

Cholinesterase Inhibitors in Non-Alzheimer Dementias

Andrew R. Gustavson, MD,* and Jeffrey L. Cummings, MD†

The treatment of Alzheimer's disease (AD) was revolutionized by the development of cholinesterase inhibitor (ChE-I) medications. For the first time, medications specifically targeted at the pathophysiological changes in the illness became available. The success of these drugs in AD led to speculation that they could also be beneficial in other types of dementia. The available evidence in vascular dementia supports this notion and is reviewed in a different section of this issue. There is some support for the use of cholinesterase inhibitors in other diseases, but the evidence supporting their use is not as well developed, and few studies have been completed. We review the available evidence regarding the use of ChE-Is in non-AD disorders and provide a theoretical framework for predicting which dementias should respond to this class of medication and the evidence relevant to this hypothesis.

There are currently 3 drugs that are approved by the U.S. Food and Drug Administration to treat the cognitive and neuropsychiatric symptoms of AD and that are widely used: donepezil (Aricept™), rivastigmine (Exelon™), and galantamine (Reminyl™). All are assumed to share a common basic mechanism of action. The ChE-Is are thought to enhance cholinergic activity in brain regions associated with both neurocognitive and neuropsychiatric symptoms in AD. All increase postsynaptic acetylcholine activity by inhibiting the main enzyme (acetylcholinesterase) responsible for catabolism of the neurotransmitter within the synaptic cleft. Diminished clearance leads to increased acetylcholine concentration in the synaptic junction and increased postsynaptic neurotransmitter activity. Based on this presumed mechanism of action, hypotheses concerning their effectiveness can be generated. First, there should be a cholinergic deficit or evidence of cholinergic dysfunction in the disease. If there is no deficit in acetylcholine function, increased acetylcholine activity would be anticipated to have little beneficial effect. In AD, which serves as a prototypic disease, there is diminished cholinergic activity related to neural death in cholinergic nuclei in the basal forebrain. Second, effectiveness would be

anticipated when there is a presynaptic deficiency in acetylcholine release rather than when there is a postsynaptic abnormality. If all available receptors are dysfunctional, then increasing the concentration of the neurotransmitter in the cleft could have little effect. In AD, there is a presynaptic deficiency as the number of cholinergic axons is decreased as a result of neuron loss. Based on this rationale the ChE-Is would be expected to exert a beneficial effect in diseases with a known presynaptic cholinergic deficit but not in diseases without these characteristics.

NORMAL SUBJECTS

Normal subjects, by definition, do not have a cholinergic deficit but there is speculation that enhanced cholinergic activity can produce enhanced memory in the absence of an abnormality. Cholinergic neurons decrease with age, and older individuals have less acetylcholine available than younger persons. Physostigmine is a cholinesterase inhibitor that increases central cholinergic activity. One controlled trial involving men 18 to 35 years of age found improved memory as measured by 15- and 20-item word-list recall 80 minutes after intravenous infusion of 1 mg of the agent. Digit span was measured concurrently to evaluate for effects on attention but did not show a similar change. Improved memory was attributed to increased cholinergic activity. The effect did not appear to be the result of enhanced attention as might be expected from stimulant properties alone. There was significant variability in the subjects' performance, however, and only single measures of memory and attention were obtained.¹ It is possible that the stimulant properties of physostigmine contributed to the memory improvement independent of attention. The degree to which verbal word-list recall generalizes to memory and cognition in general is not clear. The short-term nature of the study further limits generalizations from this study.

A randomized, placebo-controlled, double-blind, between-group study of 18 pilots found no significant improvement in retention of complex flight simulator tasks in 9 patients taking 5 mg donepezil per day for 30 days, but pilots receiving placebo had a diminished performance when retested creating a drug-placebo difference in favor of donepezil.² There was no control for general stimulant properties or enhanced attention. This study does suggest that normal individuals' cognitive skills can be stabilized by donepezil compared with placebo. The methods do not allow, however, for a conclusion concerning a specific effect of donepezil on memory.

Nathan et al.³ reported results of a double-blind, placebo-controlled, within-subject experiment with 16 healthy volunteers 18 to 31 years of age. Cognitive function was assessed with 3 well-validated neuropsychologic tests, including for-

Departments of *Neurology and †Psychiatry and Biobehavioral Science, David Geffen School of Medicine at UCLA, Los Angeles, California.

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Address correspondence to: Jeffrey L. Cummings, MD, Reed Neurological Research Center, Department of Neurology, UCLA School of Medicine, 710 Westwood Plaza, Los Angeles, CA 90095-1769. E-mail: JCummings@mednet.ucla.edu

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ward and backward Digit Span Test⁴ and Trail Making Tests A and B⁵ before and 90 minutes after administration of 5 mg donepezil and placebo. There was no difference between the active drug and the baseline or placebo conditions. The authors concluded that they failed to find any evidence that donepezil had a beneficial effect on the tests performed.

Shua-Haim and coworkers⁶ conducted a retrospective survey of family assessments of the response of individuals with age-associated cognitive deficit to treatment with donepezil. Fifty-seven percent of families thought they had observed some degree of cognitive enhancement with treatment. There was no significant change in Mini-Mental State Exam (MMSE)⁷ scores; no other cognitive measures were collected. Thirty-two percent of patients reported side effects and 5% deteriorated cognitively.

Although some studies support a possible memory or cognitive enhancing effect with ChE-I, others do not. There is currently insufficient evidence to draw any firm conclusions concerning drug-specific cognitive or memory enhancement, although the best studies to date fail to support this hypothesis. Studies of the effects of ChE-Is on test performance in normal elderly would be of substantial interest.

DOWN SYNDROME

Down syndrome is associated with early dementia with similarities in pathology and biochemistry to AD, providing a rationale for the use of ChE-Is. There is a known loss of cholinergic neurons providing input to limbic structures and cortex in both AD and Down syndrome. There is accumulation of abnormal beta-amyloid in both disorders, which presumably causes neuronal death and hence a presynaptic deficit. ChE-Is can be predicted to be helpful in this disorder. There are 2 multiple case reports of patients with Down syndrome treated with donepezil. The total number of patients reported is 7. Of the 7, 4 patients were demented. One patient improved with treatment at 5 mg per day but deteriorated at 10 mg per day. Another had improvement in activities of daily living. Two of the nondemented patients had improved socialization or communication skills.^{8,9} In contrast, the results of the only controlled study found significant improvement as measured by the Down's Dementia Rating Scale in 9 demented patients compared with 6 demented control subjects after 5 months' treatment with donepezil. This retrospective study was an open label and used carefully historical matched controls. The authors concluded that the results provide a rationale for a larger randomized, placebo-controlled study.¹⁰ Despite considerable theoretical reasons to suggest patients with Down syndrome, especially those with concurrent dementia, could derive benefit from cholinesterase inhibitor therapy, there are currently few studies reported in the literature from which to draw a conclusion. The available results to date are promising.

PARKINSON'S DISEASE WITH DEMENTIA

Of the non-AD dementias, Parkinson's disease with dementia has been studied most extensively. Parkinson's disease is associated with a loss of cholinergic neurons projecting from the basal forebrain nuclei and causing a loss of presynaptic

acetylcholine activity in cortical regions. Available studies include a double-blind, controlled trial, open-label trials, and case reports.¹¹⁻¹³ All studies report benefit in cognition with no worsening of Parkinson's symptoms. Hallucinations consistently improved if present before cholinesterase therapy. Werber and Rabey¹⁴ treated 11 patients with Parkinson's disease and dementia with ChE-Is (7 with tacrine and 4 with donepezil) in an open-label study. They observed significant improvement on cognitive measures and trends toward improvement on the MMSE and global measure. No deterioration of motor function occurred. Fabbrini and coworkers¹⁵ conducted an open-label study of the effect of donepezil on hallucinations and delusions in 8 patients with Parkinson's disease. All experienced reduction in their neuropsychiatric symptoms; 2 had worsening of motor function. In an open-label study of 8 patients with Parkinson's disease and psychosis, Bergman and Lerner¹⁶ observed marked improvement in 5 of 8 patients and 1 had minimal improvement after treatment with donepezil. No patients exhibited motor side effects. Bullock and Cameron¹⁷ treated 5 patients with Parkinson's disease, dementia, and psychosis with rivastigmine: 2 had cognitive improvement and 2 had arrest of cognitive decline; 4 of 5 manifested improvement in psychotic symptoms. In a larger open-label trial of rivastigmine including 15 patients with Parkinson's disease and hallucinations, Reading et al.¹² found a significant reduction in total Neuropsychiatric Inventory (NPI) scores and improved MMSE scores after 6 weeks of optimal dose therapy. Giladi et al.¹³ also found rivastigmine to be effective in improving cognition in patients with Parkinson's disease and dementia.

The best evidence for use of ChE-Is in patients with Parkinson's disease with dementia comes from a study conducted by Aarsland et al.¹¹ This was a randomized, double-blind, placebo-controlled, crossover study of 14 patients all with Parkinson's disease with dementia. The patients showed a mean increase in MMSE⁷ score of 2.1 points compared with 0.3 during the placebo treatment. Side effects were similar to those seen in patients with AD and related to cholinergic action of the drug (nausea, diarrhea, dizziness). Motor symptoms did not worsen during drug therapy. Patients with Parkinson's disease with dementia showed a larger response in MMSE score than is typically observed in patients with AD. All current evidence suggests ChE-Is are well tolerated in patients with Parkinson's disease, with no worsening of extrapyramidal symptoms and a potential important gain in cognitive ability. Hallucinations are the neuropsychiatric symptoms that can most benefit. These medications represent a promising new approach to treatment for Parkinson's disease with dementia. Larger-scale studies are needed.

DEMENTIA WITH LEWY BODIES

Dementia with Lewy bodies is associated with Parkinsonism, fluctuation in cognition, prominent visual hallucinations, and other neuropsychiatric symptoms such as delusions, depression, and apathy. Clinical similarities with AD and Parkinson's disease with dementia suggest ChE-Is can also be beneficial in dementia with Lewy bodies. This dementia is associated with greater neocortical cholinergic deficits than

are typical in AD.¹⁸ Cell death in cholinergic nuclei creates a presynaptic abnormality, and ChE-Is could be expected to have a beneficial effect in this illness. Studies available include a double-blind, controlled trial, open-label trials, and case reports. All report some benefit but lack consistency regarding which symptoms improved. Shea et al.¹⁹ conducted a 12-week case series of 9 patients treated with donepezil initiated at 2.5 to 5.0 mg per day and increased to 10 mg per day in 5 patients. There was a significant mean improvement of 4 points on the MMSE and 0.3-point improvement on the Geriatric Depression Inventory that approached significance ($P = 0.08$). Additionally, there was a decrease in Parkinsonism in 6 of the 9 patients and a decrease in hallucinations in 8 of the 9 patients. However, there was an increase in extrapyramidal symptoms in 3 of 9. Langtot et al.²⁰ reported the results of a case series of 7 patients treated with 5 to 10 mg donepezil for 8 weeks. Four patients discontinued treatment, 2 of which were for adverse events. Three of the 4 patients for whom data were reported experienced an improvement in MMSE score, whereas 1 remained unchanged. Before treatment, the group had a mean total score on the NPI²¹ of 42.3 and improved to 10 after treatment, suggesting a significant improvement in neuropsychiatric symptoms. Multiple and single case reports have consistently indicated improvements in cognition and behavior in patients with dementia with Lewy bodies after treatment with ChE-Is.^{22–24}

McKeith et al.¹⁸ conducted a 23-week, multicenter, double-blind, randomized, placebo-controlled trial of rivastigmine in 120 patients with dementia with Lewy bodies. Patients were treated with a maximum tolerated dose, which ranged from 6 to 12 mg per day. Primary outcome measures were NPI scores and a computerized test of cognitive speed at baseline, and weeks 12, 20, and 23. The last measure was made after 3 weeks off treatment. Both primary outcome measures showed significant improvement. During treatment, the rivastigmine group showed less apathy and anxiety, experienced fewer psychotic symptoms, and showed evidence of improved speed and performance on the computerized cognitive testing tasks. These group differences declined after treatment was stopped from weeks 20 to 23. There was a trend for improved scores on the MMSE, but the drug–placebo difference did not reach significance. Adverse events were typical of rivastigmine and related to cholinergic activity. There was no worsening of parkinsonian symptoms. In an open-label extension of this trial with 29 patients, improvement was maintained for up to 96 weeks.²⁵

All studies show some improvement in patients with dementia with Lewy bodies treated with ChE-Is. Some studies suggest that neuropsychiatric symptoms could be the most responsive to therapy. Adverse events were similar to those reported in patients treated for AD. One study found an increase in extrapyramidal symptoms with donepezil in 3 of 9 patients.^{19,25} Overall, the available evidence suggests a benefit of the ChE-Is without intolerable side effects.

PROGRESSIVE SUPRANUCLEAR PALSY

Like with dementia with Lewy bodies, common clinical features shared between Parkinson's disease and progressive supranuclear palsy led to speculation that ChE-Is could be of

benefit. However, although there is a cholinergic deficit in this disorder, it is predominantly postsynaptic,²⁶ and this argues against a therapeutic effect of the cholinesterase medications. The evidence to date supports this hypothesis. A 6-week, double-blind, placebo-controlled, crossover study of donepezil in 22 patients with progressive supranuclear palsy was reported by Litvan et al.²⁷ The outcome measures were an assessment of quality of life, the NPI, MMSE, neuropsychologic testing, and a motor symptom scale. There was no improvement in the primary outcome measures, and motor function was noted to worsen. Memory improved on a single scale during active drug treatment. Diarrhea was a significant problem occurring in 9 of 19 patients on donepezil compared with 2 of 19 on placebo.

HUNTINGTON'S DISEASE

Similar to progressive supranuclear palsy, Huntington's disease is characterized by a postsynaptic cholinergic deficit, and the scant evidence to date suggests minimal benefit of treatment with ChE-Is. There are at present no double-blind, placebo-controlled trials in this disorder. However, in an open-label trial of 8 patients treated with donepezil, Fernandez et al.²⁸ reported no significant improvement in MMSE, neuropsychologic testing, scales of behavior, independence, and functional disability. All patients tolerated the medication at 5 mg per day, but at 10 mg per day, half of the subjects discontinued treatment as a result of adverse events. Two patients experienced worsening chorea and falls, 3 experienced intolerable diarrhea, and 1 experienced anxiety and irritability. The limited preliminary evidence suggests that ChE-Is will not be beneficial in patients with Huntington's disease.

TRAUMATIC BRAIN INJURY

The effects of ChE-Is in traumatic brain injury were reviewed by Griffin et al.²⁹ They identified 13 studies through an extensive literature search that included patients treated with physostigmine, physostigmine plus lecithin, or donepezil. They noted that many of the studies were uncontrolled and failed to account for placebo effects or the effects of spontaneous recovery. Nevertheless, the studies consistently found effects on attention, memory, and executive function. Apathy and possibly other neuropsychiatric symptoms also improved. The authors hypothesized that attentional effects could be responsible for many of the benefits observed.

Traumatic brain injury is likely to produce both pre- and postsynaptic damage to the cholinergic system. Shearing injuries can damage white matter fibers ascending from the nucleus basalis creating a presynaptic deficit in cholinergic function, whereas cortical contusions, lacerations, and other direct physical damage can cause postsynaptic deficits. Thus, the response to ChE-Is could depend on the preponderance of injury type, and patient populations can be heterogeneous in terms of their responsiveness to ChE-Is.

SCHIZOPHRENIA

Patients with schizophrenia exhibit a variety of cognitive deficits in addition to psychosis, and these deficits could be

related in part to a cholinergic dysfunction.³⁰ However, unlike in AD, the deficit in schizophrenia is not clearly related to decreased presynaptic acetylcholine activity. Rather, the behavioral and cognitive abnormalities could be related to disruption of a balance between acetylcholine and dopamine activity or other secondary effects on cholinergic function. One study suggests a brief reduction in psychotic symptoms in patients with schizophrenia treated with subcutaneous physostigmine.³¹ Rosse and Deutsch³² reported a marked beneficial effect of the ChE-I galantamine on negative symptoms in a 43-year-old patient with schizophrenia and cognitive deficits. Negative symptoms improved within 1 week of initiating therapy and returned soon after treatment was discontinued. Stryker and colleagues³³ used a single blind design to assess the use of donepezil in 6 patients with schizophrenia. Improvements were noted on the MMSE and clinical global ratings. Three of the patients improved on measures of psychotic symptomatology and exhibited more significant decrement in positive than negative symptoms. However, Friedman et al.³⁰ found no such benefit for cognition or psychosis in 18 patients with schizophrenia treated with risperidone and 5 or 10 mg donepezil per day compared with 18 control patients treated with risperidone alone in a 12-week, double-blind, placebo-controlled trial. Although there could be some role for drugs that modify cholinergic function in the treatment of schizophrenia, the best evidence to date is equivocal regarding the use of ChE-Is in this disorder.

OTHER NEUROLOGIC AND NEUROPSYCHIATRIC DISORDERS

A wide range of other neurologic and neuropsychiatric disorders have been treated with ChE-Is in an attempt to identify other patient groups that could benefit from cholinomimetic therapy. Most of these studies are small, open-label studies or multiple case observations. Case reports are typically limited to those that show benefit, and the number of patients treated with ChE-Is and showing no improvement is unknown. Placebo effects can be substantial and these are typically unaccounted for. Nevertheless, these preliminary observations could identify conditions that are worthy of more rigorous investigation.

Treatment of patients with multiple sclerosis manifesting cognitive impairment with donepezil in a 12-week, open-label study indicated improvement in attention, naming, memory, and conceptualization as well as total behavioral rating scale scores.³⁴ White matter tracts arising from the nucleus basalis and projecting to distant forebrain regions could plausibly be interrupted by demyelinating plaques creating a presynaptic cholinergic deficit responsive to treatment with ChE-Is.

Delirium is commonly caused by anticholinergic toxicity, and ChE-Is could have a role in reducing attentional and cognitive abnormalities in patients with delirium. Case reports support this hypothesis and suggest that ChE-Is should be further studied for their effect in delirium.^{35,36}

Donepezil was reported to assist in the management of treatment-resistant bipolar disorder, particularly patients with mixed mood syndromes.³⁷ Donepezil has been shown to re-

duce rapid eye movement (REM) latency in patients with depression and to improve REM sleep behavior disorder.^{38,39}

A multiple case report suggested that donepezil improved behavioral symptoms and tic severity in patients with Gilles de la Tourette's syndrome with attention deficit-hyperactivity disorder.⁴⁰ Nine of 10 patients with tardive dyskinesia included in an open-label study of donepezil in this movement disorder evidenced a reduction in abnormal involuntary movements.⁴¹ Berthier and coworkers⁴² assessed the efficacy of donepezil in an open-label study of 11 patients with post-stroke aphasia. A variety of language scores improved from baseline after treatment and resolved toward baseline after withdrawal of therapy. In a study involving 29 patients with acute attacks of migraine, donepezil significantly reduced the relapse rate and the use of rescue treatments.⁴³

Many of these disorders cannot be integrated into a pre- or postsynaptic cholinergic deficit framework because little is known about the integrity of the cholinergic system in the individual conditions. If verified with large-scale, blinded studies, these pilot observations indicate that cholinergic function abnormalities could exist in a wide variety of diseases.

CONCLUSION

The study of ChE-Is as treatment for non-Alzheimer's dementias is in evolution. The available evidence suggests that illnesses characterized by a presynaptic cholinergic deficit such as AD, Down syndrome, dementia with Lewy bodies, and Parkinson's disease-related dementia improve on these medications, whereas illnesses characterized by a postsynaptic cholinergic deficit such as progressive supranuclear palsy and Huntington's disease do not. A preferential responsiveness of conditions with presynaptic cholinergic deficits is consistent with the postulated mechanism of action and forms a testable hypothesis for future studies, and could be important in choosing patient populations that might benefit from ChE-I therapy.

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