Letter to the Editor

Acetylcholinesterase Inhibitors: Treatment of Dementia-Related Behavioral Disturbances

Sir: Behavioral disturbances are seen in up to 90% of patients with Alzheimer's type dementia at some point during the illness.[1,2] There is evidence that cholinesterase inhibitors may help in controlling dementia associated behavioral disturbances.[3–5] We present a case report of a patient with behavioral disturbance associated with severe Alzheimer's dementia who showed marked improvement of the behavioral disturbance with tacrine.

Case report. Ms. A, a widowed woman, was psychiatrically evaluated nearly 5 years ago (when she was 75 years of age) at request of her primary care physician for behavioral disturbances, which included severe aggression pertaining to dementia of the Alzheimer's type (DSM-IV criteria), a diagnosis that had been made when she entered a skilled nursing facility 5 years earlier. The informant was Ms. A's brother, since she was unable to sit through an interview. Collateral information was also obtained from the nursing staff of the skilled nursing facility, where she had been residing for the previous 5 years.

At the time of the evaluation, Ms. A's brother reported that she had had a gradual decline in memory over the past 5 years. She was unable to recognize him and confused him with other people. Nursing staff reported significant difficulties during activities of care, especially aggression and sleeping problems at night. She was eating poorly, was extremely irritable, had been grabbing at staff and visitors, and was not redirectable. Ms. A had no prior history of psychiatric hospitalization or treatment. During her stay at the skilled nursing facility, she had been treated with paroxetine and haloperidol for her illness without any effect. Her medical history included peptic ulcer disease and carcinoma of the left breast for which she had undergone left mastectomy.

On mental status examination, Ms. A was appropriately dressed and well groomed, appeared her stated age, and had increased psychomotor activity. Her speech was impoverished, consisting of short sentences that had no connection. Her mood was irritable, and her affect was restricted. Her thought process was disorganized, with loosening of associations. She was unable to recall the name of the President of the United States and could not do serial *7*s, and her immediate and 5-minute recall were markedly impaired. No vegetative symptoms of depression were reported. Her judgment and insight were poor.

Laboratory tests revealed no significant findings. Ms. A was started on tacrine, 40 mg daily, in March 1996, which was increased to 40 mg q.i.d. over 4 weeks while her liver function was monitored. No side effects to tacrine were noted. Her appetite began to improve gradually, and the agitation was controlled. Trazodone, 50 mg, was added at night to improve sleep. After being on treatment with tacrine for about 2 years, the staff indicated that she was able to eat full meals and did not require assistance while eating. Her speech was more spontaneous, and her irritability was markedly reduced. She was ambulating well in the facility and was no longer as aggressive as before. She responded to redirection and also slept well at night. She continued to receive 40 mg q.i.d. of tacrine. No side effects were reported, and her liver function tests were within normal limits. The pharmacy consultant to the facility suggested discontinuing tacrine because of the cost factor; however, the nursing staff and aides were vehemently opposed to this course of action. The treating psychiatrist suggested continuing the tacrine in view of the robust response; the primary care physician agreed to continue treatment with tacrine.

Acetylcholinesterase inhibitors have been introduced as cognition-enhancing agents in the treatment of mild-to-moderate dementia. Tacrine hydrochloride,[6–8] the first acetylcholinesterase inhibitor approved by the U.S. Food and Drug Administration (FDA), was associated with liver toxicity. Tacrine was followed by donepezil hydrochloride[9,10] for the treatment of mild-to-moderate Alzheimer's dementia; donepezil is relatively safe. Rivastigmine is the most recently FDA-approved agent for this purpose. These agents block acetylcholinesterase and enhance choline acetyltransferase activity, which is decreased in patients with Alzheimer's disease. We found tacrine to be effective for treating dementia-related behavioral disturbances as demonstrated by this case from the pre-donepezil days. Today, donepezil or rivastigmine could be considered as an alternative treatment for such a patient.

A meta-analysis[11] of all randomized, double-blind, placebo-controlled trials of tacrine revealed a beneficial effect on behavioral disturbances in patients with dementia. Gauthier et al.[12] conducted a 24-week, randomized, double-blind, placebo-controlled multicenter trial (N = 144) investigating the efficacy of donepezil on neuropsychiatric symptoms in moderate-to-severe Alzheimer's disease. They found statistically significant improvement on the Neuropsychiatric Inventory with donepezil compared with placebo.[12] Cummings et al.,[13] in their study of 173 patients, demonstrated 57% improvement in behavioral symptoms with rivastigmine, with 50% of patients showing an improvement of at least 30%.

Several drugs have been used in treating behavioral symptoms in patients with dementia, e.g., anticonvulsants, neuroleptics, serotonin reuptake inhibitors, buspirone, benzodiazepines, and β-blockers. Cholinesterase inhibitors are a valuable alternative, as observed in the clinical case with tacrine reported above and in trials with donepezil and rivastigmine. Donepezil is

started at a dosage of 5 mg daily and is increased to 10 mg daily; it is usually well tolerated except for gastrointestinal side effects. Rivastigmine is administered at a dosage of 6 to 12 mg daily. Common side effects associated with rivastigmine include nausea, vomiting, diarrhea, and anorexia, which are usually rare and mild. Rivastigmine inhibits acetylcholinesterase and butyrylcholinesterase (BuChE). BuChE levels are elevated in late-stage amyloid plaques, and increased levels of BuChE have been shown to be associated with Alzheimer's disease severity.[14] This additional activity of rivastigmine in inhibiting BuChE may be responsible for its efficacy in treating behavioral disturbance, which needs to be studied systematically. We suggest that primary care physicians treating patients with dementia-related behavioral disturbances consider donepezil and rivastigmine as available alternatives.

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Correction

In the byline to the article "Hypochondriacal Concerns: Management Through Understanding" (August 2000 issue, pp. 117–121), by Vicenzio Holder-Perkins, M.D., and colleagues, Mr. Williams' first name was spelled incorrectly. The corrected name is Darvin E. Williams.