Treatment of Tardive Dyskinesia With Donepezil: A Pilot Study

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Background: Tardive dyskinesia (TD) remains a significant clinical problem for which there is no uniformly effective treatment. Earlier trials with acetylcholine precursors may have been disappointing because of underlying damage to striatal cholinergic neurons in patients with TD. In contrast, new cholinesterase inhibitors, developed for the treatment of dementia, may improve TD by directly increasing cholinergic synaptic transmission.

Method: We conducted an 8-week open-label trial of donepezil in the treatment of TD. Ten patients with schizophrenia or schizoaffective disorder who received stable doses of antipsychotics and met DSM-IV criteria for TD were treated with donepezil, 5 to 10 mg/day, for 6 weeks after a 2-week baseline period. Changes in total Abnormal Involuntary Movement Scale (AIMS) scores measured every 2 weeks were assessed for significance. Patients were also assessed using the Brief Psychiatric Rating Scale, the Mini-Mental State Examination, the Barnes Akathisia Scale, and the Simpson-Angus Scale.

Results: Total AIMS scores decreased significantly ($p = .0009$), with no changes in other measures. Nine patients showed a positive response. Improvement was greatest in orofacial and upper extremity movements. No significant interactions were noted between the total AIMS scores and age ($p > .29$), duration of TD ($p > .38$), or duration of antipsychotic treatment ($p > .14$).

Conclusion: Donepezil appeared to be effective in suppressing TD in this pilot study. However, placebo-controlled, double-blind studies are necessary before donepezil can be recommended as a treatment for TD.

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The recent development of atypical antipsychotics offers the promise of a reduction in the incidence of new cases of tardive dyskinesia (TD). However, TD remains a significant clinical problem among patients previously treated with conventional antipsychotics for which there is no uniformly effective therapy.[1–3] The rationale for the treatment of TD with cholinomimetic drugs derives from the conceptualization of this disorder as the result of a relative imbalance between cholinergic and dopaminergic systems in the basal ganglia. Unfortunately, the response of TD to treatment with the acetylcholine precursors choline, deanol, and lecithin has been disappointing.[1–3] This may reflect uncertainty concerning the efficacy of dietary precursors in stimulating central cholinergic neurotransmission in humans. Moreover, precursors may not increase cholinergic activity in the brain if presynaptic neurons are impaired in their ability to synthesize and release acetylcholine.

In support of this hypothesis, Miller and Chouinard[4] reviewed data which suggest that striatal cholinergic neurons are damaged or destroyed in patients with TD. Selective damage to large interneurons in the striatum has been observed in brains of both rats after chronic administration of antipsychotic drugs and patients with TD examined postmortem.[4,5] These large cells most likely represent striatal cholinergic neurons.[3,6,7] Miller and Chouinard[4] proposed that antipsychotic-induced dopamine receptor blockade or loss of dopaminergic activity in Parkinson's disease results in the loss of dopamine-mediated inhibition of striatal cholinergic neurons, creating a state of overactivity and vulnerability to cell damage or death. They suggested that this damage to cholinergic neurons results in the dyskinesias observed in TD patients and in patients with Parkinson's disease receiving levodopa.[4]

This model implies that cholinomimetic precursors may be ineffective in TD because antipsychotic-induced damage to presynaptic neurons may impair their ability to utilize these agents to increase acetylcholine concentrations. This reasoning is similar to that proposed for the lack of efficacy of precursors in treating cognitive deficits in Alzheimer's disease, i.e., the loss of cholinergic neurons.[8] In contrast, cholinesterase inhibitors have improved cognition in demented patients because they directly increase cholinergic transmission by inhibiting acetylcho-

linesterase in the synaptic cleft, thereby decreasing hydrolysis of acetylcholine released from surviving presynaptic neurons.[8]

By analogy, cholinesterase inhibitors may also be effective in TD. In previous investigations using physostigmine, a short-acting cholinesterase inhibitor, the severity of TD decreased transiently in at least 50% of treated patients.[9,10,12–17] However, some investigators found no effect on TD[11,18] or even worsening of dyskinetic movements after physostigmine treatment,[10,11,14,17–20] perhaps reflecting the pharmacologic heterogeneity of TD among patients. Some of these studies were limited by small patient samples, variable assessment techniques, concurrent administration of anticholinergic drugs,[11,14,15] and the discomfort, stress, and extrapyramidal symptoms[10,14–17] associated with intravenous physostigmine administration.

In 4 studies, the response of TD to physostigmine was compared with response to subsequent trials of choline[13] or deanol.[14,15,17] There was a significant correlation between responses to physostigmine and these precursors in 2 trials,[13,14] whereas a correlation was shown in some but not all patients in the other 2 reports.[15,17]

Its short duration of action, intravenous route of administration, and unpleasant systemic effects render physostigmine impractical as a treatment for TD. In contrast, recently developed cholinesterase inhibitors are long-acting, well tolerated, and effective when taken orally. Surprisingly, we found only 1 study using these agents in the treatment of TD. Ingram and Newgreen[21] reported a 43% decrease in TD ratings in 8 patients treated with 45 to 90 mg/day of tacrine for 2 weeks. Hence, we examined the response to treatment with 5 mg/day of donepezil for 4 weeks followed by an additional 2 weeks on 10 mg/day of donepezil in an open-label trial of 10 patients meeting DSM-IV criteria for TD. Positive results observed in 3 of these patients were reported previously in a case report.[22]

METHOD

Ten patients were selected who met DSM-IV criteria for TD. All patients were male; 8 were diagnosed with schizophrenia and 2 with schizoaffective disorder. The mean ± SE age was 54 ± 12 years (range, 37–77 years). The mean ± SE duration of antipsychotic drug treatment was 27 ± 10 years (range, 15–40 years), and the mean ± SE duration of diagnosed TD was 9 ± 3 years (range, 5–15 years). Patients were excluded if they had acute medical illnesses, were receiving clozapine or selegiline, could not be withdrawn from anticholinergic medications or vitamin E, or experienced a change in oral antipsychotic medications or dosage within 1 month prior to the start of the study (within 2 months for depot medications).

Patients remained on a stable dose of antipsychotics throughout the study. Any anticholinergic drugs or vitamin supplements were discontinued at the first baseline visit, 2 weeks prior to the start of donepezil treatment. Three patients were receiving haloperidol decanoate, 2 were taking trifluoperazine, 2 were taking olanzapine, 1 was taking risperidone, 1 was taking quetiapine, and 1 was receiving no antipsychotics prior to or during the study. All had received typical antipsychotics in the past. One patient (case 3) died in an unrelated accident during the study. Patients were informed of the risks and alternatives to treatment with donepezil and gave informed consent.

Patients were evaluated at 2 baseline visits 2 weeks apart before receiving 5 mg/day of donepezil for 4 weeks, followed by 10 mg/day of donepezil for 2 additional weeks. Patients were assessed at baseline and at the final visit with the Brief Psychiatric Rating Scale (BPRS)[23] and the Mini-Mental State Examination (MMSE)[24] to assess changes in psychiatric symptoms and cognition. At both baseline visits and at 2-week intervals during active treatment, patients were assessed with the Abnormal Involuntary Movement Scale (AIMS),[25] the Barnes Akathisia Scale (BAS),[26] and the modified Simpson-Angus Scale.[27] The AIMS served as the primary measure of change in TD, whereas the BAS and Simpson-Angus were used to examine whether donepezil might cause or worsen akathisia and parkinsonism, respectively. Routine blood tests and urine drug screens were conducted at the beginning and end of the study.

Data from the AIMS were analyzed using multilevel modeling adjusting for the hierarchy of clusters with nested random effects based on intent to treat, which included all patients. The analyses fall under the heading of random coefficient models.[28,29] This modeling scheme is implemented in the SAS/STAT procedure Proc Mixed, which was used in our analyses.[30] The model included 2 rates of change: we expected minimal change during the baseline period and a substantial decrease in scores after donepezil was administered. BAS and Simpson-Angus scores were analyzed using the same approach. The AIMS total scores were also analyzed using age, duration of diagnosed TD, and duration of antipsychotic drug treatment as covariates to detect any differential effect of these variables on the rate of change. The BPRS and MMSE were analyzed using paired t tests.

RESULTS

We found that the total AIMS scores decreased significantly after donepezil was initiated (Table 1; $F = 23.45$, $df = 1,9$; $p = .0009$). Nine patients showed a positive response. No significant differences were found between baseline measurements. Regarding specific anatomical areas analyzed separately, AIMS subscores decreased significantly for the face ($F = 7.86$, $df = 1,9$; $p = .02$), jaw ($F = 7.73$, $df = 1,9$; $p = .02$), lips ($F = 13.16$, $df = 1,9$; $p = .006$), tongue ($F = 10.14$, $df = 1,9$; $p = .01$), and upper extremities ($F = 29.2$, $df = 1,9$; $p = .0004$). Only scores

Table 1. Total Scores on the Abnormal Involuntary Movement Scale (AIMS)

	AIMS Score by Visit[a]				
	Baseline Visit		Donepezil Treatment Visit		
Patient	1	2	3	4	5
1	18	19	10	6	5
2	21	24	20	15	18
3[b]	15	17	12	...	...
4	10	7	4	2	2
5	5	6	3	1	2
6	11	14	1	1	1
7	16	15	9	10	4
8	7	9	2	2	1
9	9	7	3	1	1
10	12	14	10	10	15
Mean ± SE	12 ± 5	13 ± 6	7 ± 6	5 ± 5	6 ± 6

[a]Visits were at 2-week intervals.
[b]Patient 3 died in an unrelated accident during the study.

for movements in the trunk ($F = .04$, $df = 1,9$; $p = .84$) and lower extremities ($F = 4.03$, $df = 1,9$; $p = .08$) failed to decrease significantly. Ratings of global severity also decreased significantly ($F = 18.3$, $df = 1,9$; $p = .002$). No significant interactions were noted between the total AIMS scores and age ($p > .29$), duration of diagnosed TD ($p > .38$), or duration of antipsychotic drug treatment ($p > .14$).

In contrast to AIMS scores, there were no significant changes in the ratings of BAS, Simpson-Angus, BPRS, or MMSE scales.

DISCUSSION

We found that treatment for 6 weeks with donepezil, 5 to 10 mg/day, significantly decreased AIMS scores in 9 of 10 patients taking stable doses of antipsychotic medications. Changes were most marked in orofacial musculature and upper extremities. No correlations were found with age, duration of TD, or duration of prior antipsychotic treatment. No changes were noted in cognition or psychiatric symptoms, and minimal side effects were reported. No evidence was found of worsening parkinsonism or akathisia as measured by the Simpson-Angus and BAS.

The specificity of the effect of donepezil must be questioned in these cases. Two patients had either mild (case 2) or no improvement (case 10), although the latter patient was suspected of noncompliance. Changes in other patients could reflect random fluctuations of symptoms or variability and biases in ratings. Erratic use of cocaine could have accounted for changes in TD in 2 patients who tested positive for cocaine use on a drug screen (cases 4 and 10).

However, the progressive decline in TD during donepezil treatment was against a random, nonspecific effect. Furthermore, the mean difference between the 2 baseline AIMS scores, which was not statistically significant, was exceeded by the decrease in TD ratings after donepezil treatment in all 9 responders. The consistency of ratings is supported by our having previously achieved satisfactory interrater reliability for the AIMS using the intraclass correlation coefficient (0.75).[31]

Although a dose-response effect was not observed after administration of 10 mg/day of donepezil for 2 weeks, 5 mg/day may have provided maximum benefit. Alternatively, if 10-mg or higher doses had also been given for 4 weeks or more, a greater response may have been obtained.

An additional confound is raised by the effect of discontinuing anticholinergic drugs prior to donepezil treatment. This confound can only be resolved by future placebo-controlled studies. In contrast to acute extrapyramidal drug reactions, TD may be exacerbated by the administration of anticholinergic drugs. Discontinuation of these drugs may result in improvement in up to 60% of TD patients[1] and should be considered as a first step in treating TD, unless a dystonic component is present. Thus, we had to discontinue anticholinergic drugs at the first baseline visit in 5 of our patients (cases 1, 4, 6, 8, 9), which probably contributed to the decline in TD ratings. However, there was no significant change in AIMS scores between baseline visits despite discontinuation of anticholinergic therapy during that time, in contrast to the significant decline in TD ratings after initiation of donepezil. In addition, 4 patients (cases 2, 3, 5, 7) had not been taking anticholinergics prior to the study but appeared to respond to donepezil in a positive fashion. Finally, the reported beneficial effect of anticholinergic drug discontinuation in previous studies provides indirect support for the strategy of enhancing synaptic or postsynaptic cholinergic activity in TD through the use of cholinesterase inhibitors.

Consistent with previous attempts at pharmacotherapy of TD,[14,17,19,20] the response to donepezil may ultimately prove to be heterogeneous between subgroups of individuals. With donepezil, response may depend on the degree of cholinergic cell loss or damage, which may correlate with age or duration of symptoms and treatment.[4] Although we could not demonstrate any interaction between these variables and response, our study sample of chronically ill patients is too small and skewed to justify conclusions on the heterogeneity and prediction of response. It is conceivable that larger controlled studies could demonstrate that younger patients with more recent onset of TD may show a more robust response to donepezil.

If cholinesterase inhibitors are shown to be effective in TD, this finding may provide post hoc evidence supporting the hypothesis proposed by Miller and Chouinard[4] that implicates antipsychotic-induced damage to cholinergic neurons as a significant factor in the pathogenesis of TD. Similarly, it may also explain the development of dyskinesias in patients with Parkinson's disease, which suggests that trials of anticholinesterases may be worthwhile in these patients as well.[15]

Nevertheless, although donepezil appeared to be effective in suppressing TD in 9 of 10 patients who participated in this pilot study, placebo-controlled, double-blind trials are required to confirm these findings before the use of donepezil and other recently developed cholinesterase inhibitors can be recommended as a promising new strategy in the treatment of this disorder.

Drug names: choline (Trilisate), clozapine (Clozaril and others), donepezil (Aricept), haloperidol (Haldol and others), lecithin (PhosChol), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), selegiline (Eldepryl), tacrine (Cognex), trifluoperazine (Stelazine and others).

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