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REVIEW

Current and Emerging Medical Therapies for Primary Hyperhidrosis

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ABSTRACT

Hyperhidrosis is defined as the production of sweat beyond what is physiologically necessary to maintain thermal homeostasis. This disease state may (and typically does) have a significant impact on the patient's quality of life. Medications including antiperspirants, anticholinergics, and botulinum toxin have been shown to be effective in the management of hyperhidrosis. Several medical device technologies have also proven to be effective. This review article will explore the current and emerging pharmacological and medical device treatments for hyperhidrosis and provide a framework for treating patients who suffer with primary forms of hyperhidrosis.

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INTRODUCTION

Hyperhidrosis is defined as the production of sweat beyond what is physiologically necessary to maintain thermal homeostasis. This condition can be categorized as primary (idiopathic) or secondary (related to a known cause). Several studies have estimated that 1.6–2.9% of the United States population have been affected by primary hyperhidrosis [1–7]. One study conducted outside the United States has reported a prevalence as high as 16.3% of the population [3]. The pathophysiology of this disorder is poorly understood but primary hyperhidrosis has been postulated to have a genetic component. Studies have shown that 65% of patients with a diagnosis of primary focal hyperhidrosis reported a family history of the disease [8]. A genome-wide linkage analysis showed that chromosome 14q is possibly associated with hyperhidrosis [9]. This disease state likely represents a dysregulation involving both the

sympathetic and parasympathetic nervous systems [10, 11].

The diagnosis of primary focal hyperhidrosis is made via the history and physical examination with a focus on the consensus conference diagnostic criteria. The criteria require at least a 6-month history of focal and visible sweating without secondary causes [12]. In addition, at least two of the following criteria must be met: bilateral and symmetric hyperhidrosis, impairment of activities of daily living, onset at age less than 25 years old, at least one episode per week, family history of the disease, or an absence of symptoms during sleep [12]. Exclusion of medications that can cause hyperhidrosis including anticholinesterases, selective serotonin reuptake inhibitors, tricyclic antidepressants, glaucoma agents, bladder stimulants, opioids, and sialagogues remains essential to ensure proper diagnosis [13]. The marked impact of primary hyperhidrosis on a patient's quality of life has been measured in clinical trials using the validated Hyperhidrosis Disease Severity Scale [14–16]. Treatment of hyperhidrosis has focused on improving symptoms, reduction of the sweat and its inherent socially stigmatizing impact, and subsequently improving the quality of life of the patients [1]. The objective of this article is to explore the current and emerging pharmacological and medical device treatments for hyperhidrosis and to provide a framework for treating patients. Surgical options including curettage, skin excision, and sympathetic block for hyperhidrosis will be covered in a separate paper.

METHODS

A search regarding current treatments was conducted through 5 July 2016 using PubMed, The Cochrane Library, Google Scholar, Clinical Key, and Embase. The following keywords were used to research the literature for references: "hyperhidrosis", "primary hyperhidrosis", "primary focal hyperhidrosis", "sweating", "excessive sweating", "treatments for hyperhidrosis", and "treatments for excessive sweating". All relevant English-language literature was reviewed, and the reference list of articles of interest were reviewed for further citations. In addition, clinicaltrials.gov was also searched using the criteria "hyperhidrosis", and subsequent literature searches were made on all new compounds and devices being developed.

This article is a review of existing data from previously conducted studies that are publically available and does not involve any new studies of animals or human subjects performed by the authors.

CURRENT THERAPIES FOR HYPERHIDROSIS

Current therapies for hyperhidrosis are divided into several categories including topical, oral, and injectable medications and medical devices.

Topical Therapies

Antiperspirants which usually contain aluminum salts are the first-line treatment for hyperhidrosis because of their safety profile, cost-effectiveness, and efficacy [17–19]. Preparations in the United States can vary in the amount of metal salts up to 25% depending on the aluminum compound used [20]. Antiperspirants are believed to work by obstructing the distal eccrine sweat gland ducts [19, 21]. Patients with hyperhidrosis who use these products may develop miliaria due to the ongoing production of sweat inferior to the

blocked sweat duct, but long-term blockage may lead to functional and structural degeneration of the eccrine acini which does not cause harm to the patient in the process of reducing sweat production [21].

A case series published by Scholes et al., in which 65 patients treated with 20% aluminum chloride hexahydrate topically nightly for 1 week, then as needed, showed that patients reported complete control of axillary sweating. After initial treatment, most patients applied the substance every 7–21 days which correlated with epidermal renewal [22, 23]. Aluminum chloride hexahydrate has been shown to be effective in palmar hyperhidrosis in a clinical trial that reported decreased skin water vapor loss; however, the effect disappeared 48 h after stopping treatment [19]. Additionally a 6-week randomized trial of 12 patients showed that aluminum chloride hexahydrate 12.5% was equally as effective as 30% for the treatment of plantar hyperhidrosis [24].

Many patients achieve satisfactory results with aluminum chloride compounds. In a study of 691 patients treated with aluminum chloride solutions, 82% achieved satisfying results with either complete resolution or a level of sweating perceived as normal after initial treatment. In a long-term follow-up study of these patients, satisfaction levels increased to 87% with patients using maintenance therapy [23].

Skin irritation is a common limiting adverse event with aluminum chloride hexahydrate. The irritation occurs when the compound is applied to moist skin allowing the formation of weak hydrochloric acid [25]. In one study, 36% of all patients reported moderate irritation and 14% reported severe irritation [23]. Other adverse effects include itching and stinging on application which improved with continual usage [23]. Some studies have shown that application of a low-potency steroid, such as topical hydrocortisone, in the morning can decrease irritation [22, 26]. Applying aluminum chloride hexahydrate to completely dry skin greatly reduces the risk of focal skin irritation [25]. To ensure the skin is dry, some clinicians have recommended avoiding washing the axillae prior to the application of aluminum chloride hexahydrate, drying the axillae with a blow dryer on a cool setting, or applying the medication at nighttime and removing it in the morning [25].

Topical glycopyrrolate 2% is a medication believed to improve hyperhidrosis through its anticholinergic properties by competitively binding the muscarinic acetylcholine receptors [27]. Several case reports and a few randomized trials have been conducted to evaluate its efficacy in facial hyperhidrosis. One study of 25 patients with facial hyperhidrosis showed that 96% were partially or fully satisfied with the results of the medication [28]. Another study of 39 patients with facial hyperhidrosis showed a reduction of sweat production on the forehead of 25% 90 min after application with no significant improvement in the Hyperhidrosis Disease Severity Scale [29]. However, the results in axillary hyperhidrosis have been less clinically meaningful. An uncontrolled study of 35 patients with axillary hyperhidrosis who had failed aluminum chloride hexahydrate therapy was unable to show a consistent and meaningful benefit from glycopyrrolate compounded in Cetomacrogol Cream BP [30]. Glycopyrrolate may be used topically twice daily although some authors recommend applying it nightly [31]. Patients should be advised to avoid the nose, mouth, and eyes as the anticholinergic properties can prevent ocular accommodation [31].

Formaldehyde and glutaraldehyde are not commonly used in the treatment of primary focal hyperhidrosis, as these agents can cause

localized skin irritation, allergic sensitization, and central nervous system toxicity [25, 32].

Oral Therapies

Oral anticholinergics are a potential treatment for hyperhidrosis but are occasionally limited by the side effect profile. A retrospective chart review of 45 patients with hyperhidrosis who were prescribed glycopyrrolate showed a 67% response rate with 6 patients not responding to treatment and 9 patients discontinuing therapy secondary to developing adverse events including dry mouth and gastrointestinal disturbances [33]. A retrospective chart review in children has shown improvement in 90% of all patients, with the most common side effects being dry mouth (26%) and dry eyes (10%) [34]. Oxybutinin, a competitive antagonist at the postganglionic muscarinic receptors, is another potential treatment for hyperhidrosis. A prospective, randomized, placebo-controlled trial for the initial treatment of hyperhidrosis showed improvement in greater than 70% of patients with palmar and axillary hyperhidrosis and greater than 90% of patients with plantar hyperhidrosis [35]. A subsequent study showed a 60% improvement in the Hyperhidrosis Disease Severity Scale and a significant improvement in the Dermatology Life Quality Index [36]. Dosing in the literature varies greatly from 2.5 to 5 mg twice daily with dry mouth being the main dose-limiting adverse event [35, 37]. Bornaprine is an oral anticholinergic with limited commercial availability which has been studied in hyperhidrosis; however, the central nervous system adverse events limit the usage of this medication [38].

Other oral medications have been suggested to be effective in hyperhidrosis but have limited data and are of limited value given the availability of alternative therapies. These include beta-blockers, benzodiazepines, methanthelinium bromide, and clonidine. Beta-blockers, in particular propranolol, and benzodiazepines, have been reported to be successful in hyperhidrosis if the patient is believed to have an anxiety trigger [39]. Oral methanthelinium bromide 50 mg was compared in a randomized trial which showed a mean decrease in axillary sweat production of 69 mg in 5 min; however, no significant difference was seen in palmar sweat production [40]. Two case reports have shown that clonidine 0.2–0.4 mg is effective in reducing craniofacial hyperhidrosis [41].

Injectable Therapies

Botulinum toxin is an acetylcholine release inhibitor and a neuromuscular blocking agent that is commercially available in the United States [42, 43]. Each botulinum toxin (OnabotulinumtoxinA, AbobotulinumtoxinA, and IncobotulinumtoxinA) has different characteristics with variable clinical equipotency ratios that are influenced by the severity of the underlying disease [44]. A multicenter, randomized, parallel group, placebo-controlled trial of 320 patients evaluated OnabotulinumtoxinA for axillary hyperhidrosis with a primary endpoint of a greater than or equal to 50% reduction in baseline spontaneous axillary sweat production [45]. At 4 weeks, 94% of patients on active treatment had met this endpoint, with 82% maintaining this endpoint at week 16 [45]. Patients who respond to treatment can have consistent reduction of axillary sweat for greater than 5 months with repeat dosing shown to be safe with equal or potentially increased efficacy [46–48].

Other types of botulinum toxin have limited data available. Efficacy appears equal between 150 units of AbobotulinumtoxinA and 50 units

of OnabotulinumtoxinA per axilla; however, other studies have shown no difference between 100 and 200 units of AbobotulinumtoxinA [49, 50]. Several other studies have validated a variety of types of botulinum toxin for palmar and plantar hyperhidrosis [48, 51–57].

The administration of botulinum toxin requires multiple injections spaced approximately 2 cm apart which can pose many challenges, most notably pain at the injection site. In order to reduce pain from multiple injections, several studies have evaluated different techniques such as using ice, topical anesthetics, or diluting the botulinum toxin with lidocaine. The use of ice packs has been shown to decrease the discomfort associated with the multiple needle injections, and this methodology is cost-effective and non-threatening to patients [58–60]. Another cost-effective form of anesthesis is vibration, which has been shown to reduce patient discomfort during botulinum injections [61]. Other clinicians have advocated for topical anesthetics such as tetracaines or lidocaine/prilocaine cream which have been shown to be effective but need to be applied 45 min prior to the procedure [62, 63]. Some studies have even shown that diluting OnabotulinumtoxinA with lidocaine instead of normal saline decreases pain without a loss of efficacy [64, 65]. For patients with palmar hyperhidrosis who cannot tolerate a cooling technique, an ulnar, median, and radial nerve block or a modified Bier Block can be effective [66–69].

Medical Device Therapies

Iontophoresis, the passing of an ionized substance through intact skin, is a treatment method that delivers 15–20 milliamps of current through tap-water to treat hyperhidrosis [70, 71]. The exact mechanism of action is unclear, but several hypotheses exist including the inhibition of sympathetic nerve transmission, ion deposition obstructing the sweat gland, and local alterations of pH inhibiting the sweat gland [72–75]. Initial treatment of 8 sessions in a 28-day period showed a 81% reduction in sweat with maintenance therapy required to maintain the effect [76]. Common adverse events include discomfort, vesiculation, and erythema [77]. The impact of iontophoresis can be enhanced if glycopyrrolate pills are added to the trays before the iontophoresis is initiated [27, 78–81]. At least two companies, Hidrex http://www.hidrexusa.com/ and R.A. Fisher and Co http://www.rafischer.com/cat_iontophoresis in the United States, offer iontophoresis units for either sale or rental.

Microwave thermolysis has also been shown to be an effective treatment for hyperhidrosis. Microwaves heat by physical rotations of molecules with high dipole moment such as the ionic water in eccrine glands while avoiding low dipole moment molecules such as fat [16]. A study of a device using this technique in axillary hyperhidrosis showed a 89% response rate after treatment with 69% maintaining the effect at 12 months [16]. Adverse events include temporary tenderness, swelling, and numbness [82].

Adjunctive Therapies

In addition to pharmaceutical and medical device therapies, several adjunctive therapies can be helpful to patients. Educating the patient about the disease state and showing empathy are critical to increasing compliance with regimens. The International Hyperhidrosis Society hosts a website http://www.sweathelp.org which can serve as a resource for patient education on the disease state and treatment options. In addition, several companies with links on the website offer specialized shirts,

socks and other footwear that can wick moisture away and prevent wet marks and stains. To help patients sleep better, moisture-wicking bed sheets are also available.

EMERGING THERAPIES FOR HYPERHIDROSIS

Despite many approved therapies, there is still an unmet need for more effective and convenient methods for managing hyperhidrosis.

Topical Therapies

Several topical anticholinergic agents are currently in development for hyperhidrosis. Oxybutynin, which has been used off-label for hyperhidrosis in an oral formulation, is frequently associated with anticholinergic adverse events including dry mouth [83]. The adverse events are believed to be caused by an active metabolite *N*-desethyloxybutynin [84]. As a result, a transdermal gel formulation was approved in the US for overactive bladder. This gel reduces the anticholinergic adverse events associated with oral oxybutynin by avoiding gastrointestinal and hepatic first pass metabolism which reduces the level of the active metabolite [84–86]. A study is currently underway to evaluate oxybutynin gel in patients with axillary hyperhidrosis. Studies are also being conducted on umeclidinium, glycopyrrolate tosylate, and sofpironium bromide, but limited information is currently available in peer-reviewed journals.

Medical Device Therapies

Several medical device therapies are currently in development including radiofrequency thermotherapy, laser therapy, and ultrasound therapy. Radiofrequency thermotherapy is a minimally invasive therapy which utilizes a device to insert microneedles into the skin and emit bipolar thermal energy [87]. By focusing the energy with microneedles, the thermotherapy is directed to the eccrine sweat glands in the dermis with minimal trauma to the epidermis [87]. The efficacy of fractional microneedle radiofrequency thermotherapy has been shown in small randomized control trials to significantly improve the Hyperhidrosis Disease Severity Score as well as decrease sweat production [87–89]. In addition, histopathologic findings have shown a decrease in the number of sweat glands in tissue [89]. One study that followed patients for 1 year found that overweight patients may need additional treatments to maintain the effect [90].

Several different types of lasers have been studied to reduce sweat production with limited and inconsistent results to date. In a prospective case–control study of the YAG 1064-nm laser, a modified starch iodine test showed effective improvement at 9 months; however, no significant difference in eccrine glands was seen in pre- and post-treatment biopsies of the axillary skin [91]. A study of 21 patients with axillary hyperhidrosis using the 800-nm diode laser with a half-side control design showed a decrease in the sweat rate on the laser-treated sites but not statistically significantly more than on the untreated site [92]. A randomized control trial of 100 patients utilizing the 924- and 975-nm lasers simultaneously showed an improvement in the Hyperhidrosis Disease Severity Score and the modified starch iodine test at 1 and 12 months of follow-up [93]. Studies of the 1210-nm laser and the 1440-nm laser for hyperhidrosis are currently being conducted.

Ultrasound technology is another method to selectively target the glandular tissue for the

treatment of hyperhidrosis. In a randomized double-blind, sham-controlled study of 12 patients with axillary hyperhidrosis utilizing micro-focused ultrasound with visualization, 83% of all patients experienced a greater than or equal to 50% reduction in sweat production as measured using a gravimetric assessment [94]. In this study, patients followed for 12 months showed long-lasting effects [94]. Another study utilizing the VASER showed that 11 out of 13 patients had a significant reduction in sweat production and odor without recurrence in 6 months [95]. In addition, ultrasound has been reported to have been used to induce a therapeutic stellate ganglion block in a patient with efficacy for at least a few weeks [96].

DISCUSSION

Hyperhidrosis is a disorder of excess sweat production which can have a dramatic impact on a patient's quality of life. The disease state appears to have a genetic component, given the presence of a family history. Hyperhidrosis likely represents a dysregulation of the sympathetic and parasympathetic systems. More research is needed to better understand the true pathophysiology of the disease process.

A number of topical, oral, and injectable options are available to treat hyperhidrosis. Topical antiperspirants are the first-line agent and are best applied on a dry surface to prevent irritation of the skin. Second-line agents and strategies include oxybutynin, botulinum toxin, and iontophoresis. Oxybutynin has been shown to be an effective oral medication which improves the quality of life in patients with hyperhidrosis; however, dry mouth is a common adverse event that may limit the usage of the medication. Topical formulation of anticholinergics, including oxybutynin, are likely to have similar efficacy with less systemic adverse effects. Injectable botulinum toxin has also been shown to be effective, but the cost and pain associated with multiple injections can be limiting factors. Utilizing cooling agents, diluting the botulinum toxin in lidocaine, and performing a nerve block are all effective methods to reduce the pain.

Many medical device options are currently used or are in development for hyperhidrosis. Iontophoresis is a proven method which works best on palmar and plantar surfaces and can be enhanced with the addition of glycopyrrolate. Microwave technology has been shown to be effective with a long-lasting effect. Several lasers have been studied in hyperhidrosis patients; however, the results to date have been quite mixed and the role in treating hyperhidrosis remains unclear. Microneedle radiofrequency and ultrasound technology are promising new methods of treatment allowing for a focused area of thermotherapy targeting the eccrine sweat glands and potentially developing a long-term treatment.

CONCLUSION

Clinicians have many effective pharmacological and medical device options in treating patients with hyperhidrosis. While no guidelines exist in the United States, the Canadian Hyperhidrosis Advisory Committee has developed treatment algorithms for clinicians to follow [97]. Many more therapies are currently in development. Utilizing the best treatment along with education and empathy will increase a patient's compliance and lead to a meaningful clinical outcome.

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