Surrey and North West Sussex Area Prescribing Clinical Network

Surrey (East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG & Surrey Heath), Crawley CCG and Horsham & Mid-Sussex CCG

Title of paper:	**The Pharmacological Management of Hypersalivation in Children and Adults**		
Meeting date:	2nd October 2019		
Agenda item:	To be completed by PCN secretary	**Attachment(s):**	Indicate number of attachments
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Paper type	Updated guidelines		
For:	For discussion/endorsement		

Executive Summary:

The aim of this paper is to provide an updated version of the current guidelines on the Pharmacological Management of Hypersalivation in Children and Adults

Summary:

APC is asked to:

Endorse the guidelines for local adaptation and add individual drug recommendations onto the Surrey PAD.

Accompanying papers (please list):

Evidence review - Glycopyrronium for hy

Pan Mersey APC.pdf

Acknowledgement to: Pan Mersey Area Prescribing Committee

Evidence Review for the Pharmacological Management of Hypersalivation in Children and Adults

INTRODUCTION

Hypersalivation is the excessive production of saliva and may result in involuntary loss of saliva from the mouth, i.e. drooling or sialorrhoea. The pathophysiology of sialorrhoea is often not clear and in some cases, particularly neurological disorders such as cerebral palsy or Parkinson's disease, it is thought to be due to a poor swallowing mechanism and an inadequate rate of swallowing rather than increased saliva production.

First-line management of drooling should be directed at the cause, which may be multifactorial and patient-specific. Often this will require a multidisciplinary team approach, using a combination of treatments. Several options are available, including practical aids, speech therapy, behaviour therapy, physiotherapy, radiotherapy, surgery and medication. Each option has varying degrees of acceptability and success.

Drug therapy is aimed at decreasing the volume of saliva without addressing impaired swallowing. Salivation is primarily mediated by parasympathetic innervation of the salivary glands and historically, a range of drugs with antimuscarinic actions has been used in an attempt to control hypersalivation.

Blockade of cholinergic muscarinic receptors reduces salivary volume, but a lack of selectivity may result in widespread and undesirable central and peripheral effects, including drowsiness, restlessness, irritability, urinary retention, constipation, and flushing

PURPOSE

To provide Primary Care guidance on the pharmacological management of hypersalivation in children and adults.

SCOPE

This guideline provides recommendations on the medical management of adults with Parkinson's disease, children with neurodisability, cerebral palsy, long term ventilation with drooling, and drug induced hypersalivation.

It does not cover:

- **Recommendation or "preference" of one treatment over another**
- **Specialists medications or medicines regimes supplied from secondary care**
- **Non-pharmacological options. It is assumed non-pharmacological options will be exhausted initially.**
- **End of life or palliative care prescribing**
- **Botulinum Toxin or radiotherapy administered by specialist services**
- **Other non antimuscarinic drugs mentioned in case reports**
- **Treatments intended to "thin" secretions (mucolytics)**

GUIDANCE

Prescribers should use this guidance in conjunction with the medication's summary of product characteristics (SPC), British National Formulary (BNF) and NICE clinical guidelines.

ACKNOWLEDGEMENTS
This Guideline has been adopted from the Pan Mersey Area Prescribing Committee Pharmacological Management of Hypersalivation in Children and Adults

Background

The NICE guideline, Cerebral palsy in under 25s: assessment and management NG62, January 2017 recommends using anticholinergic treatments for hypersalivation, but does not choose a preference for one anticholinergic treatment over another.
A summary of NICE NG62 is included below:

1.11 Managing saliva control

1.11.1 Assess factors that may affect drooling in children and young people with cerebral palsy, such as positioning, medication history, reflux and dental issues, before starting drug therapy.

1.11.2 To reduce the severity and frequency of drooling in children and young people with cerebral palsy, consider the use of anticholinergic medication:

- *glycopyrronium bromide[3] (oral or by enteral tube)* ***or***
- *transdermal hyoscine hydrobromide[4]****or***
- *trihexyphenidyl hydrochloride[5] for children with dyskinetic cerebral palsy, but only with input from specialist services.*

When choosing which medicine to use, take into account the preferences of the child or young person and their parents or carers, and the age range and indication covered by the marketing authorisations.

1.11.3 Regularly review the effectiveness, tolerability and side effects of all drug treatments used for saliva control.
1.11.4 Refer the child or young person to a specialist service if the anticholinergic drug treatments outlined in recommendations 1.11.2 and 1.11.3 are contraindicated, not tolerated or not effective, to consider other treatments for saliva control.
1.11.5 Consider specialist assessment and use of botulinum toxin A injections[6] to the salivary glands with ultrasound guidance to reduce the severity and frequency of drooling in children and young people with cerebral palsy if anticholinergic drugs provide insufficient benefit or are not tolerated.
1.11.6 Advise children and young people and their parents or carers that high-dose botulinum toxin A injection[6] to the salivary glands can rarely cause swallowing difficulties, and so they should return to hospital immediately if breathing or swallowing difficulties occur.
1.11.7 Consider referring young people for a surgical opinion, after an assessment confirming clinically safe swallow, if there is:

- *a potential need for lifelong drug treatment* ***or***
- *insufficient benefit or non-tolerance of anticholinergic drugs and botulinum toxin A injections.*

The NICE guideline, Motor neurone disease: assessment and management NG42, February 2016 recommends considering the use of anticholinergic medication first line for the excessive drooling of saliva (sialorrhoea) patients with motor neurone disease. The guidance also recommends glycopyrronium as first line treatment for those MND patients with

cognitive impairment, because it has fewer central nervous system side effects side effects than other oral anticholinergic medications. A summary of NICE NG42 is included below:

Saliva problems

1.8.10 If a person with MND has problems with saliva, assess the volume and viscosity of the saliva and the person's respiratory function, swallowing, diet, posture and oral care. ***[new 2016]***

1.8.11 If a person with MND has problems with drooling of saliva (sialorrhoea), provide advice on swallowing, diet, posture, positioning, oral care and suctioning. ***[new 2016]***

1.8.12 Consider a trial of antimuscarinic medicine[1] as the first-line treatment for sialorrhoea in people with MND. ***[new 2016]***

1.8.13 Consider glycopyrrolate[1] as the first-line treatment for sialorrhoea in people with MND who have cognitive impairment, because it has fewer central nervous system side effects. ***[new 2016]***

1.8.14 If first-line treatment for sialorrhoea is not effective, not tolerated or contraindicated, consider referral to a specialist service for Botulinum toxin A[1]. ***[new 2016]***

1.8.15 If a person with MND has thick, tenacious saliva:

- *review all current medicines, especially any treatments for sialorrhoea*
- *provide advice on swallowing, diet, posture, positioning, oral care, suctioning and hydration*
- *consider treatment with humidification, nebulisers and carbocisteine.* ***[new 2016]***

The NICE guideline, Parkinson's disease in adults NG71, July 2017 recommends the use of glycopyrronium as a first line option in the treatment of drooling in Parkinson's disease. A summary of NICE NG71 is included below:

Drooling of saliva

1.5.26 Only consider pharmacological management for drooling of saliva in people with Parkinson's disease if non-pharmacological management (for example, speech and language therapy; see recommendation 1.7.8) is not available or has not been effective. ***[2017]***

1.5.27 Consider glycopyrronium bromide[8] to manage drooling of saliva in people with Parkinson's disease. ***[2017]***

1.5.28 If treatment for drooling of saliva with glycopyrronium bromide[8] is not effective, not tolerated or contraindicated (for example, in people with cognitive impairment, hallucinations or delusions, or a history of adverse effects following anticholinergic treatment), consider referral to a specialist service for botulinum toxin A[8]. ***[2017]***

1.5.29 Only consider anticholinergic medicines other than glycopyrronium bromide[8] to manage drooling of saliva in people with Parkinson's disease if their risk of cognitive adverse effects is thought to be minimal. Use topical preparations if possible (for example, atropine) to reduce the risk of adverse events. ***[2017]***

Cost

Drug	Typical Doses[a]	Cost per 28 days (exc VAT)[b]
Amitriptyline tablets[c]	*50mg at night*	28 tablets = £2.81
Atropine 1% eye drops[c]	*2 drops 4 times daily*	10ml = £131.87 minims 20 = £15.10
Glycopyrronium bromide oral solution 400micrograms/mL (Sialanar® 320 micrograms/ml of glycopyrronium)	*1,600 micrograms (4ml) 3 times daily*	250ml = £320.00 360ml = £460.80
Glycopyrronium bromide tablets (NB—not to be routinely used due to cost)[c]	*1mg 3 times daily*	30 tablets = £230.71 84 tablets = £645.99
Glycopyrronium bromide 1mg/5ml oral solution sugar free (Colonis®)	*1mg 3 times daily*	150ml = £91.00 450ml = £273.00
Hyoscine hydrobromide 150micrograms tablets[c]	*150 micrograms 3 times daily*	84 tablets = £12.88
Hyoscine hydrobromide 300micrograms tablets[c]	*300 micrograms 3 times daily*	84 tablets = £12.88
Hyoscine hydrobromide 100 microgram/mL oral solution (Special)[c]	*300 micrograms 3 times daily*	100ml= £32.14 270ml =£86.78
Hyoscine patch 1.5mg (Scopoderm®)[c]	*1 patch every 72 hours*	10 patches = £128.70
Ipratropium bromide nasal spray 0.03% ('off-label')[c]	*1-2 sprays twice daily*	180 dose = £6.54
Ipratropium bromide CFC free inhaler 20micrograms / actuation ('off-label')[c]	*1-2 sprays 4 times daily*	200 dose = £5.56
Procyclidine 5mg tablets	*5mg daily*	28 tablets = £2.94
Procyclidine 5mg/5ml oral solution sugar free	*5mg daily*	150ml = £21.66

Trihexyphenidyl 5mg tablets	*5mg 3 times daily*	84 tablets = £17.91
Trihexyphenidyl 5mg/5ml oral solution	*5mg 3 times daily*	200ml = £26.40 450ml =£59.40

[a] doses shown do not represent the full range that can be used and do not imply therapeutic equivalence

[b] Costs based on Drug Tariff, April 2019; excluding VAT

[c] Not licensed for the treatment of sialorrhoea; use would be off-label.

CCG Spend in 2018/19

See below the prescribing costs for oral Glycopyrronium bromide (all formulations, all indications, and all patient groups) in each CCG Mar 18 – Mar 19.

Commissioner	Actual Cost	Cost per 100,000 pop.
EAST SURREY CCG	£86,887.09	£47,292.69
GUILDFORD AND WAVERLEY CCG	£54,573.70	£24,137.29
NORTH WEST SURREY CCG	£34,143.66	£9,154.01
SURREY DOWNS CCG	£108,360.11	£35,194.88
SURREY HEATH CCG	£5,585.55	£5,769.42
CRAWLEY	£40,632.85	£30,449.82
HORSHAM AND MID SUSSEX	£123,714.27	£51,263.95

Evidence

On 5th April 2017 the PCN members noted the evidence summary from NICE ES5 - Severe sialorrhoea (drooling) in children and young people with chronic neurological disorders: oral glycopyrronium bromide, published 14 February 2017, and the PCN recommended Sialanar® glycopyrronium 320 micrograms /ml oral solution for the treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders.

A summary of NICE ES5 is included below:

A literature search was conducted by NICE which identified 62 references (see search strategy for full details). These references were screened using their titles and abstracts and 11 references were obtained and assessed for relevance

Two randomised controlled trials (RCTs) identified from the search (Mier et al. 2000 and Zeller et al. 2012a) were included in this evidence summary.

- *This evidence summary discusses 2 small randomised controlled trials (RCTs) that compared glycopyrronium bromide with placebo for the treatment of severe sialorrhoea in children and young people with chronic neurological conditions. The majority of participants had cerebral palsy.*
- *In both RCTs, participants treated with glycopyrronium bromide had statistically significantly improved drooling after 8 weeks, (measured using the modified Teacher's Drooling Scale [mTDS]), compared with placebo.*
- *Adverse effects were common with glycopyrronium bromide, mostly due to its anticholinergic action. The most commonly reported adverse effects include dry mouth, constipation, urinary retention, reduced bronchial secretions and flushing. The SPC advises that glycopyrronium bromide can cause thickening of secretions, which may increase the risk of respiratory infection and pneumonia. Glycopyrronium bromide should be used with caution in people with heart problems due to its*

potential increase in heart rate, blood pressure and rhythm disorders (SPC: glycopyrronium).

- *There is a lack of long-term safety data for glycopyrronium bromide, and the SPC recommends that the total treatment duration should be kept as short as possible.*
- *It is not possible to determine the relative effectiveness of glycopyrronium bromide compared with other treatments for severe sialorrhoea because glycopyrronium has only been compared to placebo. Because Sialanar is not bioequivalent to other formulations of glycopyrronium bromide, switching to Sialanar should only be conducted under supervision to ensure that efficacy and side effects are balanced. The effectiveness of glycopyrronium bromide should be balanced against the adverse effects associated with treatment.*

The remaining 8 references were excluded. These are listed under excluded studies in the NICE paper with reasons for their exclusion.

Comment: There are no randomised controlled comparative studies, so prescribers should consider evidence for effectiveness, potential side effects and available routes of administration when choosing between them. The absence of long-term studies means that there is no evidence for continued effectiveness or safety if used continuously for long periods.

Hypersalivation – what drug treatment options are available? Prepared by the UK Medicines Information (UKMi) pharmacists for NHS healthcare professionals found the following:

Answer

- *There are various drug treatments (see below), which have been used in the management of hypersalivation, and some are discussed in more detail in additional UKMi Q&A documents. The majority are not licensed in the UK for this indication. However, one brand of glycopyrronium oral solution (Sialanar®) is licensed for "the treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders" (9). Procyclidine (injection, tablets and oral solution) and trihexyphenidyl hydrochloride (tablets) are licensed for the treatment of the symptoms of Parkinson's disease, which include excessive salivation, or sialorrhoea/drooling (10-13).*

- *1.* ***Antimuscarinic Drugs***

- *Amitriptyline*
- *Atropine*
- *Benzatropine* (benztropine)*
- *Glycopyrronium bromide (glycopyrrolate)*
- *Hyoscine (scopolamine) hydrobromide*
- *Ipratropium bromide*
- *Procyclidine*
- *Trihexyphenidyl hydrochloride (benzhexol hydrochloride)*

- ***2. Botulinum Toxins***

- ***3. Other drugs***
- *Anti-reflux medications (e.g. ranitidine and cisapride*)*
- *Modafinil*
- *Piracetam*

- *Rotigotine*

- ** Drugs that are no longer marketed in the UK.*

- *There are few, if any, good quality studies (e.g. randomised controlled trials) to compare the different therapeutic options available for the management of sialorrhoea (4). For further discussion on the weaknesses in evidence refer to the 'Limitations' section below.*

- *An in-depth systematic review of the medical literature investigating the efficacy of anticholinergic drugs to treat drooling in children with multiple disabilities found that, because of the methodological drawbacks within the studies and the small number of reports, no general conclusion could be reached and a meta-analysis could not be performed (14). The authors concluded that there was some evidence that at least three anticholinergic drugs (benzatropine, glycopyrronium and trihexyphenidyl hydrochloride) are effective in the treatment of drooling in this patient group. However, it could not be concluded that one anticholinergic drug was preferable to others.*

- *A Cochrane review examining interventions for drooling in children with cerebral palsy identified six trials eligible for inclusion, four using botulinum toxin A, and two using the pharmacological interventions, benzatropine or glycopyrronium (15). However the reviewers were unable to reach a conclusion on the effectiveness or safety of the treatments, and insufficient evidence was found to inform clinical practice for the management of drooling in this patient group.*

- *A more recent review of management of drooling in children concluded that evidence for interventions was limited, but possible drug therapies may include transdermal hyoscine, oral glycopyrronium or salivary gland botulinum toxin injections (3). The review found that evidence of efficacy remains limited to small, short-term studies, despite the long-term nature of treatment, and that treatments were associated with adverse effects, with little data on long-term safety. A recommendation was made to ensure careful discussion of treatment decisions, and follow-up of patients to assess efficacy and adverse effects.*

- *A UK survey of 23 neurologists with a special interest in motor neuron disease identified the most popular first-line treatments for sialorrhoea in their patients as: hyoscine hydrobromide patches (65% of clinicians), amitriptyline (52%), carbocisteine (30%) and atropine eye drops topically to the tongue (26%) (16). Second-line preferences were: oral glycopyrronium (43%), botulinum toxin (39%), carbocisteine (35%), amitriptyline (30%) and subcutaneous glycopyrronium (26%). The authors noted the variation in treatment strategies, and suggested this reflected the lack of evidence based guidelines.*

- *The National Institute for Health and Care Excellence (NICE) full Clinical Guideline on the management of Parkinson's disease includes a section on sialorrhoea. Suggested treatment measures include sublingual 1% atropine ophthalmic solution twice daily and injection of salivary glands with botulinum toxin A (17). A NICE Clinical Knowledge Summary also suggests botulinum toxin A, as well as hyoscine hydrobromide patches as specialist treatment options for excessive salivation associated with Parkinson's disease (18).*
- *A NICE Clinical Knowledge Summary covering the management of oral problems in palliative care includes a section on excessive salivation (19). Specialist advice is recommended, with little data available to guide drug or dosage recommendations.*

Suggested drug treatments are based on expert opinion, and include hyoscine hydrobromide (oral, sublingual or transdermal) or amitriptyline.

- *The BNF for Children suggests oral glycopyrronium or oral/transdermal hyoscine hydrombromide as options for hypersalivation in palliative care and in children unable to control posture or with abnormal swallowing reflex (3,20).*

- *The choice of drug should be based on its pharmacological and adverse effect profile as well as the limited results of available published studies (4). Selection of a particular compound should be based on individual response and side effects (21). Clearly, larger randomised controlled trials are required before the place of each of these drugs in the management of hypersalivation can be established*

Summary

- *Hypersalivation is the excessive production of saliva and may result in drooling or sialorrhoea.*
- *Drooling is not always due to hypersalivation, and may be due to poor swallowing mechanism and an inadequate rate of swallowing. Nonetheless, drug therapy for drooling is aimed at reducing the volume of saliva.*
- *Evidence to support efficacy and safety of drug therapy in hypersalivation is limited. Drugs with antimuscarinic actions, particularly hyoscine hydrobromide and glycopyrronium, are most commonly used. Botulinum toxins are another option, as well as a selection of other drugs.*
- *Most drugs are unlicensed for this indication in the UK, although glycopyrronium oral solution (Sialanar®) is licensed for the treatment of sialorrhoea in children with neurological disorders, and procyclidine and trihexyphenidyl are licensed for excessive salivation or drooling associated with Parkinson's disease.*
- *Good quality comparative studies are lacking, so prescribers should consider evidence for effectiveness, potential side effects and available routes of administration when choosing between treatments. Specialist advice may be required, with little data available to guide drug or dosage recommendations.*
- *The various treatment options and evidence are discussed in more detail in other UKMi Q&As (links provided in this Q&A), and another Q&A discusses treatments for drug-induced hypersalivation.*

Limitations

- *To date there are no large randomised controlled trials for any drug to treat hypersalivation, so the amount of published evidence is limited. Few comparative studies are available. The evidence for the use of some of these drugs is limited to anecdotal reports only.*
- *The majority of the studies are short-term so long-term efficacy and safety data are not available.*
- *Most of the studies included small numbers of patients.*
- *The majority of the studies rely on subjective outcome measurements since it is difficult to assess saliva production objectively, particularly as there is inter-individual variation in saliva production. No single method of measurement of salivary flow and outcome presentation is available.*

Recommendations to the APC

On 5th April 2017 the PCN approved Policy No: PCN 260-2017.

The PCN recommend Sialanar® to be given a BLUE (without information sheet) traffic light status but must be initiated under recommendation from a specialist.

On 14th January 2019 the SPC for glycopyrronium bromide 1mg/5ml oral solution (Colonis®) was revised and the product is now approved for *Symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorder and for use in adults as an add-on therapy in the treatment of peptic ulcer.* This now brings it in-line with the product licence for Sialanar®.

Therefore the proposal to the APC is that glycopyrronium bromide 1mg/5ml oral solution (Colonis®) should also be given the same BLUE (without information sheet) traffic light status. For the treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders, and should be considered for use in adults as an “off label” treatment where first line alternative treatments cannot be used or are unable to be used. See separate evidence review.

The NICE guideline, Motor neurone disease (NG42) recommends the use of anticholinergic medication as a first line treatment for the excessive drooling of saliva (sialorrhoea) in people with motor neurone disease. The guidance also recommends glycopyrronium as the first line treatment for those MND patients with cognitive impairment, because it has fewer central nervous system side effects side effects than other oral anticholinergic medications.

The NICE guideline, Parkinson’s disease in adults (NG71) recommends the use of glycopyrronium as a first line option in the treatment of drooling in Parkinson’s disease.

The NICE guideline, Cerebral palsy in under 25s (NG62) recommends using anticholinergic treatments for hypersalivation, but it does not choose a preference for one anticholinergic treatment over another. It was noted during the Committee’s discussion that ipratropium bromide inhalation was being increasingly used off-license for this indication as a first-line treatment. The Committee also stated that this treatment was relatively cheap potentially dominating (less expensive and more effective) the alternatives under consideration. However, the Committee were unable to make recommendations on this treatment as it was not considered as a relevant treatment when the protocol was developed.

Based on the information from the UKMi Q&A reviews and the published NICE guidelines, the attached treatment pathway for the pharmacological management of hypersalivation in children and adults is proposed, and the formulary colour classification is recommended as follows:

Drug	Surrey PAD classification	Crawley, Horsham and Mid Sussex classification	Proposed formulary traffic light status
Amitriptyline tablets	Green (for neuropathic pain)	Green (for depression/migraine/neuropathic pain)	Green for adults- This drug is used extensively in Primary care for a range of 'off-label' indications
Atropine 1% eye drops	No classification for topical use	Blue (for hypersalivation)	Blue for adults
Glycopyrronium bromide oral solution 400micrograms/mL (Sialanar® 320 micrograms/ml of glycopyrronium) ***(Licensed Product)***	Blue	Blue	No change- Blue for children only
Glycopyrronium bromide tablets (NB—not to be routinely used due to cost)	No classification for tablets	Blue (for hypersalivation)	Blue for adults and children- despite high cost, tablets offer more acceptable patient administration
Glycopyrronium bromide 1mg/5ml oral solution sugar free (Colonis®) ***(Licensed Product)***	See separate evidence review	See separate evidence review	Suggest Blue for adults and children- Consistent with decision for Sialanar, but strength and cost more effective for adults
Hyoscine hydrobromide 150micrograms tablets	Green (for nausea/vomiting)	Green	Green for adults and children- availability of all strengths for dose variation
Hyoscine hydrobromide 300micrograms tablets[c]	Green (for nausea/vomiting)	Green	Green for adults and children

Hyoscine hydrobromide 100 microgram/mL oral solution (Special)[c]	No classification for liquid.	No classification for liquid.	Green for adults and children- liquid formulation for swallowing difficulties, enteral tubes etc
Hyoscine patch 1.5mg (Scopoderm®)[c]	Green (for nausea/vomiting)	Green	Green for adults and children
Ipratropium bromide nasal spray 0.03%	Green (for allergic rhinitis)	Green (licensed indications)	Green for adults- Experience in Primary care for other indications
Ipratropium bromide CFC free inhaler 20micrograms / actuation	No classification for inhaler.	Green (licensed indications)	Green for adults- Experience in Primary care for other indications
Procyclidine 5mg tablets	Black (for Parkinson's disease)	Blue (licensed indications)	Blue for adults- procyclidine is licensed for excessive salivation or drooling associated with Parkinson's disease
Procyclidine 5mg/5ml oral solution sugar free	Black (for Parkinson's disease)	Blue (licensed indications)	Blue for adults- procyclidine is licensed for excessive salivation or drooling associated with Parkinson's disease
Trihexyphenidyl 5mg tablets	Black (for Parkinson's disease)	Blue (licensed indications)	Blue- adults and children- trihexyphenidyl is licensed for excessive salivation or drooling associated with Parkinson's disease, but would be off-label in children.

Trihexyphenidyl 5mg/5ml oral solution	Black (for Parkinson's disease)	Blue (licensed indications)	Blue- adults and children- trihexyphenidyl is licensed for excessive salivation or drooling associated with Parkinson's disease, but would be off-label in children.

References

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