

Hypersalivation

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10.1 Introduction

The terms drooling, hypersalivation and sialorrhoea have been used interchangeably in scientific jargon. Drooling and sialorrhoea can be considered as synonymous, both indicating ‘unintentional loss of saliva from the mouth’, perhaps being more profuse in drooling. They usually refer to difficulty in swallowing, either because of pharyngeal muscle weakness, or of reduced spontaneous swallowing or incoordination, leading to excessive pooling of saliva in the anterior mouth and consequent spillage. Hypersalivation (or absolute hypersalivation) is an ‘abnormally increased production of saliva’, and does not necessarily lead to drooling, if swallowing is efficient. Drooling is sometimes simply referred to as ‘relative hypersalivation’.

10.2 Background and Clinical Description

Saliva performs a number of functions: it facilitates swallowing, keeps the mouth moist and teeth clean, conveys molecules to stimulate the taste, and has digestive and antibacterial functions. Normal daily salivary production is about 1–2 l (0.5–1.5 ml min⁻¹). The majority of daily salivary production is secreted by the parotid and submandibular glands; the parotids account for about 20 per cent of all saliva production, whilst the submandibular glands produce about 70 per cent (Table 10.1). Sympathetic impulses modulate the output of preformed components, including amylase and lysozyme, from salivary cells.

The swallowing reflex normally prevents drooling. Swallowing is a complex task requiring intact neuromuscular coordination: the mean number of swallowing actions per hour is 25.

Table 10.1. Role of the salivary glands in the production of saliva

Salivary glands	Relative contribution	Quality
Parotid	~20–25%	Watery, containing ptyalin; stimulus-induced
Submandibular and sublingual	~60–70%	Submandibular: mixed (watery and viscous); sublingual: viscous; basal
Minor glands: lingual, labial, buccal and palatal	~5–10%	Mixed (watery and viscous); basal

10.2.1 The Salivary Glands

The parotid gland is located dorsally and laterally to the mandible. Most of the gland lies superficially and can be easily detected using ultrasound anterior to the tragus, inferiorly to the zygomatic arc and behind the posterior margin of masseter muscle. Posteriorly, the gland overlaps the sternocleidomastoid muscle and anteriorly the masseter muscle. The inferior tip of the gland extends into the neck. The facial nerve enters the deep surface of the parotid gland and thereafter divides into the temporal and cervicofacial branches. Both further subdivide into five terminal branches within the gland parenchyma (Figure 10.1). The parotid duct opens into the oral cavity opposite to the upper second molar tooth. The parotid glands are made of serous cells, and therefore secrete a watery saliva containing ptyalin, particularly as a response to specific stimuli (e.g., smell or sight of food).

The submandibular glands lie behind the descendent branch of the mandible (Figure 10.2). They are rather superficial and can be easily found with ultrasound, when approached from the neck. The submandibular glands encompass mixed cell types (serous and mucinous). They are responsible for most of the basal secretion rate and, because of the anterior position of Wharton's duct, for the production of most of the spilled saliva.

The sublingual glands lie under the floor of the mouth. They are predominately mucinous, and rather secrete viscous saliva, acting as a lubricant for the oral cavity.

The salivary glands are controlled by the autonomic nervous system. Parasympathetic or sympathetic stimulations produce saliva, but acetylcholine-mediated muscarinic parasympathetic stimulation predominates, leading to the production of a watery saliva. Sympathetic impulses modulate the output of preformed components, including amylase and lysozyme, from salivary cells¹. Absence of both nerve impulses causes atrophy of the salivary gland parenchyma.

In the parotid gland, parasympathetic stimulation originates in the inferior salivatory nucleus, and enters the gland on the auriculotemporal nerve, whereas

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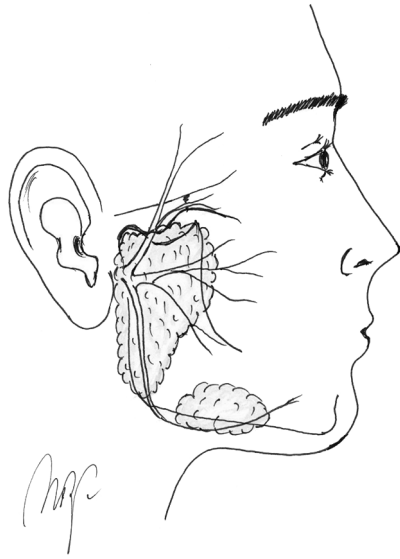


Figure 10.1 Anatomical illustration of the position of parotid and submandibular gland, with surface reperi, lateral view. Branches of the facial nerve are also shown.

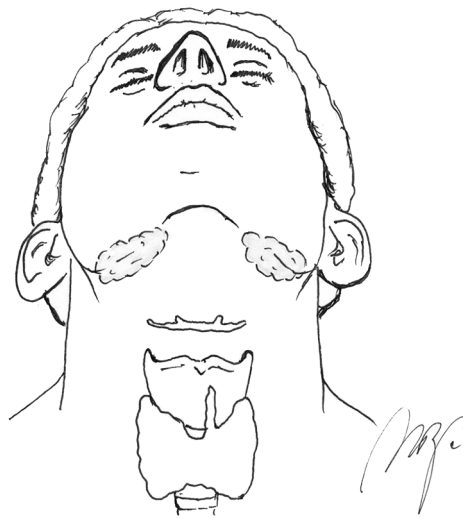


Figure 10.2 Anatomical illustration of the position of parotid and submandibular gland, with surface reperi, neck view.

sympathetic innervation lies around the carotid artery. In the submandibular gland, parasympathetic innervation originates at the superior salivatory nucleus, and enters the gland via the corda tympani and lingual nerves; instead, the sympathetic plexus innervating the gland lies around the facial artery.

10.2.2 Drooling

Drooling is normal in young infants; it usually subsides by 18 months as result of physiologic maturity of the orolingual motor function. Drooling beyond 4 years of age is considered abnormal, although otherwise normal children may occasionally achieve complete saliva control only in the early teens². Children who drool in the early stages may improve as dental age and oral musculature mature.

Absolute hypersalivation is quite rare. Transient hypersalivation follows physiological stimuli (i.e. smell or sight of food). Hypersalivation can be due to lesions or foreign bodies placed into the mouth, to rabies infections or mercurial poisoning. It can also be a pharmacological side effect of some antiepileptic drugs, or of atypical neuroleptics (such as clozapine). In the case of clozapine, it has been suggested that hypersalivation occurs in as many as 74 per cent of patients; however, the pathophysiology of clozapine-induced sialorrhoea remains unclear, as no differences in average saliva flow have been demonstrated. Hypersalivation is also observed in a rare autosomal-recessive disorder known as familial dysautonomia that exclusively affects children of Jewish Ashkenazi origin. In this case it may be the result of a combination of impaired swallowing and progressive autonomic neuropathy, leading to denervation supersensitivity and salivary hyperfunction¹. Similarly, in familial amyloid polineuropathy, which also affects the autonomic nerves, an increased secretion after gum chewing has been found and also attributed to denervation supersensitivity. Finally, a common cause of transient hypersalivation is gastro-oesophageal reflux.

Relative hypersalivation (or drooling) primarily results from infrequent or improper swallowing, dysfunctional voluntary oral motor activity, inadequate lip closure, or forward head posture. It can be seen in association with a wide number of neurological disorders in which swallowing and motility of the lower face musculature are variably affected.

Sialorrhoea occurs in about 50 per cent of patient with amyotrophic lateral sclerosis (ALS); 20 per cent of them have continuous and troublesome drooling³⁻⁵.

From 40 to 80 per cent of patients with parkinsonism may have difficulties with sialorrhoea at some point in their disease course^{6,7}. It has been hypothesized that hypersalivation in Parkinson's disease (PD) may occur as a consequence of the involvement of autonomic ganglia, as Lewy bodies have been found therein. Most probably, however, drooling in these patients is not caused by increased salivation, but rather by disturbed swallowing mainly resulting from akinesia; indeed, it has been demonstrated that PD patients have normal and often reduced salivation when compared to age-matched controls⁸. Moreover, the forward flexion of head and trunk are likely to contribute to sialorrhoea.

Other neurological disorders that can be associated with drooling are myopathies, myasthenia gravis, multiple sclerosis, post-stroke and post-traumatic encephalopathy with involvement of bulbar muscles.

Children with neurological disorders such as cerebral palsy (CP), neuromuscular diseases, autism, language disorders or mental retardation may drool. It has been reported that 10–37.5 per cent of children with CP have significant enough drooling problems as to interfere with their daily life. In a prevalence study conducted on children with CP afferent to special schools, it has been reported that 58 per cent of them had drooling, which was severe in 33 per cent, moderate in 9 per cent and, mild in 6 per cent⁹. Studies in children with CP showed normal pharyngeal and esophageal phases of deglutition, with a marked dysfunction in the oral phase, specifically in the initial suction stage, which hampered initial swallowing¹⁰. Lack of adequate strength in lip closure is also correlated to dribbling in children. Oral and pharyngeal sensory disturbances or central interruption of normal swallowing reflexes may play a role too. Absolute hypersalivation does not occur in children with CP¹⁰.

Sialorrhoea may also be secondary to sensory dysfunctions in the larynx or to surgical procedures in the upper aerodigestive tract, all resulting in dysphagia. Following oropharyngeal surgery, sialorrhoea, albeit transitory, may interfere with wound healing by leading to fistula forming.

Frey's syndrome consists in sweating from the face skin after an appropriate gustative stimulus; it is consequent to abnormal cholinergic reinnervation of denervated cutaneous sweat glands. It can occur as a complication of parotid gland surgery or after sympathetic denervation due to autonomic neuropathies (such as diabetes)¹¹.

Persistent drooling is socially stigmatizing and may affect interpersonal relationship and self-esteem, because of unpleasant smells and unhygienic appearance. Drooling leads to problems with articulation, feeding, swallowing, and work activities. In addition to irritation and ulceration of perioral skin, in some cases associated with infections, excessive drooling can cause aspiration, choking and *ab-ingestis* pulmonitis. Children and intellectually disabled patients often experience a sizable improvement in their social behavior and mood after reduction of drooling after a specific treatment of sialorrhoea.

Evaluation of Drooling

Saliva production is influenced by a number of factors, such as the time elapsed from or required to complete feeding, time of the day, concomitant medication, talking, and stressful circumstances. Some different methods have been proposed to measure drooling and evaluate treatment efficacy.

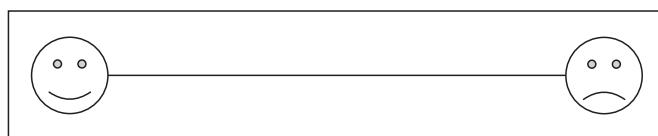


Figure 10.3 This visual analogue scale (VAS) scores the evaluation performed by the patient himself or the caregiver; one extreme indicates the best possible condition and the other is the worst possible condition. The scale line is a 10-cm long.

Subjective methods to evaluate drooling are provided by the Visual Analogic Scale (VAS) (Figure 10.3), the Drooling Frequency Scale (DFS), the Drooling Severity Scale (DSS) and the Drool Rating Scale (DRS)¹², which are based on observations performed by the patients or by their caregiver. These subjective evaluations largely rely on the patient's expectations, mood, and general conditions.

Semi-quantitative methods, aimed at measuring the daily production of saliva, include counting the number of paper handkerchiefs or the number of napkins changed in the course of the day, with evaluation of the degree of moistness (i.e., from 1 = dry to 3 = soaking wet). These methods, too, depend on subjective interpretations and variable behavior, such as the judgment on cloth wetness or the decision on when to change them¹³.

Saliva production at a given time can be measured by inserting dental cotton rolls into the mouth for a short period of time (e.g., from 2 to 5 min). The quantity of saliva produced will result from the difference between the weight of the wet and dry rolls or from the volume of saliva collected after centrifugation of the rolls. These evaluations should be performed at the same time of the day and in standardized conditions. The patient should be in the upright position, having not drunk or eaten since 1 hour before assessment; measurements should be performed after an initial swallow of saliva. In addition, specific collecting systems have been engineered. These rely on cup-like collection devices that can be connected to a system of calibrated test tubes, to measure the total volume of saliva produced¹⁰. Objective methods account only for the moment of the evaluation, not taking into account daily and weekly fluctuations in saliva production, mechanical and gustatory stimuli, emotional state or body posture. The influence of daily variability can be reduced by performing repeated measurements, possibly on different days.

Finally, ultrasound evaluation of the gland appearance and size or salivary gland scintigraphy (using [^{99m}Tc]pertechnetate) could help define changes in gland volume, consistency and activity after treatment³. These methods are not fully reliable and standardized and do not give any information on the functional impairment brought about by drooling.

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None of the methods described here are truly satisfactory: two or more of these evaluations should be performed in combination to reach an accurate estimate of treatment efficacy, ideally combining at least one subjective and one objective measure. This view is supported by a number of studies that failed to demonstrate a direct correlation between objectively measured saliva reduction and the reported subjective improvement. This discrepancy is explained not only by the inadequate accuracy of the measuring tools, but also by the fact that drooling, and most of the subjective impact of it, is only partially related to the absolute flow of saliva, as it greatly depends on the performance in swallowing and on the efficacy of the oral musculature.

10.3 Alternative Treatments

Several treatments have been used over time to treat drooling. Oral treatment as well as local and surgical interventions have been proposed. Benefit is most likely to be achieved in young children, where maturation of oral function may occur, and in adults with relatively mild problems of salivary control.

10.3.1 Anticholinergic Drugs

Various anticholinergic drugs have been used to treat sialorrhoea. These drugs act by reducing cholinergic activity that stimulates secretion of saliva, but are usually ineffective at low doses. Higher dosages, instead, often produce unacceptable systemic side effects, such as confusion, memory impairment, hallucinations, insomnia and sedation, blurred vision, exacerbation of acute angle glaucoma, urinary retention, constipation and cardiac arrhythmia. Moreover, this symptomatic treatment only produces a temporary relief. Anticholinergic drugs can be given orally, sublingually, transdermally, subcutaneously, intramuscularly or intravenously.

Glycopyrronium bromide (glycopyrrolate) is a quaternary anticholinergic that is thought to be less likely to cross the blood–brain barrier, thus producing fewer central effects. The sparse studies performed in adults and children have agreed that the benefit of orally administered glycopyrrolate is generally in the range of 70–90 per cent of improvement at doses up to 2 mg daily (or up to 0.4 mg/kg/day in children)^{13–15}. However, reported side effects are behavioral problems, urinary retention and constipation. These occurred even at lower doses and were more pronounced in children than in adults and often led to discontinuance of the treatment¹⁶. Topical application of glycopyrrolate has been proposed for the treatment of Frey's syndrome, with infrequent mild adverse events¹⁷.

Studies on benztropine mesilate and trihexyphenidyl, reported inconsistent data on efficacy and side-effects. It has been suggested that, at least in children with CP, trihexyphenidyl is more indicated than other oral drugs because of its potential benefit on dystonia associated to CP. This anticholinergic drug can be started at the dose of 0.02–0.04 mg/kg/day, and slowly increased on need.

Transdermal scopolamine has been used to treat drooling, but the results were inconsistent. It is not infrequent to observe allergic reactions to the self-adhering skin patch. Moreover, chronic treatment with scopolamine has been associated with dizziness, blurred vision, psychosis or confusion. A different route of administration has been attempted in three patients with drooling who were treated by local nebulization of 800 µg of scopolamine. Benefit without side effects has been reported, but a short-lived effect and the need for repeated prolonged applications through a mouth mask make this treatment uncomfortable¹⁸.

Significant improvement on subjective evaluation, despite a non-significant objective reduction of saliva flow, has been achieved in seven patients with sialorrhoea secondary to parkinsonism, treated with sublingual atropine twice daily. Two of them, however, experienced worsening of hallucinations⁷. Sublingual atropine was also effective in controlling clozapine-induced sialorrhoea¹⁹.

10.3.2 Surgical Treatment

Various reports have suggested that over 80 per cent of patients undergoing a surgical procedure would benefit from surgery. It has been demonstrated that, at least in children, neuromuscular oral impairment and the severity of drooling are inversely related to postoperative improvement^{20,21}. Surgical interventions are invasive and irreversible, and are therefore inadequate in young children, elderly patients with poor general conditions or when sialorrhoea is a temporary feature. In children, surgical treatments should be postponed until full dental development has been reached⁹. Those who undergo surgical procedure without additional risks are generally young, otherwise fit, patients. A number of studies have pointed out the complications that can occur during surgery and the potential long-term side-effects, such as dental caries, salivary glands calculi or a number of symptoms due to excessive dryness of the mouth (burning sensations, fissuring of commissures, tongue paresthesias). Finally, it should also be taken into account that few surgeons have adequate experience or are willing to engage themselves in these rather uncommon procedures.

Surgical treatment can be directed to each of the salivary glands or to the excretory ducts in different combinations. Excision of the parotid glands can be complicated by facial nerve palsy or by Frey's syndrome (see above); the latter occurs in up to 96 per cent of the patients, as demonstrated by the starch iodine testing (Minor test). Excision of the submandibular gland can be associated

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with ligation²² or rerouting of the parotid duct (so-called Wilkie's procedure). Benefits have been reported in up to 80–100 per cent of patients, but side effects are common (up to 30 per cent, including wound dehiscence, duct stenosis or cyst, oral/dental problems, septic parotitis, xerostomia). Furthermore, excision of the submandibular gland can be complicated by permanent (up to 7 per cent) or temporary (up to 36 per cent) damage to the marginal mandibular nerve or by damage to other nerves, such as the lingual or the hypoglossal.

Salivary duct transposition consists in rerouting of the ducts and orifices to the pharynx to bypass the oral phase of deglutition. A reasonably efficient pharyngeal phase is needed in order to avoid the risk of aspiration. Submandibular salivary duct transposition is the most common type of surgery^{20,21,23–25}. This procedure is commonly complicated by unwanted events, such as lateral neck cyst or a mucous retention pseudocystis of the sublingual ducts and gland (ranula), which could eventually require additional surgery. Duct obstruction, gland infection or transient airway obstruction have also been reported^{21,24}. Transient swelling of the cheek, the mouth floor or of the submandibular region is a common finding after this type of surgery and can last for several weeks. Recently, the transposition of parotid duct orifices using vein grafts has been introduced. This procedure is still anecdotal and requires high surgical competence and a microsurgical approach²⁶.

Surgical ligation of the parotid excretory ducts involves the danger of gland swelling and abscess formation, because of a congestion of the secretory product. The efficacy of this procedure, when performed alone, is controversial²⁷. The four-duct ligation (bilateral parotid and submandibular duct ligation) can be efficacious and less invasive than gland excision^{27,28}.

Transtympanic neurectomy produces a parasympathetic denervation of the parotid gland. Sialorrhoea control by approximately 75 per cent has been reported in the immediate, while long-term studies show a high failure rate. It is usually performed in association with a division of the corda tympani, inevitably causing loss of taste in the anterior two-thirds of the tongue.

10.3.3 Radiotherapy

Radiation-induced xerostomia is a well-known side effect of radiotherapy delivered to the head and neck region. The serous acinic cells of the salivary tissue are the target of radiation injury. Very few reports in the literature refer to the use of this technique for treating sialorrhoea. In a report on 31 cases of sialorrhoea of different origin, referred to radiotherapy after failure of medical treatment, an initial satisfactory response (complete to partial, but with drooling not interfering any longer with social activities) was achieved in 82 per cent of patient²⁹. In 64 per cent of cases, benefit was maintained for a mean follow-up

period of 39 months. Response rates were higher with electrons than with orthovoltage, and when larger fields (including both submandibular glands and the whole of parotids) were used. Twenty-six per cent of the patients reported acute side effects (oral candidiasis, skin reactions, mucositis), while 13 per cent reported permanent side effects (troublesome thick secretions and temporomandibular joint fusion). In another series, including only patients with sialorrhoea due to ALS, benefit was achieved in all the patients, but symptoms sometimes recurred after a few months. Reported side effects were erythema and burning of the skin, sore throat, nausea, and thicker secretions, all of which receded from a few hours to 4 weeks⁵.

The elderly and those in poor general conditions, or with limited life expectancy, can be offered radiation therapy. This treatment, however, should be avoided in children, because of the risk of inducing malignancies or impeding a normal growth, thereby leading to facial asymmetry or osteonecrosis.

10.3.4 Occupational, Physical and Speech Therapies

It has been suggested that facilitation of mouth closure can effectively decrease drooling. Exercises, stimulation programs or the intraoral appliance of training devices have been proposed to improve the strength of lip seal and deglutition mechanisms^{30,31}. Intraoral appliances are not suitable for children under the age of six, in whom presumably dentition is not fully completed. Vibration and/or icing have been used to improve sensation and movement. Behavioral modification programs use a conditioning technique with auditory or visual signals as cues to prompt swallowing (biofeedback). The target end-points of these programs are the child's awareness of drooling and his ability to swallow on command, which correlate with the overall treatment outcome. These techniques are time-consuming and require full cooperation, in addition to the integrity of the neuromuscular system in the facial district. Success largely depends on the intellectual ability and motivation of the patient. Motor rehabilitation should be aimed to enhance head control, improve muscle tone and stabilize the relation of body position.

10.3.5 Acupuncture

Tongue acupuncture has been proposed as a treatment of alternative medicine for children with drooling. Five of the 40 points thought to correspond somatotopically to specific skills or body regions are usually addressed. Thirty sessions are normally required for a total course of 6 weeks. Good results, according to subjective evaluations, have been obtained in 10 children. Improvement of drooling still persisted over 6-month follow-up³².

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10.4 Botulinum Toxin

10.4.1 Introduction

Autonomic symptoms of the cranial district and particularly dry mouth have been observed in the majority of patients with human botulism. In 1822 Justinus Kerner, analyzing 155 cases of food-borne botulism, made the first accurate description of botulinum toxin (BoNT)-induced autonomic failure. Kerner also developed the idea of a possible therapeutic use of the substance causing botulism, not only for muscular hypercontractions, but also for hyperhidrosis and hypersalivation³³.

Two BoNT serotypes (BoNT-A and BoNT-B) are available in the clinic; their relative potency has not been univocally assessed and therefore direct comparisons have a limited value. The possible use of BoNT for the treatment of sialorrhoea was first considered by Bushara, who proposed to inject BoNT type A into the parotid glands in patients with ALS³⁴. However only in the last few years has BoNT type A, and very recently also type B, been used for this purpose.

10.4.2 Efficacy

BoNT inhibits acetylcholine release in nerve terminals not only at the neuromuscular junction, but also in the sympathetic and parasympathetic ganglion cells and in postganglionic parasympathetic nerves. This action is exerted by blocking the fusion of acetylcholine-containing vesicles with the plasma membrane. In animals it has been demonstrated that in the parotid and submandibular glands BoNT-A inhibits the release of acetylcholine from the synaptic vesicles into the synaptic cleft, resulting in reduced function of parasympathetic controlled glands. In rats treated in just one parotid gland the acinar volume is increased in the treated gland, probably as a result of retention of the excretion products in the cell bodies. The increased number of acinar cells observed in the contralateral gland could be due to a reactive enhancement of saliva production. This phenomenon has not been observed after treatment of the submandibular glands³⁵. Studies in dogs have demonstrated that BoNT types A and D significantly decrease the production of saliva from the submandibular gland through an anticholinergic, rather than toxic, effect³⁶. BoNT-B produces similar effects at the neuromuscular junction and autonomic terminals, acting on a different intracellular target. The blockade of nerve terminals by BoNTs is irreversible; the clinical effects, however, are temporary as new nerve terminals sprout giving rise to new connections.

Anticholinergic side effects seem to be more common with BoNT-B. Trials on patients with cervical dystonia treated with BoNT-B have reported an increased incidence of dysphagia and dryness of the mouth^{37,38}. These adverse events

increase with increasing dosage³⁷ and account for up to 44 per cent of the cases treated with 10.000 NeuroBlocTM³⁸. The most frequent side effects reported with BoNT-B are dryness of the mouth (76%), impaired accommodation (36%), irritation of the conjunctiva (20%), reduced sweating, swallowing difficulties, heartburn, constipation, difficult bladder voiding, head instability, dryness of nasal mucosa or thrush^{39–41}. BoNT-A is from 10 to 50 times more potent than BoNT-B as a treatment of the motor symptoms of dystonia, although it is only 2.5–20 times more potent than BoNT-B when sudomotor blockade is considered^{41,42}. It appears that BoNT-B is clearly more potent in blocking sudomotor nerves than motor neurons in humans, probably due to a different affinity for the BoNT serotypes of cholinergic synapses of the autonomic and motor systems. A higher affinity of BoNT-B for the autonomic than somatic motor nerves could account for the higher frequency of autonomic side effects observed in patients treated for dystonia with BoNT-B. It is therefore hypothesized, albeit not yet confirmed, that less unwanted weakness of surrounding muscles could occur following injections of BoNT-B into the salivary glands.

Treatment of salivary drooling with BoNT has proven promising, especially when compared to other available treatments. Parotid was the initially targeted gland, mainly because it is easily reached. This gland, however, accounts for only about 20 per cent of all saliva production. Since the submandibular glands produce most of the saliva, the simultaneous or sequential combined treatment of the parotid and submandibular glands has been attempted. In cases in which only the parotid glands are injected, the remaining viscous secretions of the submandibular and sublingual glands is sufficient to protect against the unwanted effects due to dry mouth⁴. Still, when the parotid and submandibular glands are both injected, dry mouth is uncommon, because the basal secretion of the remaining salivary glands is sufficient. Treatment of submandibular glands alone is far less effective than combined treatments¹². No detailed reports are available concerning injection of BoNT in the sublingual glands. It has only been mentioned that dysphagia occurred in half of four patients who received direct injections into the sublingual glands without benefiting in any reduction of sialorrhoea⁴³. Salivary flow is reduced after BoNT treatment, but the secretion of salivary components is not, because BoNT does not affect adrenergic innervation⁴⁴.

The clinical efficacy of the BoNT is appreciable within 7 days and anyway within 2 weeks after treatment. The duration of the effect has not always been accurately measured and seems to vary between 6 and 30 weeks (Tables 10.2 and 10.3). Therefore, the injections must be repeated periodically. An inverse correlation has been reported between the amount of drooling before treatment and the duration and the scale of clinical benefit^{12,45}; this may suggest that BoNT doses need to be tailored on each patient. The reported duration of efficacy following BoNT

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treatment of sialorrhoea is longer than that following treatments for focal dystonia or spasticity and is similar to that of hyperhydrosis. The reason for this difference is unclear at present; one possibility is that this effect may be related to a different rate for the synthesis of the synaptic proteins inhibited by BoNT in the autonomic nerves compared to somatic motor nerves. In addition, re-sprouting in autonomic nerve endings has not been observed to date⁴⁶. It has been hypothesized that autonomic innervation may have a trophic function on glands, that would be lost following BoNT treatment⁴⁷, but histological findings on sweat glands after BoNT treatment do not reveal gland atrophy⁴⁶.

There are only two published studies on BoNT-B injections for drooling^{43,48}. The reported magnitude and duration of efficacy and the frequency of side effects are similar to those reported in trials using BoNT-A.

BoNT treatment has been successfully used also to treat clozapine-induced hypersalivation⁴⁹ and Frey's syndrome^{50,51}. In this latter condition, it has been administered subcutaneously.

Results of BoNT treatment largely depend on the accuracy of injection placement into the glands, on the dose used, on the choice of glands to inject (based on their relative role in salivary secretion), on the patient's condition and on the underlying pathology. Some studies failed to demonstrate objectively a significant saliva reduction, despite subjective improvement. This discrepancy could be explained by a placebo effect, since only two controlled studies have been conducted^{43,45,52}, or by limitations in the accuracy of the outcome measures. The variety of dosages, of toxin brands, of assessment methods, and of the causes of drooling make it very difficult to compare the available studies. In general terms, most studies reported that the overall benefit was reasonably good and capable of improving the patients' quality of life (Tables 10.2 and 10.3).

10.4.3 Injection Techniques

BoNT injections are made percutaneously into the parotid or into the submandibular gland. One pilot study has attempted to deliver BoNT directly through Stenson's duct; but, this retrograde approach has produced unacceptable side effects⁵³.

In most of the studies, the injections have been performed without guidance, but recent evidence suggests that a better outcome can be obtained when ultrasound guidance is used. This allows us to accurately reach the gland parenchyma, compensating for the anatomical variability of gland location observed in different patients. Ultrasound guidance is an essential aid to avoid vascular structures and branches of the facial nerve. It has been suggested that electromyographic guidance could prevent inadvertent injection into the masseter

Table 10.2. Synopsis of botulinum toxin treatments for sialorrhoea in adults

Patients	Gland	BoNT dose		Needle	US	Efficacy	Outcome measure	Latency of effects	Adverse events	Duration	Notes	Ref.
		(units)										
4 (1 CP, 1 PD, 1 PSP, 1 ALS)	P	20 (D)		25G (5/8)	N	Good in three cases	Subjective	7 days	1 Worsening dysphagia; 2 chewing difficulties; 1 dry mouth.	6–16 weeks	10 MU for ALS patient: no efficacy	54
5 PD	P	10 (B)		27G	N	Good in two cases, moderate in two cases, no effect in one case	Subjective	?	1 transient masseter weakness. 2 transient mouth opening weakness	17–30 weeks		55
9 PD	P	7.5 (7 pts) 15 (9 pts(B))		30G 2.5 cm	N	Good in three cases. Partial in three cases. Mean reduction 35%.	DFS, DSS rolls weigh	7–10 days	1 pain at injection site	8 weeks	Difference low/high dose not evaluated.	6
5 ALS	P ± SM	P: 6–20 SM: 5 (B)		27G (3/4)	N	Good in four cases, no effect in one case	No. handkerchiefs, DLQI, Scintigraphy UPDRS II, rolls weigh	3–5 days	1 sialorrhoea ? increase	?	Progressive additional treatment	3
11 PD	P	5 (B)		29G	N			?	No	6 weeks		58

10	(1 primary sialorrhoea, 4 ALS, 2 PD, 1 CP, 1 post- traumatic, 1 post- encephalitic). 1 CBD	P+SM P: 15-40 SM: 10-15(B)	22G	Y	Good (significant reduction)	VAS	3-8 days	1 dry mouth	17-30 weeks	Assessment made only at 1 week Dose adjusted with respect to salivation rate and body weigh	47
		P 150 (D)	21G	N	Good 55%.	No.	?	No	?		4
13	(8 post- neoplastic, 4 neurode generative, 1 post- stroke)	P+SM P: 22,5 SM: 10 (B)	26G (1/2)	Y	Good	Rolls Centrifugal, Subjective.	7 pts = within 7 days 6 pts = within 14 days	No	8-28 weeks	Lower dose for two patients	44
10	(7 PD, 3 MSA)	P+SM P: 146,25 SM: 78,75 (D)	26G	Y	Good (significant reduction DSS & DFS in)	ADL, DSS, DFS	7 days	Pain at injection site	3-6 weeks	Double-blind placebo- controlled study	45

Table 10.2. (Cont.)

Patients	Gland	BoNT dose		Needle	US	Efficacy	Outcome measure	Latency of effects	Adverse events	Duration	Notes	Ref.
		(units)	(units)									
9 (6 PD, 2 LBD, 1 MSA)	P	1000 (N)		30G	N	Good. VAS mean reduction 61%.	VAS (0–4), Rolls weigh	?	1 dry mouth	8–20 weeks		
						Weigh reduction non-significant (42%)					Increased sialorrhoea in 1 case with subjective benefit	48
32 (12 ALS, 12 PD, 4 MSA, 4 CBD)	P	a) 18.75 b) 37.5 c) 75 (D)		30G 25 mm	N	Good for c) (50%), nonsignificant for a) and b)	Rolls weigh, Subjective counter. ADL questionnaire	?	No	?	Double blind placebo controlled, dose finding study	52
16 PD	P+SM	P: 1000 SM: 250 (N)		29G 12,7 mm	N	Good.	DRS, DFS, DSS, VAS, global impression, dysphagia questionnaire, scintigraphy	DRS, DFS, DSS, 5 ± 5 days (range 1–14)	3 dry mouth, 2 gait worsening, 1 diarrhea, 1 neck pain	12–20 weeks	Double blind placebo controlled study. Duration not specifically addressed	43
1 Clozapine-induced	P	150 (D)		?	N	Good.	Subjective	2 weeks	No	> 12 weeks		49

Abbreviations: ADL = activities of daily living scale; ALS = amyotrophic lateral sclerosis; B = Botox[®]; CBD = cortico-basal degeneration; CP = cerebral palsy; D = Dysport[®]; DFS = drooling frequency scale; DLQI = dermatology life quality index; DRS = drool rating scale; DSS = drooling severity scale; LBD = Lewy body dementia; MSA = multiple system atrophy; MU = mouse units; N = NeuroBloc[™]; P = parotid; PD = Parkinson's disease; PSP = progressive supranuclear palsy; pt = patient; SM = submandibular; UPDRS = unified Parkinson's disease rating scale; US = ultrasound; VAS = visual analogic scale.

Table 10.3. Synopsis of botulinum toxin treatments for sialorrhoea in children

Patients	Gland	BoNT dose (units)	Needle	US	Efficacy	Outcome measure	Latency of effects	Adverse events	Duration	Notes	Ref.
3 CP	SM	(1) 30	25G	Y	51–63% reduction of salivary flow.	DFS, DSS, rolls weight	?	1 thick saliva	>16 weeks (2 pts)	Weight-adjusted dose: 1) <15 Kg 2) 15–25 Kg (1 pt) 3) > 25.	2
		(2) 40							4 weeks		
		(3) 50							(1 pt)		
		(B)									
17 CP	(1) SM	(1) SM: 10, 20, 30.	22G	Y	(1) benefit in 33%.	Speech therapist evaluation, radiographic swallowing evaluation	7–10 days	No	2–26 weeks	Dose escalation. Additive gland treatment. Local anesthesia.	12
	(2) SM+P	(2) SM/P: 30/20, 30/30, 30/40 (B)			(2) benefit in 80%	DRS, DQ.					
9 (6 CP, 1 congenital CMV infection, 1 chromosomal abnormality, 1 mental retardation)	P	5 (B)	30G	N	Over 75% (3 pts) 27–46% (2 pts) 15% (1 pt) No benefit (3 pts)	Rolls weight, DQ, DFS, DSS.	Within 4 weeks	1 increase of saliva production for 8 weeks (mild dysphagia?)	8–16 weeks	Local anesthesia.	56

Abbreviations: B = Botox[®]; CMV = cytomegalovirus; CP = cerebral palsy; DFS = drooling frequency scale; DQ = Drool Quotient; DRS = drool rating scale; DSS = drooling severity scale; MU = mouse units; P = parotid; pt = patient; SM = summandibular.

muscle, but this procedure can be difficult, painful and time-consuming, while comparable results can be obtained with ultrasound guidance alone.

The parotid gland can otherwise be targeted considering the surface anatomical reperi (as shown in Figure 10.4). The cholinergic innervation is equally distributed within the gland, and there is no need to target any specific area. The aim of the treatment is to reach the entire gland volume; for this purpose usually 2–3 injections are performed. The preferred injection points are:

- (1) in the space between the mandibular ascendent branch, the anterior border of mastoid process and the adjoining upper part of SCM muscle;
- (2) preauricularly, between the posterior margin of the masseter muscle, the tragus and the mandibular corner, or
- (3) between the mandibular ascendent branch and the posterior margin of the masseter muscle.

If the injections are placed in more than one site, at least one should be in the gland body, while the others could be in the tail or in the region above the masseter muscle.

The submandibular glands are targeted considering, as anatomical reperi, the margin of mandibular descendent branch (as shown in Figure 10.5). BoNT can be injected in a single site per each gland.

Injection depth in parotid glands can vary, according to the site chosen. Studies on BoNT-A diffusion show its ability to disseminate beyond fascial planes.



Figure 10.4 Suggested injection points for the parotid gland.

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Figure 10.5 Suggested injection points for the submandibular gland.

When ultrasound guidance is used, delivering the toxin in the middle of the gland can minimize the risk of diffusion, yielding a more favorable dose–response relationship. We suggest using a 55 mm 22G needle; a depth of 30 mm can be necessary to reach the center of the gland. When the injections are made without guidance, the depth should be kept around 10–15 mm, in order to avoid nervous and vascular structures within the gland. Extra-fascial parotid injections have also been proposed⁴.

The patient can be placed supine, with the head turned on one side to treat the parotids and with the head in a backward tilt to treat the submandibular glands. It is good usage to provide appropriate antisepsis and to withdraw the syringe plunger, thus ensuring that the needle has not penetrated any vessel. The diluted toxin should be injected slowly within the gland.

10.4.4 Dosage Guidelines

For the parotid gland the reported doses of BoNT-A vary between 5 and 40 Botox[®] U, usually diluted in 2 ml of saline, or 20–150 Dysport[®] U (Table 10.2). The reported doses of BoNT-B were 1000 NeuroBloc[™] U in each parotid gland. The total dose was injected in one or up to three sites. In the submandibular glands doses of 5–15 Botox[®] U were used in each gland in three studies, whereas 78.75 Dysport[®] U were injected in one study and 250 NeuroBloc[™] U were used in one study. In all these studies, the injections were placed in a single site (Table 10.2).

In order to prevent the potentially serious side effect of dysphagia in patients with bulbar symptoms it is prudent to initially begin treatment with a lower dosage (i.e., between 5 and 10 Botox[®] U) in each parotid gland, depending on the amount of drooling. If these are ineffective, higher dosages can be used in the parotid gland or the submandibular glands may be additionally injected.

Some authors attempted to determine if any features could predict the outcome of treatment. At least in adults, weight does not influence the efficacy following a fixed dose⁴⁸; some authors have suggested the adjustment of dosage in children in consideration of the low weight and the smaller dimensions of the targeted glands². This does not apply to adults where the efficacy of BoNT depends entirely on its local action without any appreciable weight influence.

10.4.5 Side Effects

Side effects are related to injection site, the dosage and dilution of the toxin used along with the patient's general conditions. Occurrence of side effects is usually higher in patients with poor physical conditions (i.e., patients with ALS in the late stages). Ultrasound guidance greatly increases the safety of the treatment, and helps avoiding vascular and nerve structures, as well as the masseter muscle. The most frequent potential side effect of this treatment is excessive dryness of the mouth; this has been reported only in six patients and has always been mild and short-lasting. In keeping with this, potential aftermaths of this side effect (such as salivary duct calculi or dental caries) have never been reported. A theoretically relevant complication could be dysphagia, due to diffusion to nearby bulbar muscles; this, however, has been reported in just one patient, who experienced mild worsening of a pre-existing dysphagia⁵⁴. Chewing can also be weakened, due to diffusion of BoNT to the masseter muscles; this has been reported in two studies in which the injections were made without guidance^{54,55}. Excessive weakness of a masseter muscle can induce dislocation of the temporo-mandibular joint.

Damage to the facial nerve or the facial artery that cross the parotid are theoretically possible complications that have never been reported, even when the injections were performed without guidance. This could be due to the common use of short and thin needles (less than 25 G), that penetrate the parotid only superficially. Infection of the salivary gland or of the salivary duct or local haematomas are also possible, theoretical, complications. Surprisingly, increase of sialorrhoea has been reported twice (in an adult and a child); this is possibly due to the occurrence of mild dysphagia and consequent further reduction of swallowing^{3,56}. Pain at the injection site is frequently reported, particularly when larger needles are used. In children, local anesthesia with anesthetic cream is useful (Table 10.3); general anesthesia has also been anecdotally used⁵⁷, but is rarely necessary. Other reported side effects following BoNT injection are gait worsening,

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diarrhea or neck pain⁴³; these are unlikely to be related to the treatment, but rather to the underlying pathology. In our experience, the frequency of side effects is very low when patients are in good general conditions and ultrasound guidance is used.

10.5 Conclusion

BoNT is an efficacious treatment of drooling, especially when it is administered in more than just one salivary gland. The safety of this treatment can be increased by using ultrasound guidance. The reduction of saliva flow in a patient with hypersalivation can increase dental caries and requires an adequate dental supervision if the treatment is prolonged in time.

In order to fully appreciate the success of BoNT treatment, the underlying pathology and the diverse individual issues are to be taken into account.

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Appendix: Rating Scales for Drooling

Drooling Frequency Scale

1	Never drools	
2	Occasional drooling	Not every day
3	Frequent drooling	Every day but not all the day
4	Constant drooling	Every day

Drooling Severity Scale

1	Dry	Never drools
2	Mild	Only lips wet
3	Moderate	Lips and chin wet
4	Severe	Clothing soiled
5	Profuse	Clothing, hands and tray most and wet

Drooling Rating Scale

Pre-injection

Salivation

- 1 Normal
- 2 Pooling in mouth
- 3 Minimal drooling
- 4 Moderate drooling
- 5 Constant drooling

Bib or shirt changes in a day as a result of excessive drooling

- 1 None
- 2 1 bib or shirt change a day

Drooling Rating Scale (Cont.)

- 3 2–3 bib/shirt changes a day
- 4 4–5 bib/shirt changes a day
- 5 6 or more bib/shirt changes a day

Drooling while eating

- 1 None
- 2 Minimal, does not interfere with eating
- 3 Moderate, slight interference with eating
- 4 Moderate-severe, obviously interferes with eating
- 5 Severe, prohibits eating

Drooling at night

- 1 None
- 2 Minimal, lips slightly moist
- 3 Moderate, lips and chin wet, pillow slightly moist
- 4 Moderate to severe, pillow obviously wet
- 5 Severe, pillow saturated, clothing wet

Choking or severe coughing episodes

- 1 Never
- 2 Has happened only once or twice
- 3 Happens occasionally
- 4 Happens often
- 5 Happens every/almost everyday

Noisy breathing or 'gurgling' caused by excess saliva

- 1 Never
- 2 Occasional (1 episode/week to 1 episode/day)
- 3 Frequent (> 2 episodes/day)
- 4 Constant

Degree of skin irritation (face/neck) from drooling

- 1 None
- 2 Slight redness, occasionally
- 3 Slight redness, always
- 4 Moderate redness, always
- 5 Severe redness, occasional breakdown

Halitosis (bad breath)

- 1 None
- 2 Slight halitosis
- 3 Moderate halitosis
- 4 Moderate-severe halitosis
- 5 Severe halitosis

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Patient self-confidence secondary to drooling

- 1 Drooling does not affect confidence
- 2 Drooling causes a slight embarrassment
- 3 Drooling causes moderate embarrassment
- 4 Drooling causes severe embarrassment

Public response to patient and drooling (please reflect)

- 1 Normal, do not shy away
- 2 Minimal, slightly reluctant to have physical contact with the patient
- 3 Moderately reluctant to have physical contact with the patient
- 4 Moderate-severe, seem extremely reluctant to touch the patient
- 5 Severe, will not even touch the patient

Ease in caring for patient related to drooling

- 1 No problem
- 2 Slight inconvenience
- 3 Moderate inconvenience
- 4 Severe inconvenience

How limiting is the patient's drooling on doing activities outside the home?

- 1 None
- 2 Very mild
- 3 Mild
- 4 Moderate
- 5 Severe

Overall, how much of an inconvenience is the caregiver by the excessive saliva and/or drooling of the patient?

- 1 Not bothered at all
- 2 Bothered a little
- 3 Bothered more than a little, but not a lot
- 4 Bothered a lot
- 5 Extremely bothered

Overall, how bothered is the patient is as a result of excessive drooling

- 1 Not bothered at all
- 2 Bothered a little
- 3 Bothered more than a little, but not a lot
- 4 Bothered a lot
- 5 Extremely bothered

Post-injection

Overall, how has the drooling been since the Botox injection?

- 1 Markedly worse
- 2 Moderately worse
- 3 Slightly worse
- 4 No change

Drooling Rating Scale (Cont.)

- 5 Slightly improved
- 6 Moderately improved
- 7 Markedly improved

If you have seen an improvement, how has it improved for you?

How would you rate your level of satisfaction with treatment for drooling?

- 1 Markedly dissatisfied
- 2 Moderately dissatisfied
- 3 Mildly dissatisfied
- 4 Mildly satisfied
- 5 Moderately satisfied
- 6 Markedly satisfied

Would you undergo botulinum toxin injections again?

- 1 Yes
 - 2 No
-