Treatment of Tardive Dyskinesia With Galantamine: A Randomized Controlled Crossover Trial

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Objective: Recent evidence suggests that tardive dyskinesia may result from antipsychotic-induced damage to striatal cholinergic neurons. To test whether cholinesterase inhibitors compensate for diminished cholinergic activity, we conducted a 30-week randomized, double-blind, placebo-controlled crossover trial of galantamine in patients with tardive dyskinesia.

Method: Patients with tardive dyskinesia were recruited between June 2001 and June 2004. After a 2-week baseline period, 35 male schizophrenia patients, on stable doses of antipsychotics, were randomly assigned to receive galantamine (8–24 mg) or placebo for two 12-week phases separated by a 4-week washout period. Patients were evaluated every 2 weeks for changes in extrapyramidal symptoms and before and after each treatment for effects on psychiatric symptoms and cognition.

Results: Galantamine reduced mean total Abnormal Involuntary Movement Scale (AIMS) scores more than placebo, but this difference was not statistically significant (p = .08). However, patients initially randomly assigned to galantamine showed a reversal of AIMS scores after switching to placebo. Simpson-Angus Scale ratings of parkinsonism were significantly higher with galantamine than placebo (p = .0005) and correlated with age. There were no significant differences between groups in akathisia, cognition, or psychiatric symptoms. More patients dropped out while receiving galantamine, but this outcome did not significantly influence the results.

Conclusions: In contrast to previous reports, reductions in tardive dyskinesia associated with galantamine were not statistically significant compared with placebo in this trial. However, galantamine was associated with a modest rebound in dyskinesia scores after discontinuation and clinically minor but statistically higher ratings of parkinsonism. These findings support the need for further investigations of cholinergic mechanisms underlying tardive dyskinesia and extrapyramidal effects of cholinesterase inhibitors when used in combination with antipsychotics in susceptible patients.

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Tardive dyskinesia is a serious complication associated with long-term administration of antipsychotic drugs.[1,2] Although liability is reduced with second-generation antipsychotics, tardive dyskinesia remains a risk in susceptible patients even with these agents.[3,4] More importantly, tardive dyskinesia persists as a legacy of treatment with first-generation antipsychotics for thousands of patients.[3,5] Unfortunately, the pathophysiology of tardive dyskinesia remains unclear, and empirical research has failed to confirm a uniformly effective treatment.[6,7]

One therapeutic strategy is suggested by the critical role of cholinergic neurons in mesostriatal circuitry and the classic concept of an imbalance between cholinergic and dopaminergic systems in extrapyramidal disorders.[8] Cholinomimetic agents could be used to compensate for dopamine supersensitivity, which has been proposed as a mechanism underlying tardive dyskinesia.[7] In prior studies,[6,9] the response of tardive dyskinesia to treatment with acetylcholine precursors was disappointing, and this approach was abandoned. However, these negative results may reflect the failure of dietary precursors to reach brain cholinergic neurons in pharmacologic concentrations or the possibility that these neurons are unable to utilize precursors in patients with tardive dyskinesia.

The latter possibility was proposed by Miller and Chouinard,[10] who suggested that patients develop tardive dyskinesia because striatal cholinergic neurons are damaged by the loss of dopamine-mediated inhibition. This hypothesis is supported by some data indicating that dopamine blockade induced by chronic antipsychotic drug

administration in rats produces excitotoxicity and degeneration of cholinergic neurons that are associated with the development of dyskinesias.[8,10–16]

If correct, the hypothesis proposed by Miller and Chouinard would suggest that cholinesterase inhibitors may be effective in suppressing tardive dyskinesia by directly enhancing synaptic cholinergic activity, thereby compensating for the loss of cholinergic neurons. Previously, physostigmine was shown to transiently decrease the severity of tardive dyskinesia in at least 50% of patients.[17–25] However, some investigators found no effect on tardive dyskinesia or even worsening of dyskinetic movements after physostigmine, perhaps reflecting the pharmacologic heterogeneity of tardive dyskinesia among patients.[19,22,25–29] Some of these studies were limited by small sample sizes, variable assessment techniques, and concurrent administration of anticholinergic drugs.[19,22–26] In addition, its short duration of action, parenteral administration, and unpleasant side effects render physostigmine impractical as a treatment for tardive dyskinesia. In contrast, recently developed cholinesterase inhibitors are long acting, well tolerated, and effective orally. A few open-label, uncontrolled reports of improvement in tardive dyskinesia associated with oral cholinesterase inhibitors have been published.[9,30–33] Galantamine, a cholinesterase inhibitor with a unique potentiating effect on nicotinic receptors, has not been utilized in trials of tardive dyskinesia.[34] To further examine this effect, we conducted a 30-week, randomized, double-blind, placebo-controlled, crossover trial of galantamine in 35 male schizophrenia patients with tardive dyskinesia.

METHOD

Thirty-eight patients with tardive dyskinesia were recruited at the Department of Veterans Affairs Medical Center in Philadelphia, Pa., between June 2001 and June 2004. Tardive dyskinesia was diagnosed in patients who fulfilled research criteria at both baseline visits 2 weeks apart, ascertained by agreement between 2 raters using the Abnormal Involuntary Movement Scale (AIMS).[35,36] There was a high level of interrater reliability achieved on the AIMS (interclass correlation coefficient = 0.94). Three patients (2 receiving placebo, 1 receiving galantamine) dropped out before the first postbaseline rating visit and were excluded from further analyses. All patients were male and met DSM-IV criteria for schizophrenia. The mean ± SD age was 56.4 ± 9.9 years. The mean ± SD durations of psychiatric illness and antipsychotic treatment were both reported to be 29.6 ± 8.0 years. Nineteen patients (54%) had tardive dyskinesia for more than 5 years, and 10 (29%) had it for more than 10 years. However, estimations of duration of illness, treatment, and tardive dyskinesia were based on patient self-report and are therefore limited in accuracy. Patients were excluded if they had acute medical illnesses, could not be withdrawn from anticholinergic medications or vitamin E–containing supplements, or experienced a change in antipsychotic medications or dosage within 1 month prior to the start of the study for oral medications and within 2 months for depot medications.

Patients remained on a stable dose of antipsychotics throughout the study. Two patients were not receiving antipsychotics during the study. Among those receiving antipsychotics, the mean ± SD daily dose in chlorpromazine equivalents was 696.0 ± 526.0 mg.[37,38] Any anticholinergic drugs or vitamin supplements were discontinued 2 weeks prior to randomization.

Patients were evaluated at 2 baseline visits 2 weeks apart before randomization. Subsequently, each patient entered a 12-week treatment phase of galantamine or placebo and then switched treatments for an additional 12-week treatment phase after a 4-week washout period between treatments. During the active treatment phase, patients received galantamine 4 mg b.i.d. for 4 weeks followed by 8 mg b.i.d. for 4 weeks, and 12 mg b.i.d. for an additional 4 weeks. Medication compliance was monitored by pill counts at each visit. Patients were evaluated at baseline and at final visits for each treatment phase with the Brief Psychiatric Rating Scale (BPRS)[39] and the Mini-Mental State Examination (MMSE)[40] to assess changes in psychiatric symptoms and cognition. At both baseline visits and at 2-week intervals during treatment, patients were assessed with the AIMS[36] by 2 raters and with the Barnes Akathisia Scale (BAS)[41] and the modified Simpson-Angus Scale (SAS)[42] by a single rater. Routine blood tests and urine toxicology screens were obtained at the beginning and end of each phase of the study. The protocol was approved by the institutional review board, and all patients were informed of the risks and alternatives to treatment and provided written consent.

Data Analysis

The primary 1-sided hypothesis was that galantamine would be significantly superior in lowering total AIMS scores (the sum of items 1–7) compared with placebo. Assuming a 30% reduction in total AIMS scores as clinically significant, the sample size for 95% power was calculated to be 22 subjects, which was exceeded in this study. The overall severity of tardive dyskinesia (AIMS item 8) was included as an additional outcome measure. Given the high level of interrater reliability on the AIMS (interclass correlation coefficient = 0.94), the means of the AIMS scores between the 2 raters were used in the analyses. Comparisons of baseline measures between treatment groups were analyzed by paired t tests. The average separation between groups for repeated outcome measures (AIMS, SAS, BAS) was tested using a linear mixed-effects model.[43] This model accounts for the correlation of repeated assessments between all outcomes within a

Table 1. Clinical Ratings of Patients With Tardive Dyskinesia Treated With Galantamine and Placebo[a]

Measure	Placebo, N = 26	Galantamine, N = 32	p Value
Total AIMS (items 1–7)			
Baseline	9.2 ± 0.7	9.4 ± 0.7	.83
Postbaseline	8.5 ± 0.6	8.1 ± 0.5	.08
AIMS severity (item 8)			
Baseline	2.7 ± 0.2	2.7 ± 0.1	.76
Postbaseline	2.4 ± 0.1	2.2 ± 0.2	.28
Simpson-Angus Scale			
Baseline	0.27 ± 0.05	0.20 ± 0.05	.32
Postbaseline	0.25 ± 0.03	0.35 ± 0.03	.0005
Barnes Akathisia Scale			
Baseline	0.7 ± 0.2	0.7 ± 0.2	.91
Postbaseline	0.7 ± 0.04	0.7 ± 0.4	.93
BPRS			
Baseline	32.1 ± 1.9	32.4 ± 2.5	.92
Postbaseline	31.9 ± 2.3	31.0 ± 1.9	.75
MMSE			
Baseline	28.2 ± 0.3	28.0 ± 0.4	.91
Postbaseline	28.7 ± 0.3	28.8 ± 0.3	.67

[a]Values for placebo and galantamine are mean ± SE.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, BPRS = Brief Psychiatric Rating Scale, MMSE = Mini-Mental State Examination.

Table 2. Total Abnormal Involuntary Movement Scale Scores Between Treatment Groups During Study Phases[a]

Phase	Group 1, N = 17	Group 2, N = 18	p Value
Phase I	[placebo]	[galantamine]	
Baseline	9.7 ± 0.7	10.9 ± 1.0	.34
Postbaseline	7.6 ± 0.7	9.1 ± 0.7	.18
Phase II	[galantamine]	[placebo]	
Baseline	7.2 ± 0.7	8.3 ± 1.4	.47
Postbaseline	7.3 ± 0.7	9.7 ± 0.8	.04

[a]Group values are estimated mean ± SE; significance determined by mixed-effects model.

patient, as well as allows for effects of phase, dose, and other covariates. We implemented a special type of linear mixed-effects model, the general mixed-model analysis of variance, by SAS 9.1 procedure PROC MIXED,[44] which examines average outcome during the longitudinal period rather than assuming a linear slope over time. To determine whether concomitant administration of first- or second-generation antipsychotics impacted treatment differentially, we included this medication factor and its interaction with treatment in our original analyses of AIMS and SAS scores.

Baseline and endpoint data (BPRS, MMSE) were analyzed by deriving a change score per phase and tested by a repeated measures model, which accommodates the correlation in the pair of change scores. Where data deviated significantly from normality (SAS, BPRS), square root transformation was performed prior to analysis. Because the majority of ratings for akathisia fell in the absent to mild categories, BAS data were reclassified as "present" or "absent." Differences between treatment groups in prestudy use of anticholinergic drugs or vitamin supplements and the proportions of dropouts during the study were compared by Fisher exact test, with the impact of dropouts on outcome measures subsequently analyzed by a pattern mixture model. To further assess the impact of dropouts, repeated measure analyses (AIMS, SAS, BAS) were replicated by a 2-timepoint last-observation-carried-forward model per phase with consistent results. Urine drug toxicology and alcohol screening were analyzed based on presence or absence of abuse.

RESULTS

For the total AIMS score, there was no significant difference between treatment groups at baseline ($p = .83$; Table 1). Although the mean total AIMS score postbaseline decreased more with galantamine, this change was not significantly different from placebo ($p = .08$). Likewise, the overall severity of tardive dyskinesia on the AIMS decreased more with galantamine, but did not reach statistical significance ($p = .28$). Including an interaction of treatment and visit, we found no significant indication of a dose effect ($p < .15$). Covariates (duration of illness, antipsychotic treatment, and tardive dyskinesia; age; baseline antipsychotic doses) were not significant in predicting outcome on the AIMS. Similarly, whether patients received first- or second-generation antipsychotics did not significantly affect treatment outcome. Finally, treatment groups did not differ in baseline discontinuation of anticholinergics (galantamine, N = 2; placebo, N = 3; Fisher exact test, $p = .66$) or vitamin supplements (galantamine, N = 4; placebo, N = 1; $p = .34$).

The treatment phase had a marginal but nonsignificant effect on between-treatment differences ($p = .08$). However, there was a significant difference between groups during the second phase of the study; patients switched from galantamine to placebo in phase 2 showed a significant increase in total AIMS scores ($p = .04$; Table 2), which was not observed in patients switched from placebo to galantamine. There was no significant difference in overall severity of tardive dyskinesia between groups during phase 2.

There were no significant baseline differences between treatment groups on square root–transformed SAS ratings ($p = .15$). However, there was a significant difference postbaseline between treatments in SAS scores ($p = .0005$; Table 1). The higher SAS scores associated with galantamine were not influenced by the generation of antipsychotics received or other covariates, except for age, which significantly predicted mean SAS scores ($p < .006$).

There were no significant differences between groups in the proportion of patients with akathisia (BAS) at baseline or subsequently ($p = .93$). On the BPRS, there were no significant differences between treatment groups (Table 1). Although there were no significant differences

Table 3. Patient Discontinuation During Treatment After Randomization[a]

Reasons	Galantamine	Placebo
Psychiatric admission	3	1
Lost to follow-up	3	1
Dizziness	2	1
Gastrointestinal symptoms	1	2
Unspecified medical illness	…	3
Addiction treatment	…	2
Tremor	1	…
Rash	…	1
Electrocardiogram changes	…	1
Shortness of breath	1	…

[a]Total N = 38, including 3 patients who were randomly assigned but who dropped out before first postbaseline rating visit and were excluded from analyses. Also includes patients who reported more than 1 reason for discontinuation.

between groups on the MMSE, this test was unlikely to be sensitive to cognitive changes in schizophrenia patients, especially given the high baseline values, which were greater than 28/30 for 24 (63.2%) of 38 patients.

Overall, 10 (31.3%) of 32 patients receiving galantamine dropped out, and 6 (23.1%) of 26 patients receiving placebo dropped out. Twelve patients dropped out during phase 1 (galantamine, N = 9; placebo, N = 3), and 4 dropped out during phase 2 (galantamine, N = 1; placebo, N = 3). Reasons for treatment discontinuation are listed in Table 3. Differences in the dropout rate between treatments were not significant (Fisher exact test, p = .31). Application of the pattern mixture model provided further evidence that the dropout pattern did not inform the differential relationship of treatments across phases for either the AIMS (p = .92) or the SAS (p = .54) findings. Similarly, analysis by last observation carried forward per phase did not change the significance of results for any of the repeated measures.

Reports of positive urine toxicology screens and instances of alcohol use were infrequent, with insufficient variability to analyze in discriminating between treatments. Over 80% of urine toxicology screens were negative for any drug of abuse, and 70% of interview screens revealed no recent use of alcohol.

DISCUSSION

In this randomized controlled trial, the hypothesis that galantamine would have a significantly greater effect in reducing tardive dyskinesia compared with placebo was not supported. These results contrast with previous reports of improvement in tardive dyskinesia associated with other cholinesterase inhibitors, although many of those studies were open-label and uncontrolled in small samples of patients followed for brief time periods.[17–25,30–33] Moreover, results from prior studies actually have been inconsistent, with some yielding no effect or even worsening of tardive dyskinesia with these agents.[19,22,25–29]

Differences between our findings and more favorable studies also may reflect sampling differences. Our study population consisted of older, chronically ill patients with longstanding antipsychotic treatment and duration of tardive dyskinesia, who could have been refractory to treatment, perhaps as a result of more pervasive and irreversible loss of cholinergic neurons. We studied only male patients with schizophrenia, such that generalizations of our findings are limited to this subgroup. Although data on factors influencing outcome of tardive dyskinesia are limited, the inclusion of females or patients with other diagnoses may have produced different results. In addition, all of our patients had generalized tardive dyskinesia with dyskinesias in either trunk or extremities in addition to oral-facial movements. It is possible that patients with milder, more recent, or more focal dyskinesias might have responded more favorably.[28,29] Furthermore, despite pill counts, noncompliance with oral medications could have obscured galantamine-placebo differences in our study.

To prevent drug interactions, we discontinued anticholinergic drugs and vitamin supplements prior to randomization. However, discontinuation of anticholinergics could have improved tardive dyskinesia, whereas discontinuation of vitamin E–containing supplements may have worsened tardive dyskinesia.[6] In fact, no patients were receiving pharmacologic doses of vitamin E, and there were no significant differences between groups in the proportions of patients who discontinued anticholinergics or vitamin supplements.

Although we discontinued adjunctive anticholinergic drugs prior to randomization, antipsychotics themselves vary in anticholinergic as well as antidopaminergic potency, such that use of different antipsychotics between studies could explain discordant results. For example, 22 (63%) of our patients were taking second-generation antipsychotics, whereas earlier studies of tardive dyskinesia included only patients taking first-generation high-potency agents with low acetylcholine receptor affinity. However, we found no significant effect of type of antipsychotic on outcome of tardive dyskinesia in our study.

It is also conceivable that cholinesterase inhibitors may differ in efficacy in suppressing dyskinesias, such that drugs used in prior studies were more effective than galantamine. Galantamine is a reversible and competitive cholinesterase inhibitor that has a unique effect as an allosteric potentiator of nicotinic receptor function.[34] Although the relative roles of cholinergic receptor subtypes in regulating movement are incompletely understood, nicotinic receptor activation appears to facilitate dopamine release in the striatum, which may aggravate dyskinesias.[8]

Despite our negative findings, the hypothesis of deficits in striatal cholinergic activity underlying the pathogenesis of tardive dyskinesia remains an appealing basis for future research by offering an explanation for several

clinical characteristics of the disorder. For example, excluding tardive dystonia, tardive dyskinesia is worsened by treatment with anticholinergics and improves in up to 60% of patients after drug discontinuation.[6] The delayed onset of tardive dyskinesia may reflect the time required for accumulation of drug-induced cell damage, which is consistent with the effects on cholinergic neurons of long-term as opposed to acute administration of antipsychotic drugs demonstrated in animal models.[10–16] The proposed loss of neurons also may explain the irreversibility of tardive dyskinesia in most cases and the increased risk of developing tardive dyskinesia with age as neurons degenerate by attrition.[45] Evidence for the selective loss of cholinergic activity and neurons in the striatum of patients with schizophrenia may explain the occurrence of spontaneous dyskinesias and the postulated synergy between schizophrenia and antipsychotic drugs in the development of tardive dyskinesia.[2,11,14,46–48] Finally, evidence from animal and human studies suggests that second-generation antipsychotics are less likely to cause alterations in activity or actual loss of striatal cholinergic neurons, which could explain their reduced liability for inducing tardive dyskinesia.[11,15,16] Thus, there is a continuing need to explore cholinergic mechanisms underlying tardive dyskinesia. Future studies should examine selective agonists targeting muscarinic or nicotinic receptor subtypes in addition to the broader effects of cholinesterase inhibitors.

The delayed reversal in total AIMS scores that we observed during phase 2 after discontinuation of galantamine has not been described previously. This pattern may be simply an artifact of the study design. However, this modest rebound in dyskinesia ratings could represent a withdrawal phenomenon, reflecting removal of a true suppressive effect of galantamine in phase 1 of the trial. Galantamine also may have suppressed increases in dyskinesias during phase 2 in the treatment group that began placebo in phase 1. The clinical significance of these findings is uncertain and requires further study.

Whereas galantamine did not significantly suppress tardive dyskinesia compared with placebo, it was associated with higher ratings of parkinsonism, although only 1 patient dropped out because of increased tremors. In addition, the clinical relevance of the small average changes in the SAS scores is unclear. Previously, Ingram and Newgreen[30] reported improvement of tardive dyskinesia with tacrine in 8 patients, only 1 of whom developed tremor. In a pilot study of donepezil in 10 patients with tardive dyskinesia, we[31] found no significant changes in SAS scores. Schopick[32] reported improvement in tardive dyskinesia in an adolescent with rivastigmine and donepezil without extrapyramidal side effects. In contrast to Bergman et al.,[33] who found improvement in ratings of tremors among 7 elderly patients on donepezil therapy, we observed increases in ratings of tremors with galantamine. Some patients, especially the elderly, developed worsening of tremor, parkinsonism, or akathisia in response to physostigmine in earlier studies of tardive dyskinesia.[19,22–24]

Contrary to our results and prior reports of increased parkinsonism, galantamine and other cholinesterase inhibitors have been well tolerated when used in clinical trials to enhance cognition in patients with schizophrenia.[49–51] This contrast in susceptibility to parkinsonian effects of cholinesterase inhibitors may reflect sampling differences. For example, compared with our patients, schizophrenia patients in cognitive trials were younger, with shorter durations of illness, included females, were observed for shorter periods of time, and received second-generation antipsychotics primarily. Moreover, we specifically selected only schizophrenia patients with dyskinesias, who may comprise a subgroup at risk for extrapyramidal side effects.

In a similar fashion, substantial prior evidence indicates that galantamine has been well tolerated by the majority of patients with neurodegenerative disorders.[52–54] However, we previously reported that a subgroup of patients with Parkinson's disease and dyskinesias were susceptible to worsening motor function from another cholinesterase inhibitor.[55] Among conceivable risk factors, the presence of dyskinesias or other preexisting motor abnormalities and concomitant treatment with antipsychotic drugs may identify patients at risk for adverse motor effects of cholinesterase inhibitors.

In conclusion, we found no statistically significant difference in the effect of galantamine versus placebo on tardive dyskinesia in a randomized controlled trial. However, in contrast to prior reports, we observed an association between galantamine and higher ratings of parkinsonism, and a possible delayed rebound in dyskinesias after drug discontinuation. The clinical relevance of these observations is uncertain. At the least, these findings suggest that galantamine and other cholinesterase inhibitors may be pharmacologically active in subcortical motor circuits with potential clinical implications. Therefore, there is a need for continued examination of motor function in patients receiving cholinesterase inhibitors combined with antipsychotic medications, particularly in elderly patients with preexisting movement disorders, some of whom may be at risk for extrapyramidal side effects.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), donepezil (Aricept), galantamine (Razadyne), rivastigmine (Exelon), tacrine (Cognex).

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