Beneficial Effect of Donepezil in the Treatment of Elderly Patients With Tardive Movement Disorders

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Background: Tardive dyskinesia and other delayed-onset abnormal involuntary movement disorders may occur as a result of the use of psychotropic drugs. A distinction is usually made between classic tardive dyskinesia (TD) (oro-buccal-lingual-facial) and tardive dystonia, tardive tremor (TT), tardive akathisia, and other related syndromes. In spite of the development of atypical antipsychotics with fewer side effects, tardive movement disorders nevertheless continue to present a significant clinical and therapeutic challenge. Several reports have suggested that donepezil may be helpful in the treatment of TD.

Method: A preliminary study was conducted of 7 patients (5 women and 2 men) enrolled over a period of 6 months who had been experiencing TT for a period of at least 1 year. The ages of the patients ranged from 64 to 79 years, and all patients were on stable antipsychotic therapy. Donepezil was added to their usual treatment for 8 weeks. The severity of patients' extrapyramidal symptoms was assessed using the tremor subscale of the Simpson-Angus Scale (SAS) and self-rated with a modification of the Clinical Global Impressions scale, the Subjective Clinical Improvement Impression scale. The clinical response was evaluated by comparing the rating scores at baseline prior to donepezil treatment and every 2 weeks thereafter.

Results: The addition of donepezil (up to 10 mg/day) was associated with a clinically significant improvement (from 37.5% to 63.6%) on the SAS tremor subscale following 4 weeks of therapy. Only 1 patient discontinued follow-up due to side effects.

Conclusion: The results suggest that donepezil may be effective in the treatment of TT, and this finding should be evaluated further by a randomized controlled study.

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Prolonged administration of psychotropic medications may lead to the development of tardive dyskinesia (TD). This term refers to a group of delayed-onset abnormal involuntary movement disorders that occur as a result of the use of psychotropic agents. There are several forms of TD. A distinction is made between classic TD (oro-buccal-lingual-facial syndrome) and other tardive syndromes such as tardive dystonia, tardive tremor (TT), tardive akathisia, tardive tics, and tardive parkinsonism.[1–5] This division into subgroups is based on the finding that the risk factors and response to treatment may differ in the various forms of the syndrome. For example, most cases of tardive dystonia have been reported in young patients, and this movement disorder frequently responds to anticholinergic medications.[6–8] In contrast, anticholinergic drugs may exaggerate TD or cause latent TD to become manifest.[9]

In spite of the development of a new generation of antipsychotics with the promise of fewer new cases of TD, this condition poses a significant clinical and therapeutic challenge in caring for patients previously treated with conventional antipsychotics, especially the elderly.

The pathophysiology of TD is not clearly understood, and there are various hypotheses that attempt to explain this phenomenon. One such theory is related to the cholinergic system and supports the use of cholinergic drugs in the management of TD. It is hypothesized that TD may result from an imbalance between the cholinergic and dopaminergic systems in the basal ganglia.[10–12] In addition, striatal cholinergic neurons have been found to be damaged or destroyed in patients with TD.[13] Therefore, attempts have been made to evaluate the treatment of TD with a short-acting cholinesterase inhibitor such as physostigmine. Some such studies have found no effect on TD,[14,15] or even an exacerbation of dyskinetic move-

ments.[16–18] However, others have reported an improvement in TD symptoms in response to treatment with physostigmine.[19–23] Recently, the longer-acting cholinesterase inhibitors such as tacrine and donepezil were shown to have some beneficial effect in the treatment of TD,[24–26] whereas another study described the opposite.[27]

We describe the preliminary results of an open-label clinical trial of donepezil as add-on therapy in 7 elderly patients suffering from TT. To the best of our knowledge, this is the first report describing the treatment of TT with donepezil.

METHOD

Seven inpatients (2 men, 5 women; age range, 64–79 years) gave their informed consent to participate in this open-label study after receiving a complete description of the trial. The patients were enrolled over a period of 6 months. Six patients were diagnosed with schizophrenia and 1 with bipolar disorder according to DSM-IV criteria.[28] All patients met DSM-IV criteria for TD and suffered from the severe, disabling TT variant.[3–5] Patients suffering from eating disorders, malnutrition, gastrointestinal absorption disorders, or any avitaminosis were excluded. Also excluded were those receiving medications influencing gastrointestinal absorption, as well as those for whom the dose of oral antipsychotic medications was altered in the month prior to commencing the study, or within 2 months for those receiving a depot form of the drug. Patients with concurrent medical illness or neurologic disorders such as Parkinson's disease and essential tremor that may have influenced the diagnosis of TT were excluded from the study. Also excluded were patients receiving vitamin supplementation. A stable dose of antipsychotic therapy was maintained for the duration of the study. Three patients were treated with olanzapine (10–15 mg/day), a further 3 were receiving risperidone (4–5 mg/day), and 1 patient was taking zuclopenthixol decanoate (200 mg/4 weeks) augmented with valproate (1000 mg/day). All patients had received typical antipsychotics previously, and none was treated with anticholinergic medications.

Mental and cognitive state was assessed by means of the Brief Psychiatric Rating Scale (BPRS)[29] and the Mini-Mental State Examination (MMSE).[30] The severity of tremor was assessed with the tremor subscale of the Simpson-Angus Scale (SAS).[31] The patients' subjective feelings regarding the degree of symptom improvement were self-rated with the Subjective Clinical Improvement Impression scale (SCII).[32] This scale is our modification of the Clinical Global Impressions scale[29] and is based on ratings from 0 to 6 (the ratings included in this scale were 0 = very much improved, 1 = much improved, 2 = minimally improved, 3 = no change, 4 = minimally worse, 5 = much worse, 6 = worst).

Clinical response was evaluated by comparing the rating scale scores at baseline prior to donepezil treatment and every 2 weeks following the initiation of treatment with donepezil. All patients were examined and rated by the same investigator (J.B.). Clinically significant improvement was defined as a reduction of at least 30% from baseline to week 8 on the rating scales. Routine blood tests were conducted at baseline and at termination of the study.

An initial dose of donepezil 5 mg/day was given and increased to 10 mg/day after clinical evaluation in the second week of treatment. Donepezil treatment was continued for 8 weeks.

Statistical analysis was performed using 1-way analysis of variance with repeated measures (matrix of time) and the Student t test.

RESULTS

Subjects' baseline characteristics and rating scale scores are presented in Table 1. The mean ± SD duration of antipsychotic drug treatment was 31.2 ± 12.3 years (range, 43–52 years), and the mean ± SD duration of diagnosed TT was 2.3 ± 1.1 years (range, 1–4 years). Donepezil was well tolerated by 6 patients, and they were able to receive the maximal dose of 10 mg/day without significant adverse effects. Two subjects developed transient cholinomimetic side effects: 1 had headache, which appeared on the second day after commencing treatment with donepezil and disappeared after 7 days, and 1 had nausea that disappeared after 14 days and did not require specific therapy. Only 1 patient withdrew from the study after the fourth week of treatment due to the appearance of headache, hypersalivation, and nausea.

One patient, who did not complete the study, was excluded from BPRS and MMSE statistical analysis. All patients showed a clinical improvement in SAS tremor subscale scores by week 4 ($F = 63.6$, $df = 4,24$; $p < .0001$). In 5 of the 7 patients, there was a reduction in SAS tremor subscale scores of between 37.5% and 42.9%, which is consistent with a moderate clinical improvement, and the remaining 2 patients showed marked improvement of 61.1% and 63.6%. At the completion of the study, total SAS tremor subscale scores for the entire group decreased by an average of 16 (a decrease of 88.9%—the initial mean SAS score was 18.0 ± 3.0 and the final mean score was 2.0 ± 1.5), representing significant clinical improvement. The SCII, on which the patients scored their impression of clinical improvement, showed similar results: by the fourth week of treatment, 3 patients reported marked improvement, 3 patients reported mild improvement, and only 1 patient felt no change. By week 8, all 6 patients who completed the study reported marked improvement.

Mean ± SD BPRS scores did not differ between baseline assessment and that following 8 weeks of donepezil

Table 1. Clinical Characteristics and Response to Donepezil in 7 Elderly Patients With Tardive Tremor

Patient	Sex	Age (y)	Diagnosis	TT Duration (y)	SAS Score, Week					SCII Score, Week				BPRS Score, Week			MMSE Score, Week		Side Effects, Week			
					0	2	4	6	8	2	4	6	8	0	8		0	8	2	4	6	8
1	M	69	BD	1	17	14	10	3	2	3	2	1	1	6	6		24	27	Headache	…	…	…
2	F	67	PS	3	21	18	13	6	4	3	2	3	1	24	23		21	24	Nausea	…	…	…
3	F	76	PS	3	16	14	10	4	4	4	2	2	1	21	23		20	24	…	…	…	…
4	F	68	RS	2	14	12	8	3	4	3	3	2	1	29	32		23	24	…	…	…	…
5	F	79	RS	4	19	15	11	DO	DO	3	1	DO	DO	19	DO		23	DO	Hypersalivation, headache, nausea	Hypersalivation, headache, nausea	DO	DO
6	M	65	RS	1	22	17	8	5	2	4	1	1	1	27	25		29	30	…	…	…	…
7	F	64	PS	2	18	12	7	4	2	3	1	1	1	17	19		30	30	…	…	…	…

Abbreviations: BD = bipolar disorder, BPRS = Brief Psychiatric Rating Scale, DO = dropout, F = female, M = male, MMSE = Mini-Mental State Examination, PS = paranoid schizophrenia, RS = residual schizophrenia, SAS = Simpson-Angus Scale, SCII = Subjective Clinical Improvement Impression scale, TT = tardive tremor.

treatment: 20.7 ± 8.4 and 21.3 ± 8.6, respectively ($p > .01$). We found that the total MMSE scores were significantly improved at the end of the trial from 24.3 (baseline) to 26.5 (endpoint) ($t = 3.16$, $df = 3$, $p = .025$). In 3 patients with cognitive decline, there was a mild improvement at the final visit (12.5% to 20.0%).

DISCUSSION

We studied patients with severe TT of relatively short duration (1–4 years). This type of tremor was postural and kinetic and not accompanied by signs of parkinsonism, as described previously.[3] Patients were treated with donepezil, a cholinesterase inhibitor. All patients studied were elderly, with 5 of them suffering from mild to moderate dementia. Although 3 experienced side effects from donepezil, only 1 patient suffered from marked side effects that necessitated the discontinuation of treatment.

We found that treatment with donepezil 10 mg/day significantly diminished movement disorders in patients receiving a stable dose of antipsychotics. There was both a subjective and an objective improvement in the severity of tremor in most subjects. It is important to note that the improvement in TT was both more rapid and more marked in 2 patients with normal cognition as compared with those with cognitive impairment (62.3% vs. 40.4%).

The pathophysiology of TD is complex. It has been suggested that different neurotransmitters may be involved, with particular interest in the cholinergic system. It is postulated that TD may result from damage to or degeneration of striatal cholinergic interneurons resulting from prolonged overactivation of cholinergic neurons, which occurs when these neurons are freed from dopaminergic inhibition following neuroleptic administration.[33,34] Movements are influenced by reciprocal inhibition between antagonist muscle groups. Destruction of cholinergic neurons in the striatum is likely to favor unimpeded movements.[35] Signs of TD are usually worsened by centrally acting anticholinergic drugs,[36] and an increase in cholinergic tone appears to reduce the signs of TD.[20]

Donepezil is a selective and potent acetylcholinesterase inhibitor developed for the treatment of Alzheimer's disease. Donepezil increases intracellular acetylcholine levels in the cerebral cortex, striatum, and hippocampus.[37] It is possible that donepezil treatment may lead to balanced dopamine-acetylcholine interactions and in this way may exert its positive therapeutic effect on TD.

Our results are consistent with previous findings[25,26] suggesting that donepezil may be efficacious in the treatment of TD. The response to cholinesterase inhibitors may depend on the degree of cholinergic cell loss or damage, which may correlate with the patient's age or the duration of symptoms of TD.[13] The response to treatment may also vary between patients.

The conclusions that may be drawn from this study are limited due to the small number of patients. Moreover, an open-label treatment design does not allow exclusion of a possible placebo effect. Nevertheless, these initial findings support the hypothesis that cholinergic neurons may play a role in the pathogenesis of tardive movement disorders. A randomized, placebo-controlled, double-blind trial is therefore required to confirm these findings before recently developed cholinesterase inhibitors can be recommended in the treatment of tardive neuroleptic-induced movement disorders.

Drug names: donepezil (Aricept), olanzapine (Zyprexa), risperidone (Risperdal), tacrine (Cognex).

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