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The Use of Botulinum Toxins to Treat Hyperhidrosis and Gustatory Sweating Syndrome†

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Hyperhidrosis is a chronic condition characterized by excessive sweating. Recent studies report that it affects approximately 2.8% of the population and typically begins during adolescence. Gustatory sweating usually occurs after parotid gland injury or surgery, and both disorders can be debilitating for those who are affected. Both diseases respond very well to botulinum toxin therapy and this article will review the use of botulinum toxins, including the serotypes used, dosing, and complications.

Keywords: Hyperhidrosis; Botulinum toxin; Frey's syndrome

INTRODUCTION

Hyperhidrosis is defined as sweating that is in excess of what is physiologically required to maintain thermoregulation of the body. Although the sweating can be generalized, hyperhidrosis is more commonly focal, affecting one or a few areas of the body. The prevalence of hyperhidrosis has been reported to be 2.8% (Strutton *et al.*, 2004)

Hyperhidrosis can be classified as primary or secondary (Hornberger *et al.*, 2004). Primary, or idiopathic, hyperhidrosis commonly affects the axilla, palms and soles. The exact etiology is unknown but there does seem to be a genetic component, with 30-50% of patients reporting positive family histories of excessive sweating. Secondary hyperhidrosis has many causes (Table I). Gustatory sweating is a well-known complication of parotid surgery and facelift surgery.

Sweating is a normal and important function that helps to maintain thermoregulation and fluid and electrolyte balance (Sato *et al.*, 1989). Eccrine sweat glands are distributed all over the body and produce a watery secretion. The rate normally varies with an individual's body temperature, and exercise. Enervation is sympathetic, but with acetylcholine as the neurotransmitter. Apocrine glands are found primarily in the axilla, areola, perineum and vermilion lip. Apocrine glands become active at puberty, with a secretion that is viscous and cloudy. The exact function of the secretion is unknown but can result in "body odor" when combined with bacteria on the skin's surface. The adrenergic nervous system primarily controls apocrine glands. A third gland, the apoeccrine gland has been identified and has features of apocrine and eccrine glands. It can produce large amounts of watery secretion. The function of this gland is not clear, but may play a role in axillary hyperhidrosis, where these glands are usually found.

Recent studies have elucidated the significance and magnitude of difficulties that hyperhidrosis causes in those affected with it (Swartling *et al.*, 2001; Naumann *et al.*, 2002). Using validated quality of life surveys, hyperhidrosis is similar in terms of negative psychological effects to other chronic diseases such as severe psoriasis, rheumatoid arthritis, and multiple sclerosis. Quality of life data indicates that all domains of life can be affected by hyperhidrosis. Individuals report that they are moderately to extremely limited in various activities due to their sweating and these include in public places, at work, in sports, with romance and intimacy, personal and work relationships, shaking hands, with family and friends and meeting people. In addition, it has been shown that treatment of hyperhidrosis with botulinum toxin type A (BoNT-A) improves health related quality of life and limitations in daily activities (Glaser *et al.*, 2004; 2005).

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DIAGNOSIS

Primary hyperhidrosis is a clinical diagnosis (Hornberger *et al.*, 2004) (Table II). Generalized forms of sweating and asymmetric patterns should be evaluated for underlying disorders. Sometimes, the history and physical exam alone is adequate to understand the underlying etiology, as with gustatory sweating.

Measuring disease severity can be a challenge. Collecting sweat for gravimetric quantification is time-consuming and not practical in the clinical setting. The amount of sweat that constitutes "excessive" has not been standardized and this tool is primarily used in clinical trials. The Minor's starch iodine test is a valuable tool to identify the area of excessive sweat production and to localize therapy (FIG. 1). More recently patient reported measures have been used to assess disease severity. As previously mentioned, several tools to measure quality of life issues are available. The Hyperhidrosis Disease Severity Scale is a simple tool that is easy to use in the office and has been validated. It is sensitive to individual differences in disease impact (Glaser *et al.*, 2006). (Table III)

TREATMENT

Several treatments are available for hyperhidrosis including topical agents such as aluminum chloride, systemic medications such as oral anticholinergic drugs and beta blockers, iontophoresis, BoNT, and surgical therapies. In general therapy should begin with the least aggressive option (FIG. 2). The choice of therapy will be dependent on the health and medication history of the patient, and the location of the excessive sweating.

This paper will focus on the use of botulinum toxins in treating hyperhidrosis.

BoNT THERAPY

The first use of BoNT to treat hyperhidrosis was reported by Bushara *et al.* in 1996. Since that time multiple studies have demonstrated that intradermal injection of BoNT is an effective and safe therapy in the treatment of hyperhidrosis. BoNT-A has been most extensively studied and used clinically for the treatment of hyperhidrosis but there are a few publications related to the use of botulinum toxin type B (BoNT-B) as well.

Table I Causes of secondary hyperhidrosis

Generalized Hyperhidrosis	**Regional Hyperhidrosis**	**Focal Hyperhidrosis**
Drugs, toxins, substance abuse	Lesions in the central or peripheral nervous system	Eccrine nevus
Cardiovascular disorders	Stroke	Gustatory sweating
Respiratory failure	Peripheral neuropathy	Frey Syndrome
Infections	Ross Syndrome	Social anxiety disorder
Malignancies	Focal nerve damage	Impaired evaporation
Endocrine/metabolic disorders		

Table II Definition and diagnostic criteria for primary focal hyperhidrosis

Excessive sweating beyond physiological needs
Focal, visible excessive sweating of at least 6 months duration without apparent cause with at least 2 of the following characteristics • Bilateral and relatively symmetric • Impairment in daily activities • Frequency of at least 1 episode per week • Age of onset less than 25 years • Positive family history • Cessation of focal sweating during sleep

Table III Hyperhidrosis Disease Severity Scale

	Which best describes the impact of sweating on daily activities?
1	Never noticeable, never interferes
2	Tolerable, sometimes interferes
3	Barely tolerable, frequently interferes
4	Intolerable, always interferes

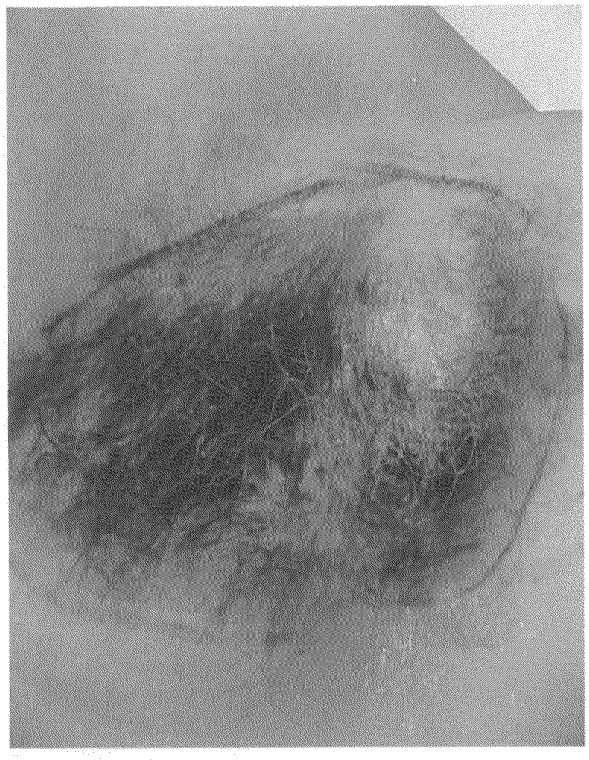

FIGURE 1 Minor's starch iodine test to identify an area of excessive sweat production and to localize therapy

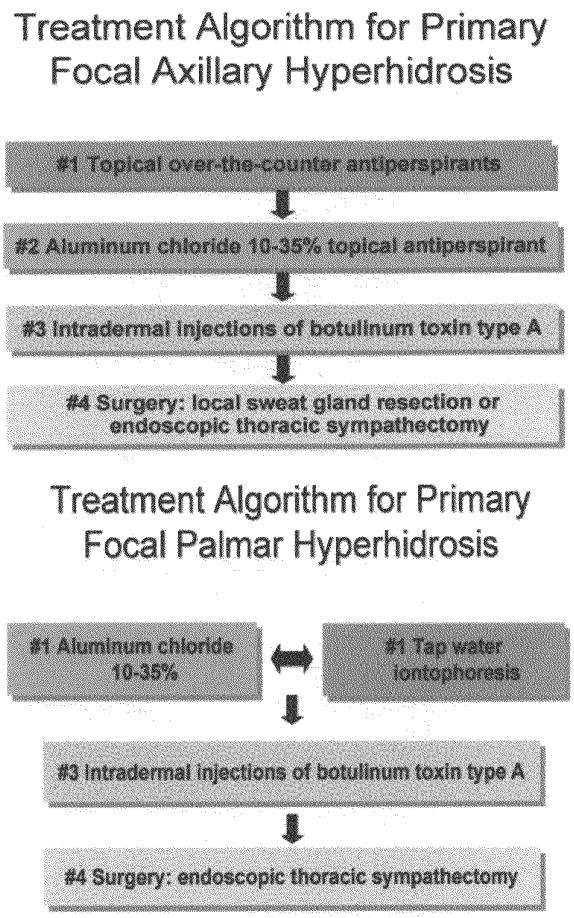

FIGURE 2 Treatment algorithm for primary focal hyperhidrosis

BoNT-A

The two preparations of BoNT-A that have most extensively been studied and used to treat hyperhidrosis throughout the world are Dysport® (Ipsen, Slough, Berkshire UK) and Botox® (Allergan, Irvine, CA, USA). As with other therapeutic challenges, the two cannot be used interchangeably as their mechanism of action is slightly different, as is their bioequivalency.

Earlier studies by Naumann and Lowe (2001) demonstrated that 50 units of Botox® injected per axilla, when compared to placebo in 307 patients, was effective and safe. Response rates were as high as 94% at 4 weeks (defined as greater than 50% reduction in sweat production) for the treatment group. Likewise, a study of 145 subjects using Dysport®, 200 units in one axilla and placebo treatment in the contralateral side, showed excellent efficacy. The placebo-treated axilla was then treated with 100 units of Dysport®. Results were maintained for about 6 months

Recent FDA-approval of Botox® brand BoNT-A for the treatment of axillary hyperhidrosis was based on a 52 week-multicenter North American trial comparing BoNT-A, 50 units in each axilla, to 75 units of BoNT-A in each axilla, or placebo. The HDSS scale was the primary endpoint of this trial involving 322 subjects. Subjects had to have an HDSS score of 3 or 4 to enroll, and responders were defined as having at least a 2-grade improvement in their HDSS score. There was a 75% response rate in the treatment groups compared to 25% response in the placebo-treated subjects ($p<0.0001$) but there was no significant difference in the response rate of the two treatment groups. Similarly high numbers of patients (80-84%) in the treatment groups had at least a 75% reduction in their sweat production compared to 21% in the placebo group. Subject satisfaction was very high in the treatment groups. The median duration was approximately 7 months (Glaser *et al.*, 2006).

BoNT-A is an effective treatment for other parts of the body, including the palms, soles, craniofacial sweating, and genital sweating. Fewer studies have been done looking at optimal dosing and duration, as with the axilla. Special considerations for these areas include the best dose, the duration of effect, pain control for the injections and possible muscle weakness, especially for palmar sweating. A typical dose for the

Table IV Methods of pain control for botulinum toxin injection of the palms and soles

Topical anesthesia
Local anesthesia
Nerve blocks
Beir block
Cold anesthesia
Vibration
General or IV sedation
None

Table V Use of botulinum toxin type A to treat gustatory sweating

Author	Year	Drug & Dosage (Mean Dose)	N	Duration
Naumann	1997	BoNT-A 1-2u/2.25cm2(21)	45	>6mo
Bjerkhoel	1997	BoNT-A 17.5-62 u (37)	15	>13 mo
Laskawi	1998	BoNT-A 2.5u/4cm (31)	19	17.3 mo
Laccourreye	1998	BoNT-A 2.5/2 cm (25-88)	14	>3-9 mo
Eckardt	2003	BoNT-A 16-80 u	33	>12 mo
Kyrmizakis	2004	BoNT-A 2.5u/3-4cm2 (15-22)	11	>16-23 m
Guntinas-Lichius	2002	DYS 148u DYS 248u	40	8 mo 16 mo
Beerens	2002	DYS 67.5-150U (100)	13	3-24 mo

BoNT-A = Botox®; DYS=Dysport®

palm is 100 units Botox® but can reach 150-200 units per hand, depending on the size of the individual's hand. Similar doses are required for the soles.

Various methods of pain control have been used to reduce the discomfort of the injections in the hands and feet (Table IV). Although some patients will use no anesthesia, many will desire some form of pain control due to the numbers of injections and the sensitivity of the palms and soles.

The basic principal of using BoNT-A for treating hyperhidrosis is to first identify and localize the affected area. The starch iodine test is most useful. Four milliliters of non-preserved saline is the recommended reconstitution of BoNT-A (package insert, Botox®) but various dilution strengths have been successfully used in clinical practice. Preserved saline is frequently used by clinicians with the belief that it reduces the stinging sensation during BoNT-A administration. A 30 gauge needle is used for the injection. The needle is inserted to the depth of the dermal-subcutaneous junction. This depth may vary by body site and within individuals, especially when it comes to the palms and soles. The injections are placed approximately every 2 cm, although there are many different patterns among different physicians.

BoNT-B

There are only a few reports of BoNT-B being used to treat hyperhidrosis. It can induce focal anhidrosis in a dose-dependent fashion. There have been far more reported side effects with the use of BoNT-B and especially systemic adverse events when treating hyperhidrosis.

Dressler and co-workers (2002) compared 100 units Botox® to 4000 units or 2000 units Neurobloc® (Elan Pharma, Shannon, Ireland) for axillary hyperhidrosis. He reported that both compounds were equally effective in the 19 patients with similar levels of improvement at 16 weeks. Side effects included severe dryness of the mouth, accommodation difficulties and conjunctival irritation. Lower doses used by Hecht *et al.* (2004) in 4 patients (250 units) resulted in no distant autonomic side effects but the duration was shorter, at 1-3 months. Excellent results were reported in 3 of his patients while one patient had "fair results".

A patient with palmar hyperhidrosis was treated with 2500 units BoNT-B in each hand. The sweating stopped within 24 hours, but two days after the injection he developed bilateral blurred vision, indigestion, dry sore throat and dysphagia (Baumann, 2003).

GUSTATORY SWEATING

Gustatory sweating can be equally debilitating for those who affected. Frey Syndrome is the classic prototype resulting from aberrant regeneration of cut parasympathetic fibres of the salivary glands. It has been reported to occur in up to 100% of the patients undergoing parotidectomy. It can occur after face lift surgery as well, with varying degrees of severity. The patient complains of sweating over the lower face and jaw, most commonly with eating.

BoNT A has been successfully used to treat gustatory

sweating (Bjerkhoel and Trobbe, 1997; Naumann *et al.*, 1997; Laccourreye *et al.*, 1998; Laskawi *et al.*, 1998; Beerens and Snow, 2002; Guntinas-Lichius, 2002; Eckardt and Kuettner, 2003; Kymizakis *et al.*, 2004). Relatively small doses are needed and results typically last more than 12-18 months (Table V). The procedure is similar to that described. The affected area is mapped out using a starch iodine test. Two to five units of Botox® is injected with a 30 gauge needle every 2-4 cm. Dysport® has also been successfully used. Side effects are minimal with weakness of the lip or mouth area occurring 0-15% of the patients.

There is one report of botulinum toxin type F being used to treat a 65 year old man with torticollis and frey syndrome (Tugnoli *et al.*, 2001). He developed immuno-resistance to BoNT-A. The F serotype was diluted 40 units in 10 ml saline. Twenty injections (2 units/10mm^2) resulted in significant reduction of the gustatory sweating within 3 days. The authors reported that the duration of benefit was 3.5 months.

FUTURE OF BoNTs TO TREAT HYPERHIDROSIS

New studies are being developed to better understand the role of BoNT therapy in adolescents with hyperhidrosis. A large multi-center trial studying BoNT-A for palmar hyperhidrosis is planned.

One exciting development is improved delivery systems for BoNTs. Several researchers have been looking at innovative methods to deliver the toxin with less discomfort to the patient without reduced efficacy. There is a report of plantar hyperhidrosis treatment using a dermojet to deliver BoNT-A without the use of analgesia (Vadoud-Seyedi, 2004). Eight of the ten subjects reported a significant decrease in their plantar sweating. One patient had a hematoma following the injection. Although there may be some loss of efficacy using such a high-pressure device, it does open the door to new research into novel injection techniques. Kavanaugh *et al.* (2004) reported successful use of an iontophoresis system to deliver BoNT-A. Drug delivery is transcutaneously via an electric current and requires water solubility, polarity and suitable molecule size.

CONCLUSION

Hyperhidrosis is a chronic condition characterized by sweating in excess of the physiologic needs of the body. It can result in significant physical, psychosocial and occupational impairment for patients. Quality of life is impaired. Several treatments are available, but BoNTs have really revolutionized the treatment of hyperhidrosis.

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