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Interventions for drooling in children with cerebral palsy (Review)

Walshe M, Smith M, Pennington L

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2012, Issue 11

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Interventions for drooling in children with cerebral palsy (Review)  
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Interventions for drooling in children with cerebral palsy

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ABSTRACT

Background

Drooling is a common problem for children with cerebral palsy (CP). This can be distressing for these children as well as for their parents and caregivers. The consequences of drooling include risk of social rejection, damp and soiled clothing, unpleasant odour, irritated chapped skin, mouth infections, dehydration, interference with speech, damage to books, communication aids, computers, and the risk of social isolation (Blasco 1992; Van der Burg 2006). A range of interventions exist that aim to reduce or eliminate drooling. There is a lack of consensus regarding which interventions are most effective for children with CP.

Objectives

(1) To evaluate the effectiveness and safety of interventions aimed at reducing or eliminating drooling in children with cerebral palsy. (2) To provide the best available evidence to inform clinical practice. (3) To assist with future research planning.

Search methods

We searched the following databases from inception to December 2010: Cochrane Central Register of Controlled Trials (CENTRAL); Medline via Ovid; EMBASE; CINAHL; ERIC; Psych INFO; Web of Science; Web of Knowledge; AMED; SCOPUS; Dissertation Abstracts.

We searched for ongoing clinical trials in the Clinical Trials website (http://clinicaltrials.gov) and in the Current Controlled Trials website (http://www.controlled-trials.com/). We hand searched a range of relevant journals and conference proceeding abstracts.

Selection criteria

Only randomised controlled trials (RCTs) and controlled clinical trials (CCTs) were included.

Data collection and analysis

Data were extracted independently by MW, MS and LP and differences resolved through discussion.

Main results

Six studies were eligible for inclusion in the review. Four of these studies were trials using botulinum toxin-A (BoNT-A) and two were trials on the pharmacological interventions, benzotropine and glycopyrrrolate. No RCTs or CCTs were retrieved on surgery, physical, oro-motor and oro-sensory therapies, behavioural interventions, intra-oral appliances or acupuncture. In the studies eligible for review,
there was considerable heterogeneity within and across interventions and a meta-analysis was not possible. A descriptive summary of each study is provided. All studies showed some statistically significant change for treatment groups up to 1 month post intervention. However, there were methodological flaws associated with all six studies.

**Authors’ conclusions**

It was not possible to reach a conclusion on the effectiveness and safety of either BoNT-A or the pharmaceutical interventions, benztropine and glycopyrrolate. There is insufficient evidence to inform clinical practice on interventions for drooling in children with CP. Directions for future research are provided.

---

**PLAIN LANGUAGE SUMMARY**

**Interventions for drooling in children with cerebral palsy**

Many children with CP have difficulty controlling saliva. Drooling varies in severity and can be distressing for the children, families and caregivers. Excessive drooling can cause constant damp soiled clothing, unpleasant odour, irritated, chapped or sore skin around the mouth and chin, skin and mouth infections, dehydration, difficulties chewing, interference with speech, damage to books, communication aids, computer and audio equipment. There is also risk of social rejection and social isolation for these children.

Many interventions are used to reduce or eliminate drooling. These include surgery, medications, botulinum toxin (BoNT-A and BoNT-B), physical therapies, therapies to improve sensory function, behavioural therapies to assist the child in managing his/her own drooling, appliances placed in the mouth, and acupuncture.

There is no clear consensus on which interventions are safe and effective in managing drooling in children with CP. This makes it hard to decide which intervention will be safest and most effective.

Only RCTs and CCTs were included in this review. Trials were identified by electronic searches of databases, searches of clinical trials registers, peer reviewed journals, published conference proceedings and reference lists of relevant articles.

Six trials were found. Four examined the safety and efficacy of BoNT-A and two examined benztropine and glycopyrrolate. No trials were found on other interventions. The quality of trials was variable. The trials all differed in the children recruited, the product used, how the product was delivered and how its effectiveness was measured. All trials reported a positive reduction in drooling and all showed some statistically significant change for treatment groups up to 1 month post intervention. Few studies examined client and/or carer satisfaction with the intervention. Some looked at side effects of the intervention but no study examined the effect of interventions on the child’s quality of life or psychological well being.

There is insufficient evidence to support the use of one intervention over another. As trials on just two kinds of interventions were retrieved, and given the variation and quality of these studies, it is not possible to conclude that one intervention is more effective than another. The lack of trials on other interventions does not suggest that these interventions are ineffective.

Adequately powered well designed trials are required across all interventions. In addition to using sensitive measures looking at change in salivary flow, measures are needed that examine client and carer satisfaction, changes in quality of life, psychological well being and in unwanted symptoms associated with drooling.
### Summary of Findings for the Main Comparison

**Outcome** | **Study** | **N in Control/Treatment** | **Standardized mean difference (SMD) where calculable** | **Quality of the Evidence (GRADE)** | **Comments** |
---|---|---|---|---|---|
Reduction in salivary flow | Jongerius 2004b | 39 Cross-over trial (39/39) | **Swab Method as Outcome Measure**<br>Scopolamine/BoNT-A<br>Mean differences: 0.0725 (SD = 0.13)<br>p < 0.05*<br>SMD = 0.56,<br>**4 Weeks**<br>Scopolamine/BoNT-A<br>Mean differences: 0.0607 (SD = 0.15)<br>p < 0.05*<br>SMD = 0.40,<br>**8 Weeks**<br>Scopolamine/BoNT-A<br>Mean differences: 0.0828 (SD = 0.13)<br>p < 0.05*<br>SMD = 0.64,<br>**16 weeks**<br>Scopolamine/BoNT-A<br>Mean difference: 0.0371 (SD = 0.15)<br>p > 0.05<br>SMD = 0.25,<br>**24 weeks**<br>Scopolamine/BoNT-A | Low | Uncertainty re risk of bias (see Figure 1)
<table>
<thead>
<tr>
<th>Study</th>
<th>Weeks</th>
<th>Intervention</th>
<th>Mean difference</th>
<th>p-value</th>
<th>SMD</th>
<th>Bias Risk</th>
<th>Risk of Bias Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin 2008</td>
<td>6</td>
<td>Method Unknown Baseline BoNT-A/Placebo</td>
<td>Mean difference: 0.0258 (SD = 0.16)</td>
<td>p &gt; 0.05</td>
<td>SMD = 0.016</td>
<td>Low</td>
<td>High risk of bias (see Figure 1) Methods of measuring saliva weight unknown</td>
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<td></td>
<td>7</td>
<td></td>
<td>Mean difference: 2.45/2.86</td>
<td>p &gt; 0.05</td>
<td>SMD = 0.38</td>
<td>Low</td>
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<tr>
<td></td>
<td>6</td>
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<td>Mean difference: 1.56/2.05</td>
<td>p &gt; 0.05</td>
<td>SMD = 0.58</td>
<td>Low</td>
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<tr>
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<td>4</td>
<td></td>
<td>Mean difference: 1.38/2.15</td>
<td>p &gt; 0.05</td>
<td>SMD = 1.11</td>
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<tr>
<td></td>
<td>6</td>
<td>BoNT-A/Placebo</td>
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<td>p &gt; 0.05</td>
<td>SMD = 1.31</td>
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<td>8</td>
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<td>SMD = 0.48</td>
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<td></td>
<td>10</td>
<td>BoNT-A/Placebo</td>
<td>Mean difference: 1.40/2.11</td>
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<td>SMD = 0.80</td>
<td>Low</td>
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</tr>
<tr>
<td>Time (Weeks)</td>
<td>Intervention</td>
<td>Mean Difference</td>
<td>p Value</td>
<td>SMD</td>
<td></td>
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<tr>
<td>(12 Weeks)</td>
<td>BoNT-A/Placebo</td>
<td>1.10/1.87</td>
<td>&lt;0.05 *</td>
<td>1.14</td>
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<td>(14 Weeks)</td>
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<td>1.49/1.95</td>
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<td>(22 Weeks)</td>
<td>BoNT-A/Placebo</td>
<td>1.58/2.21</td>
<td>&gt;0.05</td>
<td>0.54</td>
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</table>

Reduction in frequency and severity of drooling

Jongerius 2004a - 39 Cross-over trial (39/39)

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<table>
<thead>
<tr>
<th>Time (Weeks)</th>
<th>Outcome Measure</th>
<th>Mean Difference</th>
<th>p Value</th>
<th>SMD</th>
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<tbody>
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<td>(0-2 Weeks)</td>
<td>Baseline/Scopolamine</td>
<td>17.7 (SD = 21.2)</td>
<td>&lt;0.001 **</td>
<td>0.83</td>
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<tr>
<td>(2 Weeks)</td>
<td>Baseline/BoNT-A</td>
<td>21.7 (SD = 18.3)</td>
<td>&lt;0.001 **</td>
<td>1.18</td>
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<tr>
<td></td>
<td>Scopolamine /BoNT-A</td>
<td>4.1 (SD = 16.5)</td>
<td>&gt;0.05</td>
<td></td>
</tr>
</tbody>
</table>

Uncertainty re risk of bias (see Figure 1)
SMD = 0.25

(4 Weeks)
Baseline/BoNT-A
Mean difference: 16.1 (SD = 18.9)
p < 0.001**
SMD = 0.85
Scopolamine/BoNT-A
Mean difference: -1.6 (SD = 19.2)
p > 0.05
SMD = -0.08

(8 Weeks)
Baseline/BoNT-A
Mean difference: 20.0 (SD = 20.5)
p < 0.001**
SMD = 0.97
Scopolamine/BoNT-A
Mean difference: 2.4 (SD = 21.7)
p > 0.05
SMD = 0.11

(16 Weeks)
Baseline/BoNT-A
Mean difference: 15.5 (SD = 19.1)
p < 0.001**
SMD = 0.81
Scopolamine/BoNT-A
Mean difference: -2.2 (SD = 21.8)
p > 0.05
SMD = -0.1

(24 Weeks)
Baseline/BoNT-A
<table>
<thead>
<tr>
<th>Lin 2008</th>
<th>7/6</th>
<th><strong>DQ as Outcome Measure</strong></th>
<th>Low</th>
<th>High risk of bias (see Figure 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>BoNT-A/Placebo</td>
<td>Mean difference: 8.43/6.00</td>
<td>p &gt; 0.05</td>
<td>SMD = 0.80</td>
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<tr>
<td>(0-2 weeks)</td>
<td></td>
<td>p = 0.01*</td>
<td>SMD = 2.4</td>
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</tr>
<tr>
<td>(4 Weeks)</td>
<td>BoNT-A/Placebo</td>
<td>Mean difference: 5.17/9.29</td>
<td>p &gt; 0.05</td>
<td>SMD = 1.2</td>
</tr>
<tr>
<td>(6 Weeks)</td>
<td>BoNT-A/Placebo</td>
<td>Mean difference: 3.33/5.57</td>
<td>p &lt; 0.05*</td>
<td>SMD = 1.3</td>
</tr>
<tr>
<td>(8 Weeks)</td>
<td>BoNT-A/Placebo</td>
<td>Mean difference: 1.83/6.86</td>
<td>p &lt; 0.01*</td>
<td>SMD = 1.7</td>
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<tr>
<td>(10 Weeks)</td>
<td>BoNT-A/Placebo</td>
<td>Mean difference: 15.7 (SD = 16.4)</td>
<td>p &lt; 0.001**</td>
<td>SMD = 0.96</td>
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<tr>
<td>Scopolamine/BoNT-A</td>
<td>Mean difference: -2.1 (SD = 20.2)</td>
<td>p &gt; 0.05</td>
<td>SMD = -0.10</td>
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<td>BoNT-A/Placebo</td>
<td>Mean difference: 8.43/6.00</td>
<td>p &gt; 0.05</td>
<td>SMD = -0.80</td>
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<td>(0-2 weeks)</td>
<td>BoNT-A/Placebo</td>
<td>Mean difference: 2.67/6.71</td>
<td>p &lt; 0.01*</td>
<td>SMD = 2.4</td>
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<td>(4 Weeks)</td>
<td>BoNT-A/Placebo</td>
<td>Mean difference: 5.17/9.29</td>
<td>p &gt; 0.05</td>
<td>SMD = 1.2</td>
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<tr>
<td>(6 Weeks)</td>
<td>BoNT-A/Placebo</td>
<td>Mean difference: 3.33/5.57</td>
<td>p &lt; 0.05*</td>
<td>SMD = 1.3</td>
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<tr>
<td>(8 Weeks)</td>
<td>BoNT-A/Placebo</td>
<td>Mean difference: 1.83/6.86</td>
<td>p &lt; 0.01*</td>
<td>SMD = 1.7</td>
</tr>
<tr>
<td>(10 Weeks)</td>
<td>BoNT-A/Placebo</td>
<td>Mean difference: 15.7 (SD = 16.4)</td>
<td>p &lt; 0.001**</td>
<td>SMD = 0.96</td>
</tr>
<tr>
<td>Scopolamine/BoNT-A</td>
<td>Mean difference: -2.1 (SD = 20.2)</td>
<td>p &gt; 0.05</td>
<td>SMD = -0.10</td>
<td></td>
</tr>
<tr>
<td>Weeks</td>
<td>BoNT-A/Placebo</td>
<td>Dri Scale as Outcome Measure</td>
<td>Low</td>
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<tr>
<td></td>
<td>Mean difference: 4.83/6.00</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>p &gt; 0.05</td>
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<tr>
<td></td>
<td>SMD = 0.55</td>
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<td>No other data available for children with CP</td>
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<td>Limited data on children with CP</td>
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<td>Study</td>
<td>Week</td>
<td>Scale as Outcome Measure</td>
<td>Risk of Bias</td>
<td>Notes</td>
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<td>-----------</td>
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<tr>
<td>Alrefai 2009</td>
<td>13/11</td>
<td>Thomas Stonell - Greenberg</td>
<td>Low</td>
<td>High risk of bias (Figure 1)</td>
</tr>
</tbody>
</table>

**Alrefai 2009**
- **Placebo/BoNT-A**
  - Median frequency score 4/3, *p* < 0.05*
  - Median severity score 5/4, *p* < 0.05*
  - SMD not calculable from data available

**Lin 2008**
- **Baseline**
  - BoNT/Control
    - Mean difference: 6.17/6.86
    - *p* > 0.05
    - SMD = 0.54

- **(0-2 weeks)**
  - BoNT-A/Placebo
    - Mean difference: 5.33/6.29
    - *p* < 0.05*
    - SMD = 1.21

- **(4 Weeks)**
  - BoNT-A/Placebo
    - Mean difference: 5.17/6.71
    - *p* = 0.05
    - SMD = 1.8

- **(6 Weeks)**
  - BoNT-A/Placebo
    - Mean difference: 5.00/6.29
    - *p* = 0.05*
    - SMD = 1.24

- **(8 Weeks)**
  - BoNT-A/Placebo
    - Mean difference: 5.00/6.29
    - *p* = 0.05*
    - SMD = 1.24
BoNT-A/Placebo
Mean difference: 5.00/6.29
p=0.05*
SMD = 1.24
(10 Weeks)
BoNT-A/Placebo
Mean difference: 4.83/6.14
p>0.05
SMD = 0.86
(12 Weeks)
BoNT-A/Placebo
Mean difference: 5.00/6.43
p=0.05*
SMD = 0.87
(14 Weeks)
BoNT-A/Placebo
Mean difference: 5.33/6.57
p>0.05
SMD = 0.74
(18 Weeks)
BoNT-A/Placebo
Mean difference: 5.50/6.43
p>0.05
SMD = 0.45
(22 Weeks)
BoNT-A/Placebo
Mean difference: 5.67/6.43
p>0.05
SMD = 0.37

Adverse Effects to BoNT-A
Alrefai 2009 13/11
2/11 (18%) children reported transient increase in drooling at 2 weeks post treatment but not evident at one month post treatment

Low risk of bias (See Figure 1)
<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Sample Size</th>
<th>Intervention Details</th>
<th>Adverse Events</th>
<th>Uncertainty of Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jongerius 2004a</td>
<td>39/39</td>
<td>Cross-over trial</td>
<td>2/39 (5%) transient flu-like syndrome lasting &lt; 2 days, 3/39 (8%) mild difficulty swallowing</td>
<td>Low</td>
</tr>
<tr>
<td>Reid 2008</td>
<td>18/13 with CP</td>
<td>In treatment group in larger study: 1/24 (4%) developed speech, swallowing and choking difficulties in first 5 days, 1/24 (4%) developed severe chest infection on Day 5 post injection, 1/24 (4%) developed first seizure 2 days after injection, 4/24 (17%) reported more viscous saliva, “Some” reported increased difficulty swallowing dry or hard food*</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Lin 2008</td>
<td>7/6</td>
<td>None reported</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td>Alrefai 2009</td>
<td>8/24 (33%) withdrew from study, 6 from placebo and 2 from treatment group</td>
<td>Reasons given are incomplete but include lack of effect, distance for children and carers to travel to treatment centre and discomfort associated with procedure</td>
<td>Low</td>
<td></td>
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<tr>
<td>Jongerius 2004a</td>
<td>6/39 (15%) withdrew from control arm of study</td>
<td>4 children could not complete the scopolamine period, 1 changed antiepileptic medication and 1 was unable to attend for assessments due to illness reported as not related to the trial</td>
<td>Low</td>
<td></td>
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*Note: “Some” indicates the exact number is not specified.
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<thead>
<tr>
<th>Study</th>
<th>Findings</th>
<th>Quality</th>
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<tr>
<td>Lin 2008</td>
<td>Not reported</td>
<td>Low</td>
</tr>
<tr>
<td>Reid 2008</td>
<td>Not reported specifically for children with CP</td>
<td>Low</td>
</tr>
</tbody>
</table>

* = Statistically significant
** Wherever data have been published as p < 0.000, these data have been reported as p < 0.001.
*** In calculating the SMD, mean values are multiplied by -1 where relevant to correct for differences in the direction of the scale.
BACKGROUND

Description of the condition

Cerebral palsy (CP) is defined by Bax 2005 as "a group of disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, cognition, communication, perception, and/or behaviour, and/or by a seizure disorder" (p.572). Drooling is a common problem for children with CP. For the purposes of this review, we will define drooling as the unintentional loss of saliva from the mouth (Blasco 1992; Reddihough 2010 ). Other definitions include: a visually evident presence of excessive saliva (Poling 1978), saliva outside the lower lip (Lancioni 1989), spilling of saliva from the mouth onto the lips, chin, neck and clothing (Brodsky 1993), pools of saliva greater than one inch diameter (Kay 2006), saliva (either a drop or a string) present beneath the lower lip line or a string falling from the mouth for a period longer than two seconds without the individual cleaning his/her face and/or clothes (Van der Burg 2009). Prevalence figures on drooling in children with CP vary from 37.4% (Van De Heyning 1980) to 58% (Tahmassebi 2003a).

Drooling is generally not considered to be due to excessive production of saliva or sialorrhoea (Tahmassebi 2003b). It is more commonly associated with dysfunction of the oral phase of the swallow with inadequate lip closure, disorganised tongue movements exacerbated by lack of oral and perioral sensory perception, head-down posture, reduced frequency of swallowing and dysphagia (Nunn 2000; Senner 2004). In an international consensus statement on drooling, Reddihough 2010 suggested a distinction between anterior and posterior drooling for the purposes of understanding the aetiology and impact of drooling. Anterior drooling is defined as ‘saliva spilled from the mouth that is clearly visible’ (p.110) while posterior drooling is described as saliva spilling through the faucial isthmus creating a risk of aspiration.

Drooling can be distressing for children with CP, as well as for their parents and/or caregivers. Reported side effects include: risk of social rejection, constant damp and soiled clothing, unpleasant odour, irritated chapped or macerated facial skin, perioral and oral mouth infections especially candida albicans, dehydration, impaired masticatory function, interference with speech, damage to books, communication aids, electronic communication devices, computers, audio equipment, and social isolation (Blasco 1992; Van der Burg 2006). The associated dysphagia can increase the risk of chest infections and aspiration pneumonia.

Description of the intervention

A multidisciplinary team approach to the management of drooling is advisable (McAloney 2005; Crysdale 2006; Reddihough 2010). Team members can include neurologists, otolaryngologists, paediatricians, plastic surgeons, speech and language therapists, paediatric dentists, occupational therapists, psychologists, physiotherapists, nurses, and teachers. The following interventions are used in the management of drooling in children with neurological impairment.

(1) Surgery

Surgical intervention aims to either reduce or eliminate neural stimulation to the salivary glands, to redirect saliva by rerouting salivary flow, to block salivary flow and induce atrophy of the glands through ligation or to eliminate the production of saliva by excising the salivary glands. Surgical intervention can be performed unilaterally or bilaterally and involves a general anaesthetic. While each of the procedures below is described individually, published studies report a combination of methods.

Surgical interventions include the following.

(a) Sectioning of the parasympathetic neural pathway. This typically involves either sectioning of the chorda tympani nerve (Goode 1970) or tympanic neurectomy (Friedman 1974). The chorda tympani nerve carries afferent fibres of taste from the anterior two-thirds of the tongue and efferent parasympathetic nerve fibres from the inferior salivary nucleus to the submandibular and sublingual glands. Denervation works by eliminating parasympathetic stimulation to the salivary glands. Adverse side effects include hearing loss and permanent taste loss in the anterior two-thirds of the tongue as well as an increase in thick mucoid saliva. Its advantage is that there are no external excisions to the face (Reed 2009; Scully 2009).

(b) Submandibular gland rerouting. This involves transferring the submandibular ducts to approximately 1 cm behind the tongue base, directing salivary flow posteriorly. It is contraindicated in children with a history of aspiration pneumonia. Side effects include postoperative pain, ranula formation (i.e. pseudocysts on the floor of the mouth), sialoadenitis (inflammation of salivary gland) (Puravjiappan 2007) secondary haemorrhage, lingual nerve palsy, submandibular gland swelling, fibrosis at the site of the duct and aspiration pneumonia (O’Dwyer 1997).

(c) Submandibular gland ligation. This entails surgically tying the salivary gland ducts. The salivary glands continue to produce some saliva until atrophy occurs. This type of surgery is rarely carried out in isolation as the saliva produced by these glands is more viscous and more alkaline than that produced by the parotid glands. It therefore increases the risk of developing submandibular salivary gland stones due to saliva retention and saliva composition factors (Andretta 2005).

El-Hakim reports a modification of this procedure using vascular clips instead of sutures to ligate the salivary ducts (El-Hakim 2008). This procedure avoids the need for cannulation of ducts,
Thus limiting damage to the duct and avoiding leakage of saliva at the site of the duct.

**D** Submandibular gland excision. This involves surgical removal of the submandibular gland(s) which can be removed transorally (Kauffman 2009), transcervically with a 4 to 6 cm incision in the lateral neck crease approximately 2 to 3 cm below the lower edge of the mandible (Beahm 2007); or endoscopically.

Adverse side effects include xerostomia (dry mouth) with resulting impact on mastication and dental health; external scarring; and risk of facial and hypoglossal nerve damage (Burton 1991).

**E** Sublingual gland excision. This involves the removal of the sublingual gland either unilaterally or bilaterally. Such surgery is typically carried out in conjunction with submandibular gland rerouting or excision. It involves extensive floor of mouth resection and adverse side effects include potentially longer hospital stay, lingual nerve palsy, and an increased likelihood of developing a postoperative haemorrhage (Glynn 2007).

**F** Parotid duct rerouting. This redirects salivary flow in the stimulated state. It involves a general anaesthetic and side effects include the risk of developing a ranula, possible increase in aspiration (Scully 2009), wound dehiscence (splitting open of wound), parotitis, and transient parotid swelling (Faggella 1983).

**G** Parotid duct ligation. This procedure involves tying and suturing the parotid ducts transorally (El-Hakim 2008). Advantages are minimal surgical dissection and low morbidity rate (Heywood 2009). Adverse side effects include postoperative wound infection and risk of developing a ranula.

There are combinations of procedures which point to successful outcomes. Reed 2009 carried out a meta-analysis of surgical procedures used to eliminate or reduce salivary flow. This suggested that bilateral submandibular gland excision and parotid duct rerouting pioneered by Wilkie (Wilkie 1977) had a high success rate. Bilateral submandibular gland rerouting and bilateral parotid duct ligation were also reportedly to be successful.

**(2) Pharmacologic treatments**

These interventions work by decreasing the volume of saliva produced in the oral cavity and in the gastrointestinal tract. In the oral cavity, agents block cholinergic muscarinic receptors inhibiting stimulation of the salivary glands. The anticholinergic drugs most commonly used are atropine, benztpine, glycopyrrolate bromide, benzhexol hydrochloride (also known as trihexyphenidyl) and scopolamine. Medications vary in their method of delivery, dosage, frequency of delivery and length of treatment. Medications can be administered orally, intravenously, topically as dermal patches, intramuscularly, and via nebulisation (Zeppetella 1999).

Pharmacological interventions cannot selectively block stimulation of the salivary glands. As a result, unwanted side effects which can involve the central nervous system are frequently reported (Jongerius 2003).

Side effects from medications include: xerostomia, thick mucoid secretions, dehydration, urinary retention, urinary tract infections, constipation, facial flushing, skin rash, fever, dizziness, drowsiness, headache, dilated pupils, blurred vision, and epilepsy (Mier 2000). Mier et al. also reported behavioural changes (hyperactivity, restlessness, and irritability).

Gastroesophageal reflux may exacerbate drooling by stimulating the oesophagosalivary reflex. Antireflux medication decreases gastroesophageal reflux, inhibits stimulation of the oesophagosalivary reflex, and decreases salivary flow (Heinen 1996). There are no reports of adverse side effects.

**(3) Botulinum toxin**

Botulinum toxin A (BoNT-A) is the most common neurotoxin used to treat drooling. Some researchers have also used Botulinum Toxin B (BoNT-B) (Berweck 2007; Witherow 2008). Botulinum toxins act by inhibiting the release of acetylcholine at the neuromuscular junction and reducing the amount of saliva produced by the salivary glands. BoNT-A formulations available include Botox® (Allergan Inc.) and Dysport® (Ipsen Ltd). Both products differ in terms of molecular structure, manufacturing processes and use different methods for determining biological activity (Heinen 2006) The dosage varies according to the product and the weight of the child. One unit of Botox® is estimated to be comparable to three to four units of Dysport® (Fuster Torres 2007).

Adverse side effects can relate to trauma at the injection site as well as adverse effects associated with the botulinum toxin (Reddihough 2010). Adverse effects relating to trauma at the site of the injection can include pain, hematoctma, intraoral blood, swallowing difficulty associated with swelling of the salivary gland, infection, possible trauma to the facial nerve when injecting the parotid gland (Reddihough 2010), rash attributed to the ultrasound gel when ultrasound is used to identify the site of injection (Hassin-Baer 2005). Side effects associated with the botulinum toxin include excessively dry mouth, problems with chewing and swallowing as a result of toxin diffusion to muscles involved in swallowing, facial weakness, recurrent mandibular dislocation (Tan 2001) and transient fever (Ong 2009). BoNT-B is thought to have a greater affinity to autonomic receptors than BoNT-A. Studies suggest that BoNT-B can be deactivated as a result of antibody formation (Berweck 2007). BoNT-B is also reported to have a greater impact on xerostomia than BoNT-A (Tintner 2005). Side effects of BoNT-B include constipation, excessive dry mouth, velopharyngeal incompetence, and acute parotitis (Tintner 2005; Witherow 2008).

Botulinum toxin varies according to the product selected, the professional administering the injections, the dosage of neurotoxin given, the calibre of the needle used to inject the neurotoxin, the salivary glands injected, the method used to identify the site of injection (ultrasound guidance versus blind), the number of injection points, the type of anaesthesia used in the procedure (general versus local), and the duration of therapeutic effect. The safe max-
imum dosage and ideal method of application are not established (Fuster Torres 2007; Reddihough 2010).

(4) Physical, oro-motor and oro-sensory therapies
These interventions involve correction of general body posture and head posture to eliminate the anterior loss of saliva from the oral cavity, therapy to improve lip and jaw closure as well as increasing tongue control, reducing tongue thrust (McCracken 1978), normalising tone, and normalising facial and oral sensation. Therapy can be delivered either individually or in a group (Harris 1980) and varies according to the level of impairment and the ability of the child to comply with instructions. There are no reports of adverse side effects.

(5) Behavioural interventions
These interventions aim to increase target behaviours such as swallowing, wiping, head control, mouth closure, and performing self-control of drooling behaviour (Van der Burg 2007). They can be categorised into four different approaches (Van der Burg 2007): (a) instruction, prompting, and positive social reinforcement; (b) negative social reinforcement and declarative procedures; (c) cueing techniques; and (d) self-management. There are no reports of adverse side effects.

(6) Intra-oral appliances
These appliances aim to modify and improve oral motor function, thus improving oral control of saliva and its containment within the oral cavity. Appliances vary according to shape, position within the oral cavity and the length of time that the person must wear the appliance. Examples of intraoral appliances used in the management of drooling include the Exeter Lip Sensor, palatal training appliances (Selley 1985) and the Innsbruck Sensorimotor Activator and Regulator (ISMAR) (Johnson 2004). The Castillo-Morales appliance (Fischer-Brandies 1987) is used in conjunction with oro-motor therapy. Side effects include the inability to tolerate the appliances and oral discomfort.

(7) Acupuncture
Tongue acupuncture has been used in the treatment of drooling in children with neurological impairment (Wong 2001). It is based on traditional Chinese medicine and involves acupuncture performed daily to five points of the tongue for a specified number of sessions. No side effects are reported.

How the intervention might work
This range of interventions aims to either (1) reduce saliva production and/or redirect salivary flow to the posterior part of the oral cavity; (2) improve physiological oral motor function to increase containment of saliva within the oral cavity; or (3) increase the child’s ability to manage oral secretions with behaviours such as chin wiping, increased frequency of swallowing etc.

Why it is important to do this review
Clinicians currently face the difficult task of selecting an intervention for managing drooling in children with cerebral palsy. In the absence of a systematic review of the evidence, they must make clinical decisions against a background of conflicting evidence within the research literature. The long term effects of interventions are unknown.

OBJECTIVES
1. To evaluate the effectiveness and safety of interventions aimed at reducing or eliminating drooling in children with cerebral palsy.
2. To provide the best available evidence to inform clinical practice.
3. To assist with future research planning.

METHODS

Criteria for considering studies for this review

Types of studies
We evaluated all published and unpublished randomised controlled trials (RCTs) and controlled clinical trials (CCTs). We classed as RCTs all trials that involved at least one test treatment aimed at improving or eliminating drooling and one control treatment; or no treatment with concurrent enrolment and follow up of the test and control treated groups; as well as trials in which the treatment to be administered is selected by a random process, such as a random numbers table (Lefebvre 2008). We imposed no language restrictions. We defined CCTs as all trials that involved at least one test treatment aimed at improving or eliminating drooling and one control treatment; or no treatment with a non-randomised but bias free method of assigning patients to the test treatment (Lefebvre 2008). We imposed no language restrictions.
Types of participants
We included male and female children/adolescents aged 0 to 18 years with a clinical diagnosis of any type of CP and all severities of drooling in this review. We included trials of participants of mixed ages if the data allowed for data extraction on participants 0 to 18 years. We included trials of participants with other neurological conditions which included children with CP if the data allowed for data extraction on participants with CP. We did not exclude trials on account of additional impairments such as intellectual impairment, sensory impairment, epilepsy or dysphagia.

Types of interventions
We included any intervention which aimed to reduce or eliminate drooling. Interventions could occur in any setting and can be delivered by a trained person or a team. We excluded studies that involved interventions given by caregiver alone. We considered any dosages, intensity, mode of delivery, frequency, duration and timing of delivery of interventions. We considered the immediate, medium and long term improvements in drooling behaviour as well as adverse effects of interventions.

We made the following comparisons.
1. Intervention versus no intervention
2. Intervention versus placebo
3. Intervention versus other intervention.

We excluded trials that included the intervention of interest combined with another intervention as these trials would not allow the reviewers to reach clear consensus on the intervention of interest.

Types of outcome measures
We considered the following outcome measures as potential measures of success: outcome measures that signify a reduction or elimination of drooling and reflect the satisfaction of the person with CP and/or family with the intervention.

Primary outcomes
1. Reduction of volume of saliva produced
2. Reduction of frequency and severity of drooling
3. Client and/or carer satisfaction with intervention

Secondary outcomes
1. Adverse effects including increase in drooling, dysphagia, compromised medical health, compromised dental health, negative social consequences, negative psychological consequences, hospitalisation, death
2. Change in quality of life, self esteem and self-concept
3. Proxy measures of reduction in unwanted symptoms other than drooling (e.g. reduction in skin chafing, candida albicans, odour)
4. Non-compliance with intervention

We considered three time frames: (1) immediate change, (2) medium term change (three to 18 months) and (3) long term change (18 months +).

Search methods for identification of studies
We included published and unpublished studies of trials in any language in the review. There were no date restrictions on trials.

Electronic searches
We used the search strategy recommended by the Cochrane Movement Disorders Group to find relevant studies for the review. We used search terms and synonyms for ‘drooling’, ‘cerebral palsy’, ‘children’ using the controlled vocabulary used for indexing specific to each database searched. We imposed limits according to publication type when allowed by the database and filters to include clinical trials.

We searched the following databases for possible eligible reports in any language published from inception to December 2010:
- Cochrane Central Register of Controlled Trials (CENTRAL);
- Medline via Ovid; EMBASE; CINAHL; ERIC; Psych INFO; Web of Science;
- Web of Knowledge; AMED; SCOPUS; Dissertation Abstracts.

We searched for ongoing clinical trials in the Clinical Trials web site (http://clinicaltrials.gov) and in the Current Controlled Trials web site (http://www.controlled-trials.com/).

Searching other resources
We handsearched the following journals.

- American Journal of Speech-Language Pathology
- Archives of Disease in Childhood
- Brain & Development
- Clinical Otolaryngology
- Clinical Pediatrics
- Developmental Medicine and Child Neurology
- European Journal of Paediatrics
- Folia Phoniatica et Logopaeotica
- International Journal of Language and Communication Disorders
- International Journal of Paediatric Dentistry
- International Journal of Pediatric Otorhinolaryngology
- Journal of Communication Disorders
- Journal of Developmental and Physical Disabilities
- Journal of Intellectual and Developmental Disability
- Journal of Medical Speech-Language Pathology
- Journal of Oral Rehabilitation
- Journal of Speech, Language and Hearing Disorders
- Language, Speech and Hearing Services in Schools

We checked published conference proceedings of the following organisations.

- American Academy of Cerebral Palsy and Developmental Medicine (2002-2010)
Data collection and analysis

Selection of studies
We merged the search results using reference management software (EndNote) and removed duplicate records of the same report. Two authors (M Walshe and M Smith) individually examined the titles and abstracts of studies identified. We classified studies as ‘relevant’, ‘potentially relevant’, and ‘not relevant’ to this review. We excluded reports that clearly did not meet the inclusion criteria and were not relevant. We resolved disagreements on inclusion of studies through discussion.

One author (M Walshe) retrieved full texts of relevant and potentially relevant reports and linked multiple reports of the same study. All three authors (L Pennington; methodology, M Smith; content and M Walshe) examined final full texts of relevant reports for compliance with eligibility criteria. Where the eligibility of a study was in question, we contacted the authors to seek further information. The review team were not blinded to information about study authors, institutions, journal of publication or results. We resolved any disagreements through discussion. The interrater reliability for rating the eligibility of studies was found to be Kappa = 0.8 suggesting substantial agreement (Higgins 2008a).

Data extraction and management
A specifically devised form was used to extract data from study reports. The three review authors (M Walshe, M Smith, and L Pennington) independently extracted data from each report to minimise errors and reduce potential risk of bias. Data was extracted on these four main areas:
- Methods
- Participants
- Interventions
- Outcomes

We resolved disagreements through discussion and on one occasion through consultation with a member of the Cochrane Collaboration.

Assessment of risk of bias in included studies
We examined five domains of bias: selection bias, performance bias, attrition bias, detection bias and reporting bias. A Risk of Bias table was completed for each study (Characteristics of included studies) and is summarised in Figure 1.
Figure 1. Risk of bias summary: review authors’ judgements about each risk of bias item for each included study.

<table>
<thead>
<tr>
<th></th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding (performance bias and detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Other bias</th>
</tr>
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</table>
Measures of treatment effect

Dichotomous (binary) data
None of the studies included in the review used binary outcomes.

Continuous data
Studies, which reported continuous data, examined reduction of volume of saliva produced and reduction of frequency and severity of drooling using different scales. We used the standardised mean difference (SMD) where possible as a summary statistic to compare the outcomes for these studies.

Unit of analysis issues
The unit of analysis was individual children. For parallel group designs (Alrefai 2009; Lin 2008; Reid 2008) we examined whether the number of measurements in the analysis matched the number of children that were randomised to that intervention. For cross over designs (Camp-Bruno 1989; Jongerius 2004a; Mier 2000) we set out to take all measurements from intervention E (Experimental group) and all measurements from intervention C (Control group) periods and analyse them as if the trial were a parallel group trial. For parallel groups, where results were available for more than one time point, we set out to analyse separately repeated observations of participants (i.e. short term, medium term and long term follow-up outcome measures).

Dealing with missing data
The reviewers, whenever possible, contacted authors to supply any missing data from included studies. Some of the studies were over 10 years old and although we carried out Internet searches to locate the authors, we were unable to locate all authors. One of the authors contacted (Reid 2008) supplied the data on children with CP in their study. The potential impact of missing data is dealt with in the Discussion section of the review.

Assessment of heterogeneity
We analysed and present studies for each main category of intervention separately. There is clinical diversity and methodological heterogeneity within each intervention. There was not sufficient homogeneity in terms of participants, interventions, and outcome measures used to perform a meta analysis.

Assessment of reporting biases
We were unable to use funnel plots as there were insufficient numbers of studies (minimum of 10 required) available. While we can reduce reporting bias through inclusion of published and unpublished trials, grey literature, and attention to prospective trial registration, we acknowledge that this is not sufficient to reduce the risk of reporting bias.

Data synthesis
A meta analysis was not possible. Instead a descriptive summary of each study was compiled.

Subgroup analysis and investigation of heterogeneity
We grouped the results from each intervention separately. We divided botulinum toxin into subgroups taking into account the type of botulinum toxin used, the dosage given, the calibre of the needle used to inject the neurotoxin, the salivary glands injected, the method used to identify the site of injection, the number of injection points, and the type of anaesthesia used in the procedure (Table 1). We divided pharmacological interventions into subgroups according to pharmacological agent used, method of delivery, dosage, frequency of delivery, and length of treatment (Table 2).

Sensitivity analysis
We had planned to conduct a sensitivity analysis to examine the robustness of the review results but this was not possible given the small numbers of studies retrieved, the heterogeneity within interventions and the methodological quality of the included trials.

RESULTS

Description of studies
See: Characteristics of included studies; Characteristics of excluded studies.
See Characteristics of included studies; Characteristics of excluded studies.

Results of the search
Nine published studies were retrieved from the electronic searches. No additional studies were retrieved from hand searching. Two of the nine published studies were duplicate reports (Jongerius 2004a;
Included studies
Following data extraction, only six trials were eligible for inclusion in the review (see Characteristics of included studies; Characteristics of excluded studies). Four studies (Alrefai 2009; Jongerius 2004a; Lin 2008; Reid 2008) examined the efficacy of botulinum toxin A (BoNT-A) and two studies (Camp-Bruno 1989; Mier 2000) examined the pharmacological treatments, benztropine and glycopyrrolate respectively. No RCTs or CCTs were retrieved on surgical interventions, physical, oro-motor and orosensory treatments, intra-oral appliances, behavioural interventions or acupuncture. Two of the included studies (Camp-Bruno 1989; Mier 2000) did not meet fully the inclusion criteria on age. These studies also included some participants without CP and did not allow for data extraction specifically on the children with CP. The Camp-Bruno study (Camp-Bruno 1989) included adults up to 44 years. However, 14 of the 20 who completed the study were children and statistical analysis of the trial results found that age was not significantly correlated with results from outcome measures. The review authors decided to include the report in the review as this was the only RCT that examined benztropine, which is frequently used as an intervention for drooling in children with CP. The Camp-Bruno study (Camp-Bruno 1989) included adults up to 44 years. However, 14 of the 20 who completed the study were children and statistical analysis of the trial results found that age was not significantly correlated with results from outcome measures. The review authors decided to include the report in the review as this was the only RCT that examined benztropine, which is frequently used as an intervention for drooling in children with CP. One person in this study had a progressive neurological condition and the remainder had CP. Mier 2000 included children up to 19 years of age and 2 participants who completed the study did not have CP. This trial explored the efficacy of glycopyrrolate in the management of drooling and the review authors also decided to include this study in the absence of any other trials on this intervention. Both trials provided information on the use of these medications as an intervention with this population.

TRIAL DESIGN
Five of the 6 included studies were RCTs (Alrefai 2009; Camp-Bruno 1989; Lin 2008; Mier 2000; Reid 2008) and 1 was a CCT (Jongerius 2004a). Three studies used a parallel design (Alrefai 2009; Lin 2008; Reid 2008) and 3 used a cross-over design (Camp-Bruno 1989; Jongerius 2004a; Mier 2000).

SAMPLE SIZE
Approximately 198 participants were recruited in the 6 trials. The original numbers recruited for Lin 2008 are not available. A total of 162 people completed the studies. Sample size recruited ranged from 13 (Lin 2008) to 50 (Reid 2008) (mean 33; SD±12.7). The number of participants completing the studies ranged from 13 to 47 (mean 27; SD ±12.4). All of the participants in Jongerius 2004a, Alrefai 2009, and Lin 2008 had CP. Thirty one of the 50 children in Reid 2008 had CP, 26 of the 27 people recruited in Camp-Bruno 1989 had CP and 34 of the 39 children recruited into the study by Mier 2000 had CP.

SETTINGS
Five of the 6 studies were single centre studies, one was a multicentre study. One study was conducted in Taiwan (Lin 2008), one in Jordan (Alrefai 2009), one in the Netherlands (Jongerius 2004a; Jongerius 2004b) two in the USA (Camp-Bruno 1989; Mier 2000) and one in Australia (Reid 2008). Four of the studies were conducted in hospital or health settings (Alrefai 2009; Jongerius 2004a; Mier 2000; Reid 2008) one was conducted in a school environment (Camp-Bruno 1989) and one setting is unspecified (Lin 2008).

PARTICIPANTS
The age of participants across all studies ranged from 21 months to 44 years. Drooling is considered normal in children up to the age of 18 months and is only considered abnormal in the typically developing child after the age of 4 years (Fairhurst 2010). Age must therefore be considered as a confounding factor, especially when considering the results of long term outcome measures. Four of the six included studies (Alrefai 2009; Camp-Bruno 1989; Jongerius 2004a; Mier 2000) included children aged 4 years or under. The lower age range for children in the report by Lin 2008 is unknown. The youngest population of children was in the study by Alrefai 2009. In this study, children's ages ranged from 21 months to 7 years with a mean age of 3.5 years. Dental age of children with CP is considered an important factor with reports that the degree of drooling decreases as dental age increases (Tahmasebi 2003a) but is not referred to in any of the included studies. The type of CP was not specified in any of the studies. All children recruited in the trials were reported to have moderate to severe drooling. This was determined using defined criteria on the Teacher Drool Scale (Camp-Bruno 1989) or Thomas-Stonell and Greenberg Scale (Thomas-Stonell & Greenberg 1988) for three of the studies (Alrefai 2009; Camp-Bruno 1989; Jongerius 2004a). Camp-Bruno 1989 excluded children with a history of seizures. The children in the trials were heterogeneous in terms of existing co-morbidities. The children in Mier 2000 had a range of co-existing disorders and conditions, which included closed head injury, tracheostomy and hydrocephalus (see Characteristics of included studies). Jongerius 2004a excluded children with systemic disease (bronchial asthma, congenital heart failure, myasthenia gravis). Information on co-morbidities was not provided for two of the studies (Alrefai 2009; Lin 2008).
Information on the gender of children recruited as well as the gender of the children who completed the studies was not available for all studies. Some studies (Alrefai 2009; Reid 2008; Jongerius 2004a) provide information on gender of children recruited while others give either no information (Lin 2008) or information only on those completing the study (Mier 2000; Camp-Bruno 1989). The gender of the 31 children with CP in the Reid 2008 study was supplied by the authors. Overall, from the data available, there were more males than females in the trials, reflecting the prevalence of CP in males (Odding 2006). A total of 86 males and 61 females were involved in the studies, either at the point of recruitment or at point of study completion.

INTERVENTIONS

There is considerable variation in how the interventions were delivered across all 6 studies. The four interventions that examined botulinum toxin all used BoNT-A. The studies varied considerably in the products used, how these products were prepared, the salivary glands targeted, the number of injections given and the dosage given, how the dosage was determined (i.e. weight dependent), calibre of needles used for injections, methods used to identify the injection sites and the anaesthesia given to children during the procedure (see Table 1). The control interventions also differed. There was similar heterogeneity in the studies using pharmaceutical interventions (Table 2).

Treatment ranged from 5 weeks with no follow up (Camp-Bruno 1989) to 22 weeks with 1 year follow-up (Reid 2008).

OUTCOME MEASURES

All studies considered immediate change. The pharmaceutical interventions considered only immediate change. Trials on BoNT-A examined medium term (three to 18 months) change. None of the studies in this review considered long term (i.e. 18 months +) change following intervention.

Primary outcomes

Reduction of volume of saliva produced

Only two studies (Jongerius 2004b, Lin 2008) directly measured either changes in the volume of saliva produced or changes in salivary flow following intervention. Jongerius 2004b used the swab method (Table 3) to measure changes in salivary flow rate. Lin 2008 measured saliva weight but did not explain how they measured this.

Reduction of frequency and severity of drooling

All 6 studies measured the frequency and severity of drooling to some extent. Scales used are described in Table 3. They included the Drooling Frequency and Severity Scale (Thomas-Stonell 1988) the Drooling Quotient (Rapp 1980, Jongerius 2004c), the Drooling Scale (Mier 2000), a visual analogue scale (Jongerius 2004c), the Drooling Impact Scale (Reid 2008; Reid 2010) and the Teacher Drool Scale (Camp-Bruno 1989). Four studies (Alrefai 2009; Camp-Bruno 1989; Reid 2008; Mier 2000) used one outcome measure for this area, while others (Jongerius 2004a; Lin 2008) used more than one scale. Reid 2008 included just one question on the frequency of drooling (‘How frequently did your child dribble?’) and one question on the severity of drooling (‘when your child did dribble, how severe was the drooling?’) in their assessment. However, they did include other questions that related to frequency and severity of drooling such as ‘How many times a day did you have to change bibs or clothing due to drooling?’,” “How frequently did your child’s mouth need wiping?”, “How much do you have to wipe or clean saliva from household items, e.g. toys, furniture, computers, etc?”.

Reduction in the impact of drooling on child/family

Reid 2008 was the only study that included direct questions on the impact of drooling on the child and family in their outcome measure. They asked, ‘To what extent did your child’s drooling affect his or her life?’ and ‘To what extent did your child’s dribbling affect you and your family’s life?’

Client and/or carer satisfaction with intervention

None of the studies included in the review reported outcomes in this area although Reid 2008 reported that one family was ‘fairly’ satisfied with results following BoNT-A and another two ‘were not entirely disappointed’.

Secondary outcomes

Only one of the six included studies (Lin 2008) did not examine any secondary outcome.

Adverse effects.

Trials used a variety of measures to detect the presence of adverse effects to treatment. Reid 2008 asked parents to register perceived side effects of BoNT-A in a diary. Alrefai 2009 explained the anticipated side effects of BoNT-A to parents and caregivers and asked them to report these if they occurred. Jongerius 2004a asked parents to register all possible side effects of BoNT-A in a diary and discussed these
during outpatient visits. The extent of side effects was rated on a 4 point scale (0 = 'no side effect' to 3 = 'severe side effect, constantly present'). Mier 2000 gave parents a list of 15 side effects of glycopyrrolate and questioned parents every week about these as well as any other effects not on the list. These adverse effects were mainly physical and behavioural and were rated on a scale from 1 = 'not at all' to 4 = 'very much'. They also conducted a physical examination at each visit and checked for the presence of maceration or induration around the mouth, and checked weight and blood pressure. In the Camp-Bruno 1989 study, teachers were asked to report any 'unusual changes'. Nurses also observed participants for adverse effects and close contact was maintained with home caretakers regarding side-effects of medication. The Behavioral and Medical Rating scale (Table 3) was completed two to three times a week.

Change in quality of life, self-esteem and self-concept.

Only one study included a specific indirect question in this domain. In the Drooling Impact Scale, Reid 2008 asked how embarrassed the child seemed to be about his/her drooling. None of the other studies included in the review examined this area.

Proxy measures of reduction in unwanted symptoms other than drooling (e.g. reduction in skin chafing, candida albicans, odour).

Reid 2008 included a question on odour in the Drooling Impact Scale (‘How offensive was the smell of the saliva on your child?’). They also included a question on skin irritation (‘How much skin irritation has your child had due to drooling?’). In general, measures that examined adverse effects looked for the presence of new symptoms rather than a reduction in other unwanted symptoms that arise as a result of drooling.

Non-compliance with intervention

Compliance with the treatment was reported for all trials except for Lin 2008.

The methodological quality of the included studies is summarised in Table 4. Overall the methodological quality of the included studies is variable. The power to detect a true difference between intervention groups was not determined for all studies prior to analysis. Power calculations prior to recruitment were performed in two of the included studies (Jongerius 2004a; Reid 2008). Lin 2008 had a small number of participants and reports that the power of the study is reduced to 69.5% as a result. Only two of the 6 included studies (Jongerius 2004a; Reid 2008) report the confidence interval of the results. The Risk of Bias (discussed below) contributes further to the methodological weakness of the included studies.

Excluded studies

We included any intervention which aimed to reduce or eliminate drooling. We stated in our protocol (Walsh 2010) that we would exclude studies that involved interventions given by caregiver alone, or those that included the intervention of interest combined at the same time with another intervention. However, we did not come across any trials that used these methodologies. Studies retrieved were excluded because we were unable to extract data on children with CP and we were unable to obtain that data from the authors.

Risk of bias in included studies

See Figure 1 Summary assessments of risk of bias.

Allocation

Methods for recruitment varied. Children were recruited from either saliva control clinics (Reid 2008), out-patient clinics (Jongerius 2004a), or local multidisciplinary team CP clinics (Alrefai 2009). Recruitment methods were unclear in Camp-Bruno 1989 study and in Lin 2008. The children in Mier 2000 were recruited through word of mouth and by placing information signs in examination rooms. Inclusion criteria varied across studies (See Table 2).

Once recruited, the method of randomisation was unclear for all but one of the studies (Reid 2008) and selection bias is likely in all included studies. In accordance with our protocol (Walsh 2010) we considered randomisation of participants adequate where a study applied either a random number table, a computer-generated random number, coin tossing, dice throwing, selection of names from an envelope etc. We considered the risk of selection bias high if participants were selected according to non-random methods.

We specified that methods of allocation concealment must be described in full and that methods of allocation to groups must, as much as is practical, ensure that participants and researchers did not foresee the intervention although this may not always be possible but allocation of trial groups to pharmaceutical interventions must be adequately concealed from participants and investigators. The review authors judged that the two interventions included in this review (pharmacological interventions and botulinum toxin) could have used allocation concealment methods.

Reid 2008 is the only trial included in the review that describes, albeit briefly, the method used to conceal the allocation sequence. The lack of information provided in the other studies make it difficult for review authors to determine if groups allocated to interventions could have been seen in advance of, or during enrol-
Higgins 2008b advises that adequate concealment of allocation sequence safeguards those who admit participants to a study from knowing the upcoming assignments, thus reducing the risk of selection bias and improving the methodological quality of the study.

Blinding

As per the protocol (Walshe 2010) performance bias examined blinding of participants, outcome assessors and data analysts for pharmaceutical interventions. Performance bias is likely in both studies involving pharmaceutical interventions (Camp-Bruno 1989; Mier 2000). In Camp-Bruno 1989, the first week on benztpine was used for drug titration. It is possible that blinding of the treatment providers and participants could be broken during this drug titration period. Measures to prevent this are not described. In addition, it was not clear if all outcome assessors were blinded to intervention.

In Mier 2000, there was blinding of the person delivering treatment and patients receiving treatment. However, it is not clear in the report if the person performing the physical examination for side effects was blinded to the intervention.

In the protocol (Walshe 2010) it was considered that blinding of participants and healthcare providers would not be possible for interventions such as surgery, botulinum toxin, behavioural interventions, intra-oral appliances, and acupuncture and that we would examine blinding of outcome assessors and data analysts in these instances. However, in their study on botulinum toxin, Alrefai 2009 and Lin 2008 both used a placebo injection and blinding was possible in both trials.

Overall, the studies included in this review do not clarify who was and who was not blinded to the intervention. The lack of clarification on whether outcome assessors were blinded to treatments could therefore introduce observer bias. The results of the outcomes of these trials may over-estimate the effect of the intervention.

Incomplete outcome data

Incomplete outcome data can suggest attrition bias. For the majority of studies in this review it is not possible to conclude that attrition bias is absent in the reporting of the trials. We examined completeness of outcome data for each of the included studies and examined whether missing data were due to attrition or exclusion from analysis. Three primary outcomes were selected for this review: reduction of volume of saliva produced, reduction of frequency and severity of drooling, and client and/or carer satisfaction with intervention. The possible impact of incomplete data is considered for each primary outcome.

Only two studies (Jongerius 2004a; Lin 2008) examined a reduction of volume of saliva produced. Outcome data for Lin 2008 are incomplete as there is no information on how many individuals were initially recruited and whether there were withdrawals from treatment. Missing outcome data for Jongerius 2004a study are reported but reasons for the missing data at various measurement points are not explained. They report 21 missing values and deal with this missing data by using ‘last observation carried forward’ (LOCF). Given that the effects of BoNT-A can decrease over time, the use of this approach could threaten the validity of the findings. All six trials reported outcomes for the frequency and severity of drooling. Lin 2008 report outcome data for this domain but the lack of information on numbers recruited and attrition makes it difficult to decide on whether attrition bias exists. The other five studies report dropouts and withdrawals from treatment but do not consistently report at what point withdrawal from the study occurred. Withdrawals are excluded from analysis and in three studies (Camp-Bruno 1989; Jongerius 2004a; Mier 2000) withdrawals occurred because of adverse reactions to treatment. It was difficult for review authors to determine if important outcome data had been excluded from analysis.

Alrefai 2009 provide outcome data on frequency and severity of drooling for 16 of the 24 children who received the first BoNT-A injection. They excluded data for the second BoNT-A injection. They reported outcome data for the second BoNT-A injection from analysis. The caregivers of eight children declined the second injection for reasons unexplained. Although 16 children (7 in placebo and 9 in treatment arm) received the second injection 4 months later, the authors performed statistical analysis on the results of the initial injection only yielding incomplete outcome data due to exclusion from analysis.

In examining the completeness of outcome data for outcomes on client and/or carer satisfaction with intervention, only one study assessed the impact of drooling on children and their families (Reid 2008). They found a strong statistically significant difference (p<0.001) in mean scores on the Drooling Impact Scale between intervention and control groups for children with CP at 1 month. However, this scale looked at both the degree of drooling and the impact of drooling and specific information relating to impact is not available. The difference between groups for children with CP is not available at 6 months or at 1 year post intervention for the children with CP but for the main group, which included children with CP, there was a significant difference between the control and treatment group at six months. Mean drooling scores did not reach
their pre-injection levels after one year. While Reid 2008 included children with other disabilities as well as cerebral palsy and no firm conclusions can be drawn with respect to effects of BoNT-A at 6 months and one year for children with CP, there is no reason to consider that this group would respond any differently to children with intellectual disability.

Outcomes for client and carer satisfaction with interventions are not available for any of the other included studies. For the secondary outcomes selected for this review, we also examined completeness of outcome data for each of the included studies and examined whether missing data were due to attrition or exclusion from analysis. Secondary outcomes selected were adverse effects, changes in quality of life, self esteem and self-concept, proxy measures of reduction in unwanted symptoms other than drooling (e.g. reduction in skin chafing, candida albicans, odour) and non-compliance with intervention.

Outcomes for adverse effects reported in trials were largely medical and behavioural. The development of adverse effects to either the therapy or the control resulted in exclusion of participants from three (Camp-Bruno 1989; Jongerius 2004a; Mier 2000) of the included studies.

Outcomes for adverse effects in most of the included studies relied on parent/caregiver report. Scant details are provided of mechanisms used to elicit reports and observer and reporting bias are possible. Camp-Bruno 1989 assessed the medical and behavioural effects more formally but the presence of incomplete outcome data for dry mouth from 9/20 participants threaten the validity of results for the physiological side effects of benztropine. Missing data occurred because it was inadvertently omitted from assessment although included in the Behavioural and Medical Rating Scale (BMRS).

None of the six included studies set out to measure changes in quality of life, self esteem and self-concept and none reported on this outcome.

Selective reporting

Two of the included studies may give rise to concern regarding reporting bias. One study (Lin 2008) lacks detail in reporting making it impossible to gauge the overall risk of bias for that study. The failure of Alrefai 2009 to report on the outcomes for the second phase of the study also give rise to concerns regarding reporting bias. The remainder of the studies report on the pre-specified outcomes.

Other potential sources of bias

The outcome measures used to measure the frequency and severity of drooling in these studies (see Table 3) do not have established psychometric properties and may contribute to bias in measuring the response to interventions. The lack of sensitivity of outcome measures to detect change in drooling behaviour threatens the validity of study results. Measures that aim to quantify drooling over time such as the Drooling Quotient is reported to have some established validity (Jongerius 2004c; Reddihough 2010) and the content and construct validity of the Drooling Impact Scale along with test-re-test reliability and its sensitivity to change have been reported (Reid 2010).

Effects of interventions

See: Summary of findings for the main comparison Summary of Findings Table; BoNT-A; Summary of findings 2 Summary of Findings: Pharmaceutical Interventions

The included studies involved two interventions; BoNT-A and pharmaceutical interventions. (benztropine and glycopyrrolate). The effects of both interventions are reported separately (see Summary of findings for the main comparison; Summary of findings 2). Give the small number of studies for each intervention; four for BoNT-A and two for pharmaceutical interventions, the methodological flaws and the heterogeneity for all studies, a meta analysis was not possible.

In estimating the effects of interventions, we made the following comparisons:

1. Intervention versus no intervention
2. Intervention versus placebo
3. Intervention versus other intervention.

Effect of Botulinum Toxin A

One study (Reid 2008) compared intervention (BoNT-A) with no intervention. Two compared intervention (BoNT-A versus placebo (Alrefai 2009; Lin 2008) and one compared intervention versus another intervention (Jongerius 2004a).

Data for 31 children with CP were provided by Reid 2008. The mean age of the children with CP was 11.8 years (SD : 12.04 years). They found that changes in degree and impact of drooling occurred following a single weight dependent dose of BoNT-A (Botox®, Allergan) into each parotid and submandibular gland. The reduction in the degree and impact of drooling was statistically significant (t = 5.697, p<0.001, mean difference = 27.38, CI for 95% significance = 17.44-37.31) at 1 month post intervention. Reid 2008 defined a failure to respond to BoNT-A as reduction of less than 10 points on the Drooling Impact Scale. In the CP intervention group, the scores on the Drooling Impact Scale for two children increased by 6 and 12 points respectively suggesting no response or a negative response to intervention. Five children with CP had a reduction in scores of 10 to 20 points suggesting a ‘mediocre’ response to BoNT-A. The remainder of children in the intervention group (n =6) had a decrease in scores greater than 20 indicating an improvement in the degree and impact of drooling. While no follow up data are available specifically on the children with CP, Reid 2008 state that drooling increased again after 1
month for the main treated group but that mean drooling scores did not return to their pre-injection levels even after 1 year. Alrefai 2009 and Lin 2008 both used a placebo and a parallel research design. In the Alrefai 2009 study, the mean age of the participants was 3.5 years in the experimental group (SD ± 1.7 years) and 4.5 years (SD ± 2.0 years) in the control group. They found a decrease in the frequency of drooling (p = 0.034) and in the severity of drooling (p = 0.026) one month after 1 dose of Dysport® was injected into the parotid glands. Dosage was not weight adjusted. Of note, two of the eleven children in the treatment experienced an increase in drooling and did not respond to treatment at one month. Also one child in the placebo group improved scores on the outcome measure used with a decrease in frequency scores. The reason for this is unexplained.

Lin 2008 injected a single weight dependent dose of Botox® (Allergan) into one parotid and the contralateral submandibular gland. The mean age of children in the study was 14.2 years (SD ± 1.8 years). They found a statistically significant reduction in drooling frequency and severity at 2 weeks (p = 0.01), 6 weeks (p = 0.004), 8 weeks (p = 0.05) and 12 weeks (p = 0.05) following the injection. No difference from baseline was observed at 10 weeks (p = 0.08) or at 14 (p = 0.08), 18 (p = 0.21) and 22 (p = 0.28) weeks. The anomaly between the frequency and severity outcome results for weeks 10 and 12 are unaccounted for although the Drooling Quotient (DQ) scores (measuring percentage of time that a person drools in a specified time period) are statistically significant for this time period (p = 0.02). Changes in saliva weight are statistically significant only at 6 weeks (p = 0.02) and at 12 weeks post injection (p = 0.02). The only period where scores for the frequency and severity of drooling, DQ scores and saliva weight scores are all statistically significant is at 6 weeks post injection. Drooling frequency and severity and saliva weight are statistically significant at 12 weeks and there is no evidence of an effect on any outcome measure after that time period.

Jongerius 2004a compared Botox® (Allergan) with scopolamine patches in a cross over design. Participants were injected with a single weight dependent dose of Botox® (Allergan) into the submandibular glands after a trial of scopolamine patches. There was an intervening washout period of 2-4 weeks. Children recruited to the study ranged in age from 3-17 years. The mean age of children was 9.5 years (SD ± 3.7 years). Six of these children withdrew from the study. The age profile of children completing the study is unknown. A statistically significant difference in drooling (p < 0.001) was observed following BoNT-A between baseline measures on the DQ and measures at 2.4, 8, 16 and 24 weeks. There was also a statistically significant difference on VAS measures from baseline to all follow-up assessment points at 2, 4, 8, 16 (p < 0.001) and 24 weeks (p = 0.002). Drooling decreased with both the BoNT-A and scopolamine. There was no significant difference between scopolamine and BoNT-A at 24 weeks on the DQ, Teacher Drool Scale (TDS) scores were statistically significant at 8 weeks (p < 0.001) and at 24 weeks (p < 0.001) post injection. A reduction in salivary flow (Jongerius 2004b) as measured using the swab method was statistically significant at 2, 4, and 8 weeks post injection (p<0.05) but not at 16 and 24 weeks (p>0.05).

There is significant variation amongst these trials making it difficult to reach a consensus on the efficacy of BoNT-A in the treatment of drooling. Two of the included trials on botulinum toxin (Jongerius 2004a; Reid 2008) defined what they considered as ‘responders’ to treatment. (Jongerius 2004a, Jongerius 2004b) defined a ‘responder’ as one whose baseline score on the DQ decreased by 50% and had 2 point improvement on the TDS. On the swab method (Jongerius 2004b), success was defined as a decrease in submandibular salivary flow >1.0 SD within-subjects. Reid 2008 considered a change of 20 points (1 SD) on the DQ and at 1 month post injection. There is insufficient evidence to form any further conclusions.

The adverse effects to BoNT-A reported were transient increase in drooling (Alrefai 2009), transient flu like symptoms (Jongerius 2004a), chest infection (Reid 2008) swallowing difficulties (Jongerius 2004a; Reid 2008) speech difficulties, an increase in more viscous saliva, and the onset of seizure activity (Reid 2008). Overall, 18% of the children in Alrefai 2009, 13% in Jongerius 2004a, and 29% in the study reported by Reid 2008 developed side effects. It is unclear whether all adverse effects reported were directly related to the intervention. It is unknown if the children who developed adverse effects in the Reid 2008 study included children with CP (Summary of findings for the main comparison).

Pharmaceutical Interventions

Both studies on pharmaceutical interventions (Camp-Bruno 1989; Mier 2000) compared intervention versus placebo. They differed in the medications given and outcome measures used. Camp-Bruno 1989 examined reduction in salivary flow and found a statistically significant difference in salivary flow between participants (age range 4-44 years) on placebo and those taking benzotropine (p<.001) immediately after intervention.

Both studies examined the frequency and severity of drooling albeit using different outcome measures. Camp-Bruno 1989 defined a ‘responder’ as those participants who obtained a mean TDS rating of less than 3. They also defined ‘responsivity’ as a decrease of one baseline SD or greater. Mier 2000 defined an improvement of 4 points or greater in their 9 point scale as a standard for significant ‘clinical improvement’. On the Teacher Drool Scale, Camp-Bruno 1989 found a statistically significant difference between both placebo and intervention in the frequency and severity
of drooling immediately after intervention (p≤0.001). Mier 2000 using an adaptation of Thomas-Stonell and Greenberg Scale also found a statistically significant difference between the placebo and intervention immediately after intervention (p<0.001).

It is unknown how long the effects of these medications lasted in terms of reducing the quantity of saliva produced and reducing the frequency and severity of drooling.

Both studies sought information on adverse effects on medical and behavioural function. Mier 2000 found that 69% (25/36) children reported adverse effects while taking glycopyrrolate. The adverse effects of glycopyrrolate reported were behaviour changes involving hyperactivity and irritability. Medical side effect reported were constipation, diarrhoea, dry mouth, dehydration, urinary retention, urinary tract infection, headache, fever, drowsiness, dizziness, dilated pupils, blurred vision, facial flushing, rash, nasal congestion, vomiting, dehydration, thickened secretions (in child with tracheostomy), worsening of epilepsy.

The adverse effects of benztropine reported were behaviour changes such as irritability and listlessness. Medical side effects reported were insomnia, vomiting, dilated pupils, disorientation, facial flushing, ‘glassy eyes’, stomachache, and dry mouth.

Three children of the 27 (11%) children in Camp-Bruno 1989 were excluded because of adverse reactions to benztropine. Eight of the 39 (20.5%) children in Mier 2000 study dropped out because of the adverse side effects to glycopyrrolate. As with the trials on BoNT-A, it is difficult to determine whether all adverse effects reported were directly related to the medication.

Hospitalisation or death was not reported as an adverse effect of any intervention.
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Study</th>
<th>n Placebo/Exp</th>
<th>Mean Differences</th>
<th>GRADE</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in salivary flow</td>
<td>Camp-Bruno 1989</td>
<td>27/27</td>
<td><strong>Time sampling of drooling behaviour as outcome measure</strong>&lt;br&gt;0-2 Weeks&lt;br&gt;Placebo/Benztropine&lt;br&gt;Mean difference: 44.8/ 27.4&lt;br&gt;&lt;em&gt;p&lt;/em&gt; ≤ 0.001**&lt;br&gt;(2 tailed paired t test).&lt;br&gt;SMD not calculable from data given</td>
<td>Low</td>
<td>No measures beyond immediate effect</td>
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<tr>
<td></td>
<td>Mier 2000</td>
<td>39/39</td>
<td>Outcome not measured</td>
<td>Low</td>
<td>No measures beyond immediate effect</td>
</tr>
<tr>
<td>Reduction in frequency and severity of drooling</td>
<td>Camp-Bruno 1989</td>
<td></td>
<td><strong>Teacher Drool Scale as Outcome Measure</strong>&lt;br&gt;0-2 Weeks&lt;br&gt;Placebo/Benztropine&lt;br&gt;Mean difference: 3.53/ 2.38&lt;br&gt;&lt;em&gt;p&lt;/em&gt; ≤ &lt;0.001**&lt;br&gt;(2 tailed paired t test).&lt;br&gt;SMD not calculable from data given</td>
<td>Low</td>
<td>No measures beyond immediate effect</td>
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<td></td>
<td>Mier 2000</td>
<td></td>
<td><strong>Adaptation of Thomas-Stonell &amp; Greenberg Scale as Outcome Measure</strong>&lt;br&gt;0-4 Weeks&lt;br&gt;Placebo/Glycopyrrolate&lt;br&gt;Mean difference 6.33/1.85&lt;br&gt;&lt;em&gt;p&lt;/em&gt; &lt;0.001*&lt;br&gt;(2 tailed paired t test).&lt;br&gt;SMD not calculable from data given</td>
<td>Low</td>
<td>No measures beyond this time point</td>
</tr>
<tr>
<td>Adverse effects of benztrapine</td>
<td>Camp-Bruno 1989</td>
<td>3/27 (11%) withdrew because of side effects.</td>
<td>Behaviour changes: irritability, listlessness, Medical side effects: insomnia, vomiting, dilated pupils, disorientation, facial flushing, 'glassy eyes', stomachache, dry mouth</td>
<td>Low Methodological flaws and risk of bias (See Table 1)</td>
<td></td>
</tr>
<tr>
<td>Adverse effects of glycopyrolate</td>
<td>Mier 2000</td>
<td>8/39 (20.5%) withdrew because of side effects</td>
<td>Behaviour changes: hyperactivity and irritability, Medical side effects: constipation, diarrhoea, dry mouth, dehydration, urinary retention, urinary tract infection, headache, fever, drowsiness, dizziness, dilated pupils, blurred vision, facial flushing, rash, nasal congestion, vomiting, dehydration, thickened secretions (in child with tracheostomy), worsening of epilepsy</td>
<td>Low Methodological flaws and risk of bias (See Table 1)</td>
<td></td>
</tr>
<tr>
<td>Non-compliance with intervention</td>
<td>Camp-Bruno 1989</td>
<td>4/27 (15%) withdrawals</td>
<td>Withdrawals because of excessive school absence or children became ill and parents requested withdrawal from study</td>
<td>Low</td>
<td></td>
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<tr>
<td></td>
<td>Mier 2000</td>
<td>4/39 (10%) Withdrawals</td>
<td>Withdrawals because of failure to comply or because it was inconvenient for the families to continue</td>
<td>Low</td>
<td></td>
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</tbody>
</table>
DISCUSSION

Summary of main results

Six RCTs or CCTs were found comparing interventions for drooling in children with CP versus no intervention, placebo or another intervention. These trials examined only BoNT-A or pharmaceutical interventions. No trials were found on other interventions such as surgery, behavioural interventions, physical, oro-motor and oro-sensory therapies, intraoral appliances or acupuncture. All included trials involved children with moderate or severe drooling and varied significantly in interventions used and in their methodology.

Three of the four trials on BoNT-A used Botox® (Allergan) and one used Dysport®. All trials reported a positive effect of intervention on the reduction of drooling in children with CP although some children failed to respond to initial injections of BoNT-A. Some adverse effects to BoNT-A were reported. Changes in the frequency and severity of drooling occurred in the placebo groups for Alrefai 2009 and there was disparity in measures in Lin 2008 that remain un accounted for. It is suggested that closer scrutiny should be applied to factors influencing outcomes such as developmental age of the child and sensitivity and specificity of the outcome measures used.

The review authors decided to include two trials (Camp-Bruno 1989; Mier 2000) that did not meet strictly the inclusion criteria. These studies either included a small number of children without cerebral palsy (Mier 2000) or had some participants who were outside the age range (Camp-Bruno 1989) but where age was not considered an important variable in influencing outcome. These studies provide valuable data on the use of pharmacological interventions to control drooling. Both trials used different medications and adverse effects to these medications were reported.

Studies varied in the timing of outcome measurement. Trials on pharmaceutical interventions examined only the immediate effects (maximum 4 weeks) of medications, while trials of BoNT-A examined more medium effects (22 weeks to 1 year). No trials examined the effects of interventions beyond 12 months. No studies systematically examined the satisfaction of the child and/or carer with the intervention or examined the impact of the intervention on quality of life and psychological well-being of the child and/or carers.

Overall completeness and applicability of evidence

No conclusions can be reached on the efficacy and safety of either BoNT-A, benzotropine or glycopyrrolate in the treatment of drooling in children with CP. While some evidence is available for the short-term benefits of both medication and BoNT-A, the methodological quality and heterogeneity of the included studies do not allow the review authors to reach any further conclusions from the studies reviewed.

The populations of children within and across studies varied. Selection bias is likely to affect the results of all included studies. All children in these trials had moderate to severe drooling, which was often loosely defined. The studies did not include children with milder problems with drooling. It is acknowledged that children with CP and mild drooling may not seek interventions such as surgery or botulinum toxin, but may require some type of intervention. Children varied within and across trials in terms of age, gender and co morbidities. The type of CP is not provided in any of the studies. The developmental and dental age of children is not considered. The findings of the studies cannot be generalised and no conclusions can be reached on the eligibility criteria of candidates for these interventions.

The lack of trials on other interventions does not suggest that these interventions are ineffective. RCTs are not appropriate for some interventions (e.g. surgery). The fact that fewer adverse effects are reported for non invasive interventions such as physical, oro-motor, oro-sensory therapies and behavioural interventions suggest that rigorous, controlled studies are needed for these interventions. Despite the increasing popularity of botulinum toxin as an intervention for drooling in children with CP there is no evidence based consensus on the population of children with CP most suited to this intervention, the differences between products available, whether BoNT-A is preferable to BoNT-B in some populations, the salivary glands most suited for injection, the preparation of the solution, calculations of ideal dosages, maximum dosage allowed, the safest method of delivery (calibre of needle, number of injection sites etc.). Expert opinion suggests the use of ultrasound to assist in identification of the injection site (Reddihough 2010).

Quality of the evidence

The authors used the Grades of Recommendations, Assessment, Development and Evaluation Working Group (GRADE) (GRADE Working Group 2004). The quality level of all the body of evidence across all interventions was rated as ‘Low’. The high likelihood of bias across a number of domains and the presence of missing data contributed to the downgrading of evidence (see Figure 1).

Potential biases in the review process

The authors are not aware of any potential biases in the review process.

Agreements and disagreements with other studies or reviews

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Interventions for drooling in children with cerebral palsy (Review)
To the authors' knowledge, no other reviews have been published examining all interventions for drooling in children with CP.

**AUTHORS’ CONCLUSIONS**

**Implications for practice**

There is insufficient evidence to evaluate the effectiveness and safety of interventions aimed at reducing or eliminating drooling in children with cerebral palsy or to provide the best available evidence to inform clinical practice. However, there are a number of implications for research.

**Implications for research**

It is acknowledged that not all interventions will lend themselves readily to RCTs. Although two of the trials in this review (Alrefai 2009; Lin 2008) used a placebo and botulinum toxin, this may not be permitted by research ethics committees because of the trauma associated with the placebo injection. Similarly, it might not be possible to conduct RCTs on some other interventions such as surgery. In these instances the use of allocation concealment, blinding of outcome assessors and data analysts should be used. More research is needed particularly in the area of child / carer satisfaction and impact of interventions on quality of life.

The review emphasises a number of shortcomings that have significant implications for the conduct of future trials in this area:

- Firm diagnostic criteria for rating the presence and severity of drooling must be used and distinctions must be made between anterior and posterior drooling in accordance with international consensus statements (Reddihough 2010). This would allow for a reduction in adverse effects of some interventions for high risk populations (e.g. rerouting of salivary flow for children with a history of dysphagia and aspiration)

- Inclusion and exclusion criteria for studies must be clearly defined to reduce selection bias and children with CP should be categorised according to the Surveillance of Cerebral Palsy in Europe (SCPE) (Gainsborough 2008) and the Gross Motor Function Classification System (GMFCS-E & R) (Palisano 2008). This would allow clinicians to apply evidence to specific populations of children with CP.

- The developmental age of the child as well as the dental age of the child should be recorded, as this could be a confounding variable.

- The intervention and the placebo (if used) should be clearly described to allow for replication.

- For pharmacological interventions using crossover trial designs, the washout periods for medications should be established.

- The presence and severity of all adverse effects of interventions should be reported to enable investigators to calculate the number needed to harm, and so that children, families and carers can make informed decisions on the risks and side-effects associated with an intervention.

- Psychometrically sound outcome measures must be used. The use of robust measures that examine not only changes in the volume, frequency and severity of drooling but the satisfaction of child and/or carer with the intervention must also be measured. The impact of the intervention on quality of life and psychological well-being should be included in studies to examine the wider impact of intervention.

- The clients should be followed up for at least 18 months to examine the long term effects of interventions. Follow up should include examination of adverse effects.

- Longitudinal studies on the effectiveness of interventions that are pharmacological in nature should be undertaken. Studies examining the number of botulinum toxin injections, and the number of repeated doses of medication needed to manage drooling effectively should be undertaken. These studies should consider the washout period for these interventions and measure systematically the adverse effects of repeated botulinum toxin injections and repeated doses of medications. Measurement of the client/carer satisfaction with these interventions should be included in these studies.

- Power calculations should be performed on all studies with sufficient numbers of children recruited into trials thus avoiding false negative conclusions.

- Data should be analysed on an 'intention to treat" basis

- Confidence intervals must be calculated and reported for the results of outcomes.

- All trials should be reported according to the guidelines set out in the CONSORT statement (CONSORT 2010)

**ACKNOWLEDGEMENTS**
Thank you to the authors of the included studies who responded to our queries and to Susan Reid for providing us with unpublished data on children with CP. Thanks to Dr Mike Clarke of the Cochrane Collaboration for his assistance with our queries on methodology.

REFERENCES

References to studies included in this review

Alrefai 2009 [published data only]

Camp-Bruno 1989 [published data only]

Jongerius 2004a [published data only]

Lin 2008 [published data only]

Mier 2000 [published data only]

Reid 2008 [published and unpublished data]

References to studies excluded from this review

Lewis 1994 [published data only]

Mato 2010 [published data only]

Shionogi Pharma 1 [unpublished data only]

Shionogi Pharma 2 [unpublished data only]
Shionogi Pharma. Safety Study of Oral Glycopyrrolate Liquid for the Treatment of Pathologic (Chronic Moderate to Severe) Drooling in Pediatric Patients 3 to 18 Years of Age With Cerebral Palsy or Other Neurologic Condition. Clinical Trials.gov (NCT00491894) Unpublished.

Additional references

Andretta 2005

Bax 2005

Beahm 2009

Berweck 2007

Blasco 1992

Brodsky 1993

Burton 1991
CONSORT 2010

Crysdale 2006

El-Hakim 2008

Faggella 1983

Fairhurst 2010

Fischer-Brandies 1987

Friedman 1974

Fuster Torres 2007

Gainsborough 2008

Glynn 2007
Glynn F, O’Dwyer TP. Does the addition of sublingual gland excision to submandibular duct relocation give better overall results in drooling control? Clinical Otolaryngology 2007;32:103–7.

Goode 1970

GRADE Working Group 2004

Harris 1980

Hassin-Baer 2005

Heine 1996

Heinen 2006

Heywood 2009

Higgins 2008a

Higgins 2008b

Johnson 2004

Jongerius 2003

Jongerius 2004b
Interventions for drooling in children with cerebral palsy (Review)

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Palisano 2008

Poling 1978

Puravipan 2007

Rapp 1980

Reddihough 2010

Reed 2009

Reid 2010

Scully 2009

Selley 1985

Senner 2004

Tahmassebi 2003a

Tahmassebi 2003b
Tan 2001

Thomas-Stonell 1988

Tintner 2005

Van De Heyning 1980

Van der Burg 2006

Van der Burg 2007

Van der Burg 2009

Walshe 2010

Wilkie 1977

Witherow 2008

Wong 2001

Zeppetella 1999

* Indicates the major publication for the study
### Characteristics of included studies  
**[ordered by study ID]**

#### Alrefai 2009

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>Randomised controlled clinical trial. Parallel design. Allocation concealment. Blinding of person delivering treatment and patients receiving treatment. Outcome measures taken at baseline and at follow up 1-month after first injection. Second injection given 4 months later with 1-month follow-up.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Study conducted in health setting in Jordan. 34 children recruited. 26 children completed the study. Children with severe drooling scores (≥ 7 on Thomas-Stonell and Greenberg Scale) only included. Type of CP unknown. Age range: 21 months to 7 years. Mean 3.5 years. 15 boys and 9 girls. Eleven assigned to treatment group, 13 to control group. Eight did not complete the study (6 from control group and 2 in the intervention group). Co-morbidities unknown.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Treatment Group: BoNT-A. Dysport diluted with normal saline to 20U/0.1cc normal saline. Parotid glands injected bilaterally. 100 units on first visit, (50 units each gland). 140 units (70 units each gland) on second visit 4 months later. Calibre of needle used: 10mm (30G). No anaesthesia used. Blind method for identifying injection site. Placebo Group: Saline 0.9%. Method reported to be same as for BoNT. Eight (two from intervention and six from placebo group) declined the second injection for reasons unknown.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Frequency and Severity of Drooling (Thomas-Stonell 1988). Carers/Parents to note presence of possible adverse side effects.</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>&quot;Each patient was given a number and a registered nurse, independent from the investigators assigned the patients to the treatment or placebo group&quot;. Unclear if the numbers given had a non-random component</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Insufficient information to permit judgement</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Blinding of person delivering treatment and patients receiving treatment. Unclear if parents/carers taking outcome measures</td>
</tr>
</tbody>
</table>
Alrefai 2009  
(Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Risk</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High</td>
<td>Data on 16 people only provided although 24 received the first injection. No data provided for outcomes at 4 months</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High</td>
<td>Aim of the study was to evaluate the efficacy and safety of BoNT for the treatment of drooling in children with CP. Outcomes for safety (adverse effects) are reported incompletely</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Insufficient information to assess whether an important risk of bias exists</td>
</tr>
</tbody>
</table>

Camp-Bruno 1989

Methods

Randomised controlled clinical trial. Crossover design. Report states that study is 'double blind'. Participants randomly assigned to drug or placebo arm of trial. Outcome measures taken at baseline by classroom teachers. Observations made by teachers and nurses at one to two day intervals to guide dose increments of intervention drug in week 1 of 2 week of intervention period. Teacher Drool Scale (TDS) scores were taken daily and Behavioral/Medical Rating Scale was completed by the same staff 2 or 3 times a week during the trial. Research assistant observed drooling behaviour at the same time each day within 1-4 hours of drug administration. This yielded time sampling data on drooling behaviour. No follow up at the end of the trial.

Participants

Study conducted in school setting in USA. 27 participants recruited and 20 completed the study. People with severe drooling scores (4-5 on Teacher Drool Scale) only included. Exclusion criteria: People with (1) medical condition contraindicating anticholinergic medication, (2) receiving neuroleptic medication, (3) history of seizures with or without medication for at least 1 year, (4) history of poor school attendance, (5) living in households with carers who are unreliable in the administration of medication outside of school hours.

Type of CP unknown. 19 of the 20 participants who completed the study had CP, 1 had an unspecified degenerative central nervous system disease.

Age range 4-44 years Mean age not provided. 14 children and 6 adults. 11 male and 9 female. Ten assigned to treatment group either intervention-control or control-intervention group. Co-morbidities: More than half were considered to have severe or profound intellectual disability. No other details on co-morbidities.

Interventions

Benztropine 'cogentin' and placebo given for two week period separated by a minimum of one week 'washout' period.

Treatment group: Initial dose benzotropine 0.5 - 1 mg per day depending on participant's age and weight. Dosage of benztropine determined in first week of two week trial. Dose increased at 1-2 day intervals until maximum effect on drooling achieved. Mean dose 3.8 mg per day. Maximum dose: 6mg. Participants remained on most effective dose (i.e. TDS ratings of 1-2) in week 2.

Placebo Group: 2mg of placebo.
Both interventions offered as pulvrised tablets in soft food once a day on arrival at school. Caregivers administered at home at weekends.

Seven 'eliminated' from study. Two withdrawn because of excessive school absence, 3 suffered adverse effects to drug, 2 became ill and parents requested their withdrawal from the study. Unclear at what point these participants were withdrawn from the study.

### Outcomes

Teacher Drool Scale
Behavioral/Medical Rating Scale
Time sampling on observed drooling behaviour ('stream' of drooling and 'bubble' associated with drooling as well as total 'stream' and 'bubble' behaviour observed)
Observations by nurse and school staff for side effects

### User defined 1

This study involves participants beyond the age limit specified in the protocol and 1 person without CP. Data on the children with CP could not be extracted. The review authors believe that the person without CP would not significantly influence the results of the study. Statistical analysis of results found that age was not significantly correlated with either TDS ratings or total time sampling data scores.

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>No information provided on the sequence generation process.</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>No information provided to permit judgement</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Unclear risk</td>
<td>States that the study is 'double-blind'. Unclear if all staff involved in taking outcome measures were blinded to intervention. It is possible that blinding could be broken during the drug titration period. Measures to prevent this are not described</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>High risk</td>
<td>Seven children 'eliminated' from the study but no details given regarding the point at which they were excluded. Three patients developed side effects to drug and were excluded on that basis. No data is provided for these participants. Data on dry mouth is incomplete but is addressed</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>All pre-specified outcome measures reported for 20/27 children only</td>
</tr>
</tbody>
</table>
**Jongerius 2004a**

**Methods**
Controlled clinical trial, Open label, Crossover design. Sequence of interventions had fixed order. No allocation concealment. No sequence generation. No blinding of person delivering treatment and patients receiving treatment. Investigators taking Drooling Quotient (DQ) outcome measure blinded. Unclear if parents/carers taking other outcome measures are blinded.

Measures taken: (1) Swab method at baseline, 10th day after scopolamine patch, (control) and at 2, 8, 16 and 24 weeks after BoNT. (2) DQ at baseline, during the use of scopolamine, after washout at the end of the scopolamine therapy (2-4 weeks after intervention) after BoNT at 2, 8, 16 and 24 weeks. (3) VAS at baseline, during the use of scopolamine (exact time points of measurements unknown) and after BoNT at 4, 8, 16, 24 weeks. (4) TDS at baseline and after BoNT injections at 8 and 24 weeks.

**Participants**
Study conducted in an outpatient clinic in the Netherlands. 45 children with CP recruited. 39 children completed the study. No details on the children who dropped out of the study are provided. For the children recruited, the type of CP is unknown; age range 3-17 years (mean 9.5 years; SD: 3.7); 28 boys 17 girls. Co-morbidities: 34 had intellectual impairment, 22 had no verbal communication. Presence of epilepsy unclear but some children on anti-seizure medication.

**Interventions**
Treatment: Botox® (Allergan) diluted with 0.9% Sodium Chloride. Submandibular glands injected bilaterally. Single dose. 15 units per gland for children <15kg, 20 units per gland for children between 15kg-25kg, 25 units for >15kgs. Calibre of needle used: 25G. General anaesthesia used. Ultrasound for identifying injection site. Control Group: Scopolamine patch (Scopo-Dermix) 1.5 g. Patch placed topically behind the ear and changed every 72 hours. Duration of patch 10-14 days. Six withdrawals: 4 could not fulfil scopolamine patch, 1 change antiepileptic medication, 1 ‘intercurrent’ illness.

**Outcomes**
Drooling Quotient, Teacher Drool Scale, Visual Analogue Scale, Swab method.

**User defined 1**

**Notes**
Linked with Jongerius 2004b.

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
</table>

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**Risk of bias**
### Random sequence generation (selection bias)
- Unclear risk
- Insufficient information on the allocation sequence process.

### Allocation concealment (selection bias)
- Unclear risk
- Insufficient information to permit judgement.

### Blinding (performance bias and detection bias)
- High risk
- No blinding of person delivering treatment and patients receiving treatment. Investigators taking Drooling Quotient outcome measure blinded. Unclear if parents/careers measuring frequency and severity of drooling, Teacher Drool Scale (TDS), Visual Analogue Scale (VAS) and noting adverse effects after BoNT were blinded.

### Incomplete outcome data (attrition bias)
- Unclear risk
- Data adjusted by (1) carrying last observation forward and (2) by worst-case scenario system where missing data was replaced by baseline values. However, there were 6 withdrawals from intervention, 4 because of reactions to scopolamine patch. It is unclear when withdrawals occurred. These participants were excluded from analysis.

### Selective reporting (reporting bias)
- High risk
- Protocol published and outcomes collected are reported but it is unclear if all participants returned for follow-up measurements at 2, 4, 8, 16 and 24 weeks. The study design required them only to attend for at least 3 of the 5 visits within the first 24 weeks after the BoNT injection.

### Other bias
- High risk
- Scopolamine delivered before BoNT-A. No detail provided on stringency of measures used to ensure that participants did not exhibit carryover effects and had returned to baseline measures. Both arms of study not treated equally. TDS not completed while children using scopolamine. Success of therapy demanded a '2-point' decrease on the TDS'. This was not a primary measure however and other measures (DQ and VAS) completed on both groups.
**Methods**

Randomised controlled clinical trial. Parallel design. Sequence generation unclear ‘randomly assigned’. Allocation sequence concealment unclear. Blinding of person delivering treatment group unknown
Unclear if investigators taking outcome measures are blinded. Unclear if children and carers are blinded to treatment
Outcome measures taken 1 week before injections and at, 2,4,6,8,12,14,18 and 22 weeks after injection. Measures taken at 12 weeks on Frequency and Severity of Drooling (Thomas-Stonell and Greenberg Scale, 1988) and Drooling Quotient and at 22 weeks on saliva weight. Method of measuring saliva weight not provided

**Participants**

Study conducted in an unspecified setting in Taiwan.
13 children with CP. Type of CP unknown. Participants had to have severe drooling. Unclear how this was measured. Seven participants assigned to control group and 6 to treatment group. Age range unknown. Mean age 14.2 years, SD: 1.8 years. Gender unknown. Co-morbidities unknown

**Interventions**

Treatment Group: Botox® (Allergan). One parotid and contralateral submandibular gland injected. Calibre of needle used unknown. Type of anaesthesia used unknown. Ultrasound used for identifying injection site.
Placebo Group: 1.5mls saline given. Method reported to be same as for BoNT. No withdrawals from treatment reported

**Outcomes**

Frequency and Severity of Drooling (Thomas-Stonell and Greenberg Scale, 1988)
Saliva weight (unknown method)
Drooling Quotient

**User defined 1**

**Notes**

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Authors state ‘randomly assigned’ but insufficient information to permit judgement</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Insufficient information to permit judgement.</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias)</td>
<td>Unclear risk</td>
<td>States 'double-blind'. Unknown if person delivering the intervention, children, carers/parents and persons taking outcome measures are blinded to the intervention</td>
</tr>
<tr>
<td>All outcomes</td>
<td>Unclear risk</td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Unclear risk</td>
<td>No information on whether there were withdrawals from treatment. No adverse effects reported</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Lin 2008  (Continued)

<table>
<thead>
<tr>
<th>Selective reporting (reporting bias)</th>
<th>Unclear risk</th>
<th>Insufficient information to permit judgement.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Insufficient information to permit judgement.</td>
</tr>
</tbody>
</table>

Mier 2000

Methods
Randomised controlled clinical trial. Cross-over design. Allocation concealment unclear. Sequence generation unclear. Blinding of person delivering treatment and patients receiving treatment. Outcome measures taken at baseline, weekly at the same point each day - 2 hours after dose for the 8 weeks of intervention. Washout period of 1 week only. The washout period for glycopyrrolate is unclear. Not clear if person performing physical examination for side effects was blinded as to intervention. No follow up at the end of therapy

Participants
Study conducted in hospital setting in USA
39 children with neurological impairment recruited. 27 completed the study. 25 of these children had CP. Type of CP unknown. Age range of group recruited: 4 years 4 months to 19 years (mean: 10 years 9 months, SD unknown). 18 boys and 9 girls completed the study, the gender of the group recruited is unknown. Age range of the group who completed the study is unknown
Co-morbidities of recruited group: closed head injury, 2 children had tracheostomy, 1 each had Smith-Lemli-Opitz syndrome, partial trisomy 22, congenital toxoplasmosis, and spinal muscular atrophy. Children also had autism, fetal alcohol syndrome, hydrocephalus, congenital heart disease, hypothyroidism, retinitis pigmentosum. One child with tracheostomy did not complete the study

Interventions
Treatment: Glycopyrrolate; Powder form of commercially available glycopyrrolate, ground up and appropriate dosage placed in capsule by pharmacist. Children < 30kgs commenced on 0.6 mg increasing weekly to 1.2mg, 1.8 mg, and 2.4mg. Children >30kgs began at 1.2mg, increasing weekly to 1.8mg, 2.4mg and 3.0 mg, Drug given orally. If children unable to swallow capsule, capsule opened and powder placed in food Dose given three times daily in morning, early afternoon and evening. Four children had drug administered twice rather than three times daily at parents’ request
Placebo: lactose powder or cellulose prepared and given as glycopyrrolate
12 withdrawals from treatment 8 children withdrew from adverse effects to medication; 1 while receiving the placebo. 4 failed to comply with the protocol

Outcomes
Frequency and severity of drooling scale (adaptation of Thomas-Stonell and Greenberg Scale, 1988)
Physical examination at each visit to note any medical or physical side effects
Carers/Parents to note possible adverse side effects from list of 15 given as well as any additional side effects

User defined 1
Age range of children recruited to the study exceeds 18 years (19 years). Age range of the children with CP who completed the study is unknown. Two children who completed the study did not have CP but did have neurological impairment.

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Unclear. States “each child was assigned randomly to either the drug or placebo treatment arm”</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Insufficient information to permit judgement.</td>
</tr>
<tr>
<td>Blinding (performance bias and detection bias) All outcomes</td>
<td>Unclear risk</td>
<td>Blinding of person delivering treatment and patients receiving treatment. Not clear if person performing physical examination for side effects was blinded as to intervention</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>Data from 12 children who commenced the study were not included in the final analysis. No outcome measures provided for these 12 children</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Reported outcomes only on the children who completed the study</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Parents indicated that they know when their child was receiving glycopyrrolate because of the dramatic improvement in drooling</td>
</tr>
</tbody>
</table>
### Methods

Randomised controlled trial. Open label, parallel design. Allocation concealment. Sequence generation. Include criteria: age 6-18 years, have a significant problem with drooling ('significant' not defined), parents/carers able to understand study requirements and consent to study. Excluded from the study were children who any of the following; BoNT-A previously to salivary glands, previous saliva control surgery, any BoNT-A in past 6 months, unfit for general anaesthesia, unwilling to withhold oral anticholinergic medication for the length of the study and family history of poor compliance. Drooling Impact Scale measuring the degree and impact of drooling for child over previous week. taken at baseline and 1 month post injection, at monthly intervals from 2-6 months and at 1 year for treatment group and 1 month post baseline for controls.

### Participants

Multi-centre trial carried out in hospital setting in Australia. 50 children with neurological disorders, 31 children with CP. Data on children with CP provided by authors. Type of CP unknown. Eighteen children with CP assigned to control group and 13 children with CP to treatment group. Age range: 6-18 years. Mean age 11.8 years. SD: 12.04 years. 20 males, 11 females. Co-morbidities for this group (e.g. intellectual impairment, epilepsy, dysphagia etc.) unknown.

### Interventions

**Treatment Group:** Botox® (Allergan) diluted with 4ml normal saline. Bilateral sub-mandibular and parotid glands injected. One dose with 25 units per gland (1ml into centre of each salivary gland) 4 units/kg if patient’s weight less than 25kgs. Calibre of needle used unknown. General anaesthesia used. Ultrasound used for identifying injection site.

**Placebo Group:** No treatment. Two withdrawals before intervention, after randomisation. Both allocated to treatment group. Unclear if these children have CP.

### Outcomes

**Drooling Impact Scale**

Shortened version of the Drooling Impact Scale. Diary kept by parents of children in treatment group were asked to register any perceived effects of the injection in the diary.

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Low risk</td>
<td>'A set of random numbers was produced electronically in two blocks to allow matching to 56 consecutive study participants'</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Low risk</td>
<td>'The randomisation schedule was kept centrally by the study monitor; it remained concealed from all other study personnel'</td>
</tr>
</tbody>
</table>
Characteristics of excluded studies  [ordered by study ID]

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewis 1994</td>
<td>Ten developmentally delayed children with excessive drooling participated in this study. It was not possible to extract data on children with cerebral palsy</td>
</tr>
<tr>
<td>Mato 2010</td>
<td>Eleven of 30 participants had cerebral palsy. Unable to extract the data on children with cerebral palsy. Authors contacted but without response</td>
</tr>
<tr>
<td>Shionogi Pharma 1</td>
<td>Trial coordinators contacted. Unable to provide review authors with data on children with cerebral palsy until after publication</td>
</tr>
<tr>
<td>Shionogi Pharma 2</td>
<td>Trial coordinators contacted. Unable to provide review authors with data on children with cerebral palsy until after publication</td>
</tr>
</tbody>
</table>
**DATA AND ANALYSES**

This review has no analyses.

**ADDITIONAL TABLES**

Table 1. Table 1: Characteristics of methods used for treatment in studies examining BoNT-A.

<table>
<thead>
<tr>
<th>Study</th>
<th>Product used</th>
<th>Glands injected</th>
<th>Injection dosage</th>
<th>Calibre of needle used</th>
<th>Anaesthesia used</th>
<th>Method used to identify injection site</th>
<th>Person administering injection</th>
<th>Control Method</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alrefai 2009</td>
<td>Dysport diluted with normal saline</td>
<td></td>
<td></td>
<td>30G</td>
<td>No anaesthesia</td>
<td>Blind</td>
<td>Unknown</td>
<td>0.9% saline reported to be administered in the same way</td>
<td>Yes, 5 months.</td>
</tr>
<tr>
<td>Jongerius 2004</td>
<td>Botox® (Allergan) diluted with 0.9% NaCl</td>
<td>Submandibular glands bilaterally</td>
<td>Single dose weight dependant 15 units per gland for children &lt; 15kg, 20 units per gland for children between 15kg-25 kg, 25 units for &gt;15kgs.</td>
<td>25G</td>
<td>General anaesthesia</td>
<td>Ultrasound</td>
<td>Unknown</td>
<td>Scopolamine patch (Scopo-Dermis) 1.5g placed topically behind the ear and changed every 72 hours. Duration of patch 10 - 14 days</td>
<td>Yes, 24 weeks.</td>
</tr>
<tr>
<td>Lin 2008</td>
<td>Botox® (Allergan) No dilution stated.</td>
<td>One parotid and one contralateral submandibular gland.</td>
<td>Single dose weight dependant 2 units per kg body weight into each gland</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Ultrasound</td>
<td>Unknown</td>
<td>1.5ml saline given reported to be administered in the same way</td>
<td>Yes, 22 weeks.</td>
</tr>
</tbody>
</table>
Table 1. Characteristics of methods used for treatment in studies examining BoNT-A.  

<table>
<thead>
<tr>
<th>Study</th>
<th>Product used</th>
<th>Length of treatment</th>
<th>Dosage given</th>
<th>Dosage regimen</th>
<th>Method of delivery</th>
<th>Person administering drugs</th>
<th>Control</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reid 2008</td>
<td>Botox® (Al-lergan) diluted with 4mls of normal saline</td>
<td>Parotid and Sub-mandibular glands bilaterally</td>
<td>25 units per gland or 4 units per kg if child weighed less than 25kgs.</td>
<td>Unknown</td>
<td>General anaesthesia</td>
<td>Ultrasound</td>
<td>Unknown</td>
<td>No intervention</td>
</tr>
</tbody>
</table>

Table 2. Differences in methods used to deliver the pharmacological intervention

<table>
<thead>
<tr>
<th>Study</th>
<th>Product used</th>
<th>Length of treatment</th>
<th>Dosage given</th>
<th>Dosage regimen</th>
<th>Method of delivery</th>
<th>Person administering drugs</th>
<th>Control</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camp-Bruno 1989</td>
<td>Benztropine (Cogentin)</td>
<td>2 weeks</td>
<td>Week 1 taken as titration week. Week 2 on dose estimated to be most effective from week 1. Initial dose 0.5 - 1 mg depending on patient's age and weight. Dose increased at 1-2 day intervals. Mean dose 3.8 mg</td>
<td>Administered as pulverised tablets on arrival at school.</td>
<td>orally, pulverised tablets in soft food</td>
<td>Medical staff and parents, caregivers at weekends.</td>
<td>2mg placebo. No further information</td>
<td>No</td>
</tr>
</tbody>
</table>

Mier 2000 | Glycopyrrolate (commercially available powder form in gelatin capsule) | 8 weeks on treatment drug | Children < 30kgs began at 0.6 mg increasing weekly to 1.2mg, 1.8 mg, and 2.4mg. Children >30kgs | Medication given in the morning, early afternoon and evening. Four children given dose twice rather than | Orally. If children unable to swallow capsule, powder placed in food | Unclear but parent involved in administration | Placebo prepared similarly to treatment using lactose powder or cellulose in gelatin capsule | No |
Table 2. Differences in methods used to deliver the pharmacological intervention (Continued)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Purpose of the Measure</th>
<th>Method used in administration</th>
<th>Validity and Reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swab method</td>
<td>To measure changes in salivary flow rate</td>
<td>Absorbent cotton rolls are placed directly at the orifices of the sublingual, submandibular and parotid glands for 5 minutes. Subjects should be evaluated at the same time of day and by the same person. The rolls are removed from the mouth and weighed. The salivary flow rate is calculated using the formula: weight of rolls (mgs)/time of collection (mins) (Jongerius 2004b)</td>
<td>Some efforts to quantify its degree of measurement error. (Jongerius 2004c) and found to be low.</td>
</tr>
<tr>
<td>Drooling Severity and Frequency Scale (Thomas-Stonell 1988)</td>
<td>To measure the frequency and the severity of drooling</td>
<td>This 9 point scale is divided into two sections. The first section contains 4 items that relate to the frequency of drooling behaviour. A score of 1 = 'never drools' and 4 = 'constantly drools'. The second section relates to the severity of drooling. A score of 1 = 'dry (never drools) and 5 = 'profuse (hands, tray and objects wet). There are no specific guidelines on its administration</td>
<td>No</td>
</tr>
<tr>
<td>Drooling Quotient (Rapp 1980 Jongerius 2004c)</td>
<td>To measure changes in drooling behaviour</td>
<td>The Drooling Quotient (DQ) is defined as the percentage of</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Table 3: Outcome measures used in included trials

<table>
<thead>
<tr>
<th>Measure</th>
<th>Methodology</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Table 3: Outcome measures used in included trials</strong> (Continued)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time that a person drools in a specified time period. The presence or absence of saliva on the lip or dropping from the chin is recorded by a trained individual every 15 seconds during two ten minute sessions, separated by a 60 minute break. One session observed must be while the person is concentrating and the second session must be when the person is distracted. The person is evaluated in the morning at least one hour after a meal while the person is wake and sitting upright. The mean of the two observations is mapped on a numeric scale to provide an outcome measure. Response to treatment is taken as a 50% reduction from baseline values.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Visual Analogue Scale (VAS)</strong> (Jongerius 2004c)</td>
<td>To measure the severity of drooling over a specified time period. Raters mark the extent of drooling on a 10cm line. There are no visible subdivisions on the line. A mark at the left end of the scale indicates severe drooling. A mark at the right end of the scale represents no drooling. Once the scale is marked, the line is measured in millimetres on a scale from 0-100. A VAS score is obtained by measuring the position of the mark in millimetres from the right end of the scale (no drooling) to 100 (severe drooling). A reduction in 2 standard deviations from the baseline VAS score is considered clinically significant.</td>
<td>No</td>
</tr>
<tr>
<td><strong>Teacher Drool Scale</strong> (Camp-Bruno 1989).</td>
<td>To measure the frequency and severity of drooling. This is a five point ordinal scale that measures the frequency and severity of drooling. A rating of 1 indicates ‘no drooling’ where a rating of 5 means ”constant drooling, always wet’</td>
<td>No</td>
</tr>
</tbody>
</table>
Table 3. Outcome measures used in included trials (Continued)

<table>
<thead>
<tr>
<th>Table 3: Outcome measures used in included trials</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drooling Impact Scale (Reid 2008, Reid 2010)</td>
<td>To measure changes in drooling behaviour and its consequences</td>
<td>This 10 point scale consists of 10 questions that cover frequency and severity of drooling, odour, skin irritations, frequency of bib changes, impact on child as well as impact on carer and family quality of life. The questions relate to drooling behaviour and its consequences over the previous week. The scores are totaled to give a numerical rating of impact. The maximum possible score is 100</td>
</tr>
<tr>
<td>Drooling Scale (Mier 2000)</td>
<td>To measure the frequency and severity of drooling</td>
<td>This 9 point scale measures frequency and severity of drooling where 1 = “Dry, never drools” and 9 = “profuse, clothing, hands, and objects become wet frequently”</td>
</tr>
<tr>
<td>Behavioural and Medical Rating Scale (Camp-Bruno 1989)</td>
<td>To monitor potential medical and behavioural side-effects of medication</td>
<td>19 point scale with 8 behavioural and 6 physiological items rated on a 4 point scale. 1 = “Not at all” to 4 = ”Very much”</td>
</tr>
</tbody>
</table>

Table 4. Methodological Quality of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Randomisation</th>
<th>Blinding of Assessors</th>
<th>Similarities of groups at baseline</th>
<th>Explanation of withdrawals</th>
<th>Accounting in analysis of missing values</th>
<th>Intention to treat analysis</th>
<th>Power</th>
<th>Description of eligibility criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alrefai (2009)</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>C</td>
<td>C</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>Camp-Bruno (1989)</td>
<td>B</td>
<td>B</td>
<td>B</td>
<td>A</td>
<td>C</td>
<td>B</td>
<td>B</td>
<td>A</td>
</tr>
<tr>
<td>Jongerius (2004a, 2004b)</td>
<td>C</td>
<td>B</td>
<td>B Crossover design. No indication that children had returned to baseline</td>
<td>A</td>
<td>A</td>
<td>B</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Study</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>A</td>
<td>B</td>
<td>C</td>
<td>C</td>
<td>C</td>
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</tr>
<tr>
<td>Reid (2008)</td>
<td>A</td>
<td>C</td>
<td>B</td>
<td>A</td>
<td>A*</td>
<td>B</td>
<td>A</td>
<td></td>
</tr>
</tbody>
</table>
| Key           | A=Randomisation methods explained B=Randomisation methods not explained or not fully explained C=Randomisation methods not adequate A=Assessor blind at pre and post test B=Blinding not reported or not clearly reported C=Blinding methods not used A=Baseline characteristics reported B=Baseline characteristics not reported C=Baseline characteristics reported to be different A=Withdrawals accounted for B=Withdrawals not reported C=Withdrawals not accounted for A=Missing values accounted for B=No missing values shown C=Missing values discounted from analysis A=Intention to treat analysis B=Intention to treat analysis not used C=Insufficient information to make decision A=Power calculation performed and sufficient numbers recruited B=Power calculation not reported C=Power calculation completed but insufficient participants recruited A=Characteristics of all participants provided in terms of drooling behaviour and other influencing factors (e.g. medications etc.) B=Characteristics of all participants only provided in terms of
### Table 4: Methodological Quality of Included Studies (Continued)

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 September 2012</td>
<td>New citation required but conclusions have not changed</td>
<td>New citation - conclusions not changed</td>
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### WHAT’S NEW

Last assessed as up-to-date: 22 March 2011.

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### CONTRIBUTIONS OF AUTHORS

M. Walshe and M Smith carried out the searching for eligible studies. All reviewers were involved in deciding which studies were eligible for review. All reviewers were involved in data extraction from the included studies. All reviewers were involved in writing the review, M. Walshe was the primary author.

### DECLARATIONS OF INTEREST

None known.

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- No sources of support supplied

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INDEX TERMS

Medical Subject Headings (MeSH)
Benztropine [*therapeutic use]; Botulinum Toxins, Type A [adverse effects; *therapeutic use]; Cerebral Palsy [*complications]; Controlled Clinical Trials as Topic; Glycopyrrolate [*therapeutic use]; Neuromuscular Agents [adverse effects; *therapeutic use]; Randomized Controlled Trials as Topic; Sialorrhea [*drug therapy; etiology]

MeSH check words
Adolescent; Adult; Child; Child, Preschool; Female; Humans; Infant; Male; Young Adult