A Comparison of Physostigmine and Benzodiazepines for the Treatment of Anticholinergic Poisoning

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Study objective: To compare the efficacy and safety of physostigmine with benzodiazepines for the treatment of agitation and delirium associated with anticholinergic poisoning.

Methods: We conducted a retrospective study of 52 consecutive patients referred to a university hospital toxicology consultation service who were treated with physostigmine, benzodiazepines, or both for anticholinergic agitation and delirium. Patients treated with physostigmine were compared with those treated with benzodiazepines with respect to demographics, severity of poisoning, response to treatment, side effects of treatment, and complications.

Results: Physostigmine controlled agitation and reversed delirium in 96% and 87% of patients, respectively. Benzodiazepines controlled agitation in 24% of patients but were ineffective in reversing delirium. Initial treatment with physostigmine (n=30) resulted in a significant decrease in the incidence of agitation (P<.001) and level of central nervous system stimulation (P<.001), whereas initial treatment with benzodiazepines (n=22) did not (P=.03 and P=.05, respectively). Patients treated initially with physostigmine had a significantly lower incidence of complications (7% versus 46%; P<.002) and a shorter time to recovery (median, 12 versus 24 hours; P=.004) than those treated initially with benzodiazepines. There were no significant differences between these groups in the incidence of side effects (7% versus 14%; P=0.6) and length of stay (median, 32 versus 39 hours; P=.15).

Conclusion: Results suggest that physostigmine is more effective and safer than benzodiazepines for the treatment of anticholinergic agitation and delirium. A prospective controlled study is necessary to confirm such findings.

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INTRODUCTION

Physostigmine, a short-acting acetylcholinesterase inhibitor, increases synaptic acetylcholine concentrations and can overcome the postsynaptic muscarinic receptor blockade produced by anticholinergic agents. As a tertiary amine, it can pass freely into the central nervous system (CNS) and reverse both central and peripheral anticholinergic effects.

Physostigmine has been shown to be effective and safe when used to treat anticholinergic poisoning.[1-10] It was neither consistently effective nor safe when used as an antidote for undifferentiated drug-induced coma and tricyclic antidepressant (TCA) poisoning.[5,6,10-16] Although seizures were more common than asystole when physostigmine was used for patients with TCA poisoning,[10,11,14,15] the latter occurrence has led some to categorically dismiss physostigmine as a treatment option when overdose with TCAs is known or suspected.[16-18]

In 1997, US poison centers reported that only 2% of more than 7,000 patients treated in health care facilities with moderate to severe effects from anticholinergic agents other than TCAs received physostigmine.[19] Fear of potential toxicity is probably responsible for its apparent current underutilization in this setting. Although physostigmine remains the most rational treatment for anticholinergic poisoning, benzodiazepines have been recommended as the preferred therapy for agitation and delirium.[18,20] We report our experience with physostigmine and benzodiazepines for the treatment of anticholinergic agitation and delirium.

MATERIALS AND METHODS

Patients with a diagnosis of anticholinergic poisoning (*International Classification of Diseases–ninth revision*, code 971.1) were identified by reviewing toxicology consultations and discharge diagnoses at the University of Massachusetts Medical Center from April 1986 through July 1997.

Those who had agitation or delirium and were treated with physostigmine, benzodiazepines, or both were included in the study. Data abstracted from the medical record included patient demographics; drug exposure; physical and ECG findings; results of toxicology testing; nature, dose, and times of drug therapy; times of response, relapse, and recovery; length of stay; use of cranial computed tomography and lumbar puncture; side effects of treatment; and complications. Data abstraction was performed by a single investigator (MJB) using a standardized form.

Initial dose was defined as the amount of physostigmine or benzodiazepine given during the first 30 minutes of treatment. Response to therapy was defined as the maximal change in clinical status occurring within 30 minutes of initial dosing. Time to relapse was defined as the interval between response to therapy and recurrence of agitation or delirium. Time to recovery was defined as the interval between presentation and the time a patient was documented to be alert, oriented, and calm, without subsequent relapse. Length of stay was defined as the time from admission to discharge or transfer to psychiatric care.

Agitation was considered present if a patient was described as agitated or if motor hyperactivity was documented. Delirium was considered present if a patient was described as delirious or if confusion, disorientation, hallucinations, or unintelligible speech was noted. The scale used for grading the severity of CNS stimulation (Table 1) was adapted from one originally used for amphetamine posioning[21] and uses published descriptors of anticholinergic toxicity.[1,5,6,8,9]

Side effects included all adverse drug-related events occurring within 30 minutes of therapy, as well as events specifically documented as such. Complications included any adverse event that occurred during the period of medical treatment. All variables were defined and set before data abstraction; none were modified during or after data abstraction. Missing data were omitted from final analysis.

Efficacy was evaluated by comparing the incidence of agitation and delirium and the severity of CNS stimulation before and after treatment in and between patients treated initially or only with physostigmine and benzodiazepines. The magnitude of change in the incidence of agitation and level of CNS stimulation that occurred from treatment, the time to recovery, and length of stay were also compared between corresponding groups. Safety

Table 1.
Scale used for grading the severity of CNS stimulation

Severity Score	Clinical Findings
0	Relaxed, cooperative
1	Anxious, irritable, tremulous
2	Intermittently or mildly disoriented, confused, and hallucinating, moderate agitation and motor hyperactivity
3	Incomprehensible speech, marked agitation and motor hyperactivity (requiring restraints)
4	Seizures, deep coma (unresponsive to voice or pain)

was evaluated by comparing the incidence of side effects and complications between the same groups.

The approach to the treatment of anticholinergic poisoning favored by the toxicology service was to use physostigmine as the preferred agent for the control of agitation and delirium and to give benzodiazepines as adjunctive therapy or when a contraindication to physostigmine was present. An initial physostigmine dose of 1 to 2 mg (0.5 mg in children) given intravenously over 3 to 5 minutes was recommended. If the response was incomplete, additional doses of 0.5 to 1 mg every 5 minutes were given until delirium resolved or cholinergic signs (diaphoresis, salivation, vomiting, and diarrhea) occurred. A prolonged PR (>200 ms) or QRS (>100 ms and not related to bundle branch block) interval on ECG were considered the only contraindications for physostigmine use.

Data were analyzed by SPSS for Windows (version 6.1; SPSS, Inc, Chicago, IL). Two-tailed Fisher exact and Mann-Whitney *U* tests were used for independent samples. McNemar's and Wilcoxon signed rank tests were used to assess variable change over time (before and after treatment comparisons). Nonparametric testing was performed on continuous and ordinal data because they were not normally distributed. Because of multiple comparisons, statistical significance was adjusted using Bonferroni's correction. To maintain an overall type I error level of 0.05, significance was established at $P<.002$. For certain data, 95% confidence intervals were approximated using parametric testing (Student's *t* test). Repeated-measures analysis of variance was used to compare intergroup changes in the incidence of agitation and degree of CNS stimulation that occurred from treatment. The exact binomial distribution was used to compute 95% confidence intervals when the number of observed events was small.[22]

Interrater reliability was assessed by a second person (RMB) who was blinded to study intent and to investigator's findings who performed data abstraction and assessed the response to treatment on a random sample (42%) of study patients. The blinded abstractor was trained, monitored, and met periodically with the nonblinded abstractor to discuss ambiguous data. The blinded abstractor made the final decision regarding ambiguous data. The κ statistic was used to measure interrater agreement between abstractors for certain categorical data.

RESULTS

Seventy-one patients with a diagnosis of anticholinergic poisoning were identified. Sixteen patients were excluded because they did not receive physostigmine or benzodiazepines. Three patients were excluded because they were subsequently determined not to have anticholinergic poisoning. Of the remaining 52 patients, 45 (86%) were treated with physostigmine and 26 (50%) with benzodiazepines. Additional sedating agents (eg, haloperidol) were used to control agitation in 4 (8%) patients.

Median age was 26 years (25th to 75th interquartile range 18 to 39 years). Median time from drug exposure to hospital presentation was 3.8 hours (25th to 75th interquartile range 2.0 to 7.2 hours). Gastrointestinal decontamination was performed in 38 (73%) patients. Agitation and delirium were each present in 50 (96%) patients. Hallucinations were noted in 43 (83%). Nine (17%) had central anticholinergic effects without peripheral manifestations. Four (8%) patients had asthma.

Toxicology testing of blood or urine was performed in 50 (96%). Both thin-layer chromatography and gas chromatography with mass spectrometry were used in 40 cases. Drugs of abuse immunoassays were performed in 21 patients. Toxicology testing confirmed the presence of an anticholinergic agent in 40 (77%) patients. Diphenhydramine was implicated as the causative agent in 24 (46%) patients, atropine- or scopolamine-tainted heroin in 12 (23%), amitriptyline in 5, cyclobenzaprine and *Datura stramonium* in 4 each, doxylamine in 3, and benztropine, clozapine, cyproheptadine, orphenadrine, and thioridazine in 1 each. Cointoxicants were reported by history and detected by drug testing in 23 (44%) patients. Sympathomimetics were a cointoxicant in 8 (15%).

Physostigmine controlled agitation in 41 (96%) of 43 patients and reversed delirium in 39 (87%) of 45. The initial dose was administered in the emergency department in 42 (93%) and ICU in 3 (7%) patients. Mean initial dose was 2.2 mg (range 0.5 to 6 mg). Mean response time was 10.9±5.3 minutes. Relapse occurred in 32 (78%) of 41 patients who initially responded with a mean relapse time of 100±42 minutes. Twenty-six (58%) patients received multiple doses (mean 2.5±2.0 doses). Mean total dose was 3.9 mg (range 0.5 to 13.5 mg).

Side effects occurred in 5 (11%) patients treated with physostigmine: diaphoresis (n=1), emesis (n=1), diarrhea (n=1), asymptomatic sinus bradycardia (rate 51 beats/min; n=1), and increased respiratory secretions (in an intubated patient; n=1). Complications occurred in 8 (18%) patients: rhabdomyolysis (n=5), aspiration pneumonia (n=2), endotracheal intubation (n=3), and ethanol withdrawal syndrome (n=1). Rhabdomyolysis (n=2) was the only complication noted for patients treated with

physostigmine alone. Cranial computed tomography and lumbar puncture were not performed in any patient treated with physostigmine. It was specifically documented that physostigmine obviated the need to perform these tests for 5 patients.

Physostigmine controlled agitation and reversed delirium in all patients with asthma, 8 (89%) with isolated central anticholinergic poisoning, and 4 (80%) with TCA overdose. Adverse effects included diarrhea in a patient with central anticholinergic poisoning and asymptomatic sinus bradycardia in one with amitriptyline overdose. No patient with asthma developed bronchospasm after physostigmine. The incidence of cholinergic effects in those with isolated central anticholinergic poisoning (11%) was similar to that for patients with both peripheral and central manifestations (8%). All patients with TCA overdose had ingested amitriptyline at least 12 hours before physostigmine administration and none had coma, seizures, hypotension, cardiac conduction disturbances, or dysrhythmias.

Benzodiazepines controlled agitation in 6 (24%) of 25 patients but did not reverse delirium in any. Benzodiazepines were given intravenously in 28, intramuscularly in 2, and orally in 1 patient. Mean initial dose was 12.1 mg diazepam, 3.6 mg lorazepam, and 6 mg midazolam. Mean response time was 7.5±5.0 minutes. Relapse occurred in 4 (67%) of 6 patients who initially responded with a mean relapse time of 70.9±48.1 minutes. Twenty-two (85%) patients received multiple doses of benzodiazepines (mean 8.6±7.8 doses). Mean total dose was 53.1 mg diazepam, 35.5 mg lorazepam, and 31.7 mg midazolam.

Side effects occurred in 4 (15%) patients treated with benzodiazepines: excessive sedation (n=2), fecal incontinence (n=1), and paradoxical agitation (n=1). Complications occurred in 10 (38%): endotracheal intubation (n=6), aspiration pneumonia (n=4), rhabdomyolysis (n=4), delayed recovery (n=2), and ethanol withdrawal syndrome (n=1). Complications for patients treated with benzodiazepines alone included endotracheal intubation (n=3), aspiration pneumonia (n=2), delayed recovery (n=1), and rhabdomyolysis (n=1). Cranial computed tomography and lumbar puncture were performed in one patient treated with benzodiazepines alone.

Patients treated initially with physostigmine did not differ significantly from those treated initially with benzodiazepines with respect to age (P=.23), sex (P=.77), comorbidity (P=1.0), time from exposure to presentation (P=.77), the presence of cointoxicants (P=.26) including sympathomimetics (P=.06), and treatment with gastrointestinal decontamination (P=.22) and adjunctive sedating agents (eg, haloperidol; P=.03). Before treatment, there were no significant differences in the incidence of agitation (P=.50 and P=1.0, respectively) and level of CNS stimulation (P=.01 and P=.23, respectively) between patients treated initially or only with physostigmine and those treated initially or only with benzodiazepines.

After treatment, patients treated initially with physostigmine had a significantly lower incidence of agitation and degree of CNS stimulation than those treated initially with benzodiazepines (Table 2). The posttreatment incidence of agitation and level of CNS stimulation were not significantly different between patients treated with either drug alone.

After treatment, patients treated initially or only with physostigmine had a significant decrease in the incidence of agitation and level of CNS stimulation, whereas those treated initially or only with benzodiazepines did not (Table 3). The magnitude of change in the incidence of agitation and level of CNS stimulation as a result of treatment was significantly greater for patients treated initially with physostigmine than those treated initially with benzodiazepines (P<.001). There were no significant intergroup differences, however, in the magnitude of changes in these parameters for patients treated with either drug alone (P=.14).

Patients treated initially with benzodiazepines and subsequently with physostigmine had no significant change in the degree of CNS stimulation and incidence of agitation after benzodiazepine therapy, whereas a significant decrease in these parameters occurred after physostigmine therapy (Table 4).

Patients treated initially or only with physostigmine did not differ significantly from those treated initially or only with benzodiazepines with respect to the incidence of side effects and length of stay. Although not statistically significant in all groups, patients treated initially or only with physostigmine had a lower complication rate and shorter time to recovery than those treated initially or only with benzodiazepines (Table 2).

Agreement between the blinded abstractor and investigator was 93% and 89% with respect to the presence or absence of agitation and the completeness of response to treatment, respectively. Interrater agreement was excellent for assessment of agitation (κ=0.8 to 1.0) and fair for CNS stimulation scores (κ=0.5). When the blinded abstractor's data were independently analyzed, results were similar. Overall, the blinded abstractor judged treatment to have failed in 7 (88%) of 8 patients treated with benzodiazepines but in only 1 (5%) of 19 patients treated with physostigmine.

DISCUSSION

We found physostigmine to be more effective than benzodiazepines for the control of agitation and reversal of CNS stimulation and delirium associated with anticholinergic poisoning. Results were similar when physostigmine and benzodiazepines were compared as initial therapy, at separate times in the same patient, or using the blinded

Table 2.
Intergroup comparisons following physostigmine and benzodiazepine therapy.

	Initial Treatment			Sole Treatment		
Characteristics	**Physostigmine (N=30)**	**Benzodiazepines (N=22)**	**Difference (95% CI)* *P* Value†**	**Physostigmine (N=26)**	**Benzodiazepines (N=7)**	**Difference (95% CI)* *P* Value†**
CNS stimulation score‡	0.1±0.3	2.3±1.3	2.2 (1.6 to 2.7)	0.1±0.3	0.9±1.5	0.8 (–0.6 to 2.1)
Median	0	3	*P*<.001	0	0	*P*=.10
No. with agitation	1/28	16/22	(69%)	0	2	29% (–5% to 63%)
	(4%)	(73%)	(49% to 89%)	(0%)	(29%)	
			P<.001			*P*=.04
No. (incidence) of side effects	2 (6.7%)	3 (13.6%)	6.9% (–10% to 24%)	2 (8%)	0	8% (–2% to 18%)
95% CI	1.2% to 19.5%	3.8% to 34%	*P*=.64			*P*=1.0§
No. (incidence) of complications	2 (6.7%)	10 (45.5%)	38.8% (16% to 61%)	2 (8%)	4 (57%)	49% (11% to 87%)
95% CI	1.2% to 19.5%	27% to 65%	*P*<.002			*P*=.01
Time to recovery (h)‡	15.6±11.9	31.0±20.6	15.4 (4.3 to 26.5)	12.9±10.2	31.2±19.0	18.3 (0.6 to 36.1)
Median	12	24	*P*=.004	10	24	*P*=.007
Length of stay (h)‡	35.5±24.7	47.9±31.1	12.4 (–4.2 to 28.8)	34.1±26.3	56.4±35.3	22.3 (–10.9 to 55.4)
Median	32	39	*P*=.15	28	63	*P*=.14

*95% CI of difference in means and proportions.
†Significance established using Mann-Whitney *U* test.
‡Expressed as mean±SD and median.
§Group size too small for conclusive analysis.

Table 3.
Intragroup comparisons (before and after physostigmine and benzodiazepine therapy).

	Initial Treatment						Sole Treatment					
	Physostigmine (N=30)			**Benzodiazepines (N=22)**			**Physostigmine (N=26)**			**Benzodiazepines (N=7)**		
Characteristic	**Before Therapy**	**After Therapy**	**Difference (95% CI)* *P* Value†**	**Before Therapy**	**After Therapy**	**Difference (95% CI)* *P* Value†**	**Before Therapy**	**After Therapy**	**Difference (95% CI)* *P* Value†**	**Before Therapy**	**After Therapy**	**Difference (95% CI)* *P* Value†**
CNS stimulation score‡	2.5±0.6	0.1±0.3	2.4 (2.1 to 2.6)	2.8±0.4	2.3±1.3	0.5 (0 to 1.1)	2.5±0.6	0.1±0.3	2.4 (2.1 to 2.6)	2.7±0.5	0.9±1.5	1.8 (0.6 to 3.1)
Median	2	0	*P*<.001	3	3	*P*=.047	2	0	*P*<.001	3	0	*P*=.038
No. (incidence) of agitation	28 (93%)	1 (4%)	89% (56% to 100%) *P*<.001	22 (100%)	16 (73%)	27% (5% to 49%) *P*=.03	24 (92%)	0 (0%)	92% (55% to 100%) *P*<.001§	7 (100%)	2 (29%)	71% (8% to 100%) *P*=.063§

*95% CI of the difference in means and proportions.
†Wilcoxon signed rank test.
‡Expressed as mean±SD and median.
§Binomial distribution use.

abstractor's data. Although the incidence and time of initial relapse was similar between patients treated with either drug, those treated with physostigmine had fewer relapses and required fewer total drug doses than those treated with benzodiazepines. Redosing with physostigmine, but not benzodiazepines, was highly effective.

The incidence of side effects was not statistically different between treatments. Those related to physostigmine, however, were transient and did not require treatment, whereas excessive sedation from benzodiazepines resulted in delayed recovery in 2 patients. A prolonged ICU stay was necessary for both, and one required a prolonged period of mechanical ventilation.

Lower complication rates for patients treated with physostigmine were primarily related to differences in the incidence of aspiration and endotracheal intubation. Neither of these complications occurred in patients treated initially or only with physostigmine. In contrast, both developed in 3 patients treated initially with benzodiazepines and 2 treated only with benzodiazepines.

Endotracheal intubation was performed in conjunction with neuromuscular paralysis in 3 patients because initial treatment with benzodiazepines was ineffective for the control of agitation. Subsequent treatment with physostigmine allowed for prompt extubation in 2 of these patients; the third, who had been treated with benzodiazepines alone, had a delayed recovery because of prolonged CNS depression. Although aspiration occurred in 2 patients treated with physostigmine, it preceded physostigmine use in both and likely resulted from the effects of intoxicants.

Shorter recovery times for patients treated with physostigmine probably reflect both positive effects from physostigmine and negative effects from benzodiazepines. Such an interpretation is supported by our findings: patients treated with physostigmine alone had the shortest time to recovery, those treated with benzodiazepines alone had the longest time to recovery, and those treated with both agents had an intermediate time to recovery. Although physostigmine does not alter the elimination of anticholinergic agents, it may shorten their duration of action.[1] The greater incidence of sedation, aspiration, and endotracheal intubation for patients treated with benzodiazepines were most likely responsible for their slower recovery. These complications were almost certainly related to the administration of relatively high doses of benzodiazepines and the relative ineffectiveness of such therapy. Additional factors were likely responsible for the lack of a significant difference in length of stay (eg, the practicality of discharge or psychiatric disposition relative to the time of day of recovery).

The use of physostigmine may have additional benefits. A response to physostigmine for patients with suspected anticholinergic poisoning may eliminate the need to perform cranial computed tomography and lumbar puncture. Prompt control of neuromuscular hyperactivity may prevent complications of anticholinergic poisoning such as rhabdomyolysis and hyperthermia. Reversal

Table 4.
Intragroup comparisons for patients treated with both physostigmine and benzodiazepines.

	Initial Treatment Benzodiazepines (N=15)			Subsequent Treatment Physostigmine (N=15)			Initial Treatment Physostigmine (N=4)*			Subsequent Treatment Benzodiazepines (N=4)*		
Characteristic	**Before Therapy**	**After Therapy**	**Difference (95% CI)† *P* Value‡**	**Before Therapy**	**After Therapy**	**Difference (95% CI)† *P* Value‡**	**Before Therapy**	**After Therapy**	**Difference (95% CI)† *P* Value‡**	**Before Therapy**	**After Therapy**	**Difference (95% CI)† *P* Value‡**
CNS stimulation score	2.9±0.4	2.9±0.3	0 (–0.3 to 0.2)	2.9±0.3	0.1±0.3	2.8 (2.7 to 3.1)	2.5±0.6	0.2±0.5	2.3 (0.7 to 3.8)	2.5±0.6	2.0±1.4	0.5 (–1.1 to 2.1)
Median	3	3	*P*=.56	3	0	*P*<.001	2.5	0	*P*=.066	2.5	2.5	*P*=.32
No. (incidence) of agitation	15 (100%)	14 (93%)	7% (–6% to 20%) *P*=1.0	15 (100%)	1 (6.7%)	93% (44% to 100%) *P*<.001	4 (100%)	1 (25%)	75% (–10% to 100%) *P*=.25	4 (100%)	3 (75%)	25% (–25% to 74%) *P*=.1.0

*Group size too small for conclusive analysis.
†95% CI of difference in means and proportions.
‡Wilcoxon signed rank test.

of CNS dysfunction by physostigmine may obviate the need for high-dose benzodiazepine therapy, prevent associated complications, shorten the duration of toxicity, and allow for earlier discharge from medical care.

Although numbers are small, our data suggest that physostigmine is safe and effective for the treatment of anticholinergic toxicity in patients with asthma, those with isolated central anticholinergic poisoning, and in selected patients with TCA overdose (ie, those without clinical or ECG evidence of severe TCA poisoning and in whom the possibility of subsequent deterioration has been excluded by a period of observation). Our data also suggest that isolated central anticholinergic poisoning occurs more often than is generally appreciated.

Several limitations of this study merit consideration and render our conclusions tentative and preliminary. The retrospective design precluded randomization with respect to treatment and standardization of the indications for and exclusions from treatment, dose, route of administration, and agent used. The nonblinded abstractor was the consulting physician for 13 (25%) of these patients (distributed equally among treatment groups). Toxicology service treatment recommendations were not universally followed. Treating physicians often preferred using benzodiazepines and sometimes were reluctant to give physostigmine. The toxicology service was not consulted in some cases and consulted only after treatment with benzodiazepines had proved ineffective in others. Although these factors made this study possible, they may have also resulted in selection bias.

Our relatively small sample size, particularly in single-drug treatment groups, introduces the possibility of both type I and II statistical errors. For example, although the magnitude of change in the incidence of agitation and level of CNS stimulation for patients treated only with physostigmine was greater than in those treated only with benzodiazepines, it did not reach statistical significance. The small size of the benzodiazepine-only group could have resulted in a type II error. Failure of the incidence of agitation and level of CNS stimulation to decrease significantly for patients treated only with benzodiazepines could also have been related to small sample size. Similar findings in the larger group of patients treated initially with benzodiazepines, however, make the possibility of a type II error less likely.

Retrospective chart review is subject to bias in data abstraction and interpretation because of ambiguous and incomplete chart documentation. To minimize investigator bias and improve the accuracy of data collection, we used strict methodologic standards for retrospective chart review.[23] Variables and outcome parameters were defined and standardized a priori and rigidly followed during data abstraction. The reasonably high interrater reliability and similar conclusions reached after analysis of the blinded abstractor's data suggest that lack of blinding did not result in substantial investigator bias. This may not be true, however, for outcome variables not abstracted by the blinded reviewer. Although our CNS stimulation severity scale has not been validated, it used definable, logical, and previously reported severity descriptors of the anticholinergic syndrome.

Despite these limitations, our findings suggest that physostigmine is more effective and safer than benzodiazepines for the treatment of anticholinergic agitation and delirium. A prospective, randomized, multicenter study with a larger number of patients is necessary to substantiate this conclusion.

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