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Does onabotulinumtoxin type A reduce interference of daily activities for adults with hyperhidrosis?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not "Does onabotulinumtoxin type A reduce interference of daily activities for adults with hyperhidrosis?"

Study Design: A systematic review of three randomized control trials (RCTs) published after 2009 in peer-reviewed journals in the English language. These RCTs compared the efficacy of onabotulinumtoxin type A (BTX-A) to other treatment modalities in reducing the interference of daily activities for adults with hyperhidrosis.

Data Sources: Three RCTs were selected after searching the databases Pubmed, CINAHL plus, International Pharmaceutical Abstracts, and Central Register of Controlled Trials. Inclusion criteria was relevant studies published after 2009. Exclusion criteria was patients under 18 years old, too few subjects used in trial, and if the article was a systematic review or meta-analysis.

Outcomes Measured: The outcome measured was a reduction in interference of daily activities from hyperhidrosis. This was assessed via the hyperhidrosis disease severity scale (HDSS), a four-point subjective scale with a score of one correlating to no daily activity interference from sweating and a score of four correlating to constant interference.

Results: In the RCT conducted by Ibrahim et al., the mean HDSS scores were reduced by 1.55 points 3 months after the administration of onabotulinumtoxin type A ($P<.001$). In the RCT conducted by Campanati et al., every patient had a 2-point reduction in HDSS scores from baseline compared to 4 weeks after intervention with BTX-A, a statistically significant reduction ($P<.001$). The RCT conducted by Lueangarun et al., resulted in a reduction of 1.35 points on the HDSS scale four weeks after BTX-A cream application compared to baseline; when compared to the reduction of the control group this was statistically significant ($P<.001$).

Conclusion: All three RCTs found a reduction in daily activity interference due to hyperhidrosis with the implementation of onabotulinumtoxin type A. Although there were limitations to the studies, these findings suggest that onabotulinumtoxin type A is effective in reducing activity interference for those with primary hyperhidrosis.

Key words: Hyperhidrosis, Onabotulinumtoxin type A, Botulinum toxin, Botox

INTRODUCTION

Hyperhidrosis is a condition characterized by excessive perspiration extending beyond its physiologic purpose in maintaining body temperature during exercise or heat exposure. This excessive sweating typically affects the palms of the hands, soles of the feet, axilla, and face.[1,2,3] Secondary hyperhidrosis has an identifiable cause, and is related to an underlying medical condition such as infection, hormonal imbalance, or medication side effect.[2] In contrast, primary hyperhidrosis is idiopathic and chronic in nature, often with a symmetric and bilateral distribution of affected areas.[1] While the cause of primary hyperhidrosis is not well understood, evidence suggests it is due to abnormalities in the autonomic nervous system rather than increase in gland size or number.[4] Some studies postulate sympathetic nervous system overactivity, while others point to a more complex mechanism involving parasympathetic pathways as well.[4] In addition, there is a suggested genetic component, as 25% of patients suffering from the condition have a positive family history of hyperhidrosis.[3]

The suggested diagnostic criteria for primary hyperhidrosis are as follows: visible excessive sweating without an identifiable cause for at least 6 months plus at least two of the following: bilateral and symmetric distribution pattern, impairment of daily activities, sweating episode occurring at least one time weekly, age of onset under 25 years old, positive family history, and a discontinuation of sweating during sleep.[5]

Hyperhidrosis affects approximately 4.8% of the United States population, correlating to about 15.3 million people.[6] An epidemiological study found females to be affected at slightly higher rates than males (62.8% female) when analyzing records from the U.S. and Canada. This study additionally noted axillary hyperhidrosis to be the most common location for patient complaints (73% of complaints).[1] Prevalence is highest among individuals aged 18-39 and lowest

among those at the extremes of age. Of the estimated 15.3 million individuals suffering from hyperhidrosis, it is predicted that only about half will seek medical attention; the condition is both underreported and underdiagnosed.[6]

The impacts of hyperhidrosis extend far beyond the discomfort of excessive sweating. This condition can have a negative impact on many areas of life. It may lead to low self-esteem, depression, anxiety, suicidal ideation, social withdrawal, embarrassment, and can significantly interfere with daily activities, relationships, and work.[6-8] One study found that "over half of the participants (54%) claimed they would pay anything for a treatment to stop their excessive sweating".[6] Furthermore, it can significantly increase patient risk for cutaneous infections including higher risk of bacterial, fungal and viral infection, as well as increased risk of dermatophytosis and verruca.[9] The wide range of negative impacts demonstrates how significantly individuals can be affected and how important it is to find an effective and practical treatment for the condition.

Typical treatment options include topical antiperspirants such as aluminum chloride hexahydrate.[10] While these agents tend to be first line, successful treatment may require reapplication every 6-8 hours and concentrations up to 30% to be effective, often leading to skin irritation.[11] Other options include anticholinergic medications (glycopyrrolate 1-2 mg PO tid or oxybutinin 5 mg PO tid).[3,10] A systematic review demonstrated an average improvement in symptoms of 76.2% with oxybutynin therapy, however 73.4% of patients taking oxybutynin experienced dry mouth, leading a percentage of participants to cease therapy. Other adverse effects noted were headache, urinary retention, gastrointestinal upset, heart palpitations and dry eyes.[12] More invasive approaches include ganglionectomy or sympathectomy.[3] Onabotulinumtoxin type A (BTX-A) is yet another treatment option available; it is a

neuromuscular blocking agent that blocks acetylcholine release from the presynaptic membranes creating a denervation state.[13] Ordinarily, as part of the sympathetic nervous system response, acetylcholine binding to muscarinic receptors on sweat glands will activate sweating.[14] Therefore, with blockage of acetylcholine release, the sweating response is inhibited with onabotulinumtoxin. Local injection of BTX-A is being evaluated in this review due to its practicality with onset of action being 1-3 days, fast recovery time, the minimally invasive nature of the procedure, and long-lasting effects from the injection (approximately 4-6 months).[15]

OBJECTIVE

The objective of this selective EBM review is to determine whether or not "Does onabotulinumtoxin type A reduce interference of daily activities for adults with hyperhidrosis?"

METHODS

Three randomized control trials (RCTs) published in peer-reviewed journals after the date of 2009 were used in this selective evidence-based medicine (EBM) review. The patient population addressed were those suffering from primary hyperhidrosis that were over 18 years of age. The intervention applied in these studies was a form of onabotulinumtoxin type A (BTX-A). Groups receiving BTX-A were compared to groups receiving other treatment modalities (incobultinumtoxin A injections, suction-curretage procedure) and a control group (liposomal cream without botulinum toxin).[16-18] Each study chosen utilized the hyperhidrosis disease severity scale (HDSS) as part of the outcome measures. The HDSS is a subjective scale graded 1-4 based on how severely sweating interrupts daily activities.[19]

The databases Pubmed, CINAHL plus, International Pharmaceutical Abstracts, and Central Register of Controlled Trials were searched using the key words: "hyperhidrosis", "botulinum toxin" and "Botox". The selected articles were published in peer-reviewed journals

and written in the English language. Articles were selected based on their applicability to the clinical question being asked, which articles offered the greatest validity, as well as being patient-oriented outcomes that matter (POEMs). Inclusion criteria for this systematic review included RCTs published after 2009. Exclusion criteria was studies using patients under 18 years of age, studies focused on secondary hyperhidrosis, as well as if the article was a systematic review or meta-analysis. Statistics consistently used across all articles was a change from baseline of HDSS scores before and after intervention. Table 1 outlines the demographics and characteristics of the chosen studies.

OUTCOMES MEASURED

All three RCTS in this review addressed outcomes that are considered POEMs (patient-oriented evidence that matters).[16-18] The POEM being addressed in this review is a reduction in the interference of daily activities from sweating due to primary hyperhidrosis. This reduction in daily activity interference was measured using the hyperhidrosis disease severity scale (HDSS), a subjective scale graded 1-4. A score of one is least severe correlating to no daily activity interference due to sweating, while a score of four is considered the most severe, correlating to sweating "always" interfering with daily activities.[19] In the RCTs, the HDSS was administered before intervention with onabotulinumtoxin type A (BTX-A) and then re-administered after the intervention with onabotulinumtoxin type A. In two studies, mean HDSS scores were calculated both prior to intervention with BTX-A and again following intervention. These mean scores were then compared to one another to determine if the reduction was considered statistically significant, defined as a p-value $<.05$.[16,17] In Lueangarun et al., baseline and post-intervention HDSS scores were compared. However, in this study, the statistical significance was based upon the comparison in HDSS reduction of the experimental group (BTX-A) to the control group.[18]

Table 1. Demographics and Characteristics of Included Studies.[16-18]

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Ibraham O, Kakar R, Bolotin D, *et al*. 2013.[16]	RCT	20	18-65 y/o	Patients diagnosed with bilateral axillary hyperhidrosis, in "good health" and a BMI between 18.5 and 29.9.	Pregnant, lactating pts. Past suction/curettage treatment. Axillary BT-A injections 12 months prior, on blood thinners/hx of bleeding d/o. Sore or infection near procedure site. Known sensitivity to iodine, starch powder, albumin, BTX product.	0	Onabotulinum toxin type A injections versus suction-curettage treatment
Campanati A, Giuliodori K, *et al.* 2014.[17]	RCT	25	19-50 y/o	Patients with moderate to severe primary palmar hyperhidrosis that were resistant to antiperspirants that contained aluminum chloride or iontophoresis.	Pregnant or nursing women. If ever received incobotulinumtoxin or oncobotulinumtoxin type A ever in the past. Pts treated with aluminum chloride or iontophoresis less than 3 months before the study start.	0	Onabotulinum toxin type A injections versus Incobotulinum toxin type A injections.
Lueangarun S, Sermsilp C, Tempark T. 2018.[18]	RCT	20	18-50 y/o	Pts w/ symmetric bilateral primary axillary hyperhidrosis. Initial HDSS scores of 2-4, and who have not previously received specific types of treatment for the condition w/i 6 months of the trial.	Pregnancy, lactation, previous botulinum toxin injections/ microwave thermolysis/ High intensity US/hair removal laser within 6 months before screening. Pts with more than 25% asymmetry between axilla. Use of anticholinergics. Hx of specific medical conditions.	Not stated	Topical botulinum toxin type A liposomal cream versus vehicle cream without.

RESULTS

Ibrahim et al., conducted a randomized control trial composed of 20 subjects to compare the effectiveness of onabotulinumtoxin-A (BTX-A) injections to a suction-curettage procedure.[16] Patients between the ages of 18 to 65 were included if they had a prior diagnosis of bilateral axillary hyperhidrosis, were in "good health" and had a BMI between 18.5 and 29.99. Exclusion criteria omitted patients who were pregnant or lactating and those who had undergone a suction-curettage procedure in the past or had BTX-A injections within the previous 12 months. It additionally excluded anticoagulated patients, those with a sore or infection near the procedure site and patients with sensitivities to products being utilized in the study.[16] Each patient received BTX-A injections in one axilla and had the suction-curettage procedure performed on the opposing axilla. Which procedure was performed on the right versus left axilla was allocated via random sequence generation. The axilla receiving BTX-A injections had a total of 50 U of toxin given via 0.5 inch 30-guage needle; this was achieved with dermal deposits of 0.1-0.2 mL spaced evenly at 1.5-2cm apart. Due to obvious differences in procedures, blinding was unable to be achieved by patients and those administering the interventions. There were no losses to follow-up during the study. Mean HDSS scores were calculated both before any intervention, and three months following intervention. Data collected was continuous data (see Table 2). The results of the study demonstrate that the BTX-A injections were effective in achieving a statistically significant reduction in interference of daily activities ($P<.001$) following the intervention.[16] While my clinical question is not focusing on other treatments, it is of note that when comparing BTX-A versus suction curettage the mean reduction in HDSS scores at three months, the injections caused a larger decrease (0.75 point difference among groups), however it was not addressed in the article if this difference was statistically significant. Importantly, no subjects

reported discomfort or adverse reactions to the BTX-A injections, while soreness, hyperpigmentation (15% subjects), dysesthesia (5% subjects) were noted following the suction-curettage procedure.[16] These results can help guide future clinical decision making when discussing treatment options with patients in terms of efficacy and tolerability.

Table 2. Comparison of Mean Reduction in HDSS Scores of BTX-A Injections versus Suction-curettage Procedure.[16]

	Baseline mean HDSS scores (points)	3 months post intervention mean HDSS scores (points)	Mean change from baseline (points) and p-value
Axilla receiving BTX-A injections	3	1.45	1.55, *P* <.001
Axilla receiving suction-curettage procedure	3.05	2.25	0.8, *P* <.001

Table 3. Adverse Side Effects Associated with BTX-A Injections versus Suction-curettage Procedure.[16]

	Percentage experiencing hyperpigmentation after procedure	Percentage experiencing noteworthy dysesthesia after procedure
BTX-A injections	0%	0%
Suction-curettage procedure	15%	5%

Campanati et al., conducted a double-blind randomized control trial with 25 subjects comparing the efficacy of onabotulinumtoxin-A (BTX-A) injections to incobotulinumtoxin injections for patients with moderate to severe primary palmar hyperhidrosis.[17] The study included patients aged 19-50 (15 female and 10 male) that were resistant to past aluminum chloride or iontophoresis interventions. Subjects were excluded from the study if they were pregnant, nursing, had received treatment with aluminum chloride or iontophoresis within 3 months of trial, or any prior history of BTX-A or incobotulinumtoxin injections. In this trial, all patients received BTX-A injections and incobotulinumtoxin injections on contralateral hands. There was no statistically significant difference of sweating extension between hands at the start

of the trial. Reference grids were drawn on subjects' hands with square areas of 2.25 cm^2. Product was diluted in a 5mL sterile 0.9% saline solution and 0.1mL was administered by a physician in the center of each square via a 30-guage needle. Which product was injected in the right versus left hand was done in a random order with both patients and physicians blinded to the product being administered.[17] At the conclusion of the trial, no patients were lost to follow-up. Data presented was continuous. HDSS scores were obtained at baseline (prior to any intervention) and 4 weeks following injections. Mean HDSS scores at baseline were 2.45 for both groups; the mean HDSS scores for each group following intervention were not explicitly stated in the article, however it was reported that all patients experienced a 2-point decrease in their score from baseline regardless of intervention given (see Table 4). This was considered a therapeutic success for both interventions and statistically significant change from baseline following either treatment ($P<.001$).[17]

Table 4. Comparison of HDSS Sores before and after Interventions with BTX-A and Incobotulinum Toxin Injections. (Numbers in this chart are estimated based on Figure 2 in the published study).[17]

	Mean HDSS score at baseline (prior to intervention)	Mean HDSS scores 4 weeks after intervention
BTX-A injections	2.45	Not explicitly stated in article.
Incobotulinumtoxin-A injections	2.45	Not explicitly stated in article.

Lueangarun S et al., conducted a double-blind RCT comparing a topical onabotulinumtoxin type A (BTX-A) liposomal cream to a control group liposomal cream containing no active ingredient.[18] This study utilized 20 subjects with symmetric bilateral primary axillary hyperhidrosis aged 18-50 years old. To qualify, patients needed to have initial HDSS scores between 2-4. The trial excluded pregnant and lactating patients as well as those who had previous BTX-A injections, microwave thermolysis, high intensity ultrasound, or hair laser removal within 6 months of the screening process. Additionally, those with more than 25%

asymmetry between axilla, taking certain medications (CCB, anti-cholinergics, aminoglycosides) or those with certain medical conditions (CHF, DM, hyperthyroidism, myasthenia gravis) were excluded.[18] Subjects were randomly given two bottles of cream (one for each axilla, one cream with BTX-A and one without). Instructions were to use two pumps of cream from each bottle and consistently apply it to the same axilla each night for 7 days. The results were presented as continuous data. At baseline, the starting HDSS score was 3.1. After four weeks of cream use, the HDSS score was 1.75 for axilla treated with BTX-A cream versus a score of 2.65 for axilla treated with the control cream (see Table 5). This was a statistically significant reduction in scores when comparing the BTX-A cream to the control cream ($P<.001$) translating to a reduction in interference of daily activities with use of cream containing BTX-A.[18] It is presumed that these scores represent a mean score of all 20 subjects (a mean change from baseline), however this was not explicitly stated. It was also not clear that all subjects completed the trial. In this study, no adverse effects were observed with either liposomal cream; this indicated a good safety profile as no rash, pruritis, burning, changes to skin color or skin eruptions occurred during the trial.[18]

Table 5. Comparison of HDSS Scores before and after Onabotulinumtoxin type A (infused) Liposomal Cream versus Control Cream.[18]

	HDSS at baseline	HDSS after four weeks of cream usage
Liposomal cream with BTX-A	3.1	1.75
Control liposomal cream with no active ingredient	3.1	2.65
		P <.001

DISCUSSION

Primary hyperhidrosis is a chronic idiopathic condition characterized by excessive perspiration that can have debilitating psychological, health and behavioral effects on those suffering from it.[1,6] This selective EBM review sought to answer whether or not onabotulinumtoxin type A is effective in reducing the interference of daily activities for those suffering from primary hyperhidrosis. All three RCTs analyzed in this review demonstrated that BTX-A was effective in reducing HDSS scores (all statistically significant), thus correlating to a reduction in daily activity interference.

It is important to mention the multiple limitations with the studies reviewed. In all three studies the sample size was quite small (20-25 people), therefore it cannot be assumed the results of these studies are applicable to the general population.[16-18] In addition, there was no demographic information given about ethnicity in the articles chosen, thus it is unclear how ethnicity would affect the generalizability of the results. All three RCTs excluded pregnant or nursing women, so results found are not applicable to this patient population.[16-18] Additionally, Ibrahim et al., excluded those with a BMI outside of the range (18.5-29.99), and all procedures were performed at the same location by the same physician, therefore it must be kept in mind that these results may not apply to those with BMIs outside of the given range, or for those getting procedures performed at other facilities by other physicians.[16] In Campanati et al. randomization allocation was not concealed from those enrolling subjects.[17] In Lueangarun et al., 80% of subjects were female, so it is difficult to discern if the results of this study are applicable to men. Those with certain comorbidities or on specific medications were excluded, therefore efficacy and safety profiles cannot be applied to those with the exclusionary

medications and conditions. In addition, the trial was only double-blind not triple blind and losses to follow-up were not addressed.[18]

Onabotulinumtoxin type A is a neuromuscular blocking agent. It works at the neuromuscular junction by blocking acetylcholine release from presynaptic membranes creating a denervation state.[13] There are many uses for BTX-A including glabellar, forehead and canthal lines, cervical dystonia, chronic migraine, overactive bladder, and urinary incontinence to name a few.[13] Contraindications include known hypersensitivity, or infection at the injection site. Data is limited with pregnant or nursing mothers and therefore it is not recommended for those pregnant or nursing. While no serious reactions occurred in the reviewed articles,[16-18] severe reactions may occur. These include anaphylaxis, arrythmias, myocardial infarction, and systemic toxicity due to distant toxin spread. Distant toxin spread may lead to dysphagia and breathing difficulties that are life-threatening.[13] Drug interactions are noted with aminoglycosides, anticholinergic agents, muscle relaxants, and using multiple agents containing onabotulinumtoxin type A at the same time. Pricing for 100 units in the U.S. is $721.21.[13] Reimbursement and out-of-pocket expenses can vary based on insurance coverage,[20] therefore cost may be a limiting factor for some.

CONCLUSIONS

All three RCTs demonstrated that onabotulinumtoxin type A was effective in reducing the interference of daily activities for adults with primary hyperhidrosis.[16-18] Thus, it is reasonable to conclude that BTX-A is an effective and reasonable choice of intervention to enhance the daily lives of adults suffering from primary hyperhidrosis.

Future research should include larger sample sizes and have BTX-A injections performed at different sites by different providers to increase the generalizability of the research. In addition, the cream application of BTX-A is an interesting area for further studies, as it broadens

treatment options for those who are uncomfortable with needles and the pain associated with injections. If more research is done on efficacy, safety, and the most appropriate form of topical BTX-A administration, it could be a potential treatment option for patient populations that prefer a once daily application to intermittent injections.

REFERENCES

1. Lear W, Kessler E, Solish N, Glaser D. An epidemiological study of hyperhidrosis. *Dermatol Surg.* 2007; 33(1).

2. Balaji VE and Selvan AT. Retrospective review on hyperhidrosis: etiopathology and its treatment. *Int J Pharma Research.* 2017; 8(1).

3. Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J. Chapter 432: Disorders of the autonomic nervous system. In: *Harrison's Principles of Internal Medicine.* Vol II. 20th ed. New York, NY: McGraw-Hill Education; 2018:3164-3165.

4. Pathophysiology of excessive sweating. Medpage Today. 2020. Accessed November 30, 2020. https://www.medpagetoday.com/resource-centers/focus-hyperhidrosis/pathophysiology-excessive-sweating/2282.

5. Hornberger J, Grimes K, Naumann M, Glaser DA, Lowe NJ, Naver H, Ahn S, Stolman LP. Recognition, diagnosis, and treatment of primary focal hyperhidrosis. *J Am Acad Dermatol*. 2004;51(2).

6. Doolittle J, Walker P, Mills T, Thurston J. Hyperhidrosis: an update on prevalence and severity in the United States. *Arch Dermatol Res.* 2016;308(10): 743-749.

7. Leung A, Chan P, Choi M. Hyperhidrosis. *Int J Dermatol.* 2001. Doi:10.1046/j.1365-4362.1999.00609.x

8. Hamm H. Impact of hyperhidrosis on quality of life and its assessment. *Dermatol Clin.* 2014; 32(4):467-76.

9. Walling HW. Primary hyperhidrosis increases the risk of cutaneous infection: A case-control study of 387 patients. *J Am Acad Dermatol*. 2009;61(2):242-6.

10. Hyperhidrosis: Diagnosis and treatment. American Academy of Dermatology. Accessed October 5, 2020. https://www.aad.org/public/diseses/a-z/hyperhidrosis-treatment.

11. Kalantari K, Zeinalzade A, Kobarfard F, Moghadam SN. The effect and persistency of 1% aluminum chloride hexahydrate iontophoresis in the treatment of primary palmar hyperhidrosis. *Iran J Pharm Res*. 2011;10(3).

12. Cruddas L, Baker DM. Treatment of primary hyperhidrosis with oral anticholinergic medications: a systematic review. *J Eur Acad Dermatol.* 2016;31(6).

13. 18. OnabotulinumtoxinA (Lexi-Drugs). Lexicomp. 2020. Accessed November 30, 2020. httpss://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6465?cesid=8RzPT1jPkE2.

14. Costanzo LS. Chapter 2: Neurophysiology. In: *Board Review Series Physiology.* 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2018:33-66.

15. Botox Injections. Mayo Clinic. 2020. Accessed October 5, 2020. https://www.mayoclinic.org/tests-procedures/botox/about/pac-20384658.

16. Ibrahim O, Kakar R, Bolotin D, et al. The comparative effectiveness of suction-curretage and onabotulinumtoxin-A injections for the treatment of primary focal axillary hyperhidrosis: a randomized control trial. *J Am Acad Dermatol.* 2013;69(1):88-95. doi:10.1016/j.jaad2013.02.013

17. Campanati A, Giuliodori K, Martina E, Giuliano A, Ganzetti G, Offidani A. Onabotulinumtoxin type A (Botox) versus Incobotulinumtoxin type A (Xeomin) in the treatment of focal idiopathic palmar hyperhidrosis: results of a comparative double-blind clinical trial. *J Neural Transm.* 2014;121:21-26. doi:10.1007/s00702-013-1074-1

18. Lueangarun S, Sermslip C, Tempark T. Topical botulinum toxin type a liposomal cream for primary axillary hyperhidrosis: a double-blind, randomized, split-site, vehicle-controlled study. *Dermatol Surg.* 2018;44(8):1094-1101. Doi:10.1097/dss.0000000000001532

19. Solish N, Bertucci V, Dansereau A, et al. A comprehensive approach to the recognition, diagnosis and severity-based treatment of focal hyperhidrosis: Recommendations of the Canadian Hyperhidrosis Advisory Committee. *Dermatol Surg*. 2007;33(8):908-923. Doi:10.1111/j.1524-4725.2007.33192.x

20. Botox savings and insurance-Botox. Botoxseveresweating. 2020. Accessed November 29, 2020. https://www.botoxseveresweating.com/Can_botox_help/savings_insurance.