

# The Effectiveness of Glycopyrronium in Drooling Management: A Scoping Review Protocol

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**Abstract:** The management of pediatric drooling presents challenges requiring tailored therapeutic approaches. This scoping review examines the efficacy and safety of glycopyrronium in addressing drooling across diverse pediatric populations. Glycopyrronium, an anticholinergic medication, inhibits salivary gland activity, offering promise in managing drooling. Clinical trials and observational studies consistently demonstrate its effectiveness, particularly in children with neurological disabilities like cerebral palsy. Notably, glycopyrronium exhibits efficacy even at lower dosages, emphasizing personalized treatment. However, potential side effects such as dry mouth and vision changes necessitate careful monitoring. Future research should explore predictors of treatment response and include diverse patient populations to optimize management strategies. Overall, glycopyrronium emerges as a valuable therapeutic option for pediatric drooling, improving quality of life for affected children. This review underscores the importance of tailored approaches and highlights the need for further research to enhance outcomes in pediatric drooling management.

**Keywords:** Glycopyrronium, Sialorrhea, Drooling, Clinical review, Clinical protocol.

## 1. INTRODUCTION

Drooling is the unintentional loss of saliva from the mouth and can pose significant challenges for the pediatric population, affecting daily life and overall well-being. Children often experience drooling due to physiological developmental issues. However, drooling in children over the age of 4 is considered a pathological condition, often caused by underlying neuromuscular pathologies. Medications, such as antipsychotics and anticholinergics, may cause excessive salivation as a side effect [1]. It is important to understand the causes of drooling in order to develop effective management approaches that are tailored to different age groups.

To manage drooling effectively, it is crucial to assess its severity and impact [2]. Different scales have been developed for this purpose, providing clinicians with standardized tools for assessment [3]. The most used scales for measuring the impact of drooling on daily quality of life are the Drooling Impact Scale (DIS) and the modified Teacher's Drooling Scale (mTDS). The DIS considers social interactions and emotional well-being, while the mTDS is specifically designed for pediatric assessment and is a nine-point scoring system assessed by parents or caregivers [4, 5].

Managing drooling requires a comprehensive strategy that involves both pharmacological and surgical approaches. Various medications, mainly belonging to the class of anticholinergics, have been utilized to address drooling [6].

Glycopyrronium, an anticholinergic medication, has gained attention for its effectiveness in managing drooling [7]. Another pharmaceutical option is Botulinum toxin injections, which temporarily paralyze the salivary glands to reduce saliva output [8]. In cases where conservative methods prove ineffective or in more severe cases, surgical interventions may be considered. Possible surgical approaches include salivary gland duct rerouting or duct ligation [9].

The choice of a specific intervention depends on the underlying condition, severity of drooling, and individual circumstances. For patients with significant motor disabilities and severe drooling, a combination of surgical and pharmacological techniques may provide the greatest benefit.

This study endeavors to rigorously assess the efficacy and safety profile of glycopyrronium among pediatric cohorts afflicted by drooling. Central to this investigation is the critical synthesis of extant evidence, aimed at elucidating the therapeutic efficacy and potential adverse effects of glycopyrronium, thereby furnishing pivotal insights to guide clinical and investigative endeavors concerning pediatric drooling management.

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## Review Questions:

The aim of this scoping review is to synthesize evidence from trials and observational studies on the benefits of glycopyrronium across the pediatric populations dealing with drooling. Therefore, the review was guided by two questions:

- Today, what therapeutics and non-therapeutics approaches are available for pediatric patients affected by drooling?
- To what extent are studies on each treatment approach applicable in pediatric population about patient characteristics, treatment procedures, key results, and timing of follow-up?
- What is the effectiveness of glycopyrronium in pediatric populations with respect to severity of drooling?

## 2. MATERIALS AND METHODS

This scoping review followed the guidelines outlined in the JBI Manual for Evidence Synthesis [10], with pre-established protocols for evaluation and data extraction.

### 2.1. Eligibility Criteria

Inclusion and exclusion criteria are reported in Table 1.

### 2.2. Type of Sources

This scoping review will consider observational studies, clinical trials, and randomized controlled studies published in English and Italian. In addition, analytical observational studies including prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies will be considered for inclusion.

In addition, systematic reviews that meet the inclusion criteria will also be considered, depending on the research question.

### 2.3. Search Strategy

We conducted a comprehensive search of MEDLINE (via PubMed) and CENTRAL (via Cochrane Library) from the inception of each database up to our search date of January 2024, with a specific focus on English-language literature related to the management of drooling using Glycopyrronium. Distinctive combinations of keywords and Medical Subject Headings (MeSH) terms were used for each database search. The search terms included ("Glycopyrronium" OR "Glycopyrrolate") AND ("Drooling" OR "Excessive salivation" OR "Sialorrhea"), among others. In addition, we examined the reference lists of previous reviews and included trials to identify any additional relevant observational studies and trials relevant to our investigation.

### 2.4. Study Selection

All identified studies will be collated and uploaded into EndNote X9.2 and duplicates removed. Following, two researchers screened the selected citations by analysing their full text against the inclusion criteria. For the reproducibility, reasons for exclusion of sources of evidence at full text that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion, or with a third reviewer/s. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping review (PRISMA-ScR) flow diagram.

**Table 1: Selected Eligibility Criteria of the Study**

Inclusion Criteria	Exclusion Criteria
Search date of January 2024	Case reports, abstracts, and reviews
Biochemical studies describing glycopyrronium	Non-English studies with incomplete data or instances of repeated publications
Pediatric subjects	
Observational studies, clinical trials, and randomized controlled studies published in English and Italian	
All diagnosis correlated to drooling	
Treatment outcomes	

## 2.5. Data Extraction

We extracted the data from PubMed and Cochrane databases. We included specific details about the first author, publication (year, journal), objectives, domain, study design, participants and sample size, outcomes and measures, and biochemical feature of glycopyrronium. If disagreements arise among the reviewers, a consensus was reached among researcher through discussion.

## 3. RESULTS

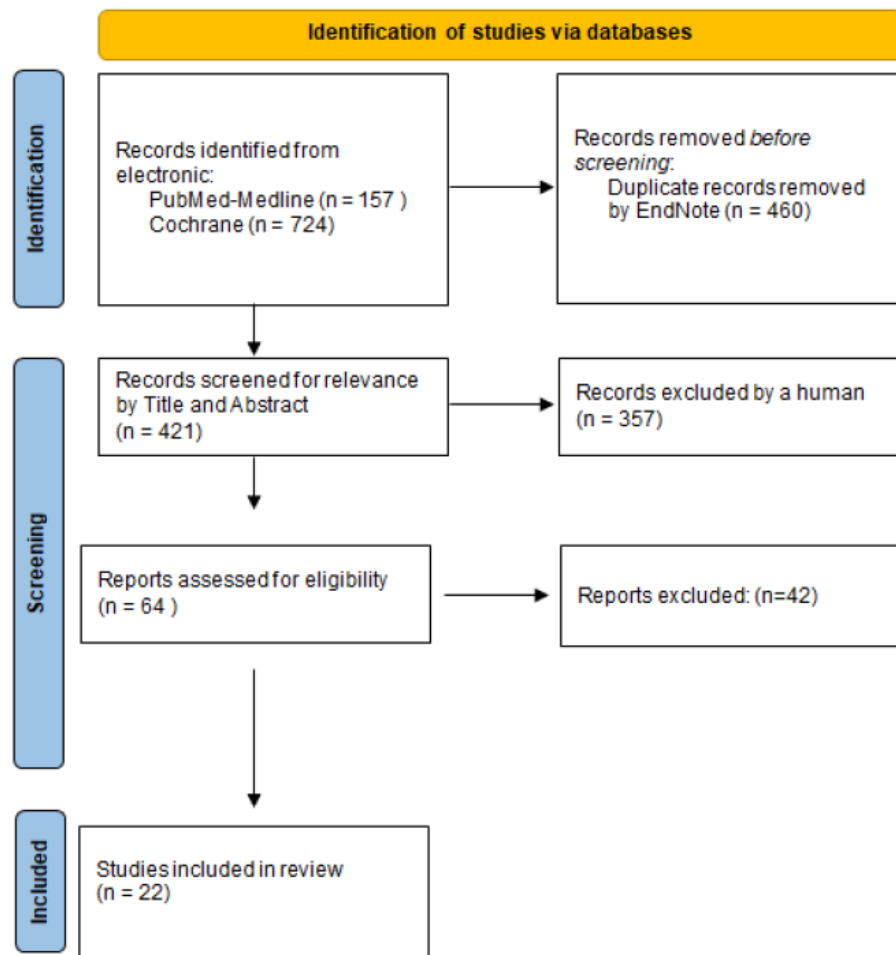
### 3.1. Search Results

A total of 881 records were recovered from MEDLINE and CENTRAL. After removing duplicate articles via EndNote 421 articles were screened using titles and abstracts, and 64 articles were selected for full-text evaluation. According to the inclusion and exclusion criteria, 22 articles were included. A PRISMA

flowchart is presented in Figure 1. Of these 8 articles were relevant for describing the biochemical features of glycopyrronium, 11 for clinical efficacy of glycopyrronium, of which 7 for evidence from clinical trials and 4 observational studies that tested the efficacy of glycopyrronium, and 3 papers for reporting information available about side effects.

#### 3.1.1. Glycopyrronium: Biochemical Features

Glycopyrronium, also known as glycopyrrolate, is an anticholinergic agent that results in a racemic mixture of two enantiomers. Its chemical composition consists of a quaternary ammonium compound containing a pyrrolidinium group [11]. The drug is available in various formulations to meet individual administration needs [11]. An oral solution of glycopyrronium is indicated for the treatment of excessive drooling associated with neurologic conditions in children [2, 6, 7, 12]. As an anticholinergic agent with an oral bioavailability, glycopyrronium inhibits acetylcholine



**Figure 1:** Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping review (PRISMA-ScR) flow diagram.

muscarinic receptors located on salivary glands, resulting in a decreased salivation rate by preventing the stimulation of these receptors [13-15]. Glycopyrronium demonstrated binding affinity to all five muscarinic acetylcholine (ACh) receptor (M1 to M5) subtypes with the highest affinity observed for the M1 (pKi = 9.60) and M3 subtypes (pKi = 9.59) [16]. Orally administered glycopyrronium was reported to have a poor absorption, with only 1.9% of the dose found in the stomach and 6.4% in the small intestine at 3 hours post-dose [17]. The bioavailability of glycopyrronium is lower in children and varies with age [12, 16]. Glycopyrronium is metabolized to the inactive M9 metabolite, which together constitutes the majority of plasma exposure [16]. The mean elimination half-life varies depending on the route of administration: 2.8 hours after oral administration, 6.2 hours after intravenous administration, and 33 to 53 hours after inhalation. Additionally, the drug and its metabolites are mostly excreted through urine [16]. The optimal dosage of glycopyrronium for managing drooling varies based on individual patient characteristics, such as age, weight, and the severity of drooling. Consulting a healthcare professional is crucial to determine the appropriate dosage regimen, as treatment is typically individualized. It is recommended to start with a low dose and gradually increase it to identify the minimum effective dose with acceptable side effects. Regular monitoring and adjustments may be necessary to optimize the therapeutic response. In accordance with FDA instructions, the initial dose of 0.02 mg/kg can be administered three times daily and titrated in increments of 0.02 mg/kg every 5-7 days, based on therapeutic response and adverse reactions. The maximum recommended dose is 0.1 mg/kg three times daily, not to exceed 1.5-3 mg per dose based on weight. It is recommended to administer the medication at least one hour before or two hours after meals [18].

### **3.1.2. Clinical Efficacy**

Since 1996, several randomized clinical trials and observational studies have consistently demonstrated the efficacy of glycopyrronium in the pediatric population (Table 1). This body of research highlights a significant commitment to comprehending and addressing the challenges posed by drooling in pediatric patients, particularly those grappling with the complexities of neurological disorders. Clinical investigations into the effectiveness of glycopyrronium's in the pediatric population have focused specifically on children affected by cerebral palsy, a condition often associated with drooling. This study presents the key findings from pivotal

randomized trials and observational studies, shedding light on the evolving landscape of clinical evidence supporting the use of glycopyrronium in pediatric drooling management.

### **3.1.3. Clinical Trial**

Following the Consensus Statement of the Consortium on Drooling, Blasco was the first to publish the results of an open-label study conducted on 40 children and young adults with motor and cognitive disabilities who were treated with glycopyrronium. The follow-up period ranged from 8 months to 4 years, during which the drug dosage varied between 0.01 and 0.82 mg/kg per day with a median dose of 0.09 mg/kg/day. Thirty-six patients (95%) showed a reduction in drooling. However, the severity of drooling was quantified using qualitative scales, and the results were based merely on subjective reports from parents [19].

The subsequent open-label study conducted by Stern involved 24 children and young adults, with an average age of 13.4 years. Patients received a daily dose ranging from 0.04 to 0.1 mg/kg, with a maximum of 0.175 mg/kg administered once a day over a period ranging from 5 weeks to 28 months. Caregivers completed a questionnaire at the end of the trial to assess the impact on drooling severity using a 5-point scale and drooling frequency on a 4-point scale. The results indicated sustained effectiveness of the therapy with minimal adverse effects [20].

Mier *et al.* conducted a randomized, placebo-controlled crossover trial involving 39 pediatric patients with developmental disabilities and sialorrhea. The study had an 8-week treatment period, separated by a one-week washout interval. Glycopyrronium doses were weight-dependent. Patients weighing under 30 kg commenced with 0.6 mg/dose and escalated weekly up to 2.4 mg. Patients weighing over 30 kg started at 1.2 mg and escalated up to 3 mg thrice daily. The study evaluated drooling severity using a 9-point drooling scale, as assessed by caregivers. The results showed a significant reduction in drooling severity of at least 4 points in the glycopyrronium group compared to the placebo group. The response exhibited a linear correlation with drug dosage, indicating a more favorable outcome with higher doses. The average highest tolerated dose of glycopyrronium was 0.11 mg/kg/dose. Interestingly, 22% of patients demonstrated optimal responses at lower doses, with one case achieving the best results at the initial dose. Although not supported by statistical analysis, the authors suggested the potential for a two-dose

**Table 1: Clinical Trials and Observational Studies Assessing the Efficacy of Glycopyrronium for the Treatment of Drooling**

Author	Study Design	Population Sample	Dose	Assessment Scale	Results
Blasco and Stansbury, 1996 [19]	Opel-label trial	40	0.01-0.82 mg/kg/day (median dose 0.09 mg/kg/day)	Qualitative scales with a subjective reports from parents	36 patients (95%) showed a reduction in drooling
Stern, 1997 [20]	Opel-label trial	24	0.04-0.1 mg/kg/day	Qualitative scales on drooling impact and frequency	Sustained effectiveness of the therapy
Bachrach <i>et al.</i> , 1998 [25]	Retrospective observational study	41	0,01-0,14 mg/kg/dose thrice a day (Median dose 0,051 mg/kg thrice a day)	Subjective five-point rating scale	Glycopyrronium improved drooling in 95% patients
Mier <i>et al.</i> , 2000 [5]	Randomized placebo-controlled trial	39	< 30 kg: 0.6 mg/dose weekly titrated up to 2.4 mg/dose thrice daily >30 kg: 1.2 mg/dose weekly titrated up to 3 mg/dose thrice daily	9-point combined qualitative-quantitative scale	Glycopyrronium: Baseline drooling score improved from 7.52 to 1.85 Placebo: Baseline drooling score improved slightly from 7.44 to 6.33
Zeller <i>et al.</i> , 2012 [21]	Randomized placebo-controlled trial	38	0.02 mg/kg thrice daily, weekly titrated up to 0.1 mg/kg or 3 mg thrice daily	mTDS	Reduction of at least 3 points in the mTDS achieved by 74% of patients in the controlled arm compared to 18% in the placebo group
Zeller <i>et al.</i> , 2012 [22]	Opel-label trial	137	0,02 mg/kg thrice daily, weekly titrated up to 0,1 mg/kg/dose	mTDS	52.3% of patients responded positively, showing a minimum three-point decrease in the mTDS from baseline
Parr <i>et al.</i> , 2018 [23]	Randomized clinical trial	90	Group 1: 0.04 mg/kg/dose. titrated up to 0.1 mg/kg not exceeding 2 mg/dose Group 2: Hyoscine	DIS, DSFS	Both hyoscine and glycopyrronium led to statistically significant reductions of drooling, however hyoscine patches were less tolerated and were associated with higher discontinuation rates
Reid <i>et al.</i> , 2019 [7]	Cohort study	110	Group 1: Benzhexol Group 2: Glycopyrronium Group 3: Scopolamine	DIS	85% of patients experienced a reduction in DIS scores with glycopyrronium, compared to 75% with benzhexol and 65% with scopolamine
Zanon <i>et al.</i> , 2021 [26]	Retrospective observational study	21	0,021 mg/kg	DIS, DSFS	72.6% of patients reported a significant reduction in drooling
Lovardi <i>et al.</i> , 2022 [12]	Retrospective observational study	18	median starting daily dose was 0.065 mg/kg/die, titrated up to 0,07 mg/kg/die in three times a day	DIS	Improvement of drooling in 94% of patients
Fayoux <i>et al.</i> , 2024 [24]	Randomized placebo-controlled trial	87	0.013 mg/kg/dose, titrated up to 0.64 mg/kg/dose not exceeding 2 mg/dose	DIS	Glycopyrronium significantly improved drooling, with a rate of good responders of 52.3% vs 16.3% in the placebo group

administration, omitting the evening dose, which some caregivers considered less necessary [5].

Zeller *et al.* conducted a randomized placebo-controlled trial to evaluate the safety and efficacy of

glycopyrronium in treating severe sialorrhea in 38 patients with neurological disabilities. Patients were treated with glycopyrronium for an average of 55.4 days, starting with an initial dose of 0.02 mg/kg administered three times a day. The dose was

increased weekly by 0.02 mg/kg, and a maximum dose of 0.1 mg/kg or 3 mg. One notable strength of this study was the use of a standardized tool to evaluate the drug's efficacy. The primary endpoint was defined as a reduction of at least 3 points on the mTDS, which was achieved by 74% of patients in the controlled arm compared to 18% in the placebo group [21].

The study's positive findings were validated in a subsequent multicenter open-label extension study. This study included an expanded cohort of 137 patients who received glycopyrronium treatment for 24 weeks. Notably, 52% of patients achieved the primary endpoint. The majority of caregivers perceived the glycopyrronium treatment to be advantageous [22].

In a recent randomized trial, the efficacy of hyoscine patches was compared with that of glycopyrronium solution in a cohort of 90 patients with neurodisabilities. The glycopyrronium treatment followed a similar protocol to previous studies, including an initial 4-week titration period starting at 0.04 mg/kg/dose. Subsequently, a steady dose was maintained for 14 weeks, with a maximum dose of 0.1 mg/kg not exceeding 2 mg/dose. The study assessed outcomes based on DIS at 4 weeks of treatment and changes in DIS and DSFS scores at baseline, week 4, and week 12. The average reduction in the 4-week DIS score was similar between the two groups, with a mean reduction of 25 points. Secondary outcomes also showed sustained improvement in drooling after 14 weeks of treatment. Furthermore, the scores on the Treatment Satisfaction Questionnaire for Medication (TSQM) were similar between the hyoscine and glycopyrronium groups at both week 4 and week 12 [23].

Earlier this year, a randomised, double-blind, placebo-controlled trial was conducted to investigate the efficacy, safety, and impact on quality of life of an oral formulation of 320 µg/mL glycopyrronium designed for children. The study analysed 87 patients. The primary endpoint was the change in total DIS score from baseline to day 84. The results showed a significant improvement with 320 µg/mL glycopyrronium compared to placebo (median [quartile 1, quartile 3] -29.5 [-44.5, 0] vs -1 [-16, 5];  $p < 0.001$ ). This effect was also observed at day 28 (median -25 vs -2;  $p < 0.01$ ). At day 84, there was a reduction in the number of bibs/clothes used per day with glycopyrronium compared to placebo (median -2 vs 0;  $p < 0.01$ ). In children with neurodisabilities and severe sialorrhoea, the specifically designed paediatric formulation of 320 µg/mL glycopyrronium significantly

improved drooling, reduced its impact on the daily life of the child and their families/caregivers, and was well tolerated [24].

### 3.1.4. Observational Studies

Observational studies have also contributed to the assessment of glycopyrronium efficacy in the paediatric population with sialorrhoea, providing valuable insights beyond controlled trials.

Bachrach and colleagues presented preliminary data from 37 patients undergoing glycopyrronium treatment. A notable 95% of the patients exhibited a favorable response to the treatment, as indicated by a reduction on a severity scale consisting of 5 points [25].

Reid and colleagues examined the efficacy of three different anticholinergic agents: benzhexol hydrochloride, glycopyrronium, and scopolamine, in a cohort of 90 patients. Follow-up data was collected for up to 52 weeks from patients recruitment or until drug discontinuation. All anticholinergic agents showed a positive response in the DIS as early as one week, with the optimal response observed between 5 to 11 weeks, depending on the specific drug. In summary, the study found that glycopyrronium was more effective than benzhexol hydrochloride and scopolamine in reducing DIS scores. Specifically, 85% of patients experienced a reduction in DIS scores with glycopyrronium, compared to 75% with benzhexol hydrochloride and 65% with scopolamine [7].

Galenic formulations of glycopyrronium have been shown to be effective in managing sialorrhoea, as reported by Zanon *et al.* According to their study, which involved 21 patients undergoing glycopyrronium therapy for 14 months, 76% demonstrated a significant improvement in symptom severity and quality of life. To assess the clinical severity of drooling and its impact on the quality of life, two specific questionnaires, the DIS and the DSFS, were administered [26].

In a recent investigation by Lovardi *et al.*, the efficacy of glycopyrronium was systematically evaluated in a pediatric cohort under the age of 3. The initial dosage, set at 0.065 mg/kg/dose, demonstrated clinical efficacy in 77% of cases. The study outcomes showed that 94% of the 18 subjects had a favorable response to treatment, as quantified by the DIS after one month [12].

### 3.1.5. Side Effects

While glycopyrronium can improve the quality of life for many individuals [2, 25], it is important to be aware

of potential side effects associated with its use. One of the most common side effects of glycopyrronium is dry mouth, also known as xerostomia. This occurs due to decreased salivary gland activity caused by the medication's inhibition of acetylcholine. Patients may experience xerostomia, a condition characterized by a dry mouth sensation and reduced saliva production. This can result in difficulties with chewing, swallowing, and speaking [27]. Further, while taking glycopyrronium, some individuals may experience changes in vision, such as blurred vision, due to the drug's anti-muscarinic effects [15]. Additionally, glycopyrronium can interfere with bladder function by reducing the frequency of urination and urine volume. This agent can also cause various gastrointestinal symptoms, including constipation, nausea, vomiting, and abdominal discomfort. In rare cases, glycopyrronium may cause hyperthermia due to impaired sweating, and allergic reactions such as hives, itching, rash, swelling, dizziness, or difficulty breathing can occur [27].

#### 4. DISCUSSION

The management of drooling in pediatric populations poses unique challenges, necessitating a comprehensive understanding of its etiology and effective therapeutic interventions. This scoping review synthesized evidence from trials and observational studies on the benefits of glycopyrronium in pediatric patients dealing with drooling. The findings underscore the significant impact of drooling on children's daily lives and the importance of tailored management strategies.

Glycopyrronium, an anticholinergic medication, has emerged as a promising therapeutic option for managing drooling in pediatric patients. Its mechanism of action involves inhibiting acetylcholine muscarinic receptors on salivary glands, thereby reducing salivation rates. Because of its chemical structure, glycopyrronium is unable to penetrate the blood-brain barrier. Consequently, it does not exert effects on the central nervous system and exhibits a prolonged duration of action.

The efficacy of glycopyrronium has been demonstrated in numerous clinical trials and observational studies, consistently showing reductions in drooling severity and improvements in quality of life for affected children.

Clinical trials and observational studies consistently demonstrate the effectiveness of glycopyrronium

treatment in managing drooling across diverse age groups, including children under the age of 3. It is a safe and efficacious therapeutic option for paediatric patients. Notably, the majority of clinical and observational studies have predominantly involved patients with cerebral palsy, showing significant improvements with glycopyrronium therapy. However, these findings are limited in their representation of broader population with diverse neuropsychological comorbidities. Therefore, larger studies are necessary to enable meaningful comparisons of efficacy under various pathological conditions.

The optimal dosage of glycopyrronium varies based on individual patient characteristics, such as age, weight, and the severity of drooling. The initial prescription of glycopyrronium oral solution is recommended at 0.02 mg/kg three times daily, with gradual titration based on therapeutic response and adverse reactions. Regular monitoring and adjustments may be necessary to optimize treatment outcomes and minimize side effects. This approach emphasizes a personalized treatment plan. However, both clinical trials and observational studies have demonstrated noteworthy efficacy even at lower dosages. This observation is particularly important considering the potential side effects of the therapy. The identification of positive effects at lower doses, although less pronounced, can still greatly improve the patient's quality of life. Indeed, it is important to note that this patient group, therapy side effects may be difficult to detect due to their communication difficulties [28].

Indeed, while glycopyrronium has shown efficacy in managing drooling, it is essential to acknowledge potential side effects associated with its use. Common adverse effects include dry mouth (xerostomia), changes in vision, gastrointestinal symptoms, and interference with bladder function. Hyperthermia and allergic reactions are rare but possible adverse events that require prompt medical attention if observed.

Additionally, future studies should play attention to predictors of efficacy. Currently, therapy selection depends on the clinician's and specialized center's experience, rather than objective data. This is due to the challenges in collecting standardized results. Identifying prognostic predictors could better guide patients towards the most effective therapy and, where necessary, potential synergies with surgical interventions.

In conclusion, glycopyrronium represents a valuable therapeutic option for managing drooling in pediatric

patients, particularly those with neurological disabilities. Observational studies have complemented clinical trials by providing real-world insights into the long-term effectiveness of glycopyrronium in pediatric populations, further supporting the use of glycopyrronium as a safe and effective treatment option for pediatric drooling.

While side effects are possible, glycopyrronium is generally well-tolerated when administered at appropriate dosages. Future research should focus on optimizing treatment protocols, exploring long-term outcomes, and identifying potential predictors of treatment response to further enhance the management of pediatric drooling.

## 5. CONCLUSIONS

The evidence presented in this scoping review highlights the efficacy of glycopyrronium in managing paediatric drooling across different age groups. The findings underscore the significant impact of drooling on children's daily lives and highlight the importance of tailored management strategies.

Glycopyrronium has demonstrated consistent efficacy in reducing drooling severity and improving quality of life outcomes across various patient populations, including those with neurological disabilities. While potential side effects exist, glycopyrronium is generally well-tolerated when administered at appropriate dosages.

Future research should include younger patients and those with varying neuropsychological comorbidities to gain a more nuanced understanding of glycopyrronium's potential. In the pursuit of personalized and optimized treatment approaches, it is important to recognize nuanced responses at lower dosages and explore predictive factors. This will shape the future landscape of paediatric drooling management, offering improved outcomes and an enhanced quality of life for patients.

## AUTHOR CONTRIBUTIONS

Conceptualization, GBD and AV.; analysis, ADL and GBD; writing-original draft preparation, GBD and ADL.; writing-review and editing, GBD, MGP and VO; supervision, AV and PS; All authors have read and agreed to the published version of the manuscript.

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## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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