Botulinum Toxin Treatment of Autonomic Disorders: Focal Hyperhidrosis and Sialorrhea

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Abstract

Primary focal hyperhidrosis is a common autonomic disorder that significantly impacts quality of life. It is characterized by excessive sweating confined to circumscribed areas, such as the axillae, palms, soles, and face. Less frequent types of focal hyperhidrosis secondary to underlying causes include gustatory sweating in Frey's syndrome and compensatory sweating in Ross' syndrome and after sympathectomy. Approval of onabotulinumtoxinA for severe primary axillary hyperhidrosis in 2004 has revolutionized the treatment of this indication. Meanwhile further type A botulinum neurotoxins like abobotulinumtoxinA and incobotulinumtoxinA, as well as the type B botulinum neurotoxin rimabotulinumtoxinB are successfully used off-label for axillary and various other types of focal hyperhidrosis. For unexplained reasons, the duration of effect differs considerably at different sites. Beside hyperhidrosis, botulinum neurotoxin is also highly valued for the treatment of sialorrhea affecting patients with Parkinson's disease, cerebral palsy, amyotrophic lateral sclerosis, motor neuron disease, and other neurologic conditions. With correct dosing and application, side effects are manageable and transient.

Keywords
- botulinum neurotoxin
- focal hyperhidrosis
- sweating
- sialorrhea
- autonomic disorders

Primary Focal Hyperhidrosis

Hyperhidrosis is an underestimated chronic autonomic disorder that affects approximately 3% of the general population in the United States—extrapolated to approximately 200 million people worldwide.[1] It is characterized by excessive sweating beyond physiological needs: amounts needed for thermoregulation. Stigmatization of patients has a profoundly negative impact on quality of life necessitating early and effective treatment.[2–4] Hyperhidrosis is classified into two main categories: primary (idiopathic) hyperhidrosis that usually starts in childhood or adolescence,[5] and secondary, often widespread or generalized hyperhidrosis in association with an underlying condition, such as endocrine and metabolic disorders, infectious diseases, heart conditions, neurologic and psychiatric disorders, medication reactions, and poisoning. Primary hyperhidrosis typically occurs focally in consequence to emotional stimuli, and predominantly affects regions with a high density of eccrine glands,[6] in order of frequency, axillae, hands, feet, face/scalp, and groin.[7] To date, the exact mechanism of excessive sweating in primary focal hyperhidrosis is unknown. According to one hypothesis, the eccrine glands are overstimulated by sympathetic postganglionic acetylcholine-releasing fibers.[6,8] Undoubtedly, there is a genetic association, with further family members affected in about half of the patients.

Treatment Options

Beside botulinum neurotoxin (BoNT), several other treatment options are available for focal hyperhidrosis. Topical antiperspirants, particularly aluminum salts forming a plug in the acrosyringium, are primarily used in patients suffering from increased focal, especially axillary sweating. Local side effects, such as skin irritation and itching, can be diminished by lower concentrations, less frequent use, or by applying a mild corticosteroid cream the day after.[9] Topical anticholinergic

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agents like glycopyrrolate solution are mainly used in craniofacial hyperhidrosis, but may be accompanied by systemic effects. Tap water iontophoresis is the most effective noninvasive therapy for palmoplantar hyperhidrosis, but is time-consuming and may be associated with discomfort during treatment and with irritation of exposed areas. Contraindications include pregnancy, metallic implants, and cardiac pacemakers. In cases of failure of local treatment and in generalized hyperhidrosis, oral anticholinergic drugs like oxybutynin, glycopyrrolate, methantheline bromide, and bornaprine hydrochloride may be considered. Typical side effects include dry mouth, blurred vision, dizziness, tachycardia, urinary retention, and constipation; however, except for xerostomia, these side effects usually occur only at higher doses.[10]

Surgery may enable a permanent cure from focal hyperhidrosis. Numerous techniques such as curettage, liposuction, or combinations of both performed under tumescent local anesthesia produce long-term reduction of axillary sweating in about two-thirds of patients, but show inferiority when compared with BoNT injections.[11] Complications include hematoma, seroma, wound infection, skin necrosis, scars, and bridle formation. Recently, microwave, radiofrequency, and microfocused ultrasound technologies aimed at the destruction of the secretary portion of the eccrine sweat glands without visible damage to the overlying skin have been developed for treating axillary hyperhidrosis. Although minimally invasive, these procedures may cause transient swelling, discomfort, altered sensation, partial hair loss, and neuropathy.[6,12,13] Endoscopic transthoracic sympathectomy is predominantly used in severe palmar hyperhidrosis[14] when less-invasive interventions have failed.[15] Success rates approach 100% in experienced centers. However, apart from perioperative complications like hemo- and pneumothorax, pain, intercostal neuralgia, and Horner's syndrome, compensatory sweating elsewhere on the body is dreaded as a major long-term side effect.[15] It is considered severe in at least 5 to 10% of patients and may occasionally be more disruptive than the primary disease.

Botulinum Toxin

Basics

Commercially available type A botulinum neurotoxin (BoNTA) products comprise onabotulinumtoxinA (onaBoNT-A; BOTOX, Allergan, Inc.), abobotulinumtoxinA (aboBoNT-A; Dysport, Galderma Laboratories, L.P.), and incobotulinumtoxinA (incoBoNT-A; Xeomin, Merz Pharmaceuticals GmbH). RimabotulinumtoxinB (rimaBoNT-B; licensed in the U.S. as MyoBloc, Solstice Neurosciences Inc., in Europe as NeuroBloc, Eisai Manufacturing Inc.) is the commercially available type B botulinum neurotoxin (BoNT-B). Botulinum neurotoxins (BoNTs) cause a long-lasting but reversible block of acetylcholine release from sympathetic nerve fibers innervating eccrine sweat glands. Depending on the treated area and the chosen BoNT dosage and preparation, axonal sprouting, degradation of BoNT and synthesis of soluble *N*-ethylmaleimide-sensitive attachment receptor (SNARE) proteins, recurrence of sweating occurs within 3 to more than 12 months after treatment.[16]

In 2004, the spectrum for the in-label usage of onaBoNT-A was extended to primary axillary hyperhidrosis. OnabotulinumtoxinA is the most widely used therapeutic agent of all BoNT serotypes in this condition[17] and in all other types of hyperhidrosis.[18] To date, onaBoNT-A has remained the only BoNT product approved for the treatment of severe primary axillary hyperhidrosis that is inadequately managed by topical agents in adult patients. However, onaBoNT-A and the other BoNT types mentioned are also effective and safe in other types of focal hyperhidrosis in which they are used off-label (►**Table 1**). Importantly, the different BoNT preparations are not interchangeable. Universally consistent and reliable conversion ratios between BoNT products do not exist.

As BoNT products consist of nonhuman proteins, there is a risk for the formation of neutralizing and nonneutralizing antibodies. Only neutralizing antibodies that are directed against the heavy chain of the core protein may inhibit the biological activity of BoNT. However, the detection of neutralizing antibodies in a patient does not necessarily mean nonresponse to treatment.[19] Therefore, in cases of nonresponse, other reasons should be excluded, such as inadequate dosing or injection failures. In general, repeated injections in short intervals (less than 2 months apart) and high doses should be avoided to reduce the risk of immunoresistance. In primary axillary hyperhidrosis, the incidence of developing neutralizing antibodies is very low. In a large survey summarizing the data in 871 patients treated with onaBoNT-A, neutralizing antibodies occurred in only four patients (0.5%), without loss of efficacy.[20,21] There is little known about the immunogenicity rates of other BoNT products used for the treatment of hyperhidrosis.

Table 1 Indications for botulinum neurotoxin (BoNT) treatment in localized autonomic disorders

Axillary hyperhidrosis[a]
Palmar hyperhidrosis
Plantar hyperhidrosis
Craniofacial hyperhidrosis (scalp, forehead, temples, nose)
Hyperhidrosis of submammary folds, inguinal folds (Hexsel's hyperhidrosis), and anal fold
Gustatory sweating (Frey's syndrome)
Compensatory sweating (Ross' syndrome, postsympathectomy)
Prosthesis-related hyperhidrosis
Eccrine sweat gland nevus
Sialorrhea

[a]To date, onabotulinumtoxinA is the only BoNT that is approved for the treatment of severe axillary hyperhidrosis in adult patients when topical treatment has failed.

Side Effects and Contraindications

With the correct dosage and administration, BoNT-A and BoNT-B injections are usually well tolerated by hyperhidrosis patients.[22] Formication, swelling, and hematomas may occur at injection sites. Some rare cases of transient botulism-like symptoms with generalized weakness and dysphagia after palmar, plantar, and axillary BoNT-A and BoNT-B injections are on record.[23–26] Hematogenic distribution and application of high doses may explain this effect. Therefore, special attention has to be paid to the intradermal injection technique, correct dosage, and exclusion of underlying neuromuscular junction disorders like myasthenia gravis. Different foci of hyperhidrosis should be treated in separate sessions.

Compensatory hyperhidrosis in untreated areas is another possible side effect that was reported in up to 5% of patients treated with onaBoNT-A for axillary hyperhidrosis.[27] In patients treated with BoNT-B, systemic symptoms such as dryness of the mouth, accommodation difficulties, eye irritation, and flu-like syndromes lasting for several weeks were observed.[18,28–30] Type B botulinum neurotoxin compared with BoNT-A seems to have a higher affinity to autonomic nerve fibers.[22,31] Moreover, due to their acid pH value, injections with BoNT-B products are more painful.

General contraindications for BoNT treatment include systemic infections, severe coagulopathy, treatment with aminoglycosides and macrolides, skin infection in areas to be treated. and diseases affecting the neuromuscular system (e.g., myasthenia gravis, Lambert-Eaton syndrome, amyotrophic lateral sclerosis).[32] Treatment of pregnant and breast feeding women should be avoided even if there are no reports on fetal harm.[33] Women of reproductive age have to be advised to execute a reliable method of contraception and to not become pregnant within 6 months of injection. Botulinum neurotoxin injections are relatively contraindicated in children and teenagers with hyperhidrosis because of limited experience.

Botulinum Toxin in Axillary Hyperhidrosis

Based on two class I[27,34] and several class II studies[35–38] (for study class definition see[39]), BoNT is considered a highly effective and safe treatment for axillary hyperhidrosis.

Botulinum neurotoxin is considered the treatment of choice if antiperspirants are ineffective or associated with intolerable irritation of the skin.[40] To date, onaBoNT-A is the only BoNT product approved for the treatment of axillary hyperhidrosis in adults (►**Fig. 1**). The efficacy and safety of onaBoNT-A in patients with axillary sweating has been convincingly demonstrated. In a large double-blind placebo-controlled European trial (class I study), 320 participants received either 50 U onaBoNT-A or placebo into each axilla.[27] More than a 50% reduction compared with gravimetrically assessed baseline sweating was noted in 94% in the verum group and in 36% in the placebo group after 4 weeks. In the onaBoNT-A-treated group, the sweat production rate decreased by an average of 83.5%. The high response rate was sustained at week 16, with 82% in the verum group compared with 21% in the placebo group. In an open 12-month follow-up trial, 207 patients received up to three more treatments, which proved to be equally effective.[41] On average, the effect lasted for approximately 7 months. Twenty-eight percent of the participants did not need reinjections within 16 months. Using the Hyperhidrosis Impact Questionnaire, patients indicated very high treatment satisfaction throughout all study visits (weeks 1, 4, 8, 12, and 16).[42] Five percent of the patients noted some kind of compensatory sweating, but no severe adverse events were reported.

In a multicenter, double-blind North American study with 322 participants suffering from axillary hyperhidrosis, the safety and efficacy of two different doses of onaBoNT-A (50 U vs. 75 U for each axilla) were compared with placebo.[38] The primary efficacy variable—reduction of Hyperhidrosis Disease Severity Score (HDSS) of at least two grades—was reached by 75% of patients of the verum group compared with 25% of the patients treated with placebo. A decrease in axillary sweat production of more than 75% was observed in 84% of participants receiving 75 U onaBoNT-A and in 80% of participants receiving 50 U onaBoNT-A, compared with 21% in the placebo group at week 4. The duration of the effect did not significantly differ between the two verum groups. No severe adverse events occurred. Most reported side effects were injection-site pain, injection-site bleeding, and compensatory sweating (incidence of at least 2% in any group). Again, treatment efficacy lasted for 7 months on average.

One prospective intraindividual double-blind head-to-head study with 51 participants compared differences in efficacy and adverse effects when 100 U or 50 U onaBoNT-A per axilla were injected.[17] Initially, patients received 100 U onaBoNT-A bilaterally with stable results for 2 years (baseline

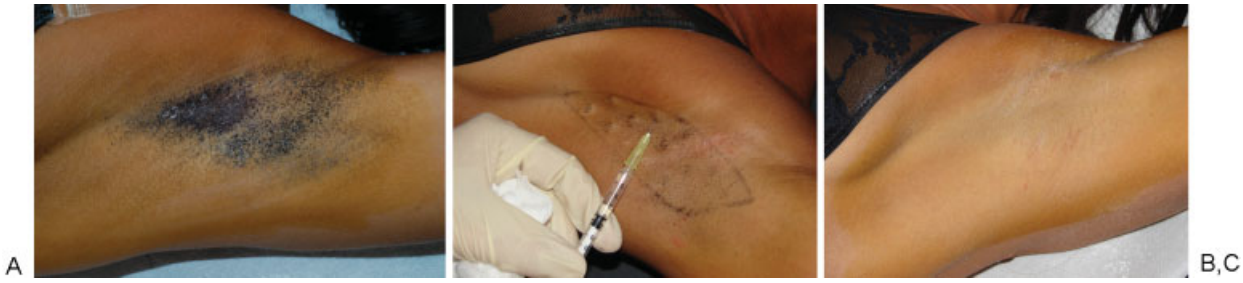

Fig. 1 Treatment of axillary hyperhidrosis with onabotulinumtoxinA (onaBoNT-A). (**A**) Demarcation of the sweating area in the left axilla by the iodine-starch test. (**B**) Intradermal injections of 3 U onaBoNT-A 1.5 cm apart (1-ml syringe, 30-gauge needle). (**C**) Negative iodine-starch test 4 weeks posttreatment. (From Hosp et al[32] with permission of Springer Science + Business Media.)

period), then 100 U onaBoNT-A in one axilla and 50 U onaBoNT-A in the other (direct comparison) before switching to 50 U onaBoNT-A in each axilla (extension period). Forty-six percent of participants estimated the treatment effect as excellent and 5% as good on a 4-item global self-assessment scale. There were no intergroup assessment differences, and even the reported duration of effect of around 3 months was equal in every group. None of the patients reported any side effect except for injection-site pain. Taken together, the lower dose of 50 U onaBoNT-A per axilla was sufficient to abolish axillary hyperhidrosis in the majority of patients, an observation confirmed by the results of most smaller studies.[17] Usually, the effect began within 1 week and lasted for approximately 6 to 7 months,[40,41,43,44] with large interindividual variation and substantial differences among trials.[45] To minimize the risk of antibody formation, the interinjection intervals are recommended not to fall below 16 weeks,[40] and the lowest effective dose should be administered.[20]

AbobotulinumtoxinA was the other BoNT product tested early in the emergence of this novel treatment option for primary axillary hyperhidrosis. An intraindividual study in 145 patients compared 100 U aboBoNT-A in one axilla with 200 U aboBoNT-A in the other axilla (class I study).[34] Reduction in the rate of sweat production was similar in both axillae with no clear advantage of the higher dose. Six months after the injections, sweat production was still below half the baseline production in 136 participants. Adverse effects were temporary and mild, including headache (2.7%), muscle soreness of the shoulder girdle (1.4%), axillary itching (0.7%), and increased facial sweating (0.7%).

In a recent French study on 83 patients with primary axillary hyperhidrosis, an increased duration of efficacy of BoNT-A with repetitive injections over 11 years was noted.[45] However, patients' data were retrospectively analyzed and no objective measurement was performed.

Only few studies directly comparing onaBoNT-A to other BoNT-A products have been performed. In a double-blind prospective intraindividual study, 10 patients received 50 U onaBoNT-A in one axilla and 150 U aboBoNT-A in the other.[36] No significant differences in sweat reduction rate and duration of treatment success were seen. In a double-blind prospective intraindividual study in 46 patients, 50 U onaBoNT-A per axilla was compared with 50 U incoBoNT-A per axilla.[37] The therapeutic effect measured on a 4-item global self-assessment scale was excellent in 89% and good in 11% of patients. Side-to-side differences of the therapeutic effect with regard to onset latency, extent, and duration were detected neither by patients nor by physicians. Side effects were not reported. As incoBoNT-A is the first BoNT that is free of complexing proteins, an advantage could potentially exist in its reduced antigenicity.

To date, there is little experience with BoNT-B products in axillary hyperhidrosis. In a small placebo-controlled, double-blind study, 20 participants received either 2500 U rimaBoNT-B or placebo in both axillae. Type B botulinum neurotoxin treatment was considered safe and efficacious.[30] In a patient-blinded intraindividual small study with 19 patients, 100 U onaBoNT-A were injected into one axilla and 2000 U (10 patients) or 4000 U (9 patients) rimaBoNT-B into the other. Significant differences were seen neither between the different BoNT subtypes nor between the different rimaBoNT-B doses.[28]

Botulinum Toxin in Palmar Hyperhidrosis

Several class II studies[18,46–49] (for study class definition see[39]) indicate that BoNT is a safe and effective treatment for palmar hyperhidrosis.

Botulinum neurotoxin is used off-label in palmar hyperhidrosis with fairly good results when topical treatment and iontophoresis have failed. Compared with axillary hyperhidrosis, the evidence level is lower due to a considerably smaller number of studied patients. Furthermore, palmar treatment is more complex, requiring higher doses and more injections; it is painful and less effective with decreasing sweat production to only about half the baseline value. Like in axillary hyperhidrosis, the best evidence exists for onaBoNT-A, as documented in several studies.[47–52] The usual dose is 100 U onaBoNT-A for palms and fingers of one hand,[52–54] but depending on the size of the hands, doses up to 160 U may be necessary.[22] The effect lasts for 2 to 9 months,[48,49,51,52,55] based on our experience with 100 U onaBoNT-A per side considerably shorter than in axillary hyperhidrosis. Interestingly, sweat reduction is greater in the nondominant hand.[56]

Transient muscle weakness beginning some days and lasting for up to 8 weeks after palmar BoNT-A injections may impair hand grip function. For most patients, this effect is hardly noticeable or insignificant, but it may be a problem for those requiring fine-motor skills such as musicians and surgeons.[2] Injections over the thenar eminence should be performed with special care as the subcutaneous layer is very thin allowing easy penetration of the toxin. The risk of muscle weakness is assumed to be further reduced when rimaBoNT-B is used on the thenar. However, injections of BoNT-B products are more painful than BoNT-A products.[18,57]

As in axillary hyperhidrosis, the largest body of experience refers to the use of onaBoNT-A in palmar hyperhidrosis. Studies on other BoNT products and comparative investigations are limited. IncobotulinumtoxinA may be considered as an equally good alternative to onaBoNT-A for palmar treatment, as shown in an intraindividual comparative study with 32 patients.[58] Both products proved similar with regard to anhidrotic effect, duration of benefit of at least 6 months determined by Minor's test, and safety profile with a slight reduction of muscle strength.

In a double-blind intraindividual study in eight patients, onaBoNT-A was compared with aboBoNT-A in a 1:4 ratio.[48] Based on subjective rating, the mean duration of effect was similar, 4 to 5 months on average. Impairment of muscle strength occurred more frequently in the hand treated with aboBoNT-A, possibly due to its greater diffusion properties. Another intraindividual comparison of onaBoNT-A and aboBoNT-A using a 1:2.5 ratio in eight patients showed no significant differences between the two toxins in sweating area scores and duration of efficacy of at least 8 months.[54]

Transient muscle weakness was the most frequent side effect and occurred in both hands.

Efficacy and safety of rimaBoNT-B in a dosage of 5000 U per palm were analyzed in a double-blind placebo-controlled study enrolling 15 patients in the verum group.[18] Injections of verum and placebo were equally painful. In the verum group, relief of symptoms began at day 7 and lasted for a mean of 3.8 months. Most rimaBoNT-B–treated patients complained about dry mouth, some about heartburn, obstipation, muscle weakness, and excessively dry hands—symptoms that do not occur after injection of BoNT-A products. Half of the participants indicated decreased hand grip strength, which could not be verified by a dynamometer. The same dosage of rimaBoNT-B (5000 U per palm) was used in an open, examiner-blinded, two-center study on 32 patients with palmar hyperhidrosis.[59] Palmar sweating was reduced for 4 to 6 months. Only local side effects occurred. Mild muscle weakness reported by three patients could not be objectified by a dynamometer. So far, no studies comparing BoNT-A with BoNT-B have been performed.

Injection pain is a major problem of BoNT treatment in palmar hyperhidrosis.[22] Therefore, some kind of anesthesia is needed. Most dermatologists use cryoanalgesia with ice packs or cooling spray as an effective, easy, and fast method. Ulnar and median nerve blocks are highly effective, but require a more complex procedure and can lead to transient paresthesias of the hands and permanent nerve damage, especially if done repeatedly.[60,61] Reconstitution of onaBoNT-A in lidocaine can reduce injection pain compared with reconstitution in normal saline.[35] However, a fatal case of anaphylaxis occurred after administration of an onaBoNT-A–lidocaine mixture for chronic neck and back pain.[62]

Botulinum Toxin in Plantar Hyperhidrosis

Data on the treatment of plantar hyperhidrosis with BoNT are scarce. Some case studies and one pilot study with onaBoNT-A[63] report favorable data. Dose recommendations vary from 50 to 250 U onaBoNT-A per sole.[56,63–66] The beneficial effect lasts between 3 to 6 months. The major problem is injection pain, which may be diminished by application of topical lidocaine 30 to 60 minutes before starting the treatment or cooling the areas before and after treatment with cool packs.[56] In contrast to the treatment of palmar hyperhidrosis, local muscle weakness has not been reported.

Botulinum Toxin in Craniofacial Hyperhidrosis

Craniofacial hyperhidrosis affects more men than women. The area of sweating may be limited to the forehead, but may also involve the scalp, temples, and other parts of the face. The affected area should therefore be visualized by an iodine-starch test before treatment.

When treating craniofacial sweating, muscle stiffness of the forehead, lowering of eyebrows, and ptosis of the upper eyelid may occur. For avoidance, a safety distance of at least 10 mm to the eyebrows and strict intracutaneous injections are recommended. In an open-label study with 10 participants suffering from frontal hyperhidrosis, we applied 20 to 30 injections of 3 U onaBoNT-A each 10 to 15 mm apart.[55] To prevent drooping of the eyelids, a minimum distance of 1 cm to the eyebrows was maintained. After treatment, half of the patients had difficulties in frowning of the forehead that lasted for several weeks. In all but one patient, the treatment effect lasted for at least 5 months and resulted in a high level of patient satisfaction.

One of our patients with hyperhidrosis of the scalp received a total dose of 200 U of onaBoNT-A distributed among 96 injection points.[67] Sweat production decreased to a fifth of the basic value and remained stable at this low level for more than 1 year.

AbobotulinumtoxinA may also be used for treatment of hyperhidrosis of the forehead. As diffusion of aboBoNT-A is greater than onaBoNT-A even with identical injection volumes, the area of anhidrosis is larger when aboBoNT-A is used, but the risk for adverse effects may be increased.[68]

Although rimaBoNT-B is thought to have a lesser effect on muscle strength, stiffness of the forehead and drooping of the eyebrows occurred in 7 out of 38 patients treated for sweating of the face and/or forehead.[31] Less frequent side effects that are unusual with BoNT-A products used at this site included compensatory hyperhidrosis, excessive dryness of the skin in the treated area, dryness of the mouth, local bruising of the skin, and worsening of migraine.

Botulinum Toxin in Gustatory Sweating (Auriculotemporal Syndrome, Frey's Syndrome)

A few class IV studies (for study class definition see[39]) demonstrated the efficacy of BoNT in the treatment of gustatory sweating.[69,70] This type of hyperhidrosis, which mostly involves areas innervated by the auriculotemporal and great auricularis nerve, appears to be particularly suited for off-label BoNT treatment. In a few studies, treatment with onaBoNT-A, aboBoNT-A, and rimaBoNT-B were shown to be highly effective and safe, with treatment benefit persisting for an exceptionally long period. Of all BoNT products, onaBoNT-A has been used most often. After visualizing the affected area by the iodine-starch test, doses of 1 to 5 U are applied 1 to 2 cm apart.[71,72] Usually, 2 to 3 U/cm^2 of onaBoNT-A are injected. Most of the patients benefit for at least 1 year, and the average duration of effect is the most long-lasting compared with all other sites of focal hyperhidrosis.[8,70,73] Side effects are rare; they include dry mouth and slight muscle weakness while chewing.[74] Similar to the treatment of craniofacial hyperhidrosis, drooping of eyebrows and upper eyelids may occur. Therefore, a safety distance of at least 40 mm to the eyebrows and strict intracutaneous injection should be ensured.[31]

Aside from onaBoNT-A, good results were obtained with aboBoNT-A in a dosage of 20 U/cm^2.[71] Patients benefited for a mean of 16.5 months. With repeated injections, subjective severity of sweating and extent of the affected area decreased and the duration of effect increased.[75] According to a small study in seven patients, BoNT-B in a dosage of 80 U/cm^2 appears to be a safe and efficacious alternative to BoNTA.[76] These preliminary data have not yet been confirmed in a larger cohort of patients.

Compensatory Hyperhidrosis

Ross' syndrome is a rare disorder characterized by the triad of unilateral tonic pupils, hyporeflexia, and segmental anhidrosis resulting in annoying compensatory sweating in circumscribed areas. An anhidrotic effect can be achieved by multiple intracutaneous BoNT injections.[77] We successfully treated several patients with 2 to 3 U onaBoNT-A per injection point 2 cm apart (►**Fig. 2**). For large affected areas, doses up to 300 U or more may be necessary. The maximum dose should not exceed 600 U in total during one session because botulism-like symptoms with generalized weakness may occur.[78] Sweating is diminished within 1 week after treatment, and the benefit lasts for 5 months on average.

Compensatory hyperhidrosis occurs in almost all patients after sympathectomy to at least a minor extent,[79] and may evolve into a serious problem in approximately 5 to 10% of patients. The back is the most commonly affected area (69%), followed by the abdomen (63%), lower extremities (43%), and chest (20%). Doses up to 500 U of onaBoNT-A fragmented to 2 to 3 U per injection point 1.5 cm apart have been shown to be efficacious and safe in selected patients.[80,81] Disadvantages include time-consuming and uncomfortable treatment, short duration of effect of only 4 months on average, and high treatment costs. The BoNT amounts required for successful treatment may be diminished when paying attention to the fact that compensatory hyperhidrosis at the back shows accentuation in the medial aspects. Therefore, higher doses are apparently required in the dorsal midline to achieve an even effect over the entire back. A study on 10 patients treated with aboBoNT-A for compensatory hyperhidrosis at the back showed a uniform anhidrotic effect when doubling the dose per injection point at the midline (10 U per injection point, 8 U beside midline, 5 U for the rest).[82]

Additional Types of Hyperhidrosis

In rare forms of focal hyperhidrosis, such as hyperhidrosis of the anal fold or prosthesis-related hyperhidrosis in patients with traumatic amputations of a limb, the administration of BoNT may also be highly effective. Good results were obtained in the treatment of hyperhidrosis of the anal fold with 1 U of onaBoNT-A 1 cm apart to an average of 30 U.[83] For relief of sweating at amputation stumps, total doses of 300 and 500 U of onaBoNT-A with 2 to 3 U per injection point 1 cm apart were chosen.[84] Similar results were achieved with injections of rimaBoNT-B in a total dose of 1750 U (20 injections 2 to 4 cm apart).[85] Inguinal hyperhidrosis (Hexsel's hyperhidrosis) is another subtype of focal hyperhidrosis often going along with other forms of hyperhidrosis. This kind of sweating was successfully treated by intradermal injections of 2 to 3 U/cm^2 of onaBoNT-A to a total dose of 100 U.[86] The duration of benefit was 6 months.

Sialorrhea

Sialorrhea is a socially disabling disorder that is frequently observed in patients with Parkinson's disease, cerebral palsy, amyotrophic lateral sclerosis, and other neurologic disorders. More than two-thirds of patients with Parkinson's disease and up to 38% of children with cerebral palsy are affected.[87,88] It compromises quality of life, but can also be harmful as it may increase the risk for saliva aspiration. In most cases, sialorrhea is based on swallowing difficulties, whereas a primarily increased saliva production is an exception. Irrespective of the cause of sialorrhea, the treatment goal is reduction of saliva production from the salivary glands. Treatment options include radiotherapy, surgical removal of salivary glands, drug therapy with anticholinergic agents, and local injections of BoNT.[39,89,90] Botulinum neurotoxin blocks the release of acetylcholine in cholinergic neurosecretory junctions of salivary glands, which reduces saliva secretion.[91]

One class I study (for study class definition see[39]) evaluated the effect of rimaBoNT-B injections into the parotid and submandibular glands in patients suffering from amyotrophic lateral sclerosis. There was a significant reduction of saliva volume and improvement of patients' global impression of change in the BoNT-treated group compared with placebo.[92] No major side effects were observed. A similarly significant reduction of drooling was found in several class II trials[93–97] performed in patients with Parkinson's disease or amyotrophic lateral sclerosis using aboBoNT-A, onaBoNT-A, or rimaBoNT-B. No severe side

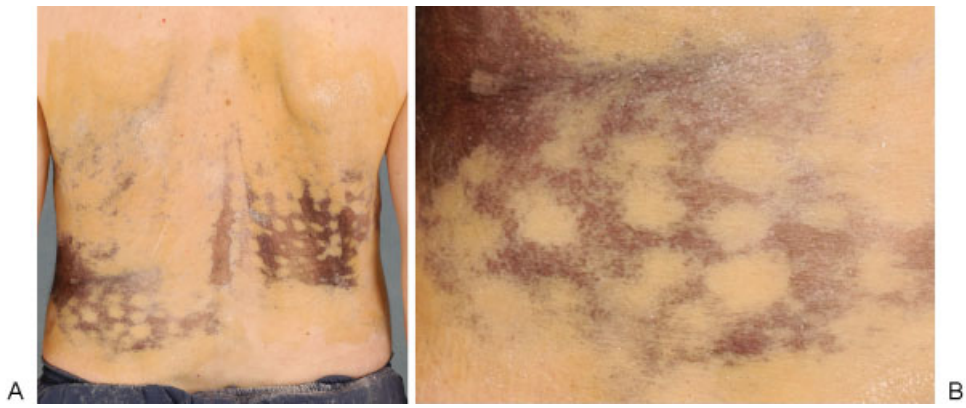

Fig. 2 A patient with Ross' syndrome and compensatory sweating in circumscribed areas at the back. Iodine-starch test performed 4 weeks after intradermal injections of 3 U of onabotulinumtoxinA (onaBoNT A) 2 cm apart. (**A**) Overview. (**B**) Close-up view of the left side of the lower back. Diffusion halos of the anhidrotic effect of A/Ona are visible within the blackened area.

effects occurred; moderate-to-mild side effects included dry mouth or transitory dysphagia. Two studies compared the effect of intraglandular injections of BoNT-A (aboBoNT-A and onaBoNT-A, respectively) with BoNT-B (rimaBoNT-B).[93,98] In one study,[93] latency to onset was shorter with BoNT-B, whereas duration, and subjective and objective measures were not significantly different between BoNT-A and BoNT-B. The other study showed no differences between BoNT-A and BoNT-B with regard to efficacy and safety.[98]

Long-term safety and efficacy of BoNT-A in sialorrhea has been analyzed in a retrospective cohort study on 69 children treated with a mean follow-up of 3.1 years.[99] Injections were performed ultrasound-guided into four glands. Nineteen percent of patients reported side effects: 14% had minor (i.e., dysphagia) and 5% had major side effects (i.e., severe dysphagia, aspiration, weakness). Forty-four percent of patients were satisfied or very satisfied with treatment; however, 45% required supplemental treatments including oral medication and surgery. Whether the risk of side effects is influenced by the dilution of the toxin used has been evaluated in a comparative study.[100] A higher concentration of onaBoNT-A (100 U in 1 ml compared with 100 U in 2 ml) was associated with less bulbar dysfunction, although efficacy was similar.

In clinical practice, there are currently no clear treatment guidelines for the treatment of drooling with respect to dose, dilution, injection technique, and selection of salivary glands. Botulinum neurotoxin is not approved for sialorrhea, and its use is off-label. Ultrasound-guided injections are recommended, particularly for the submandibular glands, to minimize side effects. Treatment could be started in both parotid glands and/or submandibular glands with low doses, and a continuous increase in dose depending on the effect on drooling and potential side effects. The duration of effect is approximately 3 to 6 months; reinjections should not be given within 8 weeks.

In sum, BoNT is a highly valuable therapeutic option in various autonomic disorders, especially in primary axillary hyperhidrosis and in gustatory sweating. Adverse effects of BoNT-A are mainly related to injection pain at palmoplantar sites and to muscle weakness at sites with little subcutaneous fat where the toxin may diffuse to striated muscles. The transience of the therapeutic effect is highly dependent on the treated location, and measures of prolongation would significantly improve the utility of BoNT treatment.

Conflict of Interest

Markus K. Naumann and Henning Hamm were principal investigators and investigators in clinical trials sponsored by Allergan Co., UK, and Ipsen Pharma, Germany. They received a research grant and speaker's honoraria from Allergan Co., UK, and PharmAllergan, Germany.

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