

Treatment of hyperhidrosis with Botox (onabotulinumtoxinA): development, insights, and impact

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Treatment of hyperhidrosis with Botox (onabotulinumtoxinA)

Development, insights, and impact

Nicholas Lowe, MD^{a,*}, Markus Naumann, MD, PhD^b, Nina Eadie, MBA^c

Abstract

Hyperhidrosis (chronic excessive sweating) may substantially affect an individual's emotional and social well-being. Therapies available before onabotulinumtoxinA were generally topical, with limited effectiveness, application-site skin reactions, and frequent, time-consuming treatments. Intradermal injection of onabotulinumtoxinA to treat sweat glands arose as a novel therapeutic approach. To develop this treatment, appropriate dosing needed to be established, and training on administration was required. Further, no previous scale existed to measure the effects of hyperhidrosis on patients' lives, leading Allergan to develop and validate the 4-point Hyperhidrosis Disease Severity Scale (HDSS), which measures the disease's impact on daily activities.

The onabotulinumtoxinA clinical development program for hyperhidrosis included 2 double-blind, placebo-controlled pivotal trials, immunogenicity studies, long-term studies of safety and efficacy, and quality of life assessments. In Europe and North America, the primary efficacy measures were, respectively, axillary sweat production measured gravimetrically and HDSS improvement. Compared with placebo, onabotulinumtoxinA treatment significantly reduced axillary sweat production and axillary hyperhidrosis severity, as measured by a 2-point or greater reduction on the HDSS. The effects of onabotulinumtoxinA occurred rapidly, within 1 week after injection, and lasted ≥ 6 months. Treatment with onabotulinumtoxinA was associated with significant quality of life improvements based on Short Form-12 physical and mental component scores. The Hyperhidrosis Impact Questionnaire also indicated greater treatment satisfaction, reduced negative impact on aspects of daily life, and improved emotional well-being with onabotulinumtoxinA versus placebo. The clinical development program and subsequent clinical experience showed that onabotulinumtoxinA treatment for hyperhidrosis was well tolerated with no new safety signals, and led to greater disease awareness.

Abbreviations: HDSS = Hyperhidrosis Disease Severity Scale, HHQ = Hyperhidrosis Impact Questionnaire, QoL = quality of life.

Keywords: axillary sweating, botulinum toxin type A, excessive sweating, neuromuscular agents, quality of life (QoL)

1. Hyperhidrosis

Sweating is a normal part of human thermoregulation; however, when it occurs uncontrollably and in excess, as is the case with hyperhidrosis, it can lead to substantial emotional and physical impairments in a person's occupation and social life.^[1–3] In fact, the negative effect on quality of life (QoL) from hyperhidrosis is of similar or greater magnitude as that of other chronic dermatologic conditions, including severe acne and psoriasis (Fig. 1).^[5] Hyperhidrosis can be classified as primary or secondary.^[6] Primary hyperhidrosis, which constitutes >90% of all cases, is idiopathic, with no identifiable underlying pathology.^[6–8] Secondary hyperhidrosis can be attributable to

an underlying cause, primarily endocrine or neurologic disease, but may also be due to medication adverse events, infection, malignancy, and metabolic/endocrine or cardiovascular disorders.^[6,9] Although the timing of onset and presentation is variable, primary hyperhidrosis typically presents before the age of 25 years, with a bilateral and symmetric distribution affecting the axillae, palms, soles, and/or craniofacial areas, and ceases during sleep.^[6,7] In contrast, secondary hyperhidrosis typically occurs at a later age, and is more likely to be unilateral, asymmetric, generalized, and present during sleep.^[6] Severely affected individuals may have physical complications, including skin maceration and secondary microbial infections.^[10] Despite the burden of hyperhidrosis, only 51% of individuals with

NL and MN contributed equally to this work.

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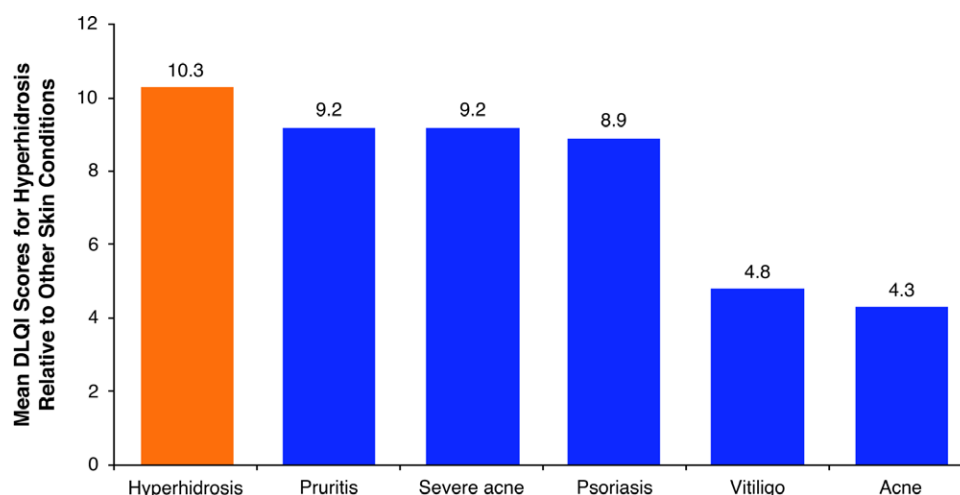


Figure 1. Mean DLQI scores for hyperhidrosis relative to other skin conditions.^[4] DLQI = Dermatology Quality of Life Index.

hyperhidrosis approached their health-care provider about their condition.^[11]

Ms. Eadie: “Individuals talked about the difficulties they had with the disease...women who talked about not wanting to pick up their babies because they were afraid that they would drop them because their hands were so sweaty. They were really moving testimonials.”

The potential QoL repercussions were evident during the onabotulinumtoxinA clinical development program.

Dr. Mitchell Brin (contributor): “The long-term study had an increased rate of pregnancies compared with other long-term studies. We ascribed this increase to enhanced social interactions post-treatment and received a compliance letter from one of the EU regulatory agencies to reinforce the contraception requirements during participation in the study.”

Although the pathophysiology of hyperhidrosis is not fully understood, it is believed to result from a malfunctioning of the autonomic nervous system that leads to hyperstimulation of otherwise normal eccrine sweat glands. Eccrine sweat glands, believed to be responsible for primary hyperhidrosis, are innervated by sympathetic cholinergic nerve fibers, and the stimulation of these fibers leads to sweating.^[12] Studies have demonstrated a genetic component to primary hyperhidrosis, with 6% to 65% of patients having a positive family history and multiple studies indicating an autosomal dominant mode of inheritance with incomplete, and variable, penetrance.^[12–17] In a recent study of 9 families affected by primary hyperhidrosis, genome-wide linkage analysis and subsequent exome sequencing revealed 4 genetic loci significantly associated with primary hyperhidrosis.^[14] These loci were localized to regions on chromosomes 1, 2 (containing 2 loci), and 15 with penetrance ranging from 60% in 1 family to 100% in 3 of the families (mean penetrance, 77.6%).^[14]

Although the etiology of primary hyperhidrosis is not yet known, hypotheses include the abnormal central control of emotional sweating occurring in response to stress, anxiety, and fear, triggered by sympathetic cholinergic nerves, or the dysregulation of the areas of the body that respond to emotion with sweating.^[12,18,19] Nevertheless, the link between emotions and hyperhidrosis via an autonomic mechanism may be incomplete. A recent controlled study examined the relationship between subjective stress reactivity (induced via a virtual standardized stress test) and markers of biological response, including sweat secretion, salivary cortisol levels, and heart rate, in individuals with primary hyperhidrosis versus unaffected subjects.^[19] Both groups showed significantly increased stress-induced sweat secretion, maximum cortisol levels, feelings of stress, and heart rate. However, whereas the primary hyperhidrosis group had secreted significantly higher quantities of sweat compared with

controls, there was no significant difference between groups in subjective feelings of stress, cortisol levels, and heart rate.^[19]

Etiologic uncertainties aside, it is evident that hyperhidrosis has distressing and debilitating effects on individuals, which include difficulty engaging in basic, everyday social interactions and a costly need to replace sweat-stained clothing, and there are demonstrated, long-lasting benefits of treatment.^[20–23] In a 2004 survey, approximately one-third of those with axillary hyperhidrosis reported that sweating was intolerable or barely tolerable, and frequently or always interfered with daily activities.^[24] Among people who seek care for axillary hyperhidrosis, QoL deficits are comparable to those experienced by people who receive inpatient care for eczema and psoriasis.^[4,21,25,26] In a study of 320 patients who had axillary hyperhidrosis that interfered with daily activities, >70% of patients indicated that they changed clothing 2 or more times per day as a result of their hyperhidrosis.^[5] This percentage decreased significantly ($P < .001$) with onabotulinumtoxinA versus placebo through week 16 (Fig. 2), remaining below 10% for most of the follow-up period.

2. Evolution of the indication

2.1. Unmet needs of earlier treatments

Treatment options for hyperhidrosis include topical application of aluminum chloride, systemic anticholinergic agents, β -blockers, and iontophoresis.^[27] These treatments may be limited by poor tolerability, lack of effectiveness, and inconvenience.^[5,11,27] The use of microwave-based energy devices to physically ablate axillary sweat glands has been evaluated for treating hyperhidrosis.^[28–31] These studies have shown significant, long-term (≥ 12 months) effects in reducing sweat severity.^[28–31] Procedure-related adverse events, including pain and swelling, were generally reported to be mild and to resolve within 2 to 3 weeks.^[28–31] Longer-term events, such as altered sensation and nodule formation, have also been reported.^[29–32] Altered sensation in the treated limb was reported in approximately 10% (8/81)^[30] and 39% (12/31)^[31] of patients in separate studies, resolving, on average, within 7 to 10 weeks. Nodules were also reported in approximately 3% (2/81)^[30] and 25% (5/20)^[29] of patients, resolving around 4 weeks. When these treatments fail, surgical removal of the sweat glands or part of the sympathetic nerve trunk in the thoracic region (i.e., endoscopic thoracic sympathectomy) is an option for axillary and palmar hyperhidrosis.^[10,11,27,33] Endoscopic thoracic sympathectomy can be associated with high rates of recurrence (up to 65%), compensatory sweating (98%), and a risk of serious complications generally associated with the site of surgery, such as Horner

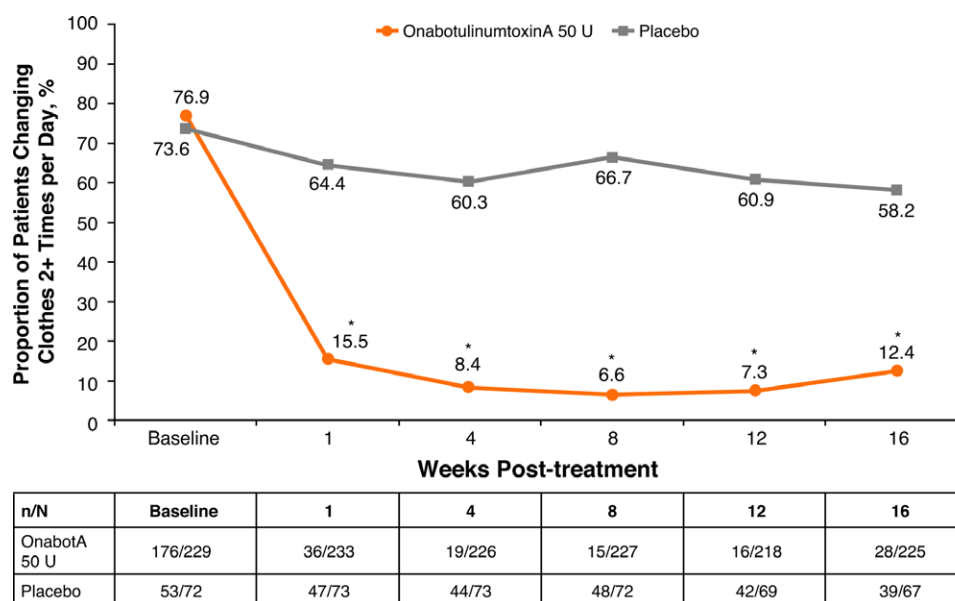


Figure 2. Proportion of patients changing clothing ≥ 2 times per day because of excessive sweating from hyperhidrosis.^[6] * $P < .001$ versus placebo. OnabotA = onabotulinumtoxinA.

syndrome, neuralgia, and pneumothorax.^[27,33] Patients reported to be most suited for sympathectomy include those who are <25 years of age and have an early onset of hyperhidrosis, body mass index <28 kg/m², and no nocturnal sweating or bradycardia, in addition to anatomical considerations.^[27]

Dr Naumann: “[Before onabotulinumtoxinA], we had a selection of local and systemic therapies as well as iontophoresis and, finally, surgery. The treatment options either were not effective enough, involved time-consuming repeat applications for the patient, or had potentially severe side effects. Cutting the sympathetic nerves was very invasive and included a significant adverse event risk.”

2.2. Development of onabotulinumtoxinA for hyperhidrosis

The use of onabotulinumtoxinA for hyperhidrosis was a logical extension of its mechanism of action: the inhibition of acetylcholine release from overactive cholinergic sympathetic neurons. Although most sympathetic postganglionic innervation is noradrenergic, there are a few organs in which innervation is cholinergic, such as the eccrine sweat glands.^[34] As early as 1951, botulinum toxin type A was shown to reduce or eliminate sweating from sudomotor nerve stimulation in preclinical experiments,^[34] thus providing rationale for onabotulinumtoxinA as a treatment for hyperhidrosis.^[33,35] Delivery of onabotulinumtoxinA for this disease required intradermal injection to reach a novel target, the cholinergic sweat gland, instead of the skeletal muscle.

Dr Lowe: “This novel delivery required training clinicians to administer a superficial dermal injection, with knowledge of the depth of the sweat glands.”

Several anecdotal reports appeared in the literature, beginning in 1996 with Bushara et al,^[36] documenting the successful use of onabotulinumtoxinA for hyperhidrosis.^[37–39] In these reports, the area of axillary, palmar, and/or plantar hyperhidrosis was identified by Minor starch–iodine test, an assessment tool first described by Minor in 1928^[40] and used in clinical studies beginning in the 1940s^[41] and 1950s.^[42] In the Minor test, an iodine solution is painted over the area of skin tested, and after the solution dries, fine rice or potato starch powder is applied, resulting in the sweat turning the mixture dark blue.

In the early anecdotal reports, sweating was reduced within 48 hours of onabotulinumtoxinA injection, and most initial

patients with axillary hyperhidrosis achieved sweating control for 12 to 28 weeks after a single procedure.^[37,38] Figure 3 depicts axillary hyperhidrosis using the Minor test before and 2 weeks after injection, showing no visible sweating after treatment with onabotulinumtoxinA.^[37] Palmar hyperhidrosis improved after 1 week and lasted up to 12 months.^[39] Injections were well tolerated in these early reports; patients reported moderate pain on injection (more commonly with palmar injections), and no compensatory sweating was reported.

Dr Lowe: “I was fortunate to collaborate with Dr John Gibson, who was Senior Vice President of Research at Allergan. We had in-depth discussions about onabotulinumtoxinA treating hyperhidrosis and developing the research protocols that led to its regulatory approval in several countries.”

For clinical development, Allergan assembled an expert panel to discuss the disease state and the design of a potential study. Of the various hyperhidrosis manifestations, axillary hyperhidrosis was the one that Allergan would ultimately develop into an approved indication. The axillae were the focus of the planned studies, rather than palms or feet, based on a variety of factors, including patient symptomatic disability (e.g., visibility of hyperhidrosis symptoms), other available treatment options, technical ability to inject into the dermis and reach the sweat glands, and patient comfort associated with the injection.

One of the challenges was that in the late 1990s, when the clinical program was being developed, the prevalence of hyperhidrosis was vastly underestimated, and estimates in the literature varied widely by country.^[11] Hyperhidrosis is both underreported by patients and underdiagnosed by physicians, which further complicates accurate assessment of the prevalence of the condition.^[11] Most international estimates of hyperhidrosis prevalence are low, ranging from 0.6% to 16.7%.^[43] However, as Dr Naumann noted, “[During the clinical studies], we all realized how common the problem was, how many patients suffer from hyperhidrosis and have no access to treatment or have no idea that they could be treated effectively.”

Dr Naumann: “The first preliminary studies that I did with Dr. Glogau on the tremendous effect of botulinum toxin on focal sweating opened the door to establish a completely new treatment perspective for hyperhidrosis patients. Botulinum toxin obviously had the potential to become a new, highly promising, effective, and safe solution for many patients suffering from focal hyperhidrosis.”

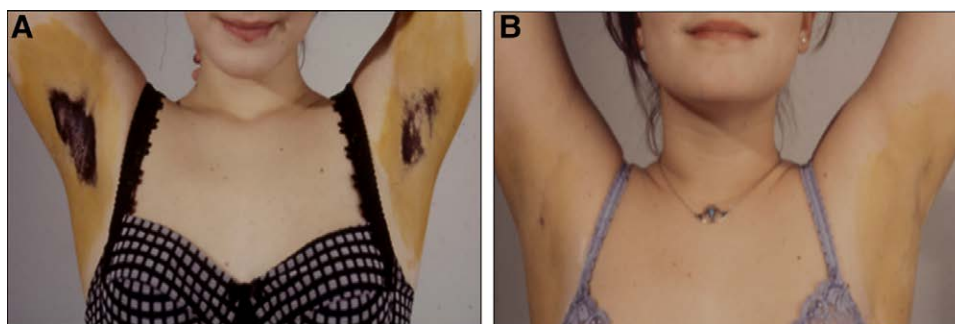


Figure 3. Axillary hyperhidrosis (A) before and (B) 2 weeks after onabotulinumtoxinA treatment, documented by the Minor starch-iodine test. Adapted with permission from: Naumann M, et al.^[37]

In the pivotal trials, the area of sweating was defined using Minor starch-iodine test. Sweat production was also measured gravimetrically by applying a filter paper to dry axillae for 5 minutes and comparing weights before and after placement of the filter paper. This method was used to identify subjects for study inclusion, defining axillary hyperhidrosis as production of at least 50 mg of sweat in each axilla at rest over 5 minutes at room temperature (limit chosen based on establishing normal sweating among volunteers self-reporting as normal sweaters).^[33] The gravimetric method had been reported previously for studies of subjects with axillary hyperhidrosis and atopic dermatitis.^[44,45]

However, for development in the United States, the US Food and Drug Administration requested an additional outcome measure for the clinical trials to show that treatment with onabotulinumtoxinA made a difference in individuals' symptoms of disease activity. Allergan therefore developed and validated the Hyperhidrosis Disease Severity Scale (HDSS; Table 1), a 4-point scale ranging from 1 (underarm sweating is never noticeable and never interferes with daily activities) to 4 (underarm sweating is intolerable and always interferes with daily activities).^[46]

Dr Naumann: "HDSS was the first questionnaire on the impact of hyperhidrosis on quality of life and is an important contribution to the disease state in general."

As a result of the novel delivery to the sweat glands, questions arose regarding the appropriate dose of onabotulinumtoxinA and its expected duration of action. Early clinical literature suggested that anhidrotic doses might be lower than those intended for skeletal muscle modulation and that the duration of effect would be longer, potentially 6 to 8 months.^[36] To address these questions, one of the pivotal studies was designed to evaluate 2 doses (50 U and 75 U) over 52 weeks.^[46] The response to both doses was similar, with a rapid decline in sweat production during the first week and a subsequent plateau of effect. Thus, the recommended

dose selected was 50 U injected intradermally in 0.1 to 0.2 mL aliquots to each axilla, evenly distributed over 10 to 15 sites approximately 1 to 2 cm apart.^[47] It is important to note that unit doses are not interchangeable among different botulinum toxin products,^[47] as each has its own dosing guidelines and clinical profile.

3. Efficacy and safety highlights

OnabotulinumtoxinA was compared with placebo in 2 prospective, randomized, double-blind, multicenter studies to demonstrate efficacy and safety for the treatment of hyperhidrosis.^[33,46,47] The first study was conducted in Europe in 1999 in subjects with persistent bilateral primary axillary hyperhidrosis; they were randomized 3:1 to onabotulinumtoxinA 50 U (n = 242) or placebo (n = 78).^[33] The proportion of subjects with at least a 50% reduction from baseline in axillary sweating was significantly greater with onabotulinumtoxinA versus placebo at week 4 and at all subsequent study visits ($P < .001$; Fig. 4). The difference between treatment groups was clinically important (>25%) at all time points. OnabotulinumtoxinA effectively reduced mean sweat production at all time points (Fig. 5). A separate 2002 publication from this trial reported the results of QoL assessments, including the Hyperhidrosis Impact Questionnaire (HHIQ).^[51] More subjects reported being somewhat or very satisfied with treatment in the onabotulinumtoxinA group at week 1 (89.4%) and throughout the 16-week study (93%) compared with the placebo group (47% and 30.4%, respectively).^[51] Substantial improvements in emotional well-being, the ability to participate in many aspects of daily life and social activities, and satisfaction with work productivity on the HHIQ were observed with onabotulinumtoxinA as early as week 1 and were sustained with little or no decline through week 16.

The second study was conducted in adults from the United States and Canada with persistent bilateral primary axillary hyperhidrosis based on gravimetric sweat production and a score of 3 or 4 on the HDSS.^[46] The primary efficacy endpoint was the proportion of subjects who reported at least a 2-point improvement from baseline HDSS score at 4 weeks after each of the first 2 treatments or who had a sustained response after their first treatment and did not receive retreatment during the 52-week study.^[46] Subjects were equally randomized to receive onabotulinumtoxinA 75 U (n = 110), onabotulinumtoxinA 50 U (n = 104), or placebo (n = 108). Treatment could be readministered after at least 8 weeks and when original study eligibility criteria were met. HDSS responder rates were significantly greater for those treated with onabotulinumtoxinA (75 U, 49%; 50 U, 55%) compared with those treated with placebo (6%; $P < .001$ for both onabotulinumtoxinA doses vs placebo). In addition, a significantly greater proportion of subjects receiving onabotulinumtoxinA (75 U, 59%; 50 U, 61%) reported complete resolution of symptoms (i.e., HDSS = 1) compared with those receiving placebo (6%) at week 4 ($P < .001$). This response was already evident in 48%, 42%, and 9% of subjects,

Table 1
Hyperhidrosis Disease Severity Scale (HDSS).

Question: How would you rate the severity of your hyperhidrosis?	Score
My underarm sweating is never noticeable and never interferes with my daily activities.	1
My underarm sweating is tolerable but sometimes interferes with my daily activities.	2
My underarm sweating is barely tolerable and frequently interferes with my daily activities.	3
My underarm sweating is intolerable and always interferes with my daily activities.	4

Reprinted from the Journal of the American Academy of Dermatology. 56(4). Lowe NJ, Glaser DA, Eadie N, Daggett S, Kowalski JW, Lai PY, North American Botox in Primary Axillary Hyperhidrosis Clinical Study Group. Botulinum toxin type A in the treatment of primary axillary hyperhidrosis: a 52-week multicenter double-blind, randomized, placebo-controlled study of efficacy and safety. pages 604-611. Copyright 2007, with permission from the American Academy of Dermatology, Inc.

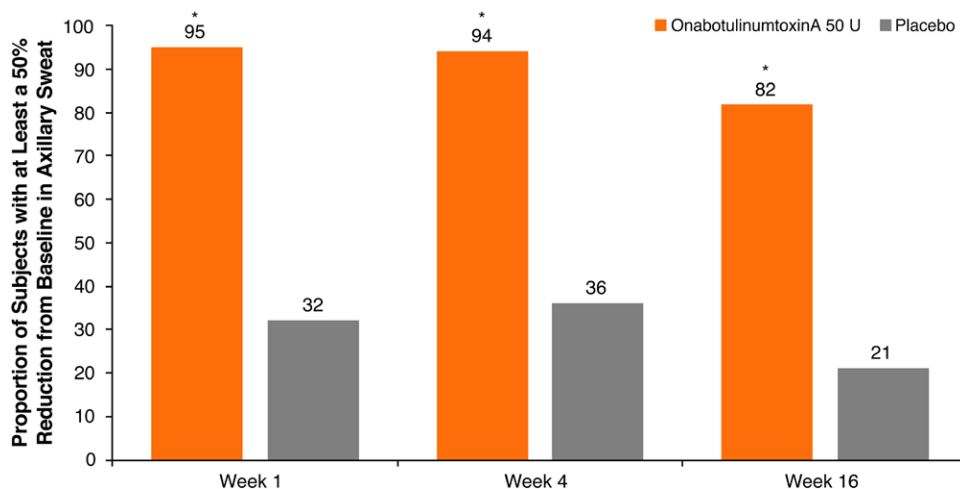


Figure 4. Proportion of subjects with at least a 50% reduction from baseline in axillary sweat, measured gravimetrically at weeks 1, 4, and 16.^[33] * $P < .001$ versus placebo.

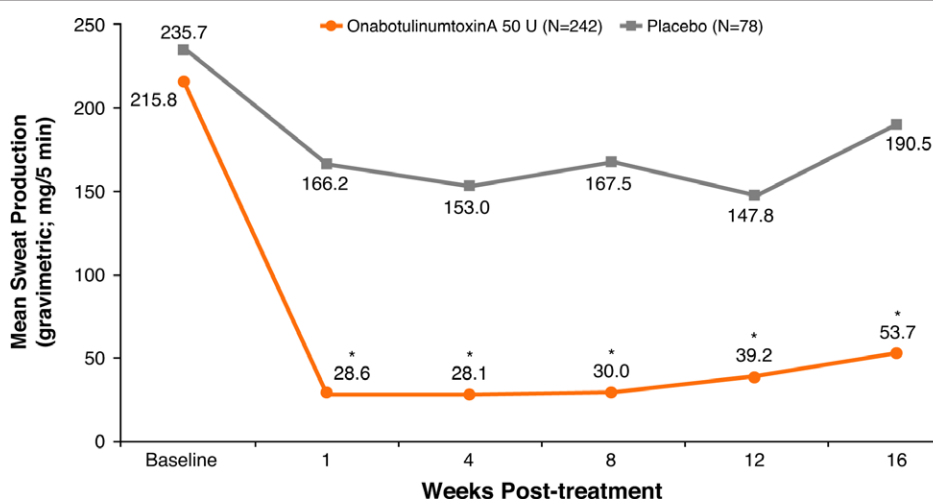


Figure 5. Effect on sweat production of botulinum toxin type A versus placebo.^[33] * $P < .001$ versus placebo.

respectively, at 1 week after the first treatment ($P < .01$; Fig. 6). It was estimated via Kaplan–Meier analyses that at least 22% of onabotulinumtoxinA-treated subjects did not return to an HDSS score of 3 or 4 at 52 weeks after their first treatment. Gravimetric measurement of sweat production also demonstrated superior efficacy of onabotulinumtoxinA 4 weeks after the first and second treatments (Fig. 7). Subjects reported significant improvements in health-related QoL, measured using the Dermatology Life Quality Index, 4 weeks after the first and second onabotulinumtoxinA treatments compared with placebo ($P < .001$), and nearly half of the subjects who reported dermatology-specific QoL impairment at baseline had no such impairment 4 weeks after onabotulinumtoxinA treatment.

OnabotulinumtoxinA treatment for hyperhidrosis was well tolerated in each study, with neither study demonstrating significant differences between onabotulinumtoxinA and placebo groups in the incidence of treatment-related adverse events.^[33,46] Nonaxillary sweating of various body sites (e.g., forehead/face and palms) was reported by 5% of subjects receiving onabotulinumtoxinA in the European study and by 6% and 10% of onabotulinumtoxinA 75 U and 50 U subjects, respectively, and 4% of placebo subjects in the US/Canadian study. In the US/Canadian study, injection site pain was reported for 9%, 12%, and 8% of subjects receiving onabotulinumtoxinA 75 U, onabotulinumtoxinA 50 U, and placebo, respectively, and persisted for a

mean of 2.4 days, with a maximum duration of 10 days. Injection-site bleeding was reported in 6%, 5%, and 3%, respectively.

The European Medicines Agency approved the use of onabotulinumtoxinA for persistent severe primary axillary hyperhidrosis in 2003. The US Food and Drug Administration approved the use of onabotulinumtoxinA for treatment of primary axillary hyperhidrosis in 2004.^[35]

4. Lessons learned and the impact of onabotulinumtoxinA in hyperhidrosis

During the 52-week registration study of onabotulinumtoxinA for hyperhidrosis,^[46] one of the most notable features was the long duration of action. In skeletal muscle, the effects of onabotulinumtoxinA typically last approximately 3 to 4 months.^[48] However, in the hyperhidrosis registration study, the median duration of response was 6 to 7 months, and many subjects did not require repeat treatment.^[46] At least 22% of subjects continued to experience therapeutic benefits for 1 year after their first treatment. These observations are supported by a 4-year longitudinal study in 193 patients with severe primary axillary hyperhidrosis who completed a 1-year randomized, controlled study followed by a 3-year open-label extension study. Patients received up to 5 injections of onabotulinumtoxinA (50 U/

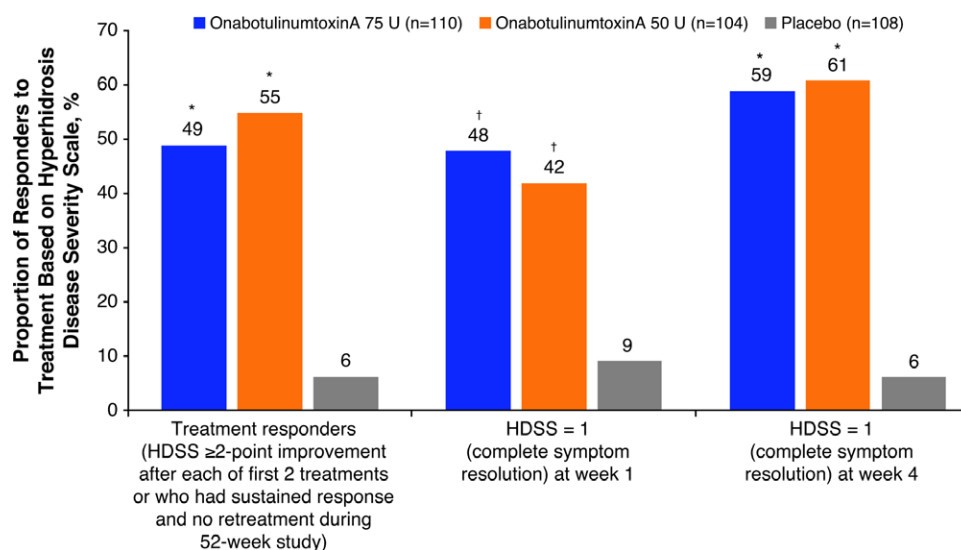


Figure 6. Key outcomes in the US/Canadian study. Week 4 data figure adapted with permission from: Lowe NJ, et al.^[46] Hyperhidrosis Disease Severity Scale (My underarm sweating is: [A] never noticeable and never interferes with my daily activities; [B] tolerable but sometimes interferes with my daily activities; [C] barely tolerable and frequently interferes with my daily activities; [D] intolerable and always interferes with my daily activities). * $P < .001$ for both onabotulinumtoxinA doses versus placebo. † $P < .01$ for both onabotulinumtoxinA doses versus placebo. HDSS = Hyperhidrosis Disease Severity Scale.

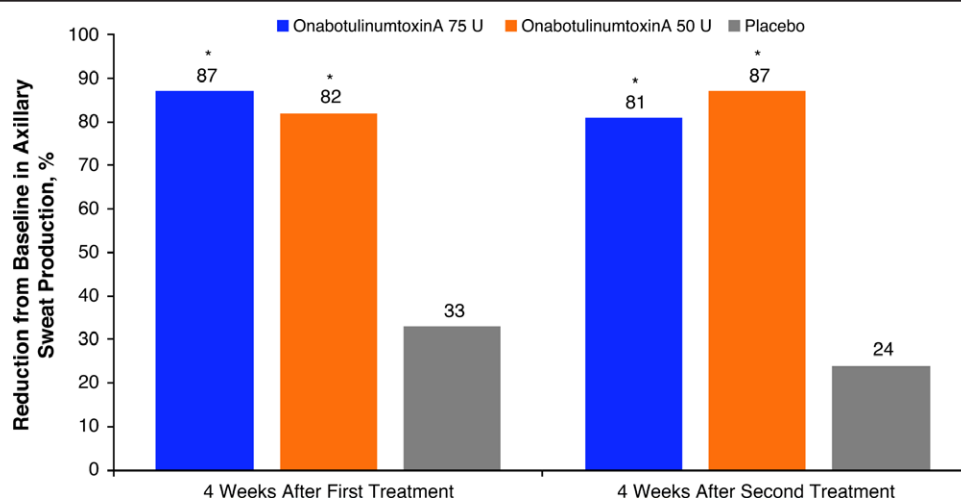


Figure 7. Percent reduction from baseline in axillary sweat production, measured gravimetrically.^[46] * $P < .001$ versus placebo.

axilla) with the possibility for retreatment 8 weeks after each injection for recurrent or persistent symptoms. In patients who had achieved a ≥ 2 -grade improvement from baseline to week 4 on the HDSS, the median duration of treatment effect ranged from 175 to 238 days for each injection up to 5 treatment sessions.^[49]

Ms. Eadie: “One of the things we were surprised about was the long duration of action, and this created some challenges in collecting repeat-treatment data because we weren’t able to acquire sufficient repeat injection data from patients in the trial to satisfy regulatory requirements.... Thus, Allergan had a commitment to complete a long-term (4-year) follow-up study during the review process.^[49]... We probably would have designed the study differently had we known about the long duration of effect at the inception of the development program.”

Dr Brin: “When I saw the topline data, I remarked to colleagues within and outside the company that there was an important mechanistic observation from the clinical trial data suggesting that the duration dimension may vary based on the type of nerve affected by onabotulinumtoxinA or the therapeutic target/disease under study.”

Dr Lowe: “We have found onabotulinumtoxinA to be highly effective and acceptable and generally predictable in excess of 9 months or longer.”

The clinical development and subsequent approval of onabotulinumtoxinA for primary axillary hyperhidrosis also provided much-needed awareness of the disease, its prevalence, and its impact on QoL.

Dr Naumann: “We learned there is a marked compromise of quality of life for individuals with hyperhidrosis...it’s not only a cosmetic problem...it’s a disease that compromises quality of life. The positive quality of life data were extremely convincing for Botox injections.”

Compelling QoL data were part of the aforementioned 2002 report on HHQ results with onabotulinumtoxinA treatment versus placebo through 16 weeks of treatment, which demonstrated significant reductions ($P < .001$) versus placebo at week 16 in the proportions of patients who reported having moderately limited daily activities and limitations at baseline with regard to going out in public and meeting people for the first time.^[5]

Dr Lowe: “In the clinical trials, we also learned that the assessment of hyperhidrosis severity is extremely varied for

Table 2**Estimates of axillary hyperhidrosis prevalence in the United States.^[11,24]**

Study	Survey type	Number of patients	Prevalence of hyperhidrosis
Strutton 2004	Mailed survey; 150,000 households	69% responded 64% provided information for prevalence estimate	By survey: 2.9% When extrapolated to US population: 2.8%
Doolittle 2016	Online; 275,904 email invitations	12,363 entered survey (4.5% response rate); 8160 provided information on hyperhidrosis	4.8% (393/8160)

individual patients [as a result of various emotional and climatic factors or related conditions that could affect their experiences of disease severity].”

Disease awareness increased substantially following use of onabotulinumtoxinA. Two studies (conducted in 2004 and 2016) surveyed people in the United States to estimate hyperhidrosis prevalence (Table 2).^[11,24] According to the 2016 report, the estimated US prevalence of hyperhidrosis had increased since 2004, validating the need for continuing to increase disease awareness. Prevalence was highest among individuals aged 18 to 39 years.^[11] In the medical community, hyperhidrosis has evolved from a subjective condition to a disease. Because of a lack of information about hyperhidrosis, health professionals have had a history of viewing the condition as more of an emotional malady than a disease.^[43] The use of onabotulinumtoxinA stimulated interest in learning more about the disease and its pathophysiology.

Dr Naumann: “It opened a window. The interest in hyperhidrosis grew dramatically. Botox stimulated interest in the pathophysiology and everything around the disease, even apart from Botox [as a treatment], and this was the fascinating thing about it.”

In fact, after publication of the first pivotal onabotulinumtoxinA study, the volume of published articles on hyperhidrosis in the PubMed/Medline database doubled during the next 10-year period (2001–2011) compared with the previous 10 years (1990–2000).

Author contributions

Conceptualization: Nicholas Lowe, Markus Naumann, Nina Eadie

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Supervision: Nicholas Lowe, Marcus Naumann

Writing – original draft: Nicholas Lowe, Marcus Naumann

Writing – review & editing: Nicholas Lowe, Markus Naumann, Nina Eadie

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