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ORIGINAL ARTICLE

Safety of Physostigmine for Pediatric Antimuscarinic Poisoning

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Abstract

Introduction Physostigmine fell out of widespread use in the 1980s due to safety concerns; however, more recent research has demonstrated that its safety profile is better than previously thought. These studies have mainly included adults. We theorized that improved safety data may lead to more acceptance. Our objectives, therefore, were to characterize current frequency of use of physostigmine in pediatric patients as well as to study adverse effect rates in a national pediatric patient population.

Methods The National Poison Data System was queried for cases of patients aged 0–18 years that involved single-substance exposures to antimuscarinic xenobiotics that were reported to a poison center between January 1, 2000, and December 31, 2020. Cases were stratified into groups by therapy received: benzodiazepines alone, benzodiazepines and physostigmine, physostigmine alone, or no physostigmine or benzodiazepines. Patient demographics, clinical effects, and medical outcomes were analyzed.

Results A total of 694,132 cases were reviewed, and 150,075 were included for analysis. Nearly 5% (7562/150,075) of patients received specific pharmacological therapy with benzodiazepines, physostigmine, or both. A benzodiazepine as a single agent was the most frequently used pharmacologic therapy (92% of 7562). Among patients receiving any pharmacological therapy, only 8.3% ($n=627$) of patients received physostigmine. Frequency of serious outcomes significantly increased across the study period among patients receiving benzodiazepines alone or with physostigmine. There was no increase in serious outcomes among patients receiving only physostigmine.

Conclusions Physostigmine frequency of use was low overall, but when used, was associated with less severe outcomes when compared to benzodiazepines.

Keywords Physostigmine · Antimuscarinic toxicity · Pediatric · Anticholinergic

Introduction

Physostigmine is a carbamate with a tertiary amine structure that reversibly inhibits acetylcholinesterase, increasing the availability of acetylcholine to act at muscarinic receptors in both the central and peripheral nervous system [1]. It is effective in reversing delirium due to antimuscarinic poisoning and can help avert costly and unnecessary diagnostic testing in patients with undifferentiated altered mental status [2]. Physostigmine was used broadly for many years for such patients as part of a mixture of medications termed the so-called coma cocktail [3]. However, the popularity of physostigmine abruptly diminished in the 1980s with the publication of a case report by Pentel and Peterson of two patients with severe tricyclic antidepressant (TCA) poisoning. Both were treated with physostigmine for TCA-induced seizures and subsequently developed severe bradyarrhythmia. After administration of atropine, both patients progressed to

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asystole [4]. Publication of these two cases led to an association of adverse cardiotoxic events with the administration of physostigmine, causing widespread opposition to its use that has endured ever since.

A later critical review of these two cases by Suchard in 2003 illustrated that both patients were relatively bradycardic (heart rates of 75 in both), already had QRS widening, and had already seized before physostigmine. Neither patient met criteria for use of physostigmine by today's standards [5]. Recent data suggest that slow rates of administration, using the lowest dose possible to achieve desired effects, and avoidance in patients with signs of cardiac toxicity or high risk of seizures result in effective treatment with minimal side effects [1, 2]. In fact, several recent case series and observational studies have demonstrated superiority of physostigmine compared to supportive care and benzodiazepines and low rates of significant side effects in adults [6–16].

However, corresponding safety and efficacy data are sparse in the pediatric population, even though the first case reports of its use were in pediatric patients [1, 2]. Several reviews have included pediatric patients in the study populations but have not reported any results on the pediatric patients as a subset of the data [7, 8, 16, 17]. Much of the pediatric-specific literature consists of small case series or case reports [18–29] and only one randomized, controlled trial [30]. The overall frequency of physostigmine use in pediatric antimuscarinic poisonings and subsequent outcomes of its use are therefore unknown. We sought to use cases reported to the National Poison Data System (NPDS) to analyze its frequency and any difference in outcomes, including morbidity and mortality, for those treated with physostigmine compared to those who were not.

Currently, physostigmine in the USA is on national shortage due to the bankruptcy of the sole domestic manufacturer [31], but internationally, supply chains differ. Importation from other countries is possible. Several medications used to treat antimuscarinic toxicity including benzodiazepines and rivastigmine patches have also suffered shortages and interruptions in availability [32], and therefore, knowledge of several alternatives and their safety profiles is imperative for the continued ability to treat patients effectively while minimizing harm.

Methods

We performed a retrospective longitudinal study using data from NPDS to characterize physostigmine use in pediatric antimuscarinic poisoning. NPDS houses records of demographic and clinical information obtained from all calls made to US poison centers. Specialists in poison information (SPIs, typically pharmacists, nurses, and physicians), who receive extensive training and certification in toxicologic patient care, accurate data collection, and outcome severity assessment, collect data during each call. Demographics, clinical effects, therapies provided, and medical outcome are coded in a standardized manner according to definitions published by America's Poison Centers (formerly the American Association of Poison Control Centers, AAPCC).

We created a list of xenobiotic agents with antimuscarinic activity using the Micromedex® (Merative; Ann Arbor, MI) antimuscarinic poisoning page [33] and searching for "drugs that cause antimuscarinic adverse reaction," performing a TOXNET (National Library of Medicine) search for "antimuscarinic" and "anticholinergic," and consulting review articles [34–36] and a reference text [37]. We then narrowed the list to the most potent antimuscarinic agents for our query by stratifying by potency using a combination of literature [34–36] and our own clinical experience. The final list of agents included for study (see Table 4) were atropine, belladonna, benztropine, brompheniramine, chlorpheniramine, cyclobenzaprine, cyproheptadine, dicyclomine, dimenhydrinate, diphenhydramine, doxylamine, hydroxyzine, hyoscyamine, loratadine, meclizine, perphenazine, quetiapine, scopolamine, trihexyphenidyl, and known antimuscarinic plants (*Datura* spp., *Brugmansia* spp., *Atropa belladonna*, *Garrya* spp., and *Hyoscyamus niger*). We then queried NPDS for cases reported to a poison center of patients aged 0–18 years with single-substance exposures to xenobiotics on our list between January 1, 2000, and December 31, 2020 (see Fig. 1). We excluded cases coded as "confirmed nonexposure" ($n = 3023$), indirect death reports (reported to the poison center posthumously, $n = 2$), and cases not receiving care at a health care facility ($n = 536{,}383$).

We stratified cases into groups by treatment received: benzodiazepines alone (BZD Only), benzodiazepines and physostigmine (BZD + Physo), physostigmine alone (Physo Only), or neither (No BZD/No Physo). Patients in any group may still have received other supportive medical therapies (such as antiemetics or analgesics) at the discretion of their medical team at the time of evaluation.

We recorded medical outcomes for each case, but specific clinical effects were not included as it is not possible to separate the effects of the ingestion from the effects of the treatment definitively using this data set.

Medical outcomes are defined in the NPDS Coding Users' Manual [38] as follows:

> Minor: minimally bothersome symptoms, usually resolve rapidly, often involve skin or mucous membrane manifestations, no residual disability or disfigurement
> Moderate: symptoms of a more pronounced, prolonged, or systemic nature than minor symptoms, treatment usually indicated, non-life threatening, no residual disability or disfigurement

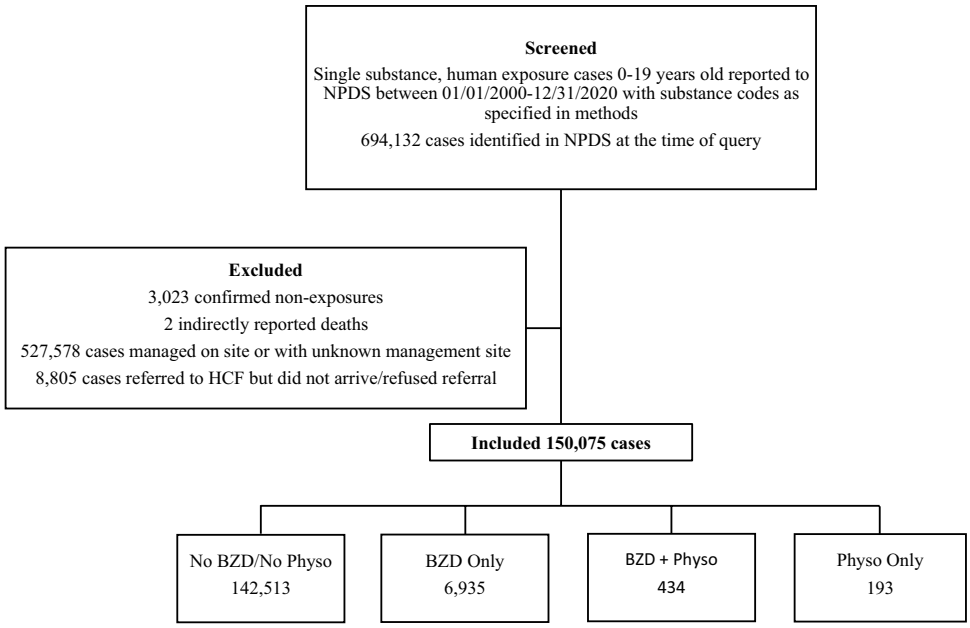

Fig. 1 Flowchart of case inclusion and exclusion.

Major: life threatening symptoms or significant residual disability or disfigurement

The Indiana University Institutional Review Board deemed the study as non-human subjects research using de-identified data.

We used descriptive statistics to determine if there were significant demographic differences between groups. Age groups were recategorized into ages 0–6 years, 7–12 years, and 13–18 years, as this is often an important variable for treating physicians to assess risk, infer reason for exposure, and formulate a treatment plan. Though exposure reason is collected as part of NPDS data, it was not examined as we focused on treatment outcomes. We performed chi-squared or Fisher's exact tests to assess the differences between treatment groups for demographics and medical outcomes. We used a Poisson regression to perform a subgroup analysis of serious outcomes, defined as a medical outcome of moderate or major severity or death (MMD), and to analyze trends in the number of cases over time between treatment groups for all levels of medical outcome. We included interaction terms in these models to assess inter-group differentials. Results were considered statistically significant if the p value was $\alpha < 0.05$. Statistical analyses were performed in Excel Professional Plus 2016 (Microsoft Corp., Redmond, WA), R Statistical Software (v.3.5.3), and RStudio v.1.1.463 (RStudio PBC, Boston, MA).

Results

Our query of NPDS returned 694,132 cases. After exclusion criteria were applied, 150,075 cases remained, of which 142,513 received No BZD/No Physo (94.96%), 6935 (4.62%) received BZD Only, 434 (0.29%) were treated with BZD + Physo, and 193 (0.13%) received Physo Only (Fig. 1). Additional demographic data may be found in Table 1.

One death occurred in each of the Physo Only and BZD/Physo groups. This is compared to seven in the benzodiazepine treatment group and eight in the No BZD/No Physo group. Patients who experienced minor clinical effects ($n = 31{,}606$) were most frequently in the No BZD/No Physo group (97.36%). Patients who experienced moderate effects ($n = 22{,}899$) were also most frequently in the No BZD/Physo group (76.19%), while 21.71% received BZD Only ($n = 4972$), 1.44% received BZD + Physo ($n = 329$), and 0.66% received Physo Only ($n = 152$). Patients who experienced major clinical effects ($n = 1795$) were most frequently treated with BZD Only (49.03%) followed by No BZD/No Physo (45.24%), and less frequently received BZD + Physo (4.74%) or Physo Only (1.00%). Patients with more severe outcomes more frequently received either physostigmine or benzodiazepines. Any

Table 1 Demographics by therapy group.

	No BZD/No Physo ($n=142,513$)	BZD Only ($n=6935$)	BZD + Physo ($n=434$)	Physo Only ($n=193$)	p value
Gender[¥]					
Male ($n=68,336$)	64,895 (94.92%)	3135 (4.59%)	108 (0.16%)	228 (0.33%)	0.006
Female ($n=81,336$)	77,283* (94.98%)	3792† (4.66%)	85 (0.1%)	206 (0.25%)	
Age (years)					
0–5 ($n=531,045$)	530,101 (99.82%)	896 (0.17%)	28 (0.01%)	20 (<0.01%)	
6–12 ($n=79,530$)	78,963 (99.29%)	519 (0.65%)	28 (0.04%)	20 (0.03%)	<0.001
13–18 ($n=80,532$)	74,472 (92.48%)	5527 (6.86%)	378 (0.47%)	155 (0.19%)	<0.001
Mean ± SD	6.9 ± 6.4	13.7 ± 4.7	14.5 ± 3.6	13.9 ± 4.3	
Median	3	15	15	15	
Reason					
Intentional suicidal intent ($n=35,431$)	31,791 (89.73%)	3363 (9.49%)	75 (0.21%)	202 (0.57%)	
Intentional misuse ($n=3351$)	3119 (93.08%)	205 (6.12%)	10 (0.03%)	17 (0.51%)	
Intentional abuse ($n=7310$)	5621 (76.89%)	1501 (20.53%)	50 (0.68%)	138 (1.89%)	
Intentional unknown ($n=2476$)	2171 (87.68%)	273 (11.03%)	6 (0.24%)	26 (1.05%)	
Unintentional ($n=91,866$)	90,311 (98.31%)	1463 (1.59%)	45 (0.05%)	47 (0.05%)	
Therapeutic error ($n=9516$)	9383 (98.6%)	123 (1.29%)	6 (0.06%)	4 (0.04%)	
Malicious ($n=125$)	117 (93.6%)	7 (5.6%)	1 (0.80%)	0 (0%)	

Physo physostigmine, *BZD* benzodiazepines

p values were calculated using chi-square/Fisher's exact tests between the two gender groups and between the youngest age group and the older two age groups

[¥]343 cases were of unknown gender across the treatment groups

[*]Includes 41 pregnancies

[†]Includes 1 pregnancy

Table 2 Medical outcomes by therapy group.

	No BZD/No Physo	BZD Only	BZD + Physo	Physo Only
Minor *n*, % ($n=31,606$)	30,773 (97.36%)	805 (2.71%)	15 (0.05%)	13 (0.04%)
Moderate *n*, % ($n=22,899$)	17,446 (76.19%)	4972 (21.71%)	329 (1.44%)	152 (0.66%)
Major *n*, % ($n=1795$)	812 (45.24%)	880 (49.03%)	85 (4.74%)	18 (1.00%)
Death *n*, % ($n=17$)	8 (47.06%)	7 (41.18%)	1 (5.88%)	1 (5.88%)
Incomplete data *n*, % ($n=28,129$)	27,991 (99.51%)	130 (0.46%)	3 (0.01%)	5 (0.02%)
Unrelated effects° *n*, % ($n=2608$)	2524 (96.78%)	79 (3.03%)	1 (0.04%)	4 (0.15%)
No effect *n*, % ($n=63,021$)	62,959 (99.90%)	62 (0.10%)	0 (0%)	0 (0%)
Total outcomes ($n=150,075$)	142,513 (94.96%)	6935† (4.62%)	434† (0.29%)	193† (0.13%)

Physo physostigmine, *BZD* benzodiazepines

[†]p value < 0.001 compared to No BZD/No Physo; p values were calculated using chi-square/Fisher's exact tests between the no treatment group and the 3 treatment groups. Percents may not add up to 100% due to rounding

°Symptoms not clearly associated with ingestion

physostigmine (Physo Only and BZD + Physo, $n=627$) was given in 11.76% of deaths, 5.74% with major outcomes, 2.10% with moderate outcomes, and 0.09% with minor outcomes. Benzodiazepines (with or without physostigmine, $n=7369$) were given in 47.06% of deaths, 53.76% of major outcomes, 23.15% of moderate outcomes, and 2.75% of minor outcomes (Table 2). Of note, the age subgroup of 13–18 years represented the largest proportion of patients receiving treatment in the form of benzodiazepines, physostigmine, or both at 80.14% of patients within these subgroups ($n=6060$ out of a total of $n=7562$). The BZD Only, Physo Only, and No BZD/No Physo groups had the same median age (15 years) and similar means which can be seen in Table 1.

Table 3 Causative agent by therapy group.

	No BZD/No Physo	BZD Only	BZD + Physo	Physo Only
Antimuscarinic drugs (excluding cough and cold preps and plants) *n*, % (*n* = 3542)	3197 (90.26%)	287 (8.10%)	32 (0.09%)	26 (0.73%)
Other antihistamines alone (excluding cough and cold preps) *n*, % (*n* = 70,872)	69,493 (98.05%)	1315 (1.86%)	35 (0.05%)	29 (0.04%)
Antispasmodics: antimuscarinic containing *n*, % (*n* = 6915)	6714 (97.09%)	184 (2.66%)	9 (0.13%)	8 (0.12%)
Cyclobenzaprine *n*, % (*n* = 17,656)	17,215 (97.5%)	423 (2.4%)	4 (0.02%)	14 (0.08%)
Phenothiazine *n*, % (*n* = 7454)	7031 (94.33%)	420 (5.63%)	1 (0.01%)	2 (0.03%)
Plants, antimuscarinics *n*, % (*n* = 4382)	3157 (72.04%)	1055 (24.08%)	127 (2.9%)	43 (0.98%)
Diphenhydramine alone (Rx) *n*, % (*n* = 1532)	1323 (86.36%)	186 (12.14%)	14 (0.91%)	9 (0.59%)
Diphenhydramine alone (OTC) *n*, % (*n* = 36,454)	33,165 (90.98%)	3021 (8.29%)	208 (0.57%)	60 (0.16%)
Antihistamine without opioids *n*, % (*n* = 1268)	1218 (96.06%)	44 (3.47)	4 (0.32%)	2 (0.16%)
Total outcomes (*n* = 150,075)	142,513 (94.96%)	6935 (4.62%)	434 (0.29%)	193 (0.13%)

Physo physostigmine, *BZD* benzodiazepines, *OTC* over the counter

Rx refers to diphenhydramine obtained via prescription

Table 4 Substances by therapy group.

Categories	AAPCC generic code	Substances included
Antimuscarinic drugs (excluding cough and cold preps and plants)	003000	Atropine*, benztropine, scopolamine*, trihexyphenidyl, dicyclomine, hyoscyamine*, belladonna*
Other antihistamines alone (excluding cough and cold preps)	003720	Brompheniramine, chlorpheniramine*, cyproheptadine, hydroxyzine, meclizine, doxylamine*
Antispasmodics: antimuscarinic containing	003830	Dicyclomine, hyoscyamine*, scopolamine*, atropine*, belladonna*
Cyclobenzaprine	003921	Cyclobenzaprine
Phenothiazine	075000	Perphenazine
Plants, antimuscarinics	087000	*Belladonna*, *Datura* spp., *Brugmansia* spp., *Atropa belladonna*, *Hyoscyamus niger*
Diphenhydramine alone (Rx)	159,850	Diphenhydramine
Diphenhydramine alone (OTC)	159,900	Diphenhydramine
Antihistamine without opioids	310,080	Doxylamine*, chlorpheniramine*

Loratadine, dimenhydrinate, *Garrya* spp., and quetiapine did not have any cases meeting the inclusion criteria

*Substances with an asterisk indicate that a drug might have been included in multiple generic codes and as such are listed in both categories

The most frequent exposure was "Other antihistamines alone (excluding cough and cold preps)," accounting for 47.22% of all cases. Diphenhydramine was the second most frequent exposure, representing 25.31% of cases, and was also the most frequent exposure in the groups that received BZD Only (46.24%), BZD + Physo (51.15%), and Physo Only (35.75%) (Table 3 and 4).

Serious outcomes (MMD) in the BZD Only group increased significantly, from 77 cases in 2000 to 602 cases in 2020, as determined by Poisson regression (p value < 0.001) (Fig. 2). Serious outcomes for the BZD + Physo and the No BZD/No Physo groups also significantly increased over the study period (p value < 0.001). There was no difference in the rate of serious outcomes over time in the Physo Only group (p value = 0.51).

Discussion

Recent studies evaluating the safety of physostigmine show a much more favorable safety profile than previously considered. Boley's 2019 review of adverse events following physostigmine administration in adults found that seizures occurred in 0.61% of cases, arrhythmias in 0.44% of cases, and cardiac arrest in 0.17% of cases. The most common adverse effect was hypersalivation, which occurred in 9%

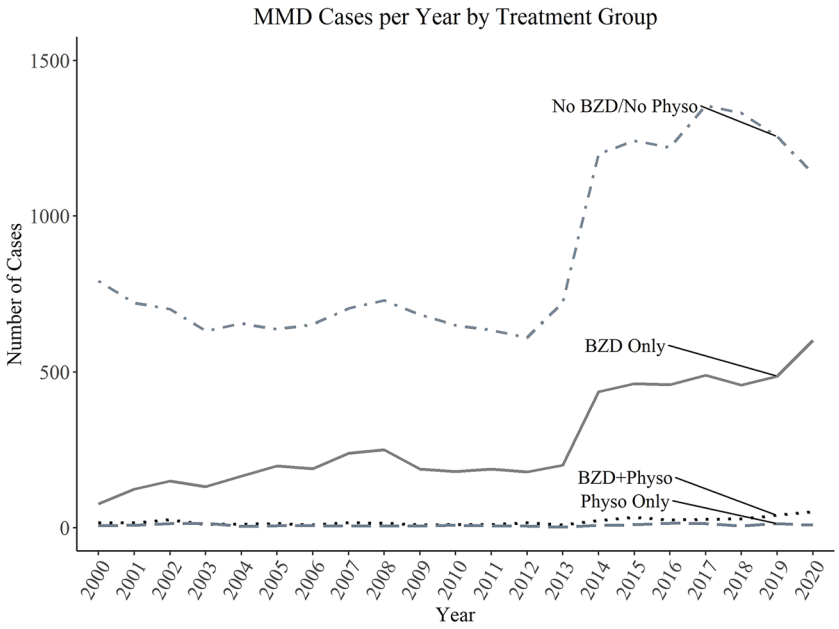

Fig. 2 Serious medical outcomes per year by therapy.

of cases [9]. Available data also suggest that the rate, but not the extent, of acetylcholinesterase inhibition correlates with adverse effects [1]; therefore, previously observed rates of adverse effects may have been related to more rapid intravenous injection than the slow (5–10 min) IV push now commonly used.

The frequency of pharmacological treatment with benzodiazepines and physostigmine for pediatric antimuscarinic poisoning in this dataset was low overall and seems to have been reserved for cases of more significant poisoning. Treatment with either physostigmine or benzodiazepines was more frequent in children aged 13–18 years, with similar mean ages among the groups that received either medication (see Table 1). Although children 0–6 years account for a majority of exposures in this study, exposures in that population are often exploratory, in contrast to the predominantly intentional exposures seen in children aged 13–18 years. We did note an increase in exposures starting in 2013; however, we are unable to ascribe a causation to this noted change.

Serious outcomes for patients treated with benzodiazepines, as well as the overall frequency of antimuscarinic poisoning by the included substances, have increased while serious outcomes for patients treated with physostigmine as monotherapy have not. Benzodiazepines and physostigmine were more likely to be used in patients with serious outcomes. Despite literature supporting the safety profile and the superior effectiveness of physostigmine to treat the agitation and delirium of antimuscarinic poisoning in adults, pediatric patients given pharmacologic therapy are still more likely to be treated with benzodiazepines alone than with physostigmine, suggesting the difference in treatment choice may be dogmatic and related to healthcare providers' perception of physostigmine. The results of this study show that patients who received physostigmine alone had less frequent serious outcomes compared to treatment with benzodiazepines.

Advocates for the use of physostigmine argue that more widespread use could reduce resource utilization, including intubation, ICU admission, and CT scans. There have been differing reports on the reduction of intubation rates associated with physostigmine administration. Boley and Stellpflug found that there was a significant reduction in intubation rates associated with physostigmine therapy in the first 24 h [10]. In contrast, Watkins et al. did not establish a significant reduction in intubation rates with any use of physostigmine, but rather a significantly lower rate was found with physostigmine monotherapy [6]. Boley and Stellpflug also found that patients treated with physostigmine had a lower rate of admission to the ICU (23%) than those who were not treated with physostigmine (39%) [10]. Additionally, a review by Doan et al. found that in cases of severe antimuscarinic toxicity, patients treated with physostigmine were more likely to fully recover within 24 h of exposure than those who did not receive physostigmine [39].

Many of the limitations of this study arise from the nature of NPDS data, which depends on patients, caregivers, healthcare providers, and others to make voluntary reports to a poison center. Therefore, there is a high likelihood that an unknown number of cases of antimuscarinic toxicity were never reported and would not be captured in our data set. These are likely to be cases with minor or no symptoms, possibly biasing our study toward more serious outcomes. Standardized coding of information for NPDS data does not include the time course of the onset of symptoms or relate

these to the administration of medications or treatments; rather, it is simply documentation that a particular therapy was or was not given. Though the data shows a higher number of MMD outcomes when benzodiazepines were used, it cannot be assumed that they were the cause of the outcomes. It can also be difficult to conclusively ascribe outcomes to a given exposure, as poison center data is generally not as complete as a hospital's electronic medical record and causality is not always evident. Limitations of the NPDS data also do not allow conclusions to be drawn regarding the rationale for administration of benzodiazepines and physostigmine to patients who were coded as having no effect from ingestion; however, we included this subset of patients as the outcomes of moderate/major/death were the primary outcomes of this study. Other variables, such as dose of medications, are not always reported and may be inaccurate when they are. Additionally, product codes were not provided in the data set provided by our research request; therefore, the therapy groups could not be further broken down by single agent. Further, the cases are not coded specifically by toxidrome, so the inquiry must be driven by a chosen list of substances, effects, treatments, or a combination of these. We combined MMD outcomes into one category, as is typical in NPDS studies, in order to compare the overall rates of severe outcomes. The proportions of each outcome may vary over time, and the analysis will not reflect this nuance. Though NPDS data does indicate the highest level of care provided, it is not possible to determine an indication for that level of care. For example, NPDS cannot differentiate between patients that require inpatient admission for psychiatric care and patients that require further medical intervention or monitoring. For this reason, assessment of level of care was excluded from our analysis. "Gender," in the context of NPDS, is only representative of biological sex and does not capture the entirety of the gender spectrum. Gender is coded based on self or secondary report and the available choices are limited to female, pregnant female, male, or unknown. Finally, the query returned small sample sizes in the BZD + Physo and Physo Only groups; further research with larger samples should be performed to corroborate the findings presented in this study.

For the purposes of this study, only single ingestion cases were included, as multi-agent exposures can present with multiple toxidromes, and isolating the events related to one toxidrome alone is not possible. This is why cough and cold preparations were not included, which may have limited the number of antimuscarinic toxidromes identified by our inclusion criteria. Similarly, agents that are only weakly antimuscarinic were not included. Adult literature has shown strong regional differences in frequency of physostigmine administration [6] and although our data does not include geographic information, it is likely that this holds true for pediatric populations as well.

Conclusions

Benzodiazepine use in antimuscarinic toxicity steadily increased throughout our study period. However, physostigmine use remained consistently low. This is despite a growing body of evidence supporting the safety and efficacy of physostigmine. Outcomes were worse with benzodiazepines than with physostigmine alone; however, causation between treatment and outcomes cannot be determined by this data. This echoes previous retrospective studies showing lower intubation rates, fewer ICU admissions, and shorter lengths of stay with physostigmine in comparison to benzodiazepine. The apparent reticence of the medical community to use physostigmine belies the current safety evidence.

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Author Contribution All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by SH, RA, AO, and SP. The first draft of the manuscript was written by SH, RA, AO, and KN, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Declarations

Conflicts of Interest None.

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