ADVANCED ULTRASOUND GUIDED BOTULINUM TOxin INJECTIONS TO SALIVARY GLANDS

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International Networking Group Executive Committee of ACRM, USA

Disclosures

I have no financial interest to disclose.

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Outline 30 min

- Definition & Impact
- Anatomy & Physiology
- Measurement
- Common Adult Conditions: Parkinson’s disease
- Evidences Based Medicine of Management
- Advanced Ultrasound Guidance Injection of Botulinum toxin

Sialorrhea is defined as the inability to control oral secretions, resulting in excessive saliva in the oropharynx. The pathogenesis of drooling in people with neuromuscular disorders does not involve excessive production of saliva but rather impairment of swallowing. Sialorrhea becomes a significant complication for the people with neuromuscular disorders. Drooling causes not only social embarrassment from anterior drooling but also aspiration pneumonia due to posterior drooling and significant swallowing problems. Physiatrists have become the main clinicians in the management of sialorrhea due to expertise in ultrasound, use of botulinum toxins, and familiarity with neuromuscular disorders. Efficacy of botulinum toxin has been significant for managing sialorrhea and preventing aspiration pneumonia with relative minor complications since 1999. The rationale for the use of Botulinum toxin (BoNT) injection to salivary glands to treat drooling is based on the blocking of cholinergic transmission that underlies the secretion of saliva. This course reviews anatomy of salivary glands and its surrounding structures, presents a video demonstration on the ultrasound technique for the salivary gland injections with botulinum toxin and includes clinical case scenarios. We will also discuss dosing of botulinum toxin, injection technique and physiology of salivary glands. We will discuss the short term and long term efficacy of this treatment and associated adverse events. Attendees will be confident in botulinum toxin injections to salivary glands upon completing this course.
Spasticity & Dystonia Clinic

1995-2018

Botulinum toxin injections

23 Years Experiences

Chart Title

4315 Patients
28995 Injections

CP Stroke HFS BS ICD WC pain Drooling
Learning Objectives

- Understand Physiology and Anatomy of Salivary Glands
- Pathophysiology and Negative Impacts of Drooling in Patients with PD and CP
- Management of Drooling
- Describe the indications, short and long term efficacy of botulinum toxin injections for salivary glands
- Delineate the techniques of ultrasound guided botulinum toxin injections to salivary glands
- Describe associated adverse events of botulinum toxin injections to salivary glands
- Evidences Based Medicine for Drooling

Definition & Impact

- Drooling is generally defined as excessive pooling and poor control of saliva in the oral cavity that might be caused by impaired salivary clearance whereas sialorrhea refers to overflow or overproduction of saliva.
- Spill saliva from their oral cavity, or Aspirate the saliva causing aspiration pneumonia.
- Drooling may occur in many neurological disorders including neuromuscular diseases such as myasthenia gravis, amyotrophic lateral sclerosis (ALS) and oculopharyngeal muscular dystrophy, neurodegenerative diseases such as Parkinson's disease (PD), multiple system atrophy (MSA), progressive supranuclear palsy (PSP), dementia with Lewy bodies (DLB) and corticobasal degeneration (CBD), cerebrovascular diseases (CVD) and traumatic brain injury (TBI).
- Other possible negative consequences are poor oral hygiene and social embarrassment.
- Nearly 40% of children with cerebral palsy and 80% of adults with Parkinson’s disease have been reported to have drooling.
- Excessive production and drooling of saliva may impair mastication and speech and can result in a poor quality of life.

- Parkinson’s disease
- Atypical parkinsonism (MSA, PSP, CBD, DLB)
- Amyotrophic lateral sclerosis
- Cerebrovascular diseases (pseudobulbar, bulbar palsy)
- Head injuries
- Muscle diseases (oculopharyngeal muscular dystrophy)
- Facial nerve paralysis
- Cerebral palsy
- Mental retardation
Complications Related to Drooling

- Poor oral and perioral hygiene (dermatitis)
- Oral odour
- Eating difficulty
- Speaking problems
- Respiratory tract infections
- Aspiration pneumonia
- Social embarrassment
- Depression and anxiety
- Poor quality of life

Relevant Anatomy and Physiology of Drooling


- 6 major salivary glands (two submandibular, two parotids, and two sublingual glands) and hundreds of minor glands located on the lips, cheek, hard palate, and tongue.
- They secrete saliva into the mouth through their excretory ducts.
- 70% of saliva at rest is produced by the submandibular glands. It is made up of a mixture of serous and mucous acini that ultimately drain to the Wharton’s duct.
- The parotid gland is the largest of the salivary glands, it produces only 25% of the saliva. Will produce 100% when eating!! It is mostly made up of serous acini that ultimately drain through Stensen’s duct, which in turn opens opposite to the second maxillary molar.
- The sublingual gland is the smallest of the three major salivary glands producing about 5% of saliva and is mostly mucinous.
- The rest of the saliva is produced by minor salivary glands.

Detail of submandibular salivary gland, showing mucous-secreting mucous cells and enzyme-secreting serous cells.

Major salivary glands and their excretory ducts.
Gland Anatomy: Parotid

- 25 g in adult
- Inferior to external auditory cranial nerve
- Sympathetic: Cervical ganglia
  - External carotid nerve plexus
- Unstimulated State
  - Contributes 26% of saliva
- Stimulated State
  - Contributes nearly 100% of saliva
Gland Anatomy: Submandibular

- 1/2 size of the parotid glands
- Inferior to the body of the mandible
- Parasympathetic: CN VII
  - Chorda tympani nerve
  - Lingual nerve
- Sympathetic: external carotid/facial artery plexus
- Unstimulated State
  - Contributes 69% of saliva
- Stimulated State
  - None

Gland Anatomy: Sublingual

- Approximately 4 g
- Anterior to submandibular glands
- Parasympathetic:
- Sympathetic:
- Unstimulated State
  - Contributes 5%
- Stimulated State
  - None
- Contributes the majority of mucous in saliva
Normal physiology of salivation and swallowing

- Salivation are controlled by both sympathetic and parasympathetic nervous systems.
- Facilitation of ingestion and swallowing are mainly contributed by the parasympathetic nervous system.
- Taste and mechanical stimuli from the tongue and other areas of the mouth excite parasympathetic nerve impulses in the afferent limbs of the salivary reflex which travel via the glosopharyngeal (CN IX), facial (CN VII), vagal (CN X) (taste) and the trigeminal (CN V) (chewing) cranial nerves. These afferent impulses are carried to the Salivary Center located approximately at the juncture of the pons and the medulla.
- The secretory response of the gland is then controlled via the glosopharyngeal nerve synapsing in the otic ganglion, the postganglionic parasympathetic fibres carrying on to the parotid gland and via the facial nerve synapsing in the submandibular ganglion and carrying on to the sublingual and submandibular glands.
Assessment

- Not easy and based on subjective assessment scales
- VAS (Visual Analog Scale) rated by patient and/or family.
- Movement Disorder Society (MDS) recommends the use of Drooling Severity and Frequency Scale (DSFS), Drooling Rating Scale, and Sialorrhea Clinical Scale for PD (SCS-PD). Evatt et al., 2009
- Objective measures used in several studies also include cotton rolls weigh or videolaryngoscopy to assess dysphagia and, indirectly, the risk of drooling.

Performance of the modified Schirmer test

The Schirmer test, which uses paper strips inserted into the eye for several minutes to measure the production of tears, is used for the evaluation of dry eye syndrome [8]. Modifying this method, salivation was evaluated by placing the Schirmer test strip (EagleVision, Memphis, TN, USA) near the submandibular gland of the patient and measuring the length of saliva permeation after 5 minutes because it was not possible to measure the weight of secreted saliva using dental rolls due to patient characteristics that included involuntary mastication and excretion saliva from dental rolls. The test was performed on all patients in the supine position.
Drooling, along with speech and swallowing issues, is included among non-movement symptoms even though the root cause is motor: decreased coordination, slowness of movement (bradykinesia) and rigidity of the muscles of the mouth and throat.

Parkinson’s causes a reduction in automatic actions, including swallowing, creating an inability to manage the flow of saliva in and around the mouth. In PD, usually the amount of saliva your body produces is normal, but swallowing difficulties – swallowing less often or not completely – lead to saliva pooling in the mouth.

When severe, drooling is an indicator of more serious difficulty with swallowing (also known as dysphagia), which can cause the person to choke on food and liquids and can even lead to aspiration pneumonia.

The oropharyngeal phase is most affected in PD patients.

### Table 1

<table>
<thead>
<tr>
<th>Year</th>
<th>Reference</th>
<th>Screening tools</th>
<th>Number surveyed</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>Siddiqui et al. [5]</td>
<td>Questionnaire: rating 0–4 point for detecting severity of symptoms: (0 = \text{normal}) (1 = \text{rare (one per month)}) (2 = \text{occasional (one per week)}) (3 = \text{frequent (one per day)}) (4 = \text{constant})</td>
<td>44</td>
<td>52</td>
</tr>
<tr>
<td>2002</td>
<td>Volonteri et al. [6]</td>
<td>Questionnaire: present or absent nocturnal salivation</td>
<td>65</td>
<td>15</td>
</tr>
<tr>
<td>2000</td>
<td>Scott et al. [7]</td>
<td>Questionnaire: present or absent drooling</td>
<td>945</td>
<td>40</td>
</tr>
<tr>
<td>1991</td>
<td>Edwards et al. [8]</td>
<td>Questionnaire: rating 0–4 point for detecting severity of symptoms: (0 = \text{normal}) (1 = \text{rare (one per month)}) (2 = \text{occasional (one per week)}) (3 = \text{frequent (one per day)}) (4 = \text{constant})</td>
<td>96</td>
<td>70</td>
</tr>
</tbody>
</table>

UPDRS: Unified Parkinson’s Disease Rating Scale; SCOPA-AUT: Scales for Outcome in Parkinson’s disease: autonomic; PD-NMSQuest: Parkinson’s disease non-motor symptoms questionnaire.
Prevalence in PD

- The most common correlations were the late-onset of the disease, higher levodopa equivalent daily doses, higher incidences of dysarthria, dysphagia and fluctuations, higher scores for the UP part III, NMSS (Nonmotor Symptoms Scale), HAMD and HAMA (Hamilton Depression and Anxiety scales, respectively), and higher scores for the mobility, activities of daily life, stigma and communication subdomains of the PDQ-39.

- Factors possibly associated with drooling were severity of PD, male gender, aging, hallucinations, duration of PD, the sum of the scores of UPDRS part II and III greater than 28 points, dysarthria, dysphagia, orthostatic hypotension, and a history of using antidepressants.

- The logistic regression analysis indicated that the strongest correlation was with dysarthria and dysphagia Ou et al., 2015.

- The prevalence of drooling ranged widely from 10% to 84% of patients. Hypersalivation may significantly result even in life-threatening consequences, like aspiration pneumonia Srivanitchapoom, Pandey, & Hallett, 2014, debilitating perioral dermatitis with erythematous, demarcated plaque, who did not tolerate oral anticholinergic and was successfully treated with BoNT Bloem, Kaft, Van Der Kerkhof, & Zwarts, 2009.

Different Mechanisms Responsible for Drooling in PD Patients Srivanitchapoom et al., 2014

- In PD, poor control of saliva may be multifactorial and mainly related not only to swallowing dysfunction (impairment of oropharyngeal phase), but also to impaired motor control of the tongue, upper esophageal dysmotility, hypomimia with involuntary mouth opening, and stooped posture with dropped head, which promotes saliva release from the mouth space.

- Drooling in PD is probably not related to overproduction of saliva. Study with the use of Tc-99 m scintigraphy to measure the parotid gland activity showed the same salivary production in PD patients and in healthy controls. Nicaretta, de Rosso, Maliska, & Costa, 2008

- Another study, using videolaryngoscopy and barium swallowing test, showed correlation between dysphagia and drooling severity. Nobrega et al., 2008

- The lesions at the striatum, globus pallidus, or its output pathway, which is the lateral mesencephalic reticular formation, could significantly decrease salivary secretion.

- A pathological study showed Lewy bodies in the superior cervical ganglion, cervical sympathetic trunk, peripheral vagus nerve, and submandibular glands.

- increasing speed of salivary excretion might partially contribute to its pathophysiology.

- Dysphagia
- Lingual bradykinesia
- Upper esophageal dysphagia
- Hypomimia
- Abnormal flexed posture
- Increasing salivary flow rate
Possible pathophysiology of drooling in Parkinson's disease.

- **Salivary Secretion**
  - Increasing salivary flow rate

- **Inability to Maintain Saliva in the Mouth**
  - Hypomimia
  - Abnormal flexed posture

- **Impairment of Salivary Clearance**
  - Lingual bradykinesia
  - Oropharyngeal dysphagia
  - Upper esophageal dysmotility

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Assessment tools for drooling in PD

- **Objective tools**: to measure the volume of saliva and salivary flow. They are time-consuming and cannot evaluate the psychosocial impairment.

- **Subjective measures**: the UPDRS part II salivary subscores to evaluate drooling treatment responses and visual analog scales (VAS) to assess the frequency, familial (VAS-FD) and social distress (VAS-SD); however, not all scales are validated.

- **Three drooling-specific rating scales** including the Drooling Severity and Frequency Scale (DSFS), Drooling Rating Scale (DRS) and Sialorrhea Clinical Scale for PD (SCS-PD) have been used to evaluate drooling in PD.

- The DSFS, a semi-quantitative scale, was used in studies to evaluate drooling in PD and cerebral palsy (CP). The scale is composed of two domains: (a) the severity of drooling rated on a five-point scale and (b) frequency of drooling rated on a four-point scale. Since the DSFS is easy to administer it is widely used. However, the limitations of this scale are no assessment of the psychosocial impact, no validation and no evidence of correlation between this scale and the objective measures of salivary secretion.

<table>
<thead>
<tr>
<th>Dripping severity</th>
<th>Dripping frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dry</td>
<td>1. Never</td>
</tr>
<tr>
<td>2. Mild</td>
<td>2. Occasionally (not every day)</td>
</tr>
<tr>
<td>3. Moderate</td>
<td>3. Frequently (part of every day)</td>
</tr>
<tr>
<td>4. Severe</td>
<td>4. Constantly</td>
</tr>
<tr>
<td>5. Profuse</td>
<td>Clothing, hands, tray, and objects are wet</td>
</tr>
</tbody>
</table>
Managing Drooling

- **Medication adjustment** – typically an increase of medication (levodopa or dopa agonists) to improve stiffness and slowness of muscles involved in swallowing including tongue, lips etc.
- **Speech therapy** - to strengthen muscles around the lips and also swallowing should also be instituted concomitantly particularly to avoid aspiration.
- **Physical/occupational therapy** - along with increase medications should also be considered to improve posture because the tendency to stoop forward with head forward and chin outward (typical Parkinson’s stance) causes pooling of saliva to front of mouth along with the help of gravity easier.
- The team of expert therapist will help instruct on proper sitting techniques as well as cues to-try to keep head up so that saliva naturally drains to the back.
- Sitting upright also helps saliva go down so once again cues can be thought to remember to do this at all times.

Managing Drooling

- Extremely important is to review medication list with your physician because some medications are known to cause increase salivation like some antipsychotics such as Clozapine.
- One trick is to suck on hard candy or chew gum, preferably sugarless. Candy and gum activate the jaw and the automatic swallowing reflex and can help clear saliva, providing temporary relief from drooling.
- Drink fluids more frequently to “wash down” saliva; preferably drink water which will also help decrease constipation.
- Do lip exercises to improve lip seal and prevent saliva dripping out – hold a wide smile (bet you makes you feel better too!) then pucker lips like you are going to blow a kiss or whistle- do these several times a day. Or suck from straw when you drink.
A suggested generic management approach to a patient with symptoms relating to oral secretions. This management approach is derived from expert clinician experience. PD, Parkinson’s disease; SM, submandibular.

**Medication Options**

- **Oral or sublingual anticholinergics medications:**
  - Blocking the parasympathetic innervation of the salivary flow.
  - The commonly used agents: Atropine, Glycopyrrolate, Ipratropium bromide. [Rickert & Blitzer, 2012]
  - Contraindicated in patients with glaucoma, provoke behavioral changes with hallucination, and cognitive impairment, confusion, drowsiness, blurred vision, urinary retention, and may influence the gastrointestinal (GI) motility resulting in constipation.
  - Many of these symptoms are present at advanced stages of PD; therefore, these medications are not useful. Approximately 30% of patients are unable to tolerate them [Rickert & Blitzer, 2012]
  - Glycopyrrolate according to MDS recommendation is the only medication considered to be effective and probably clinically useful. [Seppi, Weintraub, & Coelho, 2011]
  - Glycopyrrolate can be rated “efficacious” for the very short-term treatment of sialorrhea in PD. Although efficacious in 1-week treatment, the study provides insufficient evidence for the treatment of sialorrhea in PD exceeding 1 week.

- **Oral adrenergic receptor agonists:** Clonidine (α-2) and Modafinil (α-1) [Chau, Evatt, Hinson, & Kompoliti, 2007].
**Medications increasing saliva**

- Adrenergic receptors antagonists such as Clozapine used in PD for the treatment of psychosis may be associated with increased drooling.
- Cholinesterase inhibitors (rivastigmine, donepezil, galantamine) and quetiapine, Neuroleptics (clozapine, quetiapine) should be used for as short a period of time as possible, so discontinuation may improve drooling.
- On the other hand, cholinesterase inhibitors used for the treatment of PD-related dementia should usually be maintained for many years.
- Therefore, locally injected BoNT, are preferred in PD patients.

**Botulinum toxin A**

- Injection of botulinum toxin A into the salivary glands of the cheek and jaw decreases production of saliva without side effects, except for thickening of oral mucus secretion.
- Botulinum toxin A is not always effective, but when it works the benefit can last for several months before it wears off and re-injection is necessary.
- Botulinum toxin A can be an effective treatment for severe drooling, although pills, the patch and mouth drops should be tried first in the interest of cost saving.
- Botulinum toxin should probably be avoided when oral secretions are already deep and thick.
Botulinum toxin Therapy

- It may also inhibit the cholinergic parasympathetic secretomotor fibers of salivary glands (drooling, sialorrhea) or sympathetic nerve fibers that stimulate eccrine sweat gland, when injected intradermally (hyperhidrosis).
- There are seven serotypes (A–G) of BoNT and each acts at the specific part of the so-called SNARE (soluble N-ethylmaleimide-sensitive factor attachment receptor protein complex, including synaptobrevin, syntaxin and SNAP25 (synaptosomal-associated protein 25), which are responsible for neurotransmitter release into the synaptic cleft.
- Light chain of BoNT cleaves these proteins, which results in muscle relaxation or glandular secretion inhibition. Truong & Hallett, 2013
- After BoNT injection, the clinical improvement lasts 3–4 months when injected into striate muscles and up to 6–9 months in case of smooth muscles or eccrine sweat glands.
- The lack of permanent effect is related to neuronal sprouting with formation of temporal new synapses, and after a longer period of time even the recovery of neurotransmitter release in originally blocked terminals de Paiva, Meunier, Molgó, Aoki, & Dolly, 1999
- There are two commercially available serotypes of BoNT: A and B.

Commercially Available BoNT Preparations
(According to FDA Recommendation)

<table>
<thead>
<tr>
<th>Trade Names</th>
<th>Unique, Nonproprietary Names</th>
<th>Serotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botox</td>
<td>OnabotulinumtoxinA</td>
<td>A</td>
</tr>
<tr>
<td>Dysport</td>
<td>AbobotulinumtoxinA</td>
<td>A</td>
</tr>
<tr>
<td>Xeomin</td>
<td>IncobotulinumtoxinA</td>
<td>A</td>
</tr>
<tr>
<td>NeuroBloc/MyoBloc</td>
<td>RimabotulinumtoxinA</td>
<td>B</td>
</tr>
</tbody>
</table>

Four commercially available products have their unique names and international units which are not interchangeable among products.
Anatomical VS Ultrasound Guidance

Table 1. Accuracy of blind and ultrasound-guided injection

<table>
<thead>
<tr>
<th>No. of injections</th>
<th>Blind</th>
<th>Ultrasound-guided</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parotid gland</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site A</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician 1</td>
<td>6</td>
<td>4 (66.67)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Physician 2</td>
<td>6</td>
<td>5 (83.33)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Site B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician 1</td>
<td>6</td>
<td>5 (83.33)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Physician 2</td>
<td>6</td>
<td>5 (83.33)</td>
<td>5 (83.33)</td>
</tr>
<tr>
<td>Total</td>
<td>24</td>
<td>19 (79.17)</td>
<td>23 (95.83)</td>
</tr>
<tr>
<td>Submandibular gland</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physician 1</td>
<td>6</td>
<td>2 (33.33)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Physician 2</td>
<td>6</td>
<td>4 (66.67)</td>
<td>5 (83.33)</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>6 (50.00)</td>
<td>11 (91.67)</td>
</tr>
<tr>
<td>Overall</td>
<td>36</td>
<td>25 (69.44)</td>
<td>34 (94.44)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

Site A: location for parotid gland injection behind the ascending mandibular ramus; Site B: location for parotid gland injection infero-posterior portion of the gland, just before the mastoid process.

Table 2. Incorrect locations for blind and ultrasound-guided injections

<table>
<thead>
<tr>
<th>Blind</th>
<th>Ultrasound-guided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parotid gland</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous fat tissue (3)</td>
<td>Subcutaneous fat tissue (1)</td>
</tr>
<tr>
<td>Masseter muscle (2)</td>
<td></td>
</tr>
<tr>
<td>Submandibular gland</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous fat tissue (4)</td>
<td>Subcutaneous fat tissue (1)</td>
</tr>
<tr>
<td>Mylohyoid muscle (2)</td>
<td></td>
</tr>
</tbody>
</table>

Advanced BoNT Injections: Ultrasound plus EMG Guidance

- Intracranial gland ultrasound-guided injections are more effective and safe
- The largest is the parotid gland located in pre- and subauricular region, partially on the masseter muscle.
- The submandibular gland lies within the so-called submandibular triangle between two bellies of the digastic muscle and inferior margin of the mandible. Mylohyoid muscle divides the superficial and deep lobes. 
  
Truong, Olthoff, & Laskawi, 2013.

- Ultrasound-guided injection reduces the risk of complications. Using EMG guidance, one can avoid unintended intramuscular injection.
- In case of injecting submandibular gland, EMG guidance enables identification of mylohyoid muscle and the injection of the deep lobe. The structures to avoid within the region of the parotid gland are facial nerve, maxillary and superficial temporal artery branches, as well as retromandibular vein. Rickert & Blitzer, 2012.
Parkinson's disease (PD) is a neurodegenerative disease causing both motor and non-motor symptoms. Drooling, an excessive pooling and spillover of saliva out of the oral cavity, is one of the non-motor symptoms in PD patients that produces various negative physical and psychosocial consequences for patients and their caregivers. At present, the pathophysiology of drooling in PD is not completely certain; however, impaired intra-oral salivary clearance is likely the major contributor. There are neither standard diagnostic criteria nor standard severity assessment tools for evaluating drooling in PD. In accordance with the possible pathophysiology, dopaminergic agents have been used to improve salivary clearance; however, these agents are not completely effective in controlling drooling. Various pharmacological and non-pharmacological treatment options have been studied. Local injection with botulinum toxin serotypes A and B into major salivary glands is most effective to reduce drooling. Future research to explore the exact pathophysiology and develop standard diagnostic criteria and standard severity assessment tools are needed to formulate specific treatment options and improve patient care.
Table 1

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design</th>
<th>Disease</th>
<th>no patients included</th>
<th>Brain tissue (type and dosage)</th>
<th>US</th>
<th>Duration (weeks)</th>
<th>Latency (days)</th>
<th>Efficacy</th>
<th>Outcome measure (IUU)</th>
<th>Responders</th>
<th>Improvement</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bhuta FP et al., 1995</td>
<td>Open Label</td>
<td>Osteosarcoma, PD, P, ALS</td>
<td>4</td>
<td>A: 40 g (0 U/200 IU) ASL</td>
<td>No</td>
<td>6-16</td>
<td>7</td>
<td>Yes</td>
<td>S</td>
<td>75</td>
<td>Good</td>
<td>Dry mouth, dysphagia, chewing</td>
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<td>Jose WL et al., 1999</td>
<td>Retrospective PD</td>
<td>PD</td>
<td>5</td>
<td>A: 20 g (200 IU) ASL</td>
<td>No</td>
<td>16-28</td>
<td>Not stated</td>
<td>Yes for 4</td>
<td>S</td>
<td>80</td>
<td>Good-clean</td>
<td>No</td>
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<td>Goyal R et al., 2004</td>
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<td>8</td>
<td>A: 20 g (200 IU) ASL</td>
<td>No</td>
<td>12</td>
<td>3</td>
<td>Yes for 4</td>
<td>0.5</td>
<td>80</td>
<td>Marked (8%)</td>
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<tr>
<td>Pd PK et al., 2006</td>
<td>Open Label</td>
<td>PD</td>
<td>9</td>
<td>A: 10 g (100 IU) ASL</td>
<td>No</td>
<td>6-10</td>
<td>7</td>
<td>Yes</td>
<td>S</td>
<td>80</td>
<td>Good</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Eswaran A et al., 2007</td>
<td>Open Label</td>
<td>PD</td>
<td>11</td>
<td>A: 10 g (100 IU) ASL</td>
<td>No</td>
<td>4-6</td>
<td>7</td>
<td>Yes</td>
<td>S</td>
<td>80</td>
<td>Good</td>
<td>No</td>
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<tr>
<td>Jangwanjai PH et al., 2001</td>
<td>Case series</td>
<td>CP</td>
<td>3</td>
<td>A: 30 g (0 U) SM</td>
<td>Yes</td>
<td>16 (2-4)</td>
<td>Not stated</td>
<td>Yes for 4</td>
<td>S</td>
<td>100</td>
<td>Satisfactory</td>
<td>Salt flattening (3%)</td>
</tr>
<tr>
<td>Perla M et al., 2001</td>
<td>Open Label</td>
<td>PD, P, ALS, CP, other</td>
<td>10</td>
<td>A: 50 g (100 IU) SM</td>
<td>Yes</td>
<td>18 (range 16-20)</td>
<td>Not stated</td>
<td>Yes</td>
<td>S</td>
<td>50</td>
<td>Moderate</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Tav SEK et al., 2008</td>
<td>Case report</td>
<td>ALS</td>
<td>2</td>
<td>A: 10 g (20 U) SM</td>
<td>No</td>
<td>Not stated</td>
<td>Yes (especially with 20 U)</td>
<td>0.5</td>
<td>100</td>
<td>Moderate</td>
<td>Sublingual, chewing, jaw weakness because of salina production (1%)</td>
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<tr>
<td>Winterhalter WA et al., 2008</td>
<td>Case report</td>
<td>ALS</td>
<td>2</td>
<td>A: 50 g (100 IU) SM</td>
<td>Yes</td>
<td>4-6</td>
<td>7</td>
<td>Yes</td>
<td>S</td>
<td>100</td>
<td>Satisfactory</td>
<td>Salt flattening (3%)</td>
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<tr>
<td>Balmer JS et al., 2001</td>
<td>Open Label</td>
<td>Children neurologically impaired with mental retardation</td>
<td>9</td>
<td>A: 50 g (100 IU) SM</td>
<td>Yes</td>
<td>4-6</td>
<td>7</td>
<td>Yes (50%)</td>
<td>0.5</td>
<td>55</td>
<td>Good</td>
<td>Dry mouth</td>
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<tr>
<td>Ellis R et al., 2002</td>
<td>Open Label</td>
<td>Cerebrovascular, stroke, ischemic hypertensive</td>
<td>8</td>
<td>A: 50 g (100 IU) SM</td>
<td>Yes</td>
<td>4-6</td>
<td>10</td>
<td>Yes (50%)</td>
<td>0.5</td>
<td>55</td>
<td>Good</td>
<td>Dry mouth</td>
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<tr>
<td>Kall RL et al., 2006</td>
<td>Prospective, open Label</td>
<td>CP</td>
<td>17</td>
<td>A: 10 g (100 IU) SM</td>
<td>No</td>
<td>2-7</td>
<td>4</td>
<td>Yes</td>
<td>S</td>
<td>32</td>
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<tr>
<td>Ellis R et al., 2003</td>
<td>Open Label</td>
<td>Cerebrovascular, stroke, ischemic hypertensive</td>
<td>13</td>
<td>A: 50 g (100 IU) SM</td>
<td>Yes</td>
<td>12-14</td>
<td>14</td>
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<tr>
<td>Ipp A et al., 2004</td>
<td>Prospective double-blind, placebo-controlled, dose-finding double-blind (placebo)</td>
<td>Open Label, PD, MSA, ALS, CRD</td>
<td>20</td>
<td>A: 400 g (0 U) SM</td>
<td>Yes</td>
<td>4-7</td>
<td>Yes</td>
<td>S</td>
<td>100</td>
<td>Moderate</td>
<td>Satisfactory</td>
<td>Salt flattening (3%)</td>
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<tr>
<td>Marini F et al., 2003</td>
<td>Open Label</td>
<td>PD, MSA, ALS, CRD</td>
<td>12</td>
<td>A: 30 g (100 IU) SM</td>
<td>No</td>
<td>4-6</td>
<td>7</td>
<td>Yes</td>
<td>S</td>
<td>100</td>
<td>Satisfactory</td>
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<tr>
<td>Raves R et al., 2003</td>
<td>Open Label</td>
<td>PD, MSA, ALS, CRD</td>
<td>12</td>
<td>A: 30 g (100 IU) SM</td>
<td>No</td>
<td>4-6</td>
<td>7</td>
<td>Yes</td>
<td>S</td>
<td>100</td>
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<tr>
<td>Raves R et al., 2003</td>
<td>Open Label</td>
<td>Parkinsonism (PD, MSA, ALS)</td>
<td>0</td>
<td>A: 20 g (200 IU) SM</td>
<td>No</td>
<td>4-6</td>
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Table 2 (continued)

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<tr>
<th>Authors</th>
<th>Study design</th>
<th>Disease</th>
<th>no patients included</th>
<th>Brain tissue (type and dosage)</th>
<th>US</th>
<th>Duration (weeks)</th>
<th>Latency (days)</th>
<th>Efficacy</th>
<th>Outcome measure (IUU)</th>
<th>Responders</th>
<th>Improvement</th>
<th>Side-effects</th>
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<tbody>
<tr>
<td>Singh G et al., 2004</td>
<td>Open Label</td>
<td>Salivary neoplastic or neurological disorders</td>
<td>12</td>
<td>A: 20 g (200 IU) SM</td>
<td>Yes</td>
<td>12-16</td>
<td>7</td>
<td>Yes</td>
<td>S</td>
<td>75</td>
<td>Significant</td>
<td>Daily mouth (2 (higher in US group)</td>
</tr>
<tr>
<td>Ellis R et al., 2002</td>
<td>Open Label</td>
<td>Brainstem neoplastic or neurological disorders</td>
<td>12</td>
<td>A: 20 g (200 IU) SM</td>
<td>Yes</td>
<td>12-16</td>
<td>7</td>
<td>Yes</td>
<td>S</td>
<td>75</td>
<td>Significant</td>
<td>Daily mouth (2 (higher in US group)</td>
</tr>
<tr>
<td>Jangwanjai PH et al., 2001</td>
<td>Case report</td>
<td>Brainstem neoplastic or neurological disorders</td>
<td>12</td>
<td>A: 20 g (200 IU) SM</td>
<td>Yes</td>
<td>12-16</td>
<td>7</td>
<td>Yes</td>
<td>S</td>
<td>75</td>
<td>Significant</td>
<td>Daily mouth (2 (higher in US group)</td>
</tr>
<tr>
<td>Singha G et al., 2004</td>
<td>Open Label</td>
<td>Chronic neoplastic or neurological disorders</td>
<td>9</td>
<td>A: 10 g (50 IU) SM</td>
<td>Yes</td>
<td>4-6</td>
<td>7</td>
<td>Yes</td>
<td>S</td>
<td>75</td>
<td>Significant</td>
<td>Daily mouth (2 (higher in US group)</td>
</tr>
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<td>Montague CT et al., 2005</td>
<td>Open Label</td>
<td>Chronic neoplastic or neurological disorders</td>
<td>12</td>
<td>A: 20 g (200 IU) SM</td>
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<td>12-16</td>
<td>7</td>
<td>Yes</td>
<td>S</td>
<td>75</td>
<td>Significant</td>
<td>Daily mouth (2 (higher in US group)</td>
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<tr>
<td>Tech-Gonzalez M and Ostrom DM, 2005</td>
<td>Case report</td>
<td>Brainstem strokes</td>
<td>12</td>
<td>A: 20 g (200 IU) SM</td>
<td>Yes</td>
<td>12-16</td>
<td>7</td>
<td>Yes</td>
<td>S</td>
<td>75</td>
<td>Significant</td>
<td>Daily mouth (2 (higher in US group)</td>
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<tr>
<td>Kall RL et al., 2006</td>
<td>Prospective, open Label</td>
<td>CP</td>
<td>12</td>
<td>A: 20 g (200 IU) SM</td>
<td>Yes</td>
<td>3-12</td>
<td>1-3</td>
<td>Yes</td>
<td>S</td>
<td>50</td>
<td>Significant</td>
<td>Daily mouth (2 (higher in US group)</td>
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<tr>
<td>Laguttog R et al., 2006</td>
<td>Open Label</td>
<td>Chronic neoplastic or neurological disorders</td>
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<td>A: 20 g (200 IU) SM</td>
<td>Yes</td>
<td>3-12</td>
<td>1-3</td>
<td>Yes</td>
<td>S</td>
<td>50</td>
<td>Significant</td>
<td>Daily mouth (2 (higher in US group)</td>
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<tr>
<td>Scitole C et al., 2004</td>
<td>Prospective, open Label</td>
<td>CP</td>
<td>12</td>
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<td>Yes</td>
<td>3-12</td>
<td>1-3</td>
<td>Yes</td>
<td>S</td>
<td>50</td>
<td>Significant</td>
<td>Daily mouth (2 (higher in US group)</td>
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<td>Viesma A and Davila J, 2001</td>
<td>Prospective, open Label</td>
<td>CP</td>
<td>12</td>
<td>A: 20 g (200 IU) SM</td>
<td>Yes</td>
<td>3-12</td>
<td>1-3</td>
<td>Yes</td>
<td>S</td>
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<td>Cotugno FM et al., 2007</td>
<td>Open Label</td>
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<td>A: 20 g (200 IU) SM</td>
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<td>3-12</td>
<td>1-3</td>
<td>Yes</td>
<td>S</td>
<td>50</td>
<td>Significant</td>
<td>Daily mouth (2 (higher in US group)</td>
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<td>Capogno P et al., 2004</td>
<td>Open Label</td>
<td>Salivary neoplastic or neurological disorders</td>
<td>12</td>
<td>A: 20 g (200 IU) SM</td>
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<td>12-16</td>
<td>7</td>
<td>Yes</td>
<td>S</td>
<td>75</td>
<td>Significant</td>
<td>Daily mouth (2 (higher in US group)</td>
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29/11/2018
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<tr>
<th>Title (Uncovered)</th>
<th>Authors</th>
<th>Study design</th>
<th>Objective</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome</th>
<th>Summary</th>
<th>Therapeutic intervention</th>
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<tr>
<td>CT, MR imaging and serum CA-125</td>
<td>Comfort et al.</td>
<td>Case report</td>
<td>To evaluate the effectiveness of neoadjuvant chemotherapy in a patient with advanced ovarian cancer</td>
<td>Neoadjuvant chemotherapy</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>CT, MR imaging and serum CA-125</td>
<td>Comfort et al.</td>
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<td>To evaluate the effectiveness of neoadjuvant chemotherapy in a patient with advanced ovarian cancer</td>
<td>Neoadjuvant chemotherapy</td>
<td>No</td>
<td>No</td>
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<td>CT, MR imaging and serum CA-125</td>
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<td>To evaluate the effectiveness of neoadjuvant chemotherapy in a patient with advanced ovarian cancer</td>
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<td>No</td>
<td>No</td>
<td>Yes</td>
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<td>CT, MR imaging and serum CA-125</td>
<td>Comfort et al.</td>
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<td>Neoadjuvant chemotherapy</td>
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<td>No</td>
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<td>CT, MR imaging and serum CA-125</td>
<td>Comfort et al.</td>
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<td>No</td>
<td>No</td>
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<tr>
<td>CT, MR imaging and serum CA-125</td>
<td>Comfort et al.</td>
<td>Case report</td>
<td>To evaluate the effectiveness of neoadjuvant chemotherapy in a patient with advanced ovarian cancer</td>
<td>Neoadjuvant chemotherapy</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>CT, MR imaging and serum CA-125</td>
<td>Comfort et al.</td>
<td>Case report</td>
<td>To evaluate the effectiveness of neoadjuvant chemotherapy in a patient with advanced ovarian cancer</td>
<td>Neoadjuvant chemotherapy</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>CT, MR imaging and serum CA-125</td>
<td>Comfort et al.</td>
<td>Case report</td>
<td>To evaluate the effectiveness of neoadjuvant chemotherapy in a patient with advanced ovarian cancer</td>
<td>Neoadjuvant chemotherapy</td>
<td>No</td>
<td>No</td>
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<tr>
<td>CT, MR imaging and serum CA-125</td>
<td>Comfort et al.</td>
<td>Case report</td>
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<td>Neoadjuvant chemotherapy</td>
<td>No</td>
<td>No</td>
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<tr>
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<td>Comfort et al.</td>
<td>Case report</td>
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<td>Neoadjuvant chemotherapy</td>
<td>No</td>
<td>No</td>
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<tr>
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<td>Comfort et al.</td>
<td>Case report</td>
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<td>Neoadjuvant chemotherapy</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>CT, MR imaging and serum CA-125</td>
<td>Comfort et al.</td>
<td>Case report</td>
<td>To evaluate the effectiveness of neoadjuvant chemotherapy in a patient with advanced ovarian cancer</td>
<td>Neoadjuvant chemotherapy</td>
<td>No</td>
<td>No</td>
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</table>
Table 1 (continued)

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design</th>
<th>Disease</th>
<th>N patients included</th>
<th>BiNT (type and dosage)</th>
<th>Gland injected (P, SM, SL)</th>
<th>US Duration (weeks)</th>
<th>Latency (days)</th>
<th>Efficacy</th>
<th>Outcome measures (OS)</th>
<th>Responders (%)</th>
<th>Improvement^a</th>
<th>Side-effects</th>
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</thead>
<tbody>
<tr>
<td>Gilt T et al., 2013</td>
<td>Prospective, other neurological disorders</td>
<td>CP</td>
<td>20</td>
<td>OcA (1.5%) gland</td>
<td>Yes</td>
<td>17 (8 to 20 weeks)</td>
<td>15 (5 to 30 days)</td>
<td>Yes</td>
<td>Minimum of two point reduction in T0D scale</td>
<td>80</td>
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<tr>
<td>Corelli B et al., 2012</td>
<td>Prospective, open label</td>
<td>Patients suffering from oral cancer before surgery</td>
<td>43</td>
<td>OcA: 80 U ~ 250 U (40 U/1 g)</td>
<td>Yes</td>
<td>6</td>
<td>5 to 8</td>
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<td>Not stated</td>
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<td>Ge G et al., 2013</td>
<td>Case series</td>
<td>CP and severe learning disabilities</td>
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<td>BiNT/UA (ms) 20 to 40 U (48 U/g)</td>
<td>Yes</td>
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<td>Yes</td>
<td>87.5% (S)</td>
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<td>Ko SH et al., 2013</td>
<td>Prospective, open label</td>
<td>Tetraplegic patients with brain injury</td>
<td>8</td>
<td>OcA: 96 U, SM</td>
<td>Yes</td>
<td>12</td>
<td>Up to 21</td>
<td>Yes</td>
<td>87.5% (S)</td>
<td>Significant</td>
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<td>Reid SM et al., 2013</td>
<td>Prospective, children with developmental disability</td>
<td>Children with developmental disability</td>
<td>26</td>
<td>OcA: 100 U, P, SM U (10 U/kg)</td>
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<td>Not stated</td>
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<td>Yes</td>
<td>73 for 1 month, 60 for 2-3 months, 28 for 6 month</td>
<td>Good to excellent</td>
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<tr>
<td>Subbaramon AJ et al., 2013</td>
<td>Prospective</td>
<td>Children with various neurovascular disorders</td>
<td>20</td>
<td>OcA: 5 U, SM highdose</td>
<td>Yes for 3 pros (bilateral palpation for other pros)</td>
<td>Not stated</td>
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<td>Yes</td>
<td>O (5 added)</td>
<td>Significant</td>
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</table>

^a Improvement as described by the authors: BiNT, botulinum toxin; P, parotid; SM, submandibular; SL, sublingual; US, ultrasonography; O, objective; S, subjective; NA, not available; ms, not specified; pt, patient; pros, patients; A, Abbe, abducens nucleus; ocA, oculomotor nucleus; BNT, botulinum toxin; PD, Parkinson’s Disease; PGP, Progressive Supranuclear Palsy; ALS, Amyotrophic Lateral Sclerosis; CP, Cerebral palsy; MSA, Multiple System Atrophy; CRCA, Corneal Capsule Rupture and Cataract; DLD, Dementia with Lewy bodies; DML, electromyography; DX, diagnosis; SS, swallowing assessment; VAQ, visual analog scale.

^b Improvement as described by the authors: BiNT, botulinum toxin; P, parotid; SM, submandibular; SL, sublingual; US, ultrasonography; O, objective; S, subjective; NA, not available; ms, not specified; pt, patient; pros, patients; A, Abbe, abducens nucleus; ocA, oculomotor nucleus; BNT, botulinum toxin; PD, Parkinson’s Disease; PGP, Progressive Supranuclear Palsy; ALS, Amyotrophic Lateral Sclerosis; CP, Cerebral palsy; MSA, Multiple System Atrophy; CRCA, Corneal Capsule Rupture and Cataract; DLD, Dementia with Lewy bodies; DML, electromyography; DX, diagnosis; SS, swallowing assessment; VAQ, visual analog scale.
Pharmacological interventions for treating sialorrhea associated with neurological disorders: A mixed treatment network meta-analysis of randomized controlled trials

Kannan Sridharan a,⇑, Gowri Sivaramakrishnan b

Sialorrhea is a common distress associated with certain neurological disorders. The aim of this study is to compare the pharmacological agents used for treating sialorrhea by network meta-analysis. Electronic databases were searched for randomized clinical trials comparing active drugs with either placebo or other active drugs. Total drooling scores was the primary outcome measure. Inverse variance heterogeneity model was used for both direct and mixed treatment comparison analysis. Twenty one studies were included in the systematic review and 15 in the meta-analysis. Compared to placebo, benztropine, botulinum toxins A and B are associated with a significant reduction in the frequency and severity of drooling both in the overall neurological disorders as well as for children with cerebral palsy. Only botulinum toxin A and B were associated with significant therapeutic effects in Parkinson’s disease. Benztropine and botulinum toxins A and B were observed to be effective in reducing sialorrhea associated with neurological disorders.
Dosing Recommendation by HKIM and Areerat S.

- Onabotulinumtoxin A 1 unit/kg/gland
- Abobotulinumtoxin A 4 unit/kg/gland by Dr. Heakyung Kim
- Onabotulinumtoxin A 10 ~ 25 units/gland, Abobotulinumtoxin A 40 ~ 125 units/gland for adults by Dr. Areerat S.
- No more than total 100 /500 units/person/session
- Ultrasound (and EMG) Guidance injection

Gland selection:
- If patient is on tube feeding only, consider SM glands only
- If patient eats by mouth, consider SM+Parotid glands
  - Patients on PO feeding – may give higher dose to parotid glands

Take home messages

- Drooling is generally defined as excessive pooling and poor control of saliva in the oral cavity that might be caused by impaired salivary clearance whereas sialorrhea refers to overflow or overproduction of saliva.
- Nearly 40% of children with cerebral palsy and 80% of adults with Parkinson’s disease have been reported to have sialorrhea.
- Ultrasound-guided injection reduces the risk of complications. Using EMG guidance, one can avoid unintended intramuscular injection.
- In case of injecting submandibular gland, EMG guidance enables identification of mylohyoid muscle and the injection of the deep lobe. The structures to avoid within the region of the parotid gland are facial nerve, maxillary and superficial temporal artery branches, as well as retromandibular vein
- Both BoNT-A and -B seem to be safe and effective therapeutic options for disabling drooling in PD patients. It inhibits the cholinergic parasympathetic secretomotor fibers of salivary glands
- As BoNT acts peripherally within salivary glands, it is free of unacceptable side effects in the population of advanced PD, such as cognitive, psychotic, and GI (constipation) complications.
- Injections are relatively easy, even based on anatomical landmarks, but ultrasound-guided (and EMG) injections are recommended.
Professor Areerat Suputtitada, MD.

prof.areerat@gmail.com

Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand