JPPT | A Systematic Review

# Pharmacologic Management of Sialorrhea in Neonatal and Pediatric Patients

Caitlyn V. Bradford, PharmD; Avery M. Parman, PharmD; Peter N. Johnson, PharmD; and Jamie L. Miller, PharmD

Sialorrhea, defined as an excess flow of saliva or excessive secretions, is common in patients with cerebral palsy and other neurologic disorders and is associated with clinical complications such as increased risk of local skin reactions, infections, aspiration, pneumonia, and dehydration. Upon failure of non-pharmacologic measures, clinicians have several noninvasive pharmacologic options available to manage sialorrhea. This review of the literature provides detailed descriptions of medications used, efficacy, safety, and practical considerations for use of non-injectable pharmacologic agents. The literature search included published human studies in the English language in PubMed and Google Scholar from 1997 to 2022. Relevant citations within articles were also screened. A total of 15 studies representing 719 pediatric patients were included. Glycopyrrolate, atropine, scopolamine, and trihexyphenidyl all have a potential role for sialorrhea management in children; however, glycopyrrolate remains the most studied option with 374 (n = 52.0%) of the 719 patients included in the systematic review receiving this medication. Overall, glycopyrrolate showed similar efficacy but higher tolerability than its comparators in 2 comparative studies and is often considered the first-line agent. Patient-specific (age, route of administration) and medication-specific (dosage formulation, medication strength) considerations must be weighed when initiating a new therapy or switching to another medication upon treatment failure. Owing to the high propensity of adverse events with all agents, clinicians should consider initiating doses at the lower end of the dosage range, as previous studies have noted a dose-dependent relationship.

**ABBREVIATIONS** ADE, adverse drug event; BoNT-A, botulinum toxin type A; DIS, Drooling Impact Scale; DQ, Drooling Quotient; DSFS, Drooling Severity and Frequency Scale; FDA, US Food and Drug Administration; mTDS, modified Teacher's Drooling Scale; SL, sublingual; TDS, Teacher's Drooling Scale; VAS, Visual Analog Scale

**KEYWORDS** atropine; drooling; glycopyrrolate; hypersalivation; scopolamine; sialorrhea; trihexyphenidyl

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## Introduction

Drooling is considered developmentally normal up until the age of 18 months owing to the immaturity of motor muscles.[1] Drooling is identified as problematic and clinically important when a child reaches age 4 years of life. By definition, drooling is not a condition of increased saliva, but rather an inability to initiate an appropriate swallow, resulting in unintentional flow of saliva outside of the mouth.[2] *Sialorrhea* and *hypersalivation* are often used as synonymous terms to drooling but instead are a pathologic excess of saliva.[2] Most literature centers around management of sialorrhea and drooling in patients with cerebral palsy and other neurologic disorders. The clinical effect of sialorrhea includes increased risk of local skin reactions, infections, aspiration, pneumonia, and dehydration.[3] When saliva secretions are in excess of what is typically expected for age, measures like minimization of cholinergic medications, limitation of medications with known adverse events of increased salivation, and speech/behavioral therapy are used.[4]

The primary agents used to manage sialorrhea are agents with anti-cholinergic activity, including glycopyrrolate, scopolamine, atropine, and trihexyphenidyl. Another more invasive option is botulinum toxin type A (BoNT-A), which has a US Food and Drug Administration (FDA)–labeled indication for sialorrhea in adults.[5] However, this agent may have limitations compared with other anticholinergic agents because it requires intraglandular injections and has an FDA black box warning for spread of BoNT-A.[6] Other systematic reviews have been published on this topic, but these reviews do not include a full review of the dosage regimen, dosage forms, and adverse events.[7] Therefore, the purpose of this review is to describe the efficacy, safety, and practical considerations for use of non-injectable pharmacologic agents for the management of sialorrhea in children.

## Literature Review

Ovid Medline, PubMed, and Google Scholar were searched by using the keywords "pediatric," "sialorrhea," and "medication." Additionally, a search was done with each medication name replacing the word *medication* as a keyword. Relevant citations within articles were also screened. Results were limited to human studies published from 1997–2022 and available in the English language. One author (CVB) independently screened each article identified through the initial search. Review articles and case reports were excluded. Articles evaluating the sole use of BoNT-A or other invasive procedures were excluded, because these topics were beyond the scope of this review. Following initial review, all authors participated in the final selection process.

## Results

A total of 221 articles were identified by using the search strategies. Overall, 207 articles were excluded secondary to non-pharmacologic or invasive measures (n = 118), lack of relevance to the topic (n = 50), review article (n = 28), case report (n = 4), description of a clinical trial design (n = 1), adult population (n = 5), or animal study (n = 1). One additional study was identified by using the citations of one of these published studies. A total of 15 studies representing 719 pediatric patients were included in the review. Tables 1 to 4 provide a summary of the studies.[2,8–21]

**Tools to Evaluate Efficacy.** Several tools have been developed to subjectively and objectively evaluate the severity and/or frequency of sialorrhea and the effect on quality of life. These tools are used in the clinical setting but are also used in studies to determine efficacy of pharmacologic interventions. Table 5 includes a summary of scoring tools used to evaluate efficacy in the studies included in this review.[2,8–10,12–18,20,21] The Drooling Impact Scale (DIS) was used in 5 studies included in our review.[8,15,16,20,21] The DIS was developed to assess caregiver's assessment of severity, frequency, and quality of life over the past week.[22] Total scores of the questionnaire can range from 10 to 100, with 10 indicating no drooling or effect on quality of life and 100 indicating constant, severe drooling with significant effect on patient and caregiver quality of life. Reid and colleagues[22] validated the administration of the DIS to caregivers of children 3.5 to 18 years of age with cerebral palsy or intellectual disability and demonstrated that it can be used to quantify short- to medium-term benefits of treatment. The longitudinal nature of the scale makes it ideal for observing drooling changes after saliva-controlling interventions and provides insight into the effect of drooling on quality of life.

The Teacher's Drooling Scale (TDS) was used in 3 studies included in our review.[10,12,17] The TDS was initially introduced in 1989 for use in a study by Camp-Bruno and colleagues[23] in which teachers evaluated the severity of drooling in children with cerebral palsy and receiving benztropine after a full school-day observation. In this study, the investigators conducted an assessment of concurrent validity by correlating TDS scores with time-sampling of streams and bubbles of saliva. A modified Teacher's Drooling Scale (mTDS) was used in 2 studies included in our review.[13,14] Mier and colleagues[13] modified the TDS to be used by caregivers and provided more specific options for scoring, allowing for a more accurate description of drooling severity and frequency. Validity has not been assessed to date for the mTDS.

The Drooling Severity and Frequency Scale (DSFS), also referred to as the Drooling Rate Scale or Thomas-Stonell and Greenberg scale, was used by 6 studies in this review.[2,11,15,18,20,21] The DSFS was developed for clinician ratings and described in a 1988 study of 36 children and adults with cerebral palsy and other neurologic conditions by Thomas-Stonell and Greenberg.[24] The DSFS has concurrent validity with correlations to observational measures of drooling severity (e.g., bib count, bib weight, drooling quotient).[25]

A Visual Analog Scale (VAS) was used in 2 studies included in our review.[9,17] The use of the VAS to evaluate the severity of drooling was first reported by Brodtkorb and colleagues[26] in 1988 where a staff member marked severity of drooling on a 10-cm scale at multiple intervals after scopolamine patch placement on adults with mental disabilities. The authors did not disclose how the scale was interpreted; however, it can be inferred from the results and discussion that the highest number (e.g., 10) correlated with the most improvement in drooling, whereas the lowest number (e.g., 1) correlated with worsened drooling.[26] Since the introduction of the 10-cm VAS, researchers have begun measuring marks made on the 10-cm line and converting to millimeters to provide a final score ranging from 0 to 100 mm with lower scores indicating more severe drooling.[17] Some experts suggest that a score of 24 mm is the cutoff between moderate to severe drooling and mild drooling.[25] It should be noted that for 1 study included in this review, the VAS scale was reversed with "no drooling" on the extreme left and "severe drooling" on the extreme right; therefore, higher scores indicated more drooling.[9] The VAS has not been validated to date in clinical studies, and clinicians should pay close attention to how the VAS is oriented because it could lead to misinterpretation of results.

The Drooling Quotient (DQ) was used in 1 study included in this review.[17] The DQ includes an assessment of presence or absence of drooling every 15 seconds during a 10-minute period for a total of 40 observations.[27] The DQ is calculated by dividing the number of drooling episodes by 40 and then multiplying that by 100 to express DQ as a percentage. The DQ was validated in a 1980 study of 24 children with cerebral

**Table 1.** Summary of Atropine Reports[8–10]

| Author | Study Design (n) | Patient Population | Dose | Dosage Form | Results |
|---|---|---|---|---|---|
| Dias | Open-label (25) | Age<br>Mean ± SD: 8.6 ± 4.2 yr<br><br>Weight<br>Mean: 19.5 kg (range, 10.9–37.5) | Patients 10–19 kg:<br>One drop (0.25 mg) SL every 6 hr (max: 3 doses/day)<br><br>Patients >20 kg:<br>Two drops (0.5 mg) SL every 6 hr (max 3 doses/day) | Atropine 0.5% ophthalmic solution | - Statistically significant decrease in mean DIS score pre and post treatment, 61.8 vs 25.6 ($p < 0.0001$)<br>- Statistically significant decrease from pre to post treatment in mean score for 8 of 10 questions on DIS<br>- No ADEs noted |
| Norderyd | Open-label (11) | Age<br>Mean ± SD: 11.8 ± 4.4 yr<br><br>Weight<br>Not provided | One drop (0.5 mg) SL once daily for 4 wk, then 1 drop (0.5 mg) SL twice daily for 4 wk | Atropine 1.0% ophthalmic solution | - Statistically significant decrease in median 100-mm VAS from baseline to 4 wk of once daily dosing, 74 vs 48 ($p = 0.05$), and from once daily dosing to 4 wk of twice daily dosing, 48 vs 32 ($p = 0.026$)<br>- Decreased salivary secretion rate noted in 9 (81.8%) patients from baseline<br>- ADEs included xerostomia and behavior change |
| Azapagasi | Retrospective (20) | Age<br>Median: 25 mo (range, 3–78)<br><br>Weight<br>Not provided | 0.02 mg/kg/dose (minimum dose: 0.25 mg) SL every 4–6 hr for 7 days | Atropine intravenous solution (concentration not reported) | - Statistically significant decrease in median TDS score from 5 at baseline to 3 on day 2 ($p < 0.001$)<br>- 60% of patients with TDS score of 2 and 35% of patients with TDS score of 3 on day 2 of treatment<br>- Secretions increased 7 days after discontinuation of treatment<br>- No ADEs noted |

*ADE, adverse drug event; DIS, Drooling Impact Scale; SL, sublingual; TDS, Teacher's Drooling Scale; VAS, visual analog scale*

palsy.[27] In the validation study, a device prompter was used to collect randomized assessments totaling 40 observations over 10 minutes.[27] This was later modified by Reddihough and colleagues[28] where assessments were scheduled to be collected every 15 seconds throughout the 10-minute period. In addition, the DQ has also been correlated with DSFS.[25]

**Atropine.** A total of 3 reports were identified that described the use of atropine, representing a total of 56 patients (Table 1).[8–10] The first study was conducted by Dias and colleagues[8] who performed an open-label study of sublingual (SL) atropine for management of drooling in 25 children with a mean age of 8.6 ± 4.2 years with cerebral palsy. Thirty-three patients were initially identified and initiated on atropine; however, 8 patients were excluded from analysis owing to inappropriate use of atropine (n = 1), early discontinuation (n = 3), or adverse drug events (ADEs) (n = 4). For patients weighing between 10 and 19 kg, an atropine 0.5% ophthalmic solution was initiated at 1 drop (0.25 mg) SL 3 times daily (at 6-hour intervals), and for those ≥20 kg it was initiated at 2 drops (0.5 mg) 3 times daily (at 6-hour intervals). Efficacy of impact on drooling was assessed by using the DIS at baseline and after 30 days of treatment. A significant reduction in the mean DIS was noted from baseline to follow-up

**Table 2.** Summary of Glycopyrrolate Reports[11–16]

| Author | Study Design (n) | Patient Population | Dose | Dosage Form | Results |
|---|---|---|---|---|---|
| Stern | Retrospective (22) | Age<br>Mean: 13.4 yr (range, 3–23)<br><br>Weight<br>Not reported | 0.04–0.175 mg/kg/day enterally every 24 hr | Not specified | - Improvement in DSFS scores noted in 86.3% of patients<br>- Significant improvement in severity scores (Z = 3.6214, p = 0.0003) and frequency scores (Z = 2.7064, p = 0.0068)<br>- ADEs included constipation, pupillary dilation, flushing, and xerostomia |
| Bachrach | Retrospective review and survey (37) | Age<br>9–20 mo (Overall mean not reported)<br><br>Weight<br>Not reported | Mean: 0.051 mg/kg/dose enterally every 8 hr (range, 0.01–0.14) | Not specified | - Improvement in mean TDS in 94.9% of patients<br>- Improvement in TDS scores noted pre to post treatment, 4.59 to 2.41 (p < 0.01)<br>- 17 (45.9%) patients reported ADEs: xerostomia, urinary retention, flushing, constipation, pseudo-obstruction, and agitation/personality change<br>- No significant difference in age or weight-based dose between those with and without ADEs (p = NS) |
| Mier | Placebo-controlled, double-blind, crossover (39) | Age<br>Mean, 10.8 yr (range, 4.3–19)<br><br>Weight<br>Range: 11.5–61.9 kg (mean/median not reported) | <30 kg<br>0.6 mg enterally every 8 hr, titrated by 0.6 mg weekly to 2.4 mg every 8 hr<br><br>≥30 kg<br>1.2 mg enterally every 8 hr, titrated by 0.6 mg weekly to 3.0 mg every 8 hr | Glycopyrrolate tablets (crushed and placed in gelatin capsule to match placebo capsules) | - Mean largest tolerated dose was 0.11 mg/kg/dose (range, 0.04–0.2)<br>- Mean mTDS improved from 7.52 to 1.85 vs on placebo from 7.44 to 6.33 (p < 0.001)<br>- ADEs noted in 25 (64.1%) patients including behavioral changes, constipation, xerostomia, and urinary retention |
| Zeller | Open-label (137) | Age<br>Mean ± SD: 11 ± 4.4 yr<br><br>Weight<br>≥12.3 kg (mean/median not reported) | Initial dose<br>0.02 mg/kg enterally every 8 hr; titrated by 0.02 mg/kg every 5–7 days to max of 0.1 mg/kg every 8 hr (max: 9 mg/day)<br><br>Maximum dose<br>Mean 0.05 mg/kg/dose enterally every 8 hr | Extemporaneously prepared oral glycopyrrolate solution (0.2 mg/mL) | - 52.3% considered responders with 3-point decrease in mTDS<br>- Most responders required dose between 0.02 and 0.08 mg/kg/dose<br>- 122 (89%) patients had ≥1 ADEs including constipation, vomiting, diarrhea, pyrexia, xerostomia, flushing, and nasal congestion and severe ADEs including nystagmus, esophageal candidiasis, dehydration, and gastrointestinal motility disorder |

*(Table cont. on page 10)*

**Table 2.** Summary of Glycopyrrolate Reports[11–16] *(cont.)*

| Author | Study Design (n) | Patient Population | Dose | Dosage Form | Results |
|---|---|---|---|---|---|
| Zanon | Retrospective (21) | Age<br>Median: 12 yr (range, 2–19)<br><br>Weight<br>Not reported | 0.021 mg/kg enterally every 6–12 hr | Extemporaneously prepared oral glycopyrrolate solution (0.5 mg/mL) | - 76.2% of patients reported improvement in DIS and DSFS compared with baseline ($p < 0.001$)<br>- 66.7% of patients reported improvement in drooling severity and 47.6% reported reduction in frequency<br>- 9 (42.9%) patients reported ≥1 ADEs including xerostomia, constipation/nausea/vomiting, nasal obstruction, nasal bleeding, gastroesophageal reflux, and tachycardia |
| Lovardi | Case series (18) | Age<br>Median: 17 mo (range, 2–36)<br><br>Weight<br>Median: 9.8 kg (range, 2.5–22) | Initial dose<br>Median: 0.022 mg/kg/dose (range, 0.007–0.07) enterally every 8 hr<br><br>Maximum<br>Median: 0.023 mg/kg/dose (range, 0.007–0.09) enterally every 8 hr | Glycopyrrolate tablets (0.5 mg) | - Improvement in DIS observed in 94% of patients<br>- Significant decrease in mean DIS from baseline to 1 mo of treatment, 89 vs 61 ($p < 0.001$)<br>- No ADEs attributed to glycopyrrolate were noted |

*ADE, adverse drugs event; DIS, Drooling Impact Scale; DSFS, Drooling Severity and Frequency Scale; mTDS, modified Teacher's Drooling Scale; NS, not significant; TDS, Teacher's Drooling Scale*

at 30 days: 61.8 vs 25.6 ($p < 0.001$). In addition, the mean score for each of the 10 questions on the DIS was compared from baseline to follow-up at 30 days, and all were found to be significantly reduced, except for scores related to skin irritation and embarrassment caused by drooling. No ADEs were noted in the 25 patients included in the final analysis. However, 4 of the 33 initial patients screened were excluded because of an ADE, and it is unclear why the authors chose to exclude these patients from the final analysis.

Using the VAS scale, Norderyd and colleagues[9] conducted an open-label study of SL atropine in 11 children with mean age of 11.8 ± 4.4 years with excessive drooling. Initially, 26 children were included in the study; however, 3 left the study after the initial baseline visit and 4 left after completion of the once daily dosing phase. An additional 8 patients did not have complete data from the follow-up visits. The study was divided into 3 phases and included a 3-week baseline with no treatment, then 4 weeks of treatment with atropine 1% ophthalmic solution 1 drop (0.5 mg) administered once daily, followed by another 4-week treatment period with atropine dosing of 1 drop (0.5 mg) twice daily. Although not explicitly stated by the authors, it could be inferred that the extreme markings of the VAS had "no drooling" on the extreme left and "severe drooling" on the extreme right. Patients were evaluated at baseline, after completion of the once daily dosing (i.e., 7 weeks), and at the completion of twice daily dosing (i.e., 11 weeks). At these visits, whole saliva was collected and measured as a salivary secretion rate (mL/min), and caregiver rating of drooling was assessed with a 100-mm VAS. A statistically significant decrease in median caregiver rating on the VAS for drooling was noted from baseline to completion of once daily treatment, 74 vs 48 ($p = 0.05$), and for completion of once daily to twice daily dosing, 48 vs 32 ($p = 0.026$). A decrease in salivary secretion rate was noted for 9 (81.8%) patients from baseline to completion of twice daily dosing. The most frequently reported ADEs for the 11 patients included in the study were xerostomia (n = 4) and behavioral change (n = 1); these symptoms resolved when atropine was discontinued. Some caregivers reported difficulty with administration or issues with tolerance related to bitter taste.

Azapagasi and colleagues[10] published a retrospective evaluation of 20 hospitalized patients with

**Table 3.** Summary of Scopolamine Reports[2,17,18]

| Author | Study Design (n) | Patient Population | Dose | Dosage Form | Results |
|---|---|---|---|---|---|
| Jongerius | Prospective, open-label, crossover (45) | Age<br>Mean ± SD: 9.5 ± 3.7 yr<br><br>Weight<br>Not reported | 1.5-mg patch applied topically every 3 days | Transdermal 1.5-mg patch | - Significant improvement in sialorrhea as based on DQ and VAS scores from baseline to day 10 of scopolamine ($p < 0.001$)<br>- No significant difference in DQ ($p = 0.2$) or VAS ($p = 0.41$) with scopolamine compared with BoNT-A at 4 wk<br>- ADEs included xerostomia, behavioral changes, somnolence, and pupillary dilation |
| Franco | Case series (4) | Age<br>Range: 7–15 yr<br><br>Weight<br>Not reported | 10–17.5 mg (20–35 drops) enterally every 12 hr | Oral solution (10 mg/mL) | - All patients had improvement in frequency and severity of drooling, based on the DSFS, at 24 hr of treatment compared with baseline<br>- No ADEs reported |
| Al Jeraisy | Retrospective cohort (44) | Age<br>Median: 93 mo (IQR, 64)<br><br>Weight<br>Median: 16.8 kg (IQR, 15.9) | Initial dose<br>0.375 mg (1/4 patch) applied topically once daily; titrated patch (dosing titration not provided)<br><br>Maximum dose<br>1.5 mg (full patch) applied topically once daily | Transdermal 1.5-mg patch | - The percentage of patients with severe/very severe drooling, using the DSFS, decreased from baseline after scopolamine initiation: 87.5% to 15.6% of children ($p < 0.001$)<br>- Absolute risk reduction of 27.6% for ED visits and 35.7% for readmission visits after starting scopolamine ($p < 0.001$)<br>- ADEs included tachycardia, visual disturbance, and urinary retention |

*ADE, adverse drug event; BoNT-A, botulinum toxin; DQ, Drooling Quotient; DSFS, Drooling Severity and Frequency Scale; ED, emergency department; VAS, Visual Analog Scale*

sialorrhea treated with atropine at a median age of 25 months (range, 3–78). All patients received atropine intravenous solution via the SL route at a dose of 0.02 mg/kg (minimum dose: 0.25 mg) 4 to 6 times per day for 7 consecutive days. Thirteen patients (65%) required administration of 4 doses per day and 7 (35%) required 6 doses per day. Response to treatment was assessed with the TDS. The median TDS score at baseline was 5. By the second day of treatment, 12 (60%) patients had a reduction in the TDS score to 2 (i.e., infrequent drooling, small amount), and 7 (35%) had a reduction to 3 (i.e., occasional drooling, moderate amount). Only 1 (5%) patient had no change in score from baseline. No ADEs were noted during the 7 days of treatment. Caregivers reported an increase of secretions at the follow-up visit approximately 7 days after discontinuation of atropine.

**Atropine Summary.** All studies provided data supporting the efficacy of SL atropine. However, the dosage formulation differed because 2 studies involved ophthalmic drops (0.5% and 1.0%) and 1 involved the intravenous dosage form. The dosage regimen also varied between reports with patients receiving 0.25 to 0.5 mg/dose of atropine administered SL every 4 to 6 hours. The overall efficacy based on reduction in VAS or TDS scores was 82% to 95%, with reduction in sialorrhea noted by day 2 of treatment.[10] Clinically significant ADEs in the 56 patients included xerostomia (n = 4; 7.1%) and behavioral changes (n = 1; 1.8%).

**Table 4.** Summary of Trihexyphenidyl and Comparative Study Reports[19–21]

| Author | Study Design (n) | Patient Population | Dose | Dosage Form | Results |
|---|---|---|---|---|---|
| | | | *Trihexyphenidyl* | | |
| Carranza-del Rio | Retrospective (101) | Age<br>Mean: 7.8 yr (range, 1–18)<br>Weight<br>Not reported | Initial dose<br>Mean: 0.048 mg/kg/dose enterally every 12 hr (range, 0.005–0.21)<br>Titration<br>Increased by 10%–20% every 2 wk<br>Maximum dose<br>Mean: 0.55 mg/kg/day enterally divided every 8–12 hr (range, 0.03–3.13) | Not specified | - Sialorrhea decreased in 60.4% of patients with a sialorrhea indication<br>- Most common ADEs included constipation, decreased urinary frequency, behavioral changes, and xerostomia |
| | | | *Comparative Studies* | | |
| Parr | Randomized controlled trial (85) | Age<br>Mean: 4.9 yr (range, 3–14.5)<br>Weight<br>Median: 18.1 kg (range, 10.4–79.4) | Glycopyrrolate (n = 38):<br>*Initial dose:*0.40 mg/kg enterally every 8 hr<br>*Titration:* 0.02 mg/kg/dose enterally every 8 hr weekly, as needed<br>*Maximum dose:* 0.1 mg/kg enterally every 8 hr (max: 2 mg/dose)<br>Scopolamine (n = 47):<br>*Initial dose:* 0.375 mg (1/4 patch) applied topically every 3 days<br>*Titration:* increased by 0.375-mg (1/4 patch) patch weekly, if needed<br>*Maximum dose:* 1.5 mg (full patch) applied topically every 3 days | Glycopyrrolate: Extemporaneously prepared oral glycopyrrolate solution (concentration not reported)<br>Scopolamine: Transdermal 1.5-mg patch | - Both glycopyrrolate and scopolamine groups had significant reductions in DIS scores from baseline to wk 4 ($p < 0.001$)<br>- Noted reduction in DSFS at weeks and 12 for scopolamine and glycopyrrolate groups<br>- ADEs were "unwell," local skin reactions, skin flushing/dryness, constipation, xerostomia, and behavioral changes<br>- 24 (51.1%) patients receiving scopolamine and 7 (18.4%) receiving glycopyrrolate discontinued therapy before the end of the study owing to ADEs |
| Reid | Observational, cohort (110)* | Age<br>Mean ± SD: 8.4 ± 4.3 yr<br>Weight<br>Not reported | Dosing not reported for glycopyrrolate, scopolamine, and trihexyphenidyl | Dosage forms not specified | - DSFS scores improved from baseline to 1 wk with trihexyphenidyl, glycopyrrolate, and scopolamine: 79%, 73%, and 82%, respectively<br>- Significant improvement in DIS from baseline to wk 1 for all agents<br>- Best response noted at mean of 11.5 ± 7.2 wk for scopolamine, 1.8 ± 0.7 wk for glycopyrrolate, and 5.0 ± 8.5 wk for scopolamine<br>- ADEs noted were behavioral changes, gastrointestinal problems, skin changes, urinary symptoms, visual disturbances, swallowing difficulties, and worsening seizures<br>- Noted that 68.2% receiving trihexyphenidyl, 43.8% receiving glycopyrrolate, and 69.2% receiving scopolamine had to discontinue therapy owing to an ADE |

*ADE, adverse drug event; DIS, Drooling Impact Score; DSFS, Drooling Severity and Frequency Score*

* Patients could be included in >1 treatment group during the study, including glycopyrrolate (n = 62), scopolamine (n = 17), and trihexyphenidyl (n = 75).

**Table 5.** Summary of Scoring Tools Used in Studies Included in Review for Evaluation of Efficacy[2,8–10,12–18,20–28]

| | Description of Tool | Items Assessed | Type of Assessment | Range of Points | Validated Scale |
|---|---|---|---|---|---|
| DIS | Likert scale, 1–10, for 10 questions:<br>1. Frequency of dribbling (1 = not at all; 10 = constantly)<br>2. Severity of drooling (1 = dry; 10 = profuse)<br>3. Frequency of changing clothing/bibs (1 = once; 10 = 10 or more times)<br>4. Smell of saliva (1 = not offensive; 10 = very offensive)<br>5. Skin irritation (1 = none; 10 = severe rash)<br>6. Frequency of wiping (1 = not at all; 10 = all the time)<br>7. Embarrassment about dribbling (1 = not at all; 10 = very embarrassed)<br>8. Frequency of wiping saliva from items (1 = not at all; 10 = all the time)<br>9. Drooling impact on child's life (1 = not at all; 10 = greatly)<br>10. Drooling impact on family's life (1 = not at all; 10 = greatly) | Severity and frequency of drooling; effect on quality of life | Questionnaire | 10–100 | Yes |
| TDS | 1 = No drooling<br>2 = Infrequent drooling, small amount<br>3 = Occasional drooling, on and off all day<br>4 = Frequent drooling, but not profuse<br>5 = Constant drooling, always wet | Severity of drooling | Scale | 1–5 | Yes |
| mTDS | 1 = Dry: never drools<br>2 = Mild: only lips are wet; occasionally<br>3 = Mild: only lips are wet; frequently<br>4 = Moderate: wet on lips/chin; occasionally<br>5 = Moderate: wet on lips/chin; frequently<br>6 = Severe: clothing becomes damp; occasionally<br>7= Severe: clothing becomes damp; frequently<br>8 = Profuse: clothing/hands wet; occasionally<br>9 = Profuse: clothing/hands wet; frequently | Severity and frequency of drooling | Scale | 1–9 | No |
| DSFS | Scores from drooling severity and frequency are added to give an overall score:<br><u>Drooling Severity</u><br>1 = Never drools, dry<br>2 = Mild drooling, only lips wet<br>3 = Moderate, drool reaches lips and chin<br>4 = Severe, drool drips off chin onto clothing<br>5 = Profuse, drooling off body and onto objects<br><br><u>Drooling Frequency</u><br>1 = No drooling<br>2 = Occasional drooling<br>3 = Frequent drooling<br>4 = Constant drooling | Severity and frequency of drooling | Questionnaire | 2–9 | Yes |
| VAS | Caregivers mark the extent of drooling on a 10-cm line. Extreme left indicates "severe drooling" and extreme right indicates "no drooling." Scale broken down into 1-mm increments to give numerical score of 0–100. Lower scores indicate more severe drooling. | Severity of drooling | Visual | 0–100 | No |
| DQ | Evaluator records presence or absence of drooling every 15 sections over a 10-min period for a total of 40 observations. The number of drooling episodes observed is divided by 40, which is then multiplied by 100 and reported as a percentage. | Frequency of drooling | Direct observation, semiquantitative | 0%–100% | Yes |

*DIS, Drooling Impact Scale; DSFS, Drooling Severity and Frequency Scale; DQ, Drooling Quotient; mTDS, modified Teacher's Drooling Scale; TDS, Teacher's Drooling Scale; VAS, Visual Analog Scale*

**Glycopyrrolate.** A total of 6 reports describe the use of glycopyrrolate in 274 children (Table 2). Stern[11] conducted a retrospective study of glycopyrrolate in 22 patients with a mean age of 13.4 years. Glycopyrrolate was initiated at 0.04 mg/kg enterally once daily and increased up to 0.175 mg/kg once daily until sialorrhea was significantly decreased or controlled. The specific formulation for glycopyrrolate was not disclosed. Caregivers were asked to complete the DSFS after completion of glycopyrrolate treatment, which ranged from 5 weeks to 28 months in duration. Improvement in severity and frequency of sialorrhea was noted for 19 patients (86.3%). Overall, the author noted statistically significant improvement in severity ($p = 0.0003$) and frequency ($p = 0.0068$) of sialorrhea; however, it is unclear if this was in comparison to baseline or some other time point. Reported ADEs included xerostomia (n = 4; 18.2%), constipation (n = 2; 9.1%), pupillary dilation (n = 1; 4.5%), and flushing (n = 1; 4.5%).

Bachrach and colleagues[12] performed a retrospective chart review and survey study including 37 caregivers of children diagnosed with cerebral palsy and taking glycopyrrolate for the treatment of sialorrhea. The patients' ages ranged from 9 months to 20 years. The mean dose received was 0.051 mg/kg/dose enterally (range, 0.01–0.14), most commonly administered 3 times daily; most patients (86%) received a dose in the range of 0.02 to 0.07 mg/kg/dose. The TDS was assessed by caregivers at baseline and after treatment. Improvement in drooling was reported by caregivers for 94.9% of patients. A statistical improvement in mean TDS was noted from pre to post initiation of treatment: 4.59 vs 2.41 ($p < 0.01$). ADEs were noted in 17 (45.9%) patients, which included xerostomia (n = 7), urinary retention (n = 7), flushing (n = 4), constipation (n = 2), pseudo-obstruction (n = 1), and agitation/behavioral change (n = 1). Comparisons were made between patients with and without ADEs. No difference in age or weight-based dose was observed between groups (p = not significant). Ten (27.0%) patients stopped treatment secondary to development of ADEs.

Mier and colleagues[13] performed a placebo-controlled, double-blind, crossover study in 39 children aged 4 to 19 years (mean, 10.8) with sialorrhea. Patients were randomly assigned to receive glycopyrrolate or placebo for 8 weeks. At the end of the 8 weeks, there was a 1-week washout followed by a 1-week observation period. After the washout and observation period, patients were then initiated on the reciprocal treatment for another 8-week period. To maintain blinding, glycopyrrolate tablets were crushed into powder. The appropriate dose of glycopyrrolate or placebo was placed in a gelatin capsule. For patients who could not swallow capsules, caregivers were instructed to open the capsule and pour the powder contents in food. Patients weighing <30 kg were started at 0.6 mg enterally 3 times a day, and the dose was increased by 0.6 mg weekly over the next 3 weeks as tolerated, to a maximum of 2.4 mg/dose. Patients weighing ≥30 kg were started at 1.2 mg enterally 3 times a day, and the dose was increased by 0.6 mg weekly over the next 3 weeks as tolerated, to a maximum of 3 mg/dose. Only 27 (69.2%) patients completed the entire 18 weeks of the study. The mean glycopyrrolate dose received by these patients after titration was 0.11 mg/kg/dose 3 times a day. The response to treatment was assessed with the mTDS. Among the 27 children who completed the study, all were noted to have significant improvement in mTDS during glycopyrrolate treatment from a mean score of 7.52 to 1.85 vs mean scores during placebo treatment of 7.44 to 6.33 ($p < 0.001$). Most patients (92.6%) experienced improved drooling by at least 4 points, which was determined to be the standard for clinical improvement by the authors. Most patients (77.8%) required titration to the maximum dose to meet this standard for clinical improvement. Twenty-five (64.1%) experienced ADEs, including behavioral changes (n = 9), constipation (n = 7), xerostomia (n = 7), and urinary retention (n = 5). However, only 7 (17.9%) patients discontinued glycopyrrolate owing to ADEs. Of these 7 patients, 4 experienced ADEs at the initial dose (mean, 0.04 mg/kg/dose), while the mean dose for the remaining 3 was 0.06 mg/kg/dose.

Zeller and colleagues[14] performed an open-label study of glycopyrrolate in 137 children aged 3 to 18 years (mean, 11 ± 4.4) with sialorrhea. A compounded formulation of glycopyrrolate 0.2-mg/mL solution was developed and started at a dose of 0.02 mg/kg enterally 3 times a day. The dose was titrated over 4 weeks to an optimal maintenance dose up to a maximum dose of 0.1 mg/kg/dose (maximum: 3 mg/dose). The mean dose received by study patients was 0.05 mg/kg/dose, administered 3 times a day. Only 7.3% of patients received the maximum dose of 0.1 mg/kg/dose. The mean treatment duration was 139.8 days. The mTDS was used to determine treatment efficacy, defined as at least a 3-point change from baseline to week 24. At week 24, 52.3% of patients experienced at least a 3-point decrease in mTDS score from baseline and were considered responders to treatment. Most of the responders (83%) received a dose between 0.02 mg/kg and 0.08 mg/kg. At study completion, 15% of patients experienced cessation of drooling. There were 122 (89%) patients with ≥1 ADE; the most common ADEs included constipation (n = 28), vomiting (n = 24), diarrhea (n = 24), pyrexia (n = 20), xerostomia (n = 15), flushing (n = 15), and nasal congestion (n = 15). The severity of ADEs was considered dose dependent with most patients receiving ≥0.1 mg/kg/day of glycopyrrolate. Four patients experienced serious ADEs attributed to glycopyrrolate, which included nystagmus (n = 1), esophageal candidiasis (n = 1), dehydration (n = 1), and gastrointestinal motility disorder (n = 1). Nineteen (13.9%) patients discontinued treatment owing to ADEs.

Zanon and colleagues[15] performed a retrospective observational study of glycopyrrolate in 21 children aged 2 to 19 years (median, 12) with sialorrhea. An extemporaneously compounded 0.5 mg/mL glycopyrrolate solution was used, and patients received glycopyrrolate 0.021 mg/kg/dose enterally every 6 to 12 hours. The mean duration of treatment was 14.3 ± 13.4 months. Two (9.5%) patients received concomitant scopolamine therapy. The DIS and DSFS were used at baseline and after completion of glycopyrrolate therapy to assess efficacy. Sixteen (76.2%) patients reported improvement in DIS and DSFS when compared with baseline ($p < 0.001$). No change in score was reported for 4 (19.0%) patients and 1 (4.8%) had a worsened DIS score. Fourteen (66.7%) patients reported decreased drooling severity, and no change was noted in the remaining 7 patients. A reduction in drooling frequency was noted in 10 (47.6%) patients, and no effect on frequency was reported in the remaining 11 patients. Nine (42.9%) had ≥1 ADEs including xerostomia (n = 5), constipation/nausea/vomiting (n = 3), nasal obstruction (n = 1), nasal bleeding (n = 1), gastroesophageal reflux (n = 1), and tachycardia (n = 1). Three (14.3%) patients discontinued therapy owing to these ADEs. It is important to note that the authors did not comment on the difference in safety and efficacy outcomes in the 2 patients receiving concomitant scopolamine.

Lovardi and colleagues[16] published a case series of 18 children younger than 3 years (median, 17 months) with severe neurologic impairment. Glycopyrrolate was initiated at a median daily dose of 0.022 mg/kg/dose (range, 0.007–0.07) administered enterally TID and titrated to a median dose of 0.023 mg/kg/dose (range, 0.007–0.09) 3 times a day. In most patients (77.8%), the initial dose was continued throughout treatment. Response to treatment was assessed according to the DIS at baseline and 1 month after treatment, with statistically significant improvement in DIS noted between periods: 89 (range, 81–100) vs 61 (range, 43–78), $p < 0.001$. Improvement in DIS was observed for 94% of patients at 1 month of treatment. At a median follow-up of 31.5 months (range, 1–69) from start of treatment, 14 (77.8%) patients continued the glycopyrrolate treatment. One (5.6%) patient developed urinary retention after 9 months of glycopyrrolate therapy, but the authors commented that this was not associated with glycopyrrolate. No ADEs were reported.

**Glycopyrrolate Summary.** All studies provided data supporting the efficacy of enteral glycopyrrolate. The overall efficacy ranged from 52% to 94% based on the different sialorrhea evaluation tools used. The dosage regimen varied with the dose ranging from 0.01 to 0.14 mg/kg/dose administered every 6 to 12 hours, although most reports used 3 times daily dosing.[12–14,16] For the dosage forms included, 2 studies included patients who received a compounded oral suspension (0.2 and 0.5 mg/mL) and 2 received glycopyrrolate tablets; in 2 reports, the dosage form was not described. Clinically significant ADEs reported in the 274 patients in these 6 studies included gastrointestinal problems (n = 93; 33.9%), xerostomia (n = 33; 12.0%), pyrexia (n = 20; 7.9%), flushing (n = 20; 7.3%), nasal congestion/obstruction (n = 16; 6.3%), urinary retention (n = 12; 4.8%), behavioral changes (n = 8; 3.2%), nystagmus (n = 1; 0.4%), esophageal candidiasis (n = 1; 0.4%), dehydration (n = 1; 0.4%), nasal bleeding (n = 1; 0.4%), pupillary dilation (n = 1; 0.4%), and tachycardia (n = 1; 0.4%).

**Scopolamine.** A total of 3 reports describe the use of scopolamine in 93 children (Table 3). A prospective, open-label, crossover study was performed by Jongerius and colleagues[17] in 45 children aged 3 to 18 years (mean, 9.5 ± 3.7) with cerebral palsy. Patients were initiated on a 1.5-mg scopolamine transdermal patch for 10 days, had a washout period of 2 to 4 weeks, then received a single BoNT-A injection in the submandibular glands and were followed up for up to 24 weeks. The scopolamine patch was applied behind the ear and changed every 3 days. Sialorrhea was assessed with DQ scores by speech therapists and VAS scoring by caregivers at baseline and on day 10 of scopolamine. For the VAS, the extreme left mark represented severe drooling and the extreme right represented no drooling. A significant decrease in DQ measurements was noted from baseline to day 10 of scopolamine with a mean ± SD difference of 17.7 ± 21.2 ($p < 0.001$). Based on the investigators' definition of efficacy (decrease in DQ by ≥50%), scopolamine was efficacious in 53% of patients. The degree of drooling decreased significantly from baseline to day 10 of scopolamine, based on caregiver VAS scores with a mean difference of −34.3 (30.9) ($p < 0.001$). Of note, there was no statistical difference in DQ or VAS scores at day 10 of scopolamine compared with 4 weeks after BoNT-A injection. ADEs were reported in 82.2% of patients, including xerostomia (n = 30; 66.7%), behavioral changes (n = 25; 55.6%), somnolence (n = 16; 35.6%), and pupillary dilation (n = 9; 20.0%). Four (8.9%) patients discontinued scopolamine early owing to ADEs.

Franco and colleagues[2] published a case series on 4 children ranging in age from 7 to 15 years and receiving scopolamine oral solution for sialorrhea. These children received a 10-mg/mL oral solution, and the weight was not reported for any of the patients. Three of the 4 patients, ages 5 to 8 years, received 10 mg (20 drops) of the oral solution every 12 hours enterally, whereas the remaining patient, age 15 years, received 17.5 mg (35 drops) every 12 hours. The authors used the DSFS at baseline and 24 hours after treatment; all patients had improvement on the DSFS after receiving treatment for 24 hours, and severity and frequency were rated as a "1" for all patients. No ADEs were reported.

Al Jeraisy and colleagues[18] evaluated 44 pediatric patients receiving scopolamine; patients included were 3 to 14 years of age with nonprogressive

neurodevelopmental disability and with failed glycopyrrolate therapy of 1-week duration. Scopolamine was initiated at 0.375 mg (1/4 patch) and titrated to the full 1.5-mg patch once daily or the maximum tolerated dose for a treatment period ≥1 year. Authors disclosed that patients were able to receive increments of patches by covering the backing of the patch, using an occlusive dressing to expose only the prescribed portion, but they did not describe what occlusive dressing was used or the exact titration method. Body-weight dosing was not provided, but the median weight was 16.8 kg. Sialorrhea was assessed via caregiver perceptions of severity of drooling, using the DSFS from baseline to ≥1 year following scopolamine initiation. In addition, caregiver satisfaction with use of scopolamine was assessed on a Likert scale of "1 to 5" to assess 4 different aspects of sialorrhea (i.e., frequency of drooling, frequency of wiping of child's mouth, frequency of bib/clothing changes, and choking/aspiration), with "1" representing "not satisfied" and "5" representing "very satisfied." They noted a significant reduction in all 4 aspects of sialorrhea assessed ($p < 0.001$). Using the DSFS, a significant reduction in the percentage of patients with very severe/severe drooling from baseline, compared with ≥1 year after scopolamine therapy, was reported: 87.5% vs 15.6% ($p < 0.001$). They also noted an absolute risk reduction of emergency department visits and hospital readmissions for management of drooling of 27.6% (95% CI, 9.4%–45.6%; $p < 0.001$) and 35.7% (95% CI, 15.7%–55.7%; $p < 0.001$), respectively. ADEs reported included tachycardia (n = 16), visual disturbances (n = 6), and urinary retention (n = 4).

***Scopolamine Summary.*** All studies provided data supporting the efficacy of scopolamine in the reduction of days with or severity of sialorrhea. There was variability in dosage forms used with 2 reports with transdermal scopolamine and 1 with an enteral solution. It is difficult to evaluate the dosing used in these reports given that 2 of the reports did not describe the weight of the patients and the differences in absorption that would occur with transdermal vs enteral administration. This information would be helpful given that younger patients with smaller size would receive a larger dose (mg/kg/dose). In addition, the study of Al Jeraisy and colleagues[18] used an initial dose of 0.375 mg or 1/4 of the 1.5-mg transdermal patch. However, the authors of this study did not describe how they titrated the dose up to the 1.5-mg patch. Clinically significant ADEs reported in the 93 patients in these 3 reports included xerostomia (n = 30; 32.3%), behavioral changes (n = 25; 26.9%), somnolence (n = 16; 17.2%), tachycardia (n = 16; 17.2%), visual disturbances (n = 13; 14.0%), urinary retention (n = 4; 4.3%), increased mouthing behaviors (n = 3; 3.2%), and removal of transdermal patch (n = 3; 3.2%).

***Trihexyphenidyl.*** Only 1 study has evaluated the use of trihexyphenidyl in pediatric patients. Carranza-del Rio and colleagues[19] retrospectively evaluated 101 patients with cerebral palsy with a mean age of 7.8 years who received trihexyphenidyl to treat sialorrhea (n = 6; 5.9%), dystonia and sialorrhea (n = 66; 65.4%), or dystonia (n = 29; 28.7%). No details were provided on the dosage form used; the mean initial dose was 0.048 mg/kg/dose every 12 hours enterally. Patients had their trihexyphenidyl titrated every 2 weeks in 10% to 20% increments until a benefit or intolerable ADEs were observed. The mean maximum dose achieved was 0.55 mg/kg/day enterally divided every 8 to 12 hours. The mean duration of treatment was 3.6 years (range, 0–10.8). They did not use a validated tool to assess sialorrhea. However, based on caregiver reports, improvement was noted in 60.4% of patients who were initiated on trihexyphenidyl for sialorrhea. ADEs were observed in 70 (69.3%) patients, and the most common ADEs included constipation (n = 43; 42.6%), urinary retention (n = 19; 18.8%), behavioral changes (n = 13; 12.9%), and xerostomia (n = 7; 6.9%). Treatment was discontinued in 8 (7.9%) patients owing to intolerable ADEs, which resolved after discontinuing trihexyphenidyl.

***Trihexyphenidyl Summary.*** This study provided some evidence for improvement for sialorrhea, but most patients developed ADEs. The application of the results of this study may be difficult to apply to clinical practice. First, the study included patients with 2 different indications, sialorrhea or dystonia. The inclusions of multiple indications could affect the dosing required, duration of treatment, and the potential for corresponding ADEs. Next, the authors did not provide details on the dosage formulation used, which could limit the clinical use of trihexyphenidyl. Last, this study is also limited in that the authors did not use a validated tool to assess sialorrhea, and efficacy was based on subjective caregiver reporting.

***Comparative Studies.*** Two reports including 200 patients compared the efficacy and safety of several agents for children with sialorrhea. Parr and colleagues[20] conducted a randomized controlled trial in children with a mean age of 4.9 years to glycopyrrolate (n = 38) vs scopolamine (n = 47) for sialorrhea management. For children randomly assigned to receive scopolamine, a 1.5-mg transdermal patch was used, and they were initiated on 0.375 mg (1/4 patch) for week 1. Their dose was titrated as tolerated on the basis of clinical response and development of ADEs to 0.75 mg (1/2 patch) for week 2; 1.125 mg (3/4 patch) for week 3; and up to 1.5 mg (full patch) for week 4; and their maximal tolerated dose was continued up to week 12. In these patients, the scopolamine patch was placed behind the ear, replaced every 3 days, and increments of the patch were achieved through manipulation of the plastic patch backing to expose only the prescribed portion. Patients who were randomly assigned to receive glycopyrrolate started therapy at 0.04 mg/kg/dose enterally every 8 hours for week 1,

using an extemporaneously prepared solution. Their dose was titrated as tolerated to 0.06 mg/kg/dose every 8 hours for week 2; 0.08 mg/kg/dose every 8 hours for week 3; and 0.1 mg/kg/dose (maximum: 2 mg/dose) every 8 hours for week 4; and their maximally tolerated dose was continued through week 12. The investigators assessed efficacy for sialorrhea by using the DIS and DSFS. The authors did not comment on the number of patients who reached the maximally tolerated dose of each agent. Both therapies led to a significant reduction from baseline with mean change in DIS of 25.0 ± 22.2 (95% CI, 1.6–15.3) for scopolamine and 26.6 ± 16.0 (95% CI, 20.5–32.7) for glycopyrrolate. They did note reduction in the DSFS at weeks 4 and 12 for scopolamine and glycopyrrolate, but statistical analyses were not performed. ADEs were noted more commonly in the scopolamine than in the glycopyrrolate group, 51% vs 18.4%; no statistical comparison was performed. The ADEs for scopolamine were "unwell" (n = 14), local skin reactions (n = 11), skin flushing/dryness (n = 8), gastrointestinal problems (n = 5), and xerostomia (n = 3). In addition, the authors noted that 4 patients repeatedly pulled off their patches. For glycopyrrolate, the ADEs included "unwell" (n = 15), gastrointestinal problems (n = 12), xerostomia (n = 7), skin flushing/dryness (n = 3), and behavioral changes (n = 1). They noted that 24 (51.1%) patients receiving scopolamine and 7 (18.4%) patients receiving glycopyrrolate had their therapy discontinued before week 12 because of ADEs. The authors noted no difference in efficacy, but based on the differences in ADEs between medications, they recommended the use of glycopyrrolate for first-line use in children with sialorrhea.

Reid and colleagues[21] conducted an observational study trial in 110 children with mean age of 8.4 ± 4.3 years and receiving trihexyphenidyl (n = 75), glycopyrrolate (n = 62), or scopolamine (n = 17) with follow-up at weeks 1, 2, 4, 13, 26, and 52. Trihexyphenidyl was the first-line option in the investigators' practice setting, but if patients discontinued one therapy, they could be initiated on another therapy and re-enrolled in the study. The dosage regimen was not disclosed; medications were titrated over 2 to 4 weeks until efficacy was achieved based on sialorrhea control or ADEs occurrence. The DIS and DSFS were used to assess efficacy. They noted improvement in DSFS from baseline to 1 week with trihexyphenidyl, glycopyrrolate, and scopolamine, in 79%, 73%, and 82% of patients, respectively. Significant improvement in DIS scores (mean ± SD) from baseline to week 1 was noted with trihexyphenidyl (59.5 ± 13.9 to 42.3 ± 15.3, $p < 0.001$), glycopyrrolate (59.9 ± 13 to 44 ± 16.7, $p < 0.001$), and scopolamine (63.8 ± 14.4 to 43.2 ± 17.8, $p = 0.023$). The time of best response based on DIS scores for each agent was a mean of 5 weeks for trihexyphenidyl, 11.5 weeks for glycopyrrolate, and 1.8 weeks for scopolamine. They noted that 66 (88%) trihexyphenidyl patients experienced ADEs; these included behavioral changes (n = 43), gastrointestinal problems (n = 29), skin changes (i.e., redness, dryness) (n = 18), urinary retention (n = 9), visual disturbances (n = 6), and swallowing difficulties (n = 5). Forty-five (68.2%) of the 66 patients who experienced ADEs discontinued trihexyphenidyl. Forty-eight (77%) patients receiving glycopyrrolate experienced ADEs including gastrointestinal problems (n = 22), behavioral changes (n = 20), urinary retention (n = 12), skin changes (n = 9), worsening seizures (n = 4), and swallowing difficulties (n = 4); 21 (43.8%) of the 48 patients who experienced ADEs discontinued glycopyrrolate. Thirteen (76.5%) patients receiving scopolamine experienced an ADE, which included behavioral changes (n = 9), skin changes (n = 8), and gastrointestinal problems (n = 4); 9 (69.2%) of the 13 patients with ADEs discontinued scopolamine therapy. Based on the overall efficacy and reported ADEs, the authors concluded that glycopyrrolate had the lowest failure rate and fewest ADEs requiring discontinuation.

***Comparative Studies Summary.*** The application of these comparative studies is limited because minimal information about dosing, specifically maximum tolerated doses, is provided. The overall efficacy for each agent reported in these 2 studies is similar to that reported in the previous studies of individual agents. Likewise, the reported rates of ADEs and discontinuation secondary to ADEs are similar to those reported in the previous studies. The investigators in both comparative studies indicate that glycopyrrolate should be considered first-line as based on efficacy and safety.

## Discussion

There is no definitive pharmacologic treatment for the management of sialorrhea in children. Riva and colleagues[3] published recommendations for drooling in children with neurological disorders, based on an expert opinion from a consensus panel. These experts noted the importance of progressive escalation of therapy from behavioral/rehabilitation therapy to oral pharmacologic therapy to more invasive procedures like administration of intraglandular BoNT-A. As noted in the findings of our systematic review, only 2 comparative studies have assessed outcomes with patients receiving glycopyrrolate, scopolamine, or trihexyphenidyl. No study has compared outcomes with SL atropine. It is difficult to make direct comparisons between the individual studies on atropine, scopolamine, trihexyphenidyl, and glycopyrrolate included in our systematic review owing to different sialorrhea scoring tools used, broad age range represented, and different or undisclosed dosage regimens and formulations.

Table 6 provides a summary of the dosage regimen and dosage forms of the anticholinergics included in the systematic review. With all 4 agents, there was variability in the dosage regimens used between the different studies, and as a result it is difficult to provide definitive

**Table 6.** Summary of Dosing Regimens, Dosage Formulations, and Adverse Drug Events Described in Reported Studies[2,6,8–21]

| Agent | Total No. of Patients | Dosing Range | Commercially Available Formulations in United States | Adverse Drug Events (Incidence in Published Studies)* |
|---|---|---|---|---|
| Atropine | 56 | 1–2 drops (0.25–0.5 mg) SL daily to every 4 hr | - 1% ophthalmic solution<br>- 0.4-mg/mL intravenous solution | Xerostomia (7.1%); behavioral changes (1.8%) |
| Glycopyrrolate | 374 | 0.02–0.14 mg/kg/dose† enterally every 8 hr‡ (max of 3 mg/dose) | - 0.2-mg/mL oral solution<br>- 1-, 1.5-, and 2-mg tablets<br>- 0.2-mg/mL intravenous solution | Gastrointestinal problems§ (34.0%); xerostomia (10.7%); behavioral changes (7.8%); urinary retention (6.4%); flushing (6.1%); pyrexia (5.3%); nasal problems¶ (4.5%); unwell (4.0%); skin changes (2.4%) |
| Scopolamine | 157 | 0.375 mg (1/4 patch) to 1.5 mg (full patch) re-applied once daily to every 3 days# | - 1-mg transdermal patch | Behavioral changes (21.7%); xerostomia (21.0%); somnolence (10.2%); tachycardia (10.2%); unwell (8.9%); visual disturbances (8.3%); local skin reactions (7.0%); gastrointestinal problems (5.7%); flushing (5.1%); skin changes (5.1%); inadvertent patch removal (4.5%); urinary retention (2.5%) |
| Trihexyphenidyl | 176 | Mean 0.048–0.2 mg/kg/dose enterally every 8–12 hr | - 0.4-mg/mL oral solution<br>- 2- and 5-mg tablets | Gastrointestinal problems (40.9%); behavioral changes (31.8%); urinary retention (15.9%); skin changes (10.2%); swallowing difficulties (2.8%); visual disturbances (3.4%); xerostomia (4.0%) |

*SL, sublingual*

* Table depicts only adverse drug events occurring in >2% of patients in published studies including in the review.
† The smallest dose reported in most studies was 0.02 mg/kg/dose; 1 report included a patient receiving 0.01 mg/kg/dose.[12]
‡ Patients in most reports received glycopyrrolate every 8 hours; 1 study reported up to 0.175 mg/kg/dose daily.[11]
§ Gastrointestinal problems are adverse drug events with symptoms including nausea, vomiting, and constipation.
¶ Nasal problems are adverse drug events with symptoms including congestion, obstruction, and bleeding.
# Most patients received transdermal scopolamine in the studies included in the systematic review.

dosing recommendations. Some of the studies included dosage formulations that are not commercially available in the United States. For instance, 1 study used scopolamine enteral drops.[2] In addition, several of the glycopyrrolate studies included an extemporaneously formulated glycopyrrolate oral suspension, and there could be variability in preparation and stability.[6,13–15,20] There is now a commercially available 0.2-mg/mL oral solution in the United States, and as a result compounded formulations should not be used. Owing to the high propensity of ADEs, clinicians should consider initiating doses at the lower end of the dosage range, because previous studies have noted increased ADEs with larger doses. For example, 1 study with glycopyrrolate noted a parallel relationship with glycopyrrolate dose ≥0.1 mg/kg/day and increased ADEs.[14] Once initiated, validated sialorrhea tools can be used to titrate the dose for efficacy while minimizing ADEs.

Several factors should be considered when selecting an agent for sialorrhea management. First, glycopyrrolate should be considered the first-line option because this was the most studied agent with 374 (n = 52.0%) of the 719 patients included in our systematic review. The authors of both of the comparator studies included in the review noted that glycopyrrolate should be considered as a first-line option owing to similar efficacy but greater tolerability than other agents.[20,21] Second, for patients whose first-line therapy initially fails, some providers may add an adjunct agent to achieve greater efficacy. Only 1 study by Zanon and colleagues[15] described 2 patients who received combination glycopyrrolate and transdermal scopolamine patches. Based on their summary, it is difficult to elucidate the potential effect of dual therapy on efficacy or safety. Caution should be used with combination agents because this would increase the potential risk of ADEs, and the authors recommend switching to a different medication upon initial medication failure rather than using combination agents. Third, for patients who are not tolerating enteral medications, providers may

need to use transdermal scopolamine or SL atropine. Alternatively, providers could switch to intravenous glycopyrrolate, though it should be noted that none of the studies included in this review evaluated intravenous glycopyrrolate. If this route of administration is considered, providers should note that the bioavailability of enteral glycopyrrolate is poor, and the dosing of intravenous glycopyrrolate is significantly smaller than for the enteral formulation.[6] Fourth, the age of the patient should also be considered. For instance, scopolamine patches should be used with caution in neonates and infants <1 year. In this population, several factors increase the topical absorption of medications, including a larger body surface to weight ratio, enhanced skin hydration, and increased capillary density in the skin when compared with older patients.[29] The enhanced absorption in young infants could increase the risk of ADEs and may result in need for more frequent re-administration of patches.

A few additional practical considerations should be explored with SL atropine and transdermal scopolamine. For the 3 reports evaluating SL atropine, the investigators used the ophthalmic (0.5% or 1%) or intravenous solution.[8–10] The 0.5% atropine ophthalmic solution (0.25 mg/drop) is not available in the United States, and if providers use the 1% solution, then the smallest possible dose is 1 drop, which equates to 0.5 mg.[6] In the 2 atropine studies evaluating sialorrhea in infants and young children, a minimum dose of 0.25 mg was used.[8,10] If using atropine 1% ophthalmic solution, consider limiting use to patients ≥25 kg to align with the weight-based dosing of 0.02 mg/kg studied by Azapagasi and colleagues.[10]

For transdermal scopolamine, there are also several considerations that should be noted when applying the findings of our systematic review. First, several of the published reports of transdermal scopolamine have used the 1.5-mg patch.[17,18,20] Although the patch contains 1.5 mg of scopolamine, in recent years the patch has been relabeled as 1 mg/3 days to better reflect that a total of 1 mg is delivered over 3 days.[30] In recent years, this formulation change has created some confusion in prescribing, dispensing, and administration of scopolamine patches with several reports provided to the Institute of Safe Medication Practices.[31] Second, the published reports describe various methods of titration with patients receiving 0.375 mg (1/4 patch), 0.75 mg (1/2 patch), or 1.5 mg (full patch) applied behind the ears and changed either once daily or every 3 days. However, Parr and colleagues[20] and Al Jeraisy and colleagues[18] were the only authors that described how they delivered a partial dose; they mentioned that the patch backing was cut to expose the prescribed portion of the patch. It is not recommended to cut the patch to reach these increments owing to the medication delivery system.[30,31] Instead, a transparent film dressing could be applied to occlude a portion of the patches to achieve the partial dose. However, providers should be mindful that this may affect the adhesive properties of the patch and increase the likelihood of its inadvertent removal. This may be evident by the fact that 4.5% of patients who received scopolamine had inadvertent removal of their patch (Table 6).

Table 6 also provides an overview of ADEs that occurred in >2% of the patients included in the reports. All 4 agents had a number of expected common anticholinergic ADEs including gastrointestinal problems (e.g., constipation), urinary retention, xerostomia, tachycardia, and vision changes. The agent with the lowest number of ADEs was SL atropine, but it is difficult to elucidate further given that this agent had the smallest sample size of patients. In both comparator studies included in this review (Table 4), glycopyrrolate was noted to have fewer ADEs that resulted in discontinuation of the agent.[20,21] In addition to the more commonly anticipated ADEs, all agents were noted to be associated with behavioral changes, reported in 1.8% to 31.8% of patients. Several reports also provided a description of ADEs that were hard to interpret. For example, one study comparing glycopyrrolate and scopolamine listed “unwell” as a general descriptor for an ADE but did not define what this meant.[20] In terms of management of ADEs, some reports noted that providers decreased the dose or discontinued the agents to manage symptoms. However, there was inconsistent information provided with each article.

## Conclusions

Based on our review, glycopyrrolate, atropine, scopolamine, and trihexyphenidyl have a potential role for sialorrhea management in children. This review does have limitations including the following: 1) most available literature reported single center, non-comparator studies; 2) different tools were used to assess sialorrhea; 3) not all studies provided weight-based dosing information; 4) some reports provided incomplete information on dosage formulations; and 5) there was variability in the description and management of ADEs within the reports.

This systematic review provides evidence for the safety and efficacy of anticholinergics for the management of sialorrhea. Based on similar efficacy, potential for fewer ADEs resulting in discontinuation, and a commercially available dosing form that can deliver a patient-specific mg/kg dose compared with other agents, many experts consider glycopyrrolate as the first-line agent. The selection of alternative agents should be based on patient-specific factors including ability to take enteral medications and age/size. Concomitant use of dual anticholinergic agents should be avoided owing to the increased risk of ADEs and lack of data to support efficacy. It is the authors’ opinion that scopolamine patches should be reserved for patients >1 year of age, and providers should use transparent film dressing over portions of a patch to deliver the

0.375- (1/4 patch) or 0.75-mg (1/2 patch) doses rather than cut the patches. In addition, the authors recommend that SL atropine 1% ophthalmic solution be reserved for patients >25 kg to achieve the recommended weight-based dosing of 0.02 mg/kg. For all agents, the smallest possible dose should be used to minimize ADEs. Dose titrations should be based on adjustments, using validated sialorrhea tools listed in Table 5 to achieve efficacy and minimize ADEs.

## Article Information

**Affiliations.** Department of Pharmacy, Clinical and Administrative Sciences (AMP, JLM, PNJ), University of Oklahoma College of Pharmacy, Oklahoma City, OK; Department of Pharmacy Practice (CVB), Philadelphia College of Pharmacy at Saint Joseph's University, Philadelphia, PA.

**Correspondence.** Peter N. Johnson, PharmD; peterjohnson@ouhsc.edu

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