

REVIEW ARTICLE

The place of botulinum toxin type A in the treatment of focal hyperhidrosis

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Summary

Background Hyperhidrosis (primary or secondary) is excessive sweating beyond that required to return body temperature to normal. It can be localized or generalized, commonly affecting the axillae, palms, soles or face, and can have a substantial negative effect on a patient's quality of life.

Impact of disease Objective evaluation comprising quantitative assessment (gravimetric and Minor's iodine starch test) and subjective evaluation (Dermatology Quality of Life Index and Hyperhidrosis Impact Questionnaire) allow accurate assessment of the impact of hyperhidrosis on patients.

Botulinum toxin type A Botulinum toxin type A acts by inhibiting the release of acetylcholine at the presynaptic membrane of cholinergic neurones. It has proved useful in treating a number of diseases relating to muscular dystonia and is now proving beneficial in treating hyperhidrosis. Clinical trials investigating botulinum toxin type A use in axillary and palmar hyperhidrosis show significant benefits with few side-effects reported, with a favourable impact also being seen on patient quality of life. Botulinum toxin type A injections are generally well-tolerated with beneficial results lasting from 4 to 16 months.

Conclusions Botulinum toxin type A injections are an effective and well-tolerated treatment for hyperhidrosis. This paper proposes a positioning of this treatment along with current established treatments, and highlights the role of botulinum toxin type A as a valuable therapy for the treatment of hyperhidrosis.

Key words: axillary, botulinum toxin type A, hyperhidrosis, palmar, quality of life

Background

The eccrine sweat glands are concentrated in the palms, soles and axillary areas of the body and it is estimated that each person has around 2–4 million of such glands.¹ The eccrine gland consists of a layer of single cells arranged in a coil, with this coil of cells surrounded by myoepithelial cells that contract on stimulation from sympathetic nerves. These nerves use

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Table 1. Examples of causes of hyperhidrosis (from Stolman⁷)

Generalized (essential or primary)	
Environment	Heat, humidity, exercise
Febrile disease	Acute and chronic infections, neoplasia
Metabolic	Thyrotoxicosis, diabetes mellitus, hypoglycaemia, gout, pheochromocytoma, hyperpituitarism, menopause
Sympathetic discharge	Shock and syncope, intense pain, alcohol, drug withdrawal
Neurological	Riley–Day syndrome, irritative hypothalamic lesions
Drugs	Propranolol, physostigmine, pilocarpine, tricyclic antidepressants, venlafaxine
Localized	
Extrinsic	Heat, olfactory
Gustatory	Citric acid, coffee, chocolate, peanut butter, spicy food
Neurological	Lesions, primary or essential hyperhidrosis

acetylcholine as their neurotransmitter.^{1,2} Thus, sweating is under the control of both circulating catecholamines and sympathetic innervation, although studies at the cellular level have also shown the involvement of cyclic adenosine monophosphate (cAMP) in sweating.³ In the majority of hyperhidrotic patients the sweat glands are morphologically normal, but what is abnormal is the neurological response to stimuli in the hypothalamic sweat centres.¹ However, in some patients (both with and without hyperhidrosis) an unusual hybrid sweat gland has been described that has both eccrine and apocrine elements and has been found to be capable of a secretory rate 10 times higher than a normal eccrine gland.⁴

Hyperhidrosis may be defined as excessive sweating beyond what is required to return elevated body temperature to normal.⁵ It may be primary (idiopathic, essential) or secondary to a number of medical conditions or prescribed drugs.² Hyperhidrosis can be local or generalized, and commonly affects the underarms (axillary hyperhidrosis), palms of the hands (palmar hyperhidrosis), the soles of the feet (plantar hyperhidrosis) and the face (facial hyperhidrosis).⁶ Causes of hyperhidrosis include genetic, metabolic, hormonal or idiopathic pathology, with the main causes being shown in Table 1. There seems to be a genetic predisposition to primary hyperhidrosis and it often manifests itself in childhood or puberty. Essential or focal hyperhidrosis characteristically does not occur during sleep, but is made worse by heat and emotional situations, since it is thought that the hypothalamic sweat centres are more sensitive to emotional stimuli than in nonhyperhidrotic subjects.⁷

Table 2. Levels of evidence (from US Agency for Health Care Policy and Research^{4,8})

Ia	Evidence obtained from meta-analysis of randomized controlled trials
Ib	Evidence obtained from at least one randomized controlled trial
IIa	Evidence obtained from at least one well-designed controlled study without randomization
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study
III	Evidence obtained from well-designed non-experimental descriptive studies such as comparative studies, correlation studies and case-control studies
IV	Evidence obtained from expert committee reports or opinions and/or clinical evidence of respected authorities

Sweat rates are highly variable between individuals and are thought to be a factor of acclimatization, sex, age and possibly diet.⁸ However, it is estimated that 0.6–1.0% of the population suffers from primary or essential hyperhidrosis⁷ and in many it can become chronic and can lead to significant disruption in both social and professional life, leading to a marked impact on the patient's quality of life (QOL). Patients find the symptoms embarrassing and often complain that the anticipation of sweating leads to avoidance of certain activities.³ In particular, axillary sweating causes social embarrassment and can cause staining and rotting of clothes. In addition, the profuse sweating can also result in odour production,⁹ and in severe cases can lead to painful skin maceration, which can, in turn, lead to secondary infection, such as tinea pedis, viral warts and dermatitis.¹⁰

It is imperative to strive continually to improve the quality of clinical trials and the subsequent standards of care provided to patients. In this respect, a guide is provided for assessing the evidence base for each of the clinical studies under review using a scale for the quality of evidence comprising categories Ia–IV (see Table 2).

Impact of disease

The line between 'normal' sweating and hyperhidrosis is poorly defined and objective evaluations of the disease are needed before treatment can be justified and evaluated. Subjective measurements can be used, as well as objective assessments such as gravimetric assessment of sweat production and Minor's iodine starch test; however, one of the main criteria for determining whether treatment is justified is the effect of the condition on the patient's QOL.¹¹

It has always been known that dermatological conditions have a detrimental effect on patients' lives but it has only relatively recently been measured in a standardized, repeatable way. The effects of hyperhidrosis have been assessed on various QOL scales, such as the Dermatology Life Quality Index (DLQI) (a simple, practical method of scoring the impact of skin disease using 10 questions, each with four possible answers)¹² and the Hyperhidrosis Impact Questionnaire[®] (HHIQ).^{6,13} The DLQI is a validated measure that allows comparison of hyperhidrosis with other dermatological conditions, whereas the HHIQ focuses specifically on how hyperhidrosis affects patients. Studies using both scales have shown that hyperhidrosis has a significant impact on patients' lives; however, there is still a low awareness of it as a true medical condition, and as such there is also a paucity of knowledge on the prevalence of the condition and a lack of information on the treatment options available. In some cases there is also a lack of clarity on the referral pathways for these patients and local reimbursement guidelines.

Axillary hyperhidrosis

Treatment options

Topical treatments. Topical medications are the least invasive treatments, and as such should be used as first-line therapy where practical. Topical use of aluminium salts is the preferred method and this treatment is effective for many patients, particularly those with moderate hyperhidrosis, when used in the evening before going to bed. The effect of topical aluminium salts is thought to be caused by mechanical obstruction of the eccrine sweat gland, although atrophy of the secretory cells is also thought to contribute to the effect following long-term use.^{3,7} However, this treatment only lasts approximately 48 h and it can cause skin irritation in up to 50% of patients as contact with water results in hydrochloric acid formation (Evidence levels: 1b, IIb).^{3,6} Minor irritation can be relieved by use of hydrocortisone cream. Alternatively, aluminium chlorhydroxide in purified water rather than aluminium chloride in alcoholic solution can be used, which avoids this problem.

Oral treatments. Oral anticholinergic drugs can be used to treat hyperhidrosis, although response to treatment is variable and systemic side-effects are common, such as dry mouth and blurred vision (Evidence level: IIb).^{1,7} Glycopyrrolate (glycopyrronium bromide) has been

found to be useful as an adjunct to other therapies and iontophoresis (Evidence level: IIb).³ Phenoxybenzamine, an α -adrenergic blocking agent, has also been used with some success, with its mechanism thought to be via blockage of cholinergic stimulation of the sweat glands and inhibition of the uptake of neurochemical transmitters, such as norepinephrine, at the postsynaptic site.³ However, side-effects include orthostatic hypotension and inhibition of ejaculation, as well as general lethargy and nausea.

Where hyperhidrosis is stress-induced, diazepam can have an ameliorating effect (Evidence level: IIb).⁷ The nonsteroidal anti-inflammatory drug indomethacin has also caused a reduction in sweating, possibly due to its effect on prostaglandin E (Evidence level: IIb).⁷ Clonidine, a centrally active α -adrenergic autoreceptor stimulant, has also proved useful in the treatment of tricyclic-induced hyperhidrosis and also in hyperhidrosis linked to menopause (Evidence level: IIb).⁷ Oral propoxyphene hydrochloride, a narcotic and weak ganglionic blocking agent, may also improve hyperhidrosis in patients with autonomic dysreflexia (Evidence level: III).¹⁴

Surgery/curettage/liposuction. Local surgery, subcutaneous curettage and liposuction may be performed under local anaesthesia and have been shown to be effective in reducing axillary hyperhidrosis, with patients experiencing a subsequent reduction in sweating. Direct excision, though, can create unacceptable scarring and contractures which are associated with significant morbidity, prolonged recovery and limitations to mobility.^{1,3} Subcutaneous curettage and liposuction offer permanent efficacy but far fewer side-effects and less scarring compared with local excisional procedures (Evidence level: IIa).^{15,16}

Botulinum toxin type A. Botulinum toxin is produced by the anaerobic bacillus *Clostridium botulinum* and is the cause of the clinical signs and symptoms of botulism.¹⁷ Its mechanism of action is to inhibit the release of acetylcholine at the presynaptic membrane of cholinergic neurones.¹⁸ This is achieved by the injection of the drug in areas of excessive sweating, causing a localized, long-lasting but reversible decrease in cholinergic transmission.

Botulinum toxin type A has been used for a variety of conditions, ranging from the treatment of spasticity to blepharospasm and strabismus and it has been shown to have substantial benefits in the treatment of axillary hyperhidrosis, where it should be considered the

treatment of choice if topical treatments prove ineffective. Currently BOTOX[®] (Allergan Inc.) is the only botulinum toxin type A formulation to be licensed for axillary hyperhidrosis and as such the majority of the data below and the recommendations refer to BOTOX[®] only. Given differences in dosing and safety profiles of different botulinum toxin formulations, the results should not be extrapolated to other botulinum toxin formulations or serotypes.

In a large multicentre, double-blind, placebo-controlled study patients treated with botulinum toxin type A (BOTOX[®]) 50 U per axilla or placebo were assessed for 16 weeks following treatment. A total of 320 patients were randomized (242 treated with botulinum toxin type A and 78 treated with placebo), with results showing a consistently high and rapid response rate in the botulinum toxin type A group at all time points (from 81.8% to 95.0%) compared with the placebo group (response rates ranging from 20.5% to 37.2%). Subjects also rated their satisfaction with the treatment following botulinum toxin type A highly (Evidence level: Ib).¹⁹

In an extension to this study, patients were followed for a further 12 months, during which time a further three botulinum toxin type A treatments could be given if required by the subject, with a minimum of 16 weeks between each treatment. A high response rate was seen following each treatment, with the outcome being similar after successive treatments (mean reduction in sweat production of 82% at week 4 following the first treatment and 80% following the second treatment). Patient satisfaction with treatment remained high following subsequent treatment cycles. Analysis of the duration of effect showed that the mean time between the first and second treatments was 30.6 weeks (range 15.4–51.3 weeks). However, it should be noted that this calculation applies only to subjects who received at least two botulinum toxin type A treatments: 28% of subjects did not qualify for retreatment, based on subject demand and sweat production, thus indicating that in a substantial proportion of patients the duration of effect may be considerably longer (Evidence level: Ib).²⁰

Lowe *et al.* also demonstrated long-term efficacy of botulinum toxin type A (BOTOX[®]) in the suppression of axillary hyperhidrosis, with five of 20 patients requiring only one injection in 18 months of follow-up, without emergence of significant side-effects. The mean duration of effect between consecutive treatments was approximately 6 months and the duration of benefit conferred by the first injection could provide a broad

guideline to the patient as to the expected frequency of reinjection (Evidence level: IIa).²¹

The efficacy of botulinum toxin type A (Dysport[®]; Ipsen) in axillary hyperhidrosis has been shown in a multicentre trial in 145 patients previously unresponsive to topical therapy where a significant ($P < 0.001$) decrease in sweat production compared with placebo occurred 2 weeks postinjection and was maintained 24 weeks postinjection (Evidence level: IIa).²² Treatment was well tolerated and 98% of patients said they would recommend botulinum toxin therapy to others.

Treatment with botulinum toxin type A in axillary hyperhidrosis was also seen to have a significant favourable impact on patient QOL. In a study carried out to assess the effects of axillary hyperhidrosis on daily life using the HHIQ, 68% of patients felt it interfered when they met new people, 55% felt it interfered with their personal relationships, 58% felt it limited them at work and 39% felt they were less effective at work as a result of their hyperhidrosis.⁶ Fifty percent of patients had to change clothes twice or more each day and 20% had to shower or bath twice or more per day because of their hyperhidrosis. Importantly, 72% of patients said it made them feel less confident and 51% of patients had changed their leisure activities as a result of their condition. Following treatment with botulinum toxin type A (BOTOX[®]), significant improvements in all QOL measures were noted compared with placebo treatment, with the most dramatic changes being seen in the degree of limitation on being in public places and on meeting people for the first time. The positive effects of treatment were observed within 1 week of treatment, and the effects were carried over from one treatment to the next. In fact, botulinum toxin type A treatment resulted in a greater level of overall treatment satisfaction than any other hyperhidrosis treatment (Evidence level: Ib).⁶

The positive benefits of botulinum toxin type A on QOL in patients with axillary, palmar or plantar hyperhidrosis have also been demonstrated using the Dermatology Life Quality Index (DLQI). In a study by Swartling *et al.*, 53 patients were assessed before and after treatment with botulinum toxin type A (Evidence level: IIa).²³ This study showed that treatment resulted in a clinically significant improvement in QOL (mean reduction in DLQI from 9.9 to 2.4) for patients who had not relapsed at a median of 5 months post-treatment. Similar results were seen in a study by Campanati *et al.* where 41 patients with focal hyperhidrosis were treated with botulinum toxin type A and showed a significant improvement in QOL following assessment

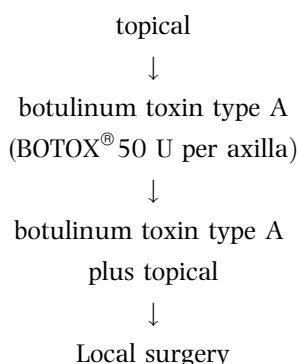
pretreatment and post-treatment using the DLQI (Evidence level: IIa).²⁴

Botulinum toxin type A injections have been shown to be generally well tolerated (Evidence level: IIb),²⁵ with no unexpected adverse events being noted in the trials to date. In studies of axillary hyperhidrosis, isolated cases of perceived increases in nonaxillary sweating have been noted but in a very small number of individuals (< 5%). Occasional, transient, generalized muscle weakness in the hands has been reported following treatment for axillary hyperhidrosis. No severe allergic reactions have been reported.²⁵

The development of neutralizing antibodies against botulinum toxin has been reported in patients administered long-term treatment (up to 10 years); however, Schneider *et al.* found that repeated botulinum toxin type A injections over 3 years were as effective as the first set of injections and the production of neutralizing antibodies did not play a major role (Evidence level: IIa).²⁶ Lowe *et al.* also found that repeated botulinum toxin type A injections provided the same duration of benefits without development of disease resistance or serum antibody production (Evidence level: IIa).²¹ Despite this finding, the authors recommend using the most appropriate dose that achieves efficacy while minimizing the risk of antibody formation.²⁷

Recommendations

A simple algorithm has been developed for the treatment of patients presenting with axillary hyperhidrosis based on published data:



The current recommended initial dose for axillary hyperhidrosis is 50 U BOTOX® per axilla, which has been shown in clinical trials to be an efficacious and safe dose. However, it should be noted that dose adjustments may be required for subsequent treatments, dependent upon patient response (Evidence level: Ib).²⁸ There is little evidence for recommending a

higher initial dose, and there are also cost implications for increasing the dose. From clinical experience to date the injection interval seems to be consistent for an individual patient, which is very valuable from a patient management perspective. Patients should be retreated when the sweating returns at a level of concern for the patient, although retreatment within 16 weeks is not recommended. When sweating starts to return, it is initially recommended the patients use a topical preparation twice a week, which can extend the time interval between injections.

It is very important to identify areas of hyperhidrosis objectively before commencing treatment with botulinum toxin type A. Minor's iodine starch test or gravimetric tests should be used to delineate both the hyperhidrotic area and symptom intensity and will distinguish between those patients with severe hyperhidrosis requiring treatment with botulinum toxin type A from those with delusional hyperhidrosis (e.g. botulinophilia) who display no significant objective dermatological pathology.²⁹ Although these techniques are not difficult, there are tricks to performing them accurately and the nursing team should be trained to do the preparatory work. The development of a practical guide and checklists are also a useful part of the training plan.

Palmar hyperhidrosis

Treatment options

Topical treatments. The main topical treatments for palmar hyperhidrosis are aluminium salts, glutaraldehyde, formaldehyde and tannic acid (strong tea), which have been shown to have beneficial effects, although they are effective only in mild hyperhidrosis. In addition, brown staining of the skin, and in the case of formaldehyde, its sensitizing potential, are limiting side-effects (Evidence level: IIb).³

Oral treatments. The oral agents discussed under axillary hyperhidrosis are also applicable for patients presenting with palmar hyperhidrosis.

Sympathectomy. Traditionally, sympathectomy surgery was carried out as upper thoracic (T2) ganglionectomy, but this is a radical treatment for hyperhidrosis and should be used only when other options have failed. Lumbar sympathectomy surgery is not usually recommended due to the risk of sexual dysfunction.⁷ Sympathectomy surgery is particularly successful in

palmar hyperhidrosis, with success rates of 92–99%, but the complications are significant, including compensatory sweating in 24–100% of patients, pneumothorax, wound infection, haemothorax, permanent Horner's syndrome, gustatory sweating and intercostal neuralgia (Evidence level: IIb).⁷ The advent of endoscopic transthoracic sympathectomy (ETS) made this initially the treatment of choice (Evidence level: IIb)³⁰ and has reduced some of the risks, but the technique still has to be carried out under general anaesthesia and may not be successful, with approximately 20% of patients being dissatisfied with the outcome following ETS (Evidence levels: IIb).^{31,32} One of the primary reasons for dissatisfaction among patients is compensatory sweating, which can occur in up to 26% of patients following ETS (Evidence level: IIb)³³ and which may cause more of a problem than the initial condition being treated.

Iontophoresis. Tap-water iontophoresis using direct current (DC) or DC plus alternating current (AC) has been shown to be an effective treatment for palmar hyperhidrosis, with a reduction in sweating lasting 3–4 days (Evidence level: Ib).³⁴ The procedure is well tolerated and is usually repeated five to six times a week until the degree of sweating has been reduced to an acceptable level, whereupon maintenance treatment has to be continued once or twice weekly. Iontophoresis is thought to work by blockage of the sweat gland at the stratum corneum level, although structural changes have not been shown.³ It has also been suggested that the mechanism of action is due to interruption of the stimulus–secretion–coupling, which then leads to a functional disturbance of sweat secretion.³⁴ However, iontophoresis can cause discomfort (burning and tingling) and skin irritation, including erythema and vesicles, and incorrect use can cause burns at the sites of minor skin injury as well as cutaneous necrosis.³⁵ Care also has to be taken to avoid electric shock in case of incorrect use.^{34,36}

Botulinum toxin type A. Although the majority of work has been carried out in axillary hyperhidrosis, botulinum toxin type A has shown efficacy in other types of hyperhidrosis, although only a limited number of patients have been treated to date. In a study by Solomon and Hayman, 20 subjects with recalcitrant palmar and digital hyperhidrosis were treated with botulinum toxin type A (BOTOX[®]), 165 U per hand. Treatment was shown to reduce sweat production significantly in the treated areas, with anhidrosis

lasting from 4 to 9 months, although reduced sweating continued in all patients for the 12-month evaluation period. The greatest reduction in sweating was seen in the nondominant hand (Evidence level: IIa).³⁷

Another recent study by Bodokh and Branger compared the effectiveness of treatment with BOTOX[®] in one hand compared with no treatment in the other control hand. Assessments included subjective and objective measurements using gravimetric scales and Minor's iodine starch test. This study showed a significant improvement in 15/20 (75%) patients treated for palmar hyperhidrosis, with no serious adverse events observed (Evidence levels: IIa, III).^{35,38}

Some concern has been expressed that botulinum toxin type A injections in the palm may impede the release of acetylcholine at the neuromuscular junctions, thereby decreasing muscle tone and motor function in the hand; however, this has not been found to be the case (Evidence level: IIb).³⁹ Lowe *et al.* investigated the use of BOTOX[®] vs. placebo for the treatment of palmar hyperhidrosis in 19 patients and concluded that patients experienced a significant improvement in palmar hyperhidrosis without a concomitant decrease in grip strength, significant finger dexterity, or the occurrence of notable adverse events (Evidence level: Ib).⁴⁰

Occasional, transient, generalized muscle weakness in the hands has been reported following treatment for palmar hyperhidrosis, as has pain during injection. Pain during injection can be addressed through application of ice packs, use of the Dermojet delivery system or anaesthetic procedures. Hayton *et al.* and Naumann *et al.* conclude that patient preference is for local anaesthetic blockade rather than topical anaesthesia techniques and ice packs.^{39,41}

There is a good body of clinical evidence to recommend the use of botulinum toxin type A for the long-term treatment of axillary hyperhidrosis. However, the long-term effects of botulinum toxin type A injections in palmar hyperhidrosis need further investigation, but this treatment appears promising based on current research.

Recommendations

There is more inconsistency in the treatment of palmar hyperhidrosis than in axillary hyperhidrosis and currently no licence exists for botulinum toxin in the treatment of palmar hyperhidrosis. Treatment of palmar hyperhidrosis can be variable due to difficulty in maintaining consistency of injection technique and, as

such, the following algorithm is recommended for subjects presenting with palmar hyperhidrosis:

Iontophoresis or botulinum toxin type A

(BOTOX® 60–100 U per palm)



Sympathectomy

From clinical experience there seems to be a wider range of individual susceptibility to treatment in palmar hyperhidrosis compared with axillary, so the dose needed is more variable. Hayton *et al.* gives an outline of the neural anatomy relevant to the palmar injection of botulinum toxin type A and provides guidance on appropriate injection techniques.³⁹ Also, giving botulinum toxin type A injections through the densely innervated skin of the palms is often painful and can deter the patients from repeated treatments. Injections with a Dermojet have been tried in palmar hyperhidrosis in order to reduce the pain, but this technique is not recommended due to the potential for damage to the superficial palmar nerves and vessels.^{13,41,42} Therefore, for palmar hyperhidrosis, regional blocking of the ulnar and median nerves at the wrist level with 1% lidocaine is recommended before administering botulinum toxin injections (although training in nerve block techniques should be given to anyone undertaking such techniques).⁴¹

Other types of focal hyperhidrosis

Botulinum toxin type A treatment has been used to treat a variety of other hyperhidrosis conditions and in the treatment of distinct dermatological disorders or syndromes associated with hyperhidrosis. Doses of 30 U botulinum toxin type A injected into the hyperhidrotic area of the forearm in a patient with localized unilateral hyperhidrosis revealed complete anhidrosis (Evidence level: III).⁵ Botulinum toxin type A is also widely used with excellent efficacy for gustatory sweating (Frey's syndrome) and some recommend this option as first-line treatment (Evidence level: IIB).⁴³ Its use has also been suggested in the treatment of Ross syndrome (progressive segmental anhidrosis) (Evidence levels: IIB, III).^{44,45}

Frontal hyperhidrosis has been successfully treated with botulinum toxin type A, with a reduction in sweating of approximately 75% seen for a period of at least 5 months (Evidence level: IIB).⁴⁶ Schnider *et al.* also demonstrated that BOTOX® significantly reduces

sweat production in focal hyperhidrosis over a period of 13 weeks following a single injection (Evidence level: Ib).⁴⁷

Summary

Botulinum toxin type A injections are an effective and well-tolerated treatment for hyperhidrosis. This paper outlines the current treatment options for hyperhidrosis and proposes a positioning for botulinum toxin type A based on the clinical evidence from published trials. Botulinum toxin type A is a valuable therapy for the treatment of hyperhidrosis, and future research will continue to expand the indications for which it is licensed.

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