

**Drug Treatments to Control Drooling in Pediatric Patients with
Cerebral Palsy: An Evidence-Based Review of the Literature**

Written By:

Voyle Bagley, Molly Gareh, Katherine Lee, Jordana Platt, Emily Singer
and Carolyn Tuffner

University of Toronto

Word Count: 1553

Submitted March 30, 2006

Abstract

The purpose of this literature review was to determine the best drug treatment for drooling in pediatric patients with cerebral palsy by identifying the strongest evidence amongst the various treatment options. The primary method searched electronic journal databases; the secondary method examined the references of relevant articles; the tertiary method included conversations with experts in the field of pharmacology. The electronic databases PubMed and Ovid were searched and yielded 56 and 38 articles, respectively. A second search using the Cochrane Database and Web of Science yielded no new articles. After examining the references from articles deemed relevant (see criteria below), two more potentially relevant articles were found. The three articles that met the inclusion criteria were then scored based on a “Checklist to Assess Evidence of Efficacy of Therapy” developed by Leake¹¹ (see Table 1). The highest possible score was 16. Each article was assessed by two independent reviewers who collaborated to reach a final agreement when discrepancies were noted. Due to the weaknesses in study design, it is difficult to make a reliable drug recommendation to treat drooling in CP children. The studies available did not utilize a proper control nor possess blinding of the investigator and patients. The strongest evidence (though Level II and thus relatively weak) suggests that treatment with Botox injections into salivary glands might have therapeutic benefit in the treatment of drooling in this group with limited adverse effects. However, there are weaknesses in the study design of even the ‘strongest’ evidence and a lack of sufficient evidence from reliable studies on other treatment options. Therefore future studies of improved design are needed before a confident recommendation about the best treatment option can be made. Stronger evidence for other frequently utilized drugs such as

glycopyrrolate should be carried out to ensure that all available treatment options can be effectively analyzed and compared.

Key words: sialorrhea, hypersalivation, drooling, cerebral palsy, children, drug, anticholinergic, botulinum toxin, botox, scopolamine, glycopyrrolate, benzhexol hydrochloride, atropine, antireflux, ranitidine, cisapride, benztropine.

Excessive salivation, a common and often debilitating problem in dentistry, can be divided into two main etiologies. The first, true hypersalivation, is defined as the over secretion of salivary glands resulting in excess production of saliva. This condition is relatively rare.¹ A much more common disorder of salivation is drooling, a neuromuscular clearance deficiency where the individual cannot effectively clear saliva. This often leads to pooling in the mouth and an outward flow of fluid. Drooling can be a common problem in individuals with neurological impairment, as seen in children born with cerebral palsy.

Cerebral palsy (CP) refers to a group of disorders caused by faulty development of or damage to motor areas in the brain that disrupts the brain's ability to control movement and posture. It is one of the most prevalent handicapping disorder in Canada³, and 13.7 % of children in Canada affected with CP will suffer from chronic drooling.⁴ A combination of three independent factors lead to difficulty clearing saliva including infrequent swallowing, inadequate lip closure, and poor head posture.^{4,7} Drooling is associated with many adverse effects such as social stigma, decreased self-esteem, impaired speech and increased caregiver burden.^{4,10} Additionally, many other skills remain underdeveloped due to excess time devoted to manage drooling. Furthermore, the constant saliva resting on extra-oral soft tissue can predispose individuals to perioral skin macerations and infections with a possibility of transmission of infections or systemic manifestations.⁴

Four main treatment modalities have been explored to manage drooling in these patients. Primary treatment options, which are the least invasive, include behavioural modification and/or physiotherapy which stresses positive reinforcement and

sensorimotor development.¹ Most of the literature exploring these options was in the form of case studies and results showed effects to be only in the short term, consequently long term intensive therapy would still be required.⁴ The second option for treatment is the use of functional appliances. These appliances stimulate oral musculature to correct the myofunctional disbalance.¹ Again, many of these studies looked only at individual cases and thus the evidence was deemed weak. Pharmacological means is a third, well explored option with the majority of evidence focusing on the use of anticholinergic medications. Researched drugs include scopolamine, botulinum toxin (Botox), antireflux, benzotropine, benzhexol hydrochloride, atropine, and glycopyrrolate. A fourth treatment option, often viewed as a last resort if other methods have failed, is the use of surgical therapy, specifically gland excision or salivary duct relocation to the nasopharynx.^{1,7} Although each of the above treatments can be utilized in isolation, most agree that optimal management of drooling stems from a team approach employing a speech pathologist, physiotherapist and dentist.^{1,6,9,10}

The purpose of this literature review was to determine the best drug treatment option for drooling seen in children with cerebral palsy by identifying the strongest sources of evidence that exist in the literature.

Method

To identify potentially relevant published journal articles, three types of searches were employed. The primary method searched electronic journal databases; the secondary method examined the cited references of relevant articles; the tertiary method included conversations with experts in the field of pharmacology. The following key

words were searched: sialorrhea, hypersalivation, drooling, cerebral palsy, children, drug, anticholinergic, botulinum toxin, Botox, scopolamine, glycopyrrolate, benzhexol hydrochloride, atropine, antireflux, ranitidine, cisapride, benztropine. The electronic databases PubMed (1966 to the present) and Ovid (1966 to the present) were searched and yielded 56 and 38 articles, respectively. A second search using the Cochrane Database and Web of Science yielded no new articles. After examining the reference list from articles deemed relevant (see criteria below) two more potential articles were found.

After elimination of duplicate articles from overlapping electronic databases and elimination based on title alone, 32 articles were identified. The articles were subjected to the following inclusion criteria: 1) All subjects in the study must be children aged <18yrs; 2) >80% of subjects in the study had CP; 3) The study was published in English; 4) The study used humans subjects only; 4) The articles were accessible online or at a library; 5) The study design was a randomized controlled trial or prospective study; 6) The study used an objective measure of drooling observed by the operator.

The three articles that met all six criteria were then scored based on a “Checklist to Assess Evidence of Efficacy of Therapy” developed by Leake¹¹ (see Table 1). The highest possible score was 16. Each article was assessed by two independent reviewers who collaborated to reach a final agreement when discrepancies were noted.

Results

Heine et al., 1996⁷ (see Table 2) examined the effects of antireflux medication on drooling of patients with cerebral palsy based on the hypothesis that acid reflux in the distal portion of the esophagus may induce saliva and result in drooling in this

population. Patients were given either a combination of two antireflux medications or a placebo. Drooling was measured by a semiquantitative observation (drooling quotient) for two 15 minute periods separated by a 1 hour interval. No significant differences between groups ($p=0.74$) were found and investigators concluded that antireflux medications did not significantly decrease drooling in these patients. The power of the study was not reported nor could be calculated from the results reported. The investigators used a strong study design -- a double blinded randomized controlled trial with a valid control group. However, the evidence was considered weak due to a small sample size as only nine patients demonstrated reflux and were included in the final study. Additionally, only a small population of CP patients display gastroesophageal reflux, therefore a recommendation on the use of this medication might be invalid for the general population suffering from this problem.

Jongerius et al.,⁸ 2004 (see Table 2) studied the effects of two anticholinergic agents, scopolamine and Botox. Each subject wore a transdermal scopolamine patch for a two week period and drooling was recorded on the tenth day by weighing dental (cotton) rolls placed at the orifices of salivary glands. After a reliable washout period, patients received Botox injections in both submandibular glands and dental roll weights were measured at 2, 4, 8, 16 and 24 weeks post-injection. A greater mean reduction in flow with Botox as compared with scopolamine ($p<0.05$) was found, but overall success rates were greater for scopolamine ($p=0.002$). Despite overall success with scopolamine, 82.2% of patients reported significant adverse effects and nine subjects had to discontinue treatment as a result. Conversely, adverse effects following Botox injections were mild and were found in only 7.6% of subjects. The authors concluded that Botox

provided a greater reduction in amount of drooling than scopolamine and that despite lower overall success rates, the adverse effects associated with scopolamine warrant a recommendation of Botox as a superior treatment. The investigators controlled for confounding variables, included extensive criteria for admitting subjects, and used a concrete quantitative measure of drooling. However, the study design was weak since neither the subjects, nor the investigators were blinded and no control group or valid placebo was utilized.

The study by Saverese et al.,⁴ 2004 (see Table 2) examined Botox injection into the parotid glands. Researchers compared pre- and post-treatment dental roll weights and reported a significant decrease in amount of saliva produced up to two months post-treatment. No adverse effects were reported. This study did employ a valid objective measure to quantify drooling, however the study was non-blinded with no placebo group. The poor study design coupled with a limited sample size weakened the evidence and thus the recommendation.

Discussion

Due to the weaknesses in study design, it is difficult to make a reliable drug recommendation to treat drooling in CP children. The studies available did not utilize a proper control or blinding of the investigator and patients. Moreover, confounding variables such as hunger and hydration were not controlled in the present studies. Although the studies reported adverse effects experienced by the patients while taking the medications, no evidence was available on the long-term effects of these drugs. Therefore, follow up studies investigating the long-term adverse effects, specifically for

relatively new drugs such as Botox, should be employed before a recommendation can be established. It is difficult to effectively compare the various treatments due to variability in the measurement of drooling, and thus a standard measure of drooling needs to be established. Furthermore, these studies examined different salivary glands, which produce different amounts of saliva when at rest and when stimulated, further complicating the comparison of treatments.

In conclusion, the strongest evidence (though Level II and thus relatively weak) suggests that treatment with Botox injections into salivary glands might have a therapeutic benefit in the treatment of drooling in CP patients with limited adverse effects. However, due to insufficient evidence regarding other available treatment options as well as weaknesses in study design of even the 'strongest' evidence, it is recommended that further studies of improved design be carried out before a confident recommendation about the best treatment option can be made. Some suggestions for future research include performing double blinded randomized controlled trials, using larger sample sizes and the development of a standard measure to assess drooling. Additionally, it is important to find optimum dosage of drugs before conducting studies and therefore, dose response trails should be investigated. Finally, stronger evidence for other frequently utilized drugs such as glycopyrrolate should be carried out to ensure that all available treatment options can be effectively analyzed and compared.

Table 1: Checklist to Assess Evidence of Efficacy of Therapy

1. Was the study ethical?
2. Was a strong design used to assess efficacy?
3. Were outcomes validly and reliably measured?
4. Were interventions validly and reliably measured?
5. What were the results?
 - Was the treatment effect large enough to be clinically important
 - Was the estimate of the treatment effect beyond chance and relatively precise?
 - If the findings were “no difference” was the power of the study 80% or better?
6. Are the results of the study valid:
 - Was the assignment of patients to treatments randomized?
 - Were all patients who entered the trial properly accounted for and attributed at its conclusion?
 - Was the study of sufficient duration?
 - Were patients, health workers and study personnel “blind” to treatment?
 - Were the groups similar at the start of the trial?
 - Aside from the experimental intervention, were the groups treated equally?
 - Was care received outside the study identified and controlled for?
7. Will the results help in caring for your patients?
 - Were all clinically important outcomes considered?
 - Are the likely benefits of treatment worth the potential harms and costs?

Table 2: Studies Showing the Strongest Evidence for Drug Treatments for CP patients

Author, Date, Study Design	Heine et al., 1996 RCT	Jongerius et al., 2004 Prospective Open Labelled Clinical Trial	Saverese et al., 2004 Prospective Open Labelled Clinical Trial
Population [total (final sample)]	CP children aged 4.5 to 18.6 yrs [24 (9)]	CP children aged 3 to 16 yrs with severe drooling [45 (39)]	Children with CP aged 5-18 yrs [21 (19)]
Treatment	Two Antireflux medications (Ranitidine & Cisapride)	1.5 mg transdermal scopolamine patch worn for 10-14 days BoNT injections in bilateral submand glands (dosage by wt)	BoNT injected into parotid gland at 2 sites
Control	Placebo	No control group Each subject compared to own baseline values	No control group Each subject compared to own baseline values
Measure	Drooling Quotient: observed drooling every 15 sec for 2 15 min periods	Dental roll weights recorded at baseline, 10th day of SCP and 2, 4, 8, 16, 24 wks post BoNT	Compared pre and post treatment dental roll weights after 2-5 min in mouth
Outcome	No significant differences between groups (p=0.74)	Higher mean reduction of flow with BoNT (42.4%) over SCP (24.7%) up to 8 wks after BoNT (p<0.05) Higher overall success rates with SCP (p=0.002)	Significant decrease in amount of saliva produced was reported up to 2 months (53% marked, 21% mod, 15% slight) (p=0.012)
Adverse Effects (% dropout)	No significant adverse effects reported (0%)	SCP: 82.2% adverse effects Incl. dry mouth, blurred vision and confusion (9%) BoNT: 7.6% reported mild temp, flu-like syndrome, swallowing problems (0%)	No reports of adverse effects (0%)
Grade, Level of Evidence	I-E	II-1, B	II-3, B
Conclusions	Antireflux medications do not significantly reduce drooling in these patients	BoNT provides greater reduction in drooling than SCP but with lower overall success rates	Injection of BoNT into parotid glands significantly improved drooling for up to 2 months
Score	11/16	11/16	10/16

References

1. Hussein I, Fayle S, Kershaw A, Tahmassebi J. The management of drooling in children and patients with mental and physical disabilities: a literature review. *International J. of Paediatric Dentistry* 1998; 8: 3-11.
2. National Institute of Neurological Disorders and Stroke. Available from URL: <http://www.ninds.nih.gov/disorders/cerebral_palsy/cerebral_palsy.htm> Accessed March 9, 2006.
3. Ontario Federation for Cerebral Palsy. Available from URL: <<http://www.ofcp.on.ca>> Accessed March 9, 2006.
4. Savarese R, Elovic E, Martin D, Scott M. Intraparotid injection of botulinum toxin A as a treatment to control sialorrhea in children with cerebral palsy. *Am. J. Phys. Med. Rehabil* 2004; 83(4): 304-311.
5. Bhidayasiri R, Truong DD. Expanding use of botulinum toxin. *J Neurol Sci* 2005; 235(1-2):1-9.
6. Brei TJ. Management of drooling. *Semin Pediatr Neurol.* 2003; 10(4):265-70.
7. Heine RG, Catto-Smith AG, Reddihough DS. Effect of antireflux medication on salivary drooling in children with cerebral palsy. *Dev Med and Child Neurol.* 1996; 38:1030-36.
8. Jongerius PH, Rotteveel JJ, van Limbeek J, Gabreels FJM, van Hulst K, van den Hoogen FJA. Botulinum toxin effect on salivary flow rate in children with cerebral palsy. *Neurology* 2004; 63:1371-75.
9. Crysedale WS, Greenberg J, Koheil R, Moren R. The drooling patient: a team evaluation and management. *Int J Pediatr Otorhinolarhngol.* 1985; 9(3):241-8.

10. Meningaud JP, Pitak-Arnop P, Chikhani L, Bertrand JC. Drooling of saliva: a review of the etiology and management options. *Oral Surg Oral Med Oral Oathol Oral Radiol Endod.* 2006; 101(1):48-57.
11. Leake JL, Department of Biological and Diagnostic Sciences, Faculty of Dentistry, University of Toronto. Unpublished document. Course Notes DENT 300Y 2005. The checklist was adapted from Fletcher RH, Fletcher SW, Wagner EH. *Clinical epidemiology. The essentials.* 3rd ed. Baltimore: Williams and Wilkins, 1996; and Sackett DL, Richardson WS, Rosenberg W, Haynes RB. *Evidence-based medicine: how to practice and teach. EBM.* 2nd ed. New York: Churchill Livingstone, 1997.