Treatment of Sialorrhoea / Drooling in paediatrics: Cost-effective treatment options

Drug option	Evidence base	Cost	License
1.) Hyoscine hydrobromide	NICE NG62 recommendation	Scopoderm® 1.5mg patch £23.19 for 28 days	Not licensed for this indication. Only licensed from age 10 for travel sickness. Change patch every 72 hrs
2.) Trihexyphenidyl tablets (for dyskinetic cerebral palsy)	NICE NG62 recommendation	2mg tablets x 84 £4.40 5mg tablets x 84 £17.91 Oral solution 5mg/5ml x 200ml (Rosemont): £22.00	Not licensed for this indication. "Not recommended" for children in the SPC. But is listed in the BNF for children. 1mg bd titrated up to 2mg tds (see UKMI Q&A 53 in references)
3.) Glycopyrronium	NICE NG62 recommendation	**Sialanar®**: £430.08 for 28 days (£320 per 250ml) Drug Tariff prices of other forms: • 2mg tabs £237 per 30 tabs • 1mg/5ml oral solution £91 per 150ml • 1mg tabs £237 per 30 tabs	Sialanar® is licensed for symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders (short term intermittent use)
4.) Botulinum A injections	Long term safety unknown	List price (HRG admin tariff to be added) 50 Units/vial=£77.50. 100 Units/vial=£138.20. 200 Units/vial=£276.40.	Not licensed for this indication
Other options with less evidence base			
Atropine eye drops 1% (used sub-lingually)	Pilot study 2017 & case report in UKMI Q & A 53	10ml £98.23	Not licensed for this indication
Ipratropium (nebulised or inhaler used sub-lingually	UKMI Q & A 53 & 2010 BMJ paper	20mcg inhaler £5.56 (200 dose) 250micrograms/1ml nebuliser UDVs x 20 £4.51, 500mcg/ml UDVs £3.20	Not licensed for this indication
Modafinil	Case reports UKMI Q & A 53	100mg tabs x 30 £5.68 200mg tabs x 30 £13.20	Not licensed for this indication. MHRA safety warning August 2010

Summary of evidence base:

There is insufficient evidence to inform clinical practice for the management of drooling in the paediatric patient group.

There are no randomised double-blind studies that compare the different therapeutic options available for the management of sialorrhoea. 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. 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.[1]
More recently, a Cochrane review examining interventions for drooling in children with cerebral palsy was unable to reach a conclusion on the effectiveness or safety of either botulinum toxin A, benzatropine or glycopyrronium.[1]

Choice of treatment
The choice of drug should be based on its pharmacological and adverse effect profile, individual response as well as the limited results of available published studies.[1]
First-line management of drooling should be directed at the cause, which may be multifactorial and patient-specific. Several options are available, including practical aids, speech therapy, physiotherapy, surgery and medication. Each option has varying degrees of acceptability and success.

There is now one product that has been licensed in the UK as follows:
Sialanar®: glycopyrronium 320 micrograms /ml oral solution[2]

This is licensed for "Symptomatic treatment of severe sialorrhoea (chronic pathological drooling) in children and adolescents aged 3 years and older with chronic neurological disorders".
Due to the lack of long term safety data, Sialanar® is recommended for short -term intermittent use and costs £320 per 250ml. At a dose of 1600mcg (4ml) TDS the 28 day cost is £430.08 (33kg child at a dose of 48mcg/kg). Once opened, a bottle has a shelf-life of 28 days.
Published safety data are not available beyond 24 weeks treatment duration. Given the limited long-term safety data available and the uncertainties around the potential risk for carcinogenicity, total treatment duration should be kept as short as possible. If continuous treatment is needed (eg in a palliative setting) or the treatment is repeated intermittently (e.g. in the non-palliative setting treating chronic disease) benefits and risks should be carefully considered on a case by case basis and treatment should be closely monitored.
Due to the low likelihood of benefit and the known adverse effect profile, Sialanar should not be given to children with mild to moderate sialorrhoea.

NICE NG62 on cerebral palsy in under 25s (Jan 17)[3] https://www.nice.org.uk/guidance/ng62:

1.11 Managing saliva control (p21-22)
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 (oral or by enteral tube)

or

- transdermal hyoscine hydrobromide

or

- trihexyphenidyl hydrochloride 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.

Consider specialist assessment and use of botulinum toxin A injections 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.

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.

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Drugs that have been used to treat drooling[1]:

1. Antimuscarinic Drugs

- Amitriptyline
- Atropine
- Benzatropine
- Trihexyphenidyl hydrochloride (benzhexol hydrochloride)
- Glycopyrronium bromide (glycopyrrolate): oral, nebulized and subcutaneous
- Hyoscine hydrobromide (scopolamine hydrobromide): oral, topical, subcutaneous and nebulized

2. Beta-Blockers

3. Botulinum Toxin

4. Other drugs e.g. modafinil

Atropine[4]:

The authors of one small non-comparative study suggest that the advantages of sublingually administered **atropine** include its availability as a ready-made solution (eye drops) and reversibility. However, some patients may have difficulty manipulating the dropper to ensure proper dosing and there is the potential for accidental overdose with drops. The exact dose of sublingual atropine has not been established and atropine should not be used in patients with cognitive impairment, dementia and hallucinations. One small randomised placebo-controlled trial which evaluated the effectiveness of sublingual atropine sulfate drops for the management of hypersalivation failed to demonstrate any significant benefits.

A recent pilot study over 11 weeks of the use of atropine eye drops in children (n=26) with excessive drooling concluded that atropine used in this manner showed promising results.[5]

Beta-blockers[4]: In one small, uncontrolled pilot study, sixteen bulbar amyotrophic lateral sclerosis/motor neuron disease patients, who were complaining of thick tenacious secretions, were treated with either oral propranolol 10mg twice daily or oral metoprolol 25mg twice daily. They were already taking maximal anticholinergic medications (hyoscyamine or amitriptyline). The authors hypothesise that, in these patients, the source of secretions is a combination of serous and mucus outflow from the salivary glands plus mucus from the nose and lungs, and that selective combination drug therapy involving anticholinergics and beta-blockers may be necessary. Based on subjective responses, 12 of the 16 patients (75%) reported a significant reduction in their thick secretions within one week. The other 4 patients noticed no change. Follow-up ranged from 2 to 9 months, with one patient experiencing a progressive reduction in responsiveness to the treatment after 9 months despite gradual increases in the beta-blocker dose.

I am not sure if there is any specific evidence base about the use of this option in children.

Benzatropine: Benzatropine tablets are no longer available in the UK & so can only be imported from abroad which is prohibitively expensive.

Botulinum Toxin[4]:

In the NICE full Clinical Guideline on the management of Parkinson's disease[6], injection of salivary glands with botulinum toxin A is one option suggested for the treatment of hypersalivation.

Systematic reviews and meta-analyses of botulinum toxin in the management of hypersalivation have been published. An international consensus statement defining the assessment, intervention and aftercare of patients with drooling treated with botulinum toxin A is also available.

Since the administration of botulinum toxin is invasive and requires specialized expertise to perform the intervention, patient access to treatment is restricted. The effect of repeated injections of botulinum toxin over time, or the risk of developing antibodies, are not known.

A review of the management of drooling in children from 2010[7] points out that potential side-effects are major, particularly thickening of secretions and dysphagia.

Such use of botulinum is off-label but has been recognised in peer-reviewed documents such as the European Consensus statement as causing reproducible benefit.[7]

A systematic review from 2012[8] of the use of botulinum for drooling in children concluded that botulinum injections are an effective, temporary treatment for sialorrhoea in children with cerebral palsy. It stated that more studies were needed to adress the safety and to compare botulinum with other treatment options.

The following information is from Great Ormond's Street Hospital about botulinum injections[9]:
Almost all salivary gland injections are carried out as a day case while your child is under general anaesthetic.
Salivary gland injections with botulinum toxin are not a permanent solution to excessive dribbling and drooling and they are not effective for every child. If they are effective, you should notice a reduction in your child's dribbling and drooling between three and eight days after the injections. It may take longer for positive effects to show in some children, occasionally taking two to four weeks. Some children may only show partial effects. The effects of the injections last between three and six months so the procedure may need to be repeated in future.
Surgery to re-position the salivary gland duct (opening into the mouth) to the back of the mouth is also possible. This procedure is called a bilateral submandibular duct transposition (BSMDT).

Glycopyrronium[4]:
Benefits of using glycopyrronium include its long duration of action and its inability to cross the blood-brain barrier thus reducing central adverse effects (e.g. sedation, restlessness).
Glycopyrronium is slower in onset and produces less tachycardia than atropine or hyoscine.
The published data available are mainly limited to the use of oral glycopyrronium in children and young adults with neurodevelopmental disabilities, where it has been used with some success in relatively small studies. Dosage used has been variable. However, in three of the six studies, at least 20% of patients are reported to have discontinued the medication due to side effects.
The authors of a NICE Evidence Summary[10] evaluated the three published randomised controlled trials (RCTs) and concluded that there is moderate evidence that oral glycopyrronium bromide reduces hypersalivation or drooling, but these RCTs do not provide evidence for the efficacy or safety of long-term use of oral glycopyrronium bromide for treating adults, children and young people with hypersalivation. Further larger RCTs are required.
There has also been recently published a NICE evidence summary[11] of the new licensed glycopyrronium liquid, Sialanar® which outlines the limited evidence base for this product.
Isolated case reports have been published describing the use of nebulized or subcutaneous glycopyrronium[12].

Hyoscine Hydrobromide[4]:
Transdermal hyoscine patches offer several advantages over other treatments including ease of administration, maintenance of steady state concentrations and a low incidence of systemic side effects compared with other anticholinergics. Hyoscine hydrobromide can also be given by non-topical routes but there is less evidence to support this.

Ipratropium Bromide[4]
One randomised, double-blind, placebo-controlled, crossover study investigated the safety, tolerability and efficacy of ipratropium bromide spray in the management of Parkinson's disease related hypersalivation. In the study 17 patients were recruited and 15 completed the trial. Patients used one or two metered doses (sprays) of ipratropium bromide (21 microgram/metered dose) or placebo sublingually up to four times per day for 2 weeks, with a one week washout before crossover. Ipratropium bromide had no significant effect on the amount of saliva produced, but was well tolerated.
A review of the management of drooling in children from 2010[7] points out that nebulised ipratropium is generally well tolerated & easy to give. However at that point there had been no trials reported in paediatric literature.

Modafinil[4]
In two children (aged 13 and 6 years) with spastic cerebral palsy, treatment with modafinil for spasticity resulted in a dramatic improvement in drooling. In the first case, the modafinil was gradually increased from 50mg daily to 200mg daily over several months, and drooling stopped, although irritability developed at this dose. This resolved on discontinuation of treatment and modafinil was then restarted at 100mg every other day with a view to increasing the dose stepwise back to 150mg in the morning. In the second case, modafinil was started at 25mg in the morning and was gradually increased to 100mg in the morning over a few months. No side effects are mentioned and it is reported that the patient stopped drooling.
There has however been a Drug Safety Update from 2010[13], where the safety of modafinil was reviewed & it was decided that it should only be used within its narrower license for narcolepsy only, so this option would not be recommended.

Trihexyphenidyl[4]

A study of 20 children (aged 3-12 years) with cerebral palsy revealed that trihexyphenidyl improved drooling in 17 recipients. One child showed no difference and two had increased drooling. Patients were treated for a minimum of 3 months and adverse effects were reported infrequently despite some patients continuing treatment for up to 2 years.

A retrospective chart review was carried out for 101 children (aged 1-18 years) with cerebral palsy, who received trihexyphenidyl for dystonia (28.7%), sialorrhoea (5.9%) or both (65.4%). Side effects were reported in 69.3% of patients including constipation, decreased urinary frequency, behavioural changes and excessive dry mouth. Thirty-six patients (35.6%) discontinued treatment including 8% due to intolerable side effects and 8.9% due to lack of efficacy. Sialorrhoea was reduced in 60.4% of patients.

The authors of the retrospective chart review suggest that trihexyphenidyl should be started at a low dose with a gradual stepwise increase over several weeks to promote tolerability and to account for a potentially delayed response to treatment.

References:

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