptoms.[41] For example, 6-month clinical trials in patients with mild to moderate AD showed a mean treatment difference of 0.34 points in favor of rivastigmine[16] and 1.36 points in favor of donepezil[14] on the MMSE. One-year clinical trials in patients with mild to moderate AD showed a mean treatment difference of 1.6 points on the MMSE in favor of donepezil.[42,43] In contrast to the preservative effect seen in these clinical trials, Ms. A's cognition was greatly enhanced at the 6- and 12-month assessments of her treatment. Over the course of 1 year, her mean response to treatment was 5 points on the MMSE. Of note, her initial score of 8/30 indicated that she was suffering from severe AD. After treatment with donepezil, her MMSE scores at 6 and 12 months indicated mild to moderate AD. Ms. A's marked improvement in cognition was accompanied by the alleviation of her depressive symptoms and a renewed interest in social activity. Her case history suggests that ChE inhibitors may offer significant behavioral as well as cognitive benefits to patients with AD.

Table 3. Nonpharmacologic Interventions for Reducing Behavioral Disturbances in Alzheimer's Disease (AD)

Reassurance[44]
Distraction[44]
Maintaining routine[44]
Structured activities (eg, bingo, group singing)[45]
Music[46]
Unstructured activities (eg, sorting, walking)[47]
Exercise[48]
Bright light therapy[49]
Simulated presence therapy (eg, audiotapes or videotapes of family events)[50]
Touch therapy (eg, hand massages, back rubs)[51]
Pet therapy[52]
Gardening[31]
Behavioral interventions[53]
One-to-one therapy[54]

STRATEGIES FOR TREATING BEHAVIORAL DISTURBANCES

Because behavioral disturbances may change in nature, frequency, intensity, and duration over the disease course, caregivers should be questioned regarding continued symptoms and the emergence of new behaviors. Target symptoms should be identified and their frequency and severity clearly defined. Accurate and detailed pretreatment profiles of patients with AD may optimize management of behavioral symptoms by identifying troublesome behaviors and tracking their response to therapy.[34]

Various nonpharmacologic interventions have value in treating behavioral disturbances in AD (Table 3),[44–57] and many of these interventions can improve the patient's quality of life. Commonly described interventions provide sensory stimulation, activities, and social contacts because patients with dementia benefit when their social energy is channeled into positive activities that may relieve the distress of boredom and loneliness.[44] Activities that require simple thought, such as bingo or sorting easily distinguishable objects, provide calming distraction.[44,45,47] Playing music preferred by the patient and engaging in regular exercise may decrease agitation.[46,48] Since patients with AD do not cope well with change, establishing a daily routine and limiting environmental changes can reduce stress.[44]

Pharmacologic interventions may be helpful when nonpharmacologic strategies fail to reduce behavioral symptoms sufficiently. Specific target symptoms dictate

the choice of pharmacologic agent. Traditional pharmacologic therapy for severe behavioral disturbances such as delusions and hallucinations includes the typical and atypical neuroleptic agents, with a preference for the atypical neuroleptics due to more favorable side effect profiles.[58] The American Academy of Neurology currently recommends the use of antipsychotics for agitation or psychosis.[18] Although less commonly used, there is evidence to support the use of other agents such as anticonvulsants, benzodiazepines, antihistamines, monoamine oxidase inhibitors, or selective serotonin reuptake inhibitors (SSRIs) for agitation or psychosis.[18] SSRIs also offer some benefit for the treatment of depression with better tolerability than other antidepressants.[18] Serotonin-norepinephrine reuptake inhibitors may offer additional benefits over SSRIs because they have shown favorable safety and tolerability, analgesic effects, and efficacy in treating all symptoms of depression.[59] In addition, there is an accumulating body of evidence that ChE inhibitors improve behavioral symptoms, and these drugs are increasingly being considered by many experts as effective first-line treatment for behavioral disturbances in AD.[25,40,44]

In keeping with the principles of geriatric psychopharmacology, pharmacologic agents should be started at a low dose and then slowly increased until a sufficient response occurs or side effects emerge. Potential drug interactions should be considered. After behavioral disturbances have been controlled for 4 to 6 months, the dosage of pharmacologic agent should be reduced periodically to determine whether continued pharmacotherapy is required.

It is important to regularly evaluate the patient for drug toxicity as well as medical, psychosocial, or environmental problems that may underlie behavioral changes. For example, a symptom such as agitation may reflect an underlying infection or a change in the patient's routine.

In addition to addressing the direct needs of the patient with AD, physicians should provide caregivers with emotional support and encourage them to utilize private and community resources such as the Alzheimer's Association, support groups, and legal services.

CONCLUSIONS

Growing evidence supports the hypothesis that cholinergic deficits observed in AD contribute to the behavioral manifestations of AD. Nonpharmacologic treatments may alleviate these behavioral disturbances. When nonpharmacologic treatments alone are not sufficient, they may be used in conjunction with therapies that enhance cholinergic function or other pharmacotherapies, and behavior may be improved. In the case example provided, significant benefits on cognition and behavioral disturbances were observed with donepezil treatment. At the first visit, the patient showed symptoms of apathy, depression, and a general withdrawal from normal activities. After starting donepezil therapy, the patient showed greater involvement in social activities, her depressive symptoms subsided, and her behavior continued to improve and then remained stable throughout treatment with donepezil.

While pivotal clinical trials of the ChE inhibitors demonstrated benefits in cognition and global function, the behavioral benefits were not as apparent, as these studies enrolled patients with mild to moderate AD who, in general, do not suffer severe behavioral disturbances. In addition, these studies did not include uniform behavioral measures. Recent studies enrolling more advanced patients have provided compelling data demonstrating benefits for behavioral symptoms of AD.[30] The behavioral efficacy of ChE inhibitors in patients with AD provides support for a proposed role of a cholinergic deficiency in neuropsychiatric AD symptoms[29] and further emphasizes the importance of ChE inhibitors as a therapeutic treatment option for the management of behavioral disturbances in AD.

Drug names: donepezil (Aricept), galantamine (Reminyl), meclizine (Antivert and others), megestrol (Megace and others), metoclopramide (Reglan and others), rivastigmine (Exelon), tacrine (Cognex).

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