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Primary hyperhidrosis in children: A review of therapeutics

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Abstract

Primary hyperhidrosis, an idiopathic disease that commonly affects the palms, soles, axillae, and/or craniofacial region, is characterized by perspiration in excess of what is required for physiologic cooling. This disease begins in childhood or adolescence and negatively impacts emotional, physical, and psychological well-being. This review explores current therapeutic options for primary hyperhidrosis in the pediatric population, including topical therapies, oral therapies, non-surgical and procedural interventions, and adjunctive therapies. In addition, this review identifies new and emerging treatments and highlights the need for further research and therapeutic options for this impactful disease.

Introduction

Hyperhidrosis is perspiration that exceeds what is required for physiologic cooling. Further categorization of hyperhidrosis depends upon the presence or absence of an underlying, identifiable cause. Primary hyperhidrosis is idiopathic in etiology and characterized by bilateral, focal or multifocal involvement. In contrast, secondary hyperhidrosis results from an underlying cause, such as a medical condition or medication, and often manifests by generalized (rather than focal) sweating. Prior to discerning a diagnosis of primary hyperhidrosis, secondary hyperhidrosis should be ruled out.

The exact cause of primary hyperhidrosis has not been elucidated, though a genetic predisposition has been suggested.[1] Physiologically, overactivity of the sympathetic nervous system is thought to cause excessive stimulation of the eccrine glands and the resultant increased sweating characteristic of primary hyperhidrosis.[1] The anatomic sites most commonly affected by primary hyperhidrosis are the axillae, craniofacial region, palms, and soles; less frequently the back, chest, or area under the breast may be involved.[2] As of 2016, Doolittle et al reported primary hyperhidrosis had a prevalence of 4.8% in the United States (U.S.), though this is lower than other countries and may reflect underreporting.[2]

Hyperhidrosis interferes with multiple aspects of life and causes significant patient distress. Excessive perspiration adversely affects social interactions, such as shaking hands; athletic activities, such as gripping sports equipment; and activities of daily living, such as writing and using touch technology. Further impacts may be felt on extracurricular pursuits, such as playing video games, learning an instrument, or participating in fine arts. These daily challenges negatively impact emotional well-being and mental health. One recent study demonstrated a positive correlation between hyperhidrosis severity and rates of anxiety and

depression.[3] In these patients, the prevalence of anxiety and depression was reported to be 21.3% and 27.2%, respectively; in patients not suffering from hyperhidrosis, the rates for anxiety and depression were 7.5% and 9.7%, respectively.[3]

Primary hyperhidrosis usually starts prior to 20 years of age.[2] Patients with involvement of the palms and soles have the earliest mean age of onset.[2] Furthermore, patients under 21 years of age are more likely than adults to bring their concerns regarding excess sweating to the attention of a healthcare provider.[2] Thus, providers who care for pediatric and young adult populations must be knowledgeable regarding management of this impactful medical condition. This review summarizes the current therapeutic options for the pediatric patient suffering from primary hyperhidrosis.

Topical Medications

Topical therapies are considered first-line treatment for mild to moderate primary hyperhidrosis, though long-term adherence may be challenging. General limitations of topical treatments include local irritation and, for some interventions, a relatively short duration of action.

Aluminum salts

Aluminum salts work by precipitating ions that clog eccrine ducts, thereby physically blocking sweat from reaching the surface of the skin.[4] Secondary changes to the sweat gland may occur, such as atrophy and necrosis.[4] Due to the destruction of secretory units within the eccrine sweat glands, future sweat production may be decreased, and the patient may require less frequent treatments.[4] The application of aluminum salts is generally limited to use on the axillae, palms, soles, or craniofacial region. Over-the-counter formulations may have active concentrations up to 12.5% aluminum chloride hexahydrate or 20% aluminum zirconium salts,

while medical providers can prescribe aluminum chloride hexahydrate up to 20%, though the concentration may be higher depending on the vehicle of delivery.[5] These must be applied to clean, dry skin once daily at night, when hyperhidrosis is at its lowest level, then washed off in the morning.[5] Home administration is a major benefit of this treatment option; however, the necessity of long-term usage may negatively impact adherence. Skin irritation is a limiting adverse effect, but this can be mitigated with correct application to completely dry skin in the evenings and use of low potency topical corticosteroids as needed.[5]

Glycopyrronium Tosylate

Topical glycopyrronium tosylate was approved by the Food and Drug Administration (FDA) in June 2018 to treat primary axillary hyperhidrosis in patients 9 years of age and older.[6] This anticholinergic agent exerts a local effect that decreases neuronal transduction of acetylcholine at eccrine sweat glands.[7] Significant research has been recently performed evaluating the safety and efficacy of topical glycopyrronium tosylate.[6,8,9] One such study that pooled two study groups found 79% of pediatric study participants experienced a 50% decrease in sweating, compared to approximately 54% in the control group.[9] These authors found a relatively tolerable and predictable side effect profile, which included xerophthalmia, xerostomia, and mydriasis; similar to that experienced with oral dosing of anticholinergics, but generally less severe.[9] Application is once daily to cleaned axillae using a pre-moistened cloth containing 2.4% glycopyrronium tosylate.[6] Topical application makes it suitable for use on the axillae, but these studies note patients should be counseled to avoid touching their eyes after using the moistened towelette, as this behavior was associated with unilateral or bilateral mydriasis in patients across the age spectrum.[6,9]

Oxybutynin

Oxybutynin is an anticholinergic that works by competitively preventing acetylcholine from binding with muscarinic receptors.[10] In recent studies, the transdermal application of oxybutynin is shown to have a half-life of 62-84 hours, suggesting it may be a suitable option for use in hyperhidrosis.[10] Due to topical delivery, first-pass metabolism is bypassed and systemic effects may be minimized.[10] Research on oxybutynin in pediatric hyperhidrosis is limited, though it has been studied in oral formulations for pediatric nocturnal enuresis. Nguyen and colleagues conducted a small trial using topical oxybutynin in pediatric patients suffering from axillary hyperhidrosis.[11] This limited sample of 10 pediatric participants applied 1 g oxybutynin 3% gel to the axillae every morning for four weeks.[11] The authors note this study did not enroll the target number of participants and three subjects dropped out, leaving just seven participants to complete the study.[11] All seven subjects reported an improvement in their hyperhidrosis, while six of seven patients reported an improved quality of life score.[11] Patients reported side effects most commonly associated with anticholinergics: xerostomia, constipation, and blurred vision.[11] Further research is necessary to better elucidate the potential role of topical oxybutynin in the treatment of primary hyperhidrosis.

Systemic Medications

When topical treatments are unsuccessful in alleviating symptoms of primary hyperhidrosis, systemic medications can be used and may offer relief for excessive sweating. Currently, oral anticholinergics represent the mainstay of systemic therapy. These may be particularly beneficial for multifocal primary hyperhidrosis, as the medication exerts its effects on all sweating sites.

Glycopyrrolate

Glycopyrrolate is a synthetic anticholinergic that blocks acetylcholine from binding to receptors.[12] The quaternary structure prevents this drug from crossing the blood-brain barrier, resulting in little to no central nervous system effects.[12] This anticholinergic agent can be used for any site of hyperhidrosis and is an affordable and effective treatment for hyperhidrosis. One retrospective study of pediatric patients evaluated the use of oral glycopyrrolate in primary hyperhidrosis and suggested dosing of 1 to 3 mg twice daily, and titrating as required.[13] A majority of study participants experienced a decrease in sweating with a dose of 2 mg twice daily, but the results only lasted as long as patients took the medication.[13] A separate retrospective analysis of 12 adolescent patients with primary hyperhidrosis found high patient satisfaction, with 11 of the 12 study participants experiencing symptom improvement.[14] In this study, a majority of patients used a dose of 1 mg once daily, but the authors note these dosages were often adjusted to balance efficacy with side effects.[14] The most common side effects are xerostomia and xerophthalmia, which appear to increase in a dose dependent manner.[13]

Oxybutynin

Oral oxybutynin, another systemic anticholinergic, has been studied previously in pediatric populations for nocturnal enuresis and can be used for primary hyperhidrosis..[15] Due to its tertiary structure, this medication can cross the blood-brain barrier more easily than glycopyrrolate and can have more significant antimuscarinic side effects, such as tachycardia, cognitive dysfunction, and confusion.[15] Wolosker and colleagues studied doses of 2.5 mg/day up to 10 mg/day and found this to be an effective treatment for palmar hyperhidrosis in children under 14 years of age, with dose dependent adverse effects such as xerostomia.[16] A majority of study subjects experienced improvement after six weeks of treatment, but more rigorous trials are necessary to support this data.[16]

Non-Surgical and Procedural Interventions

Beyond topical and oral medications, other devices, procedures, and surgical interventions are available that may provide relief from excessive perspiration. Some are used off-label for pediatric hyperhidrosis, while others are not utilized in pediatric patients and are more suitable for consideration as they mature to adulthood.

Iontophoresis

The mechanism of action of iontophoresis is as yet undetermined. One theory suggests increased keratinization, plugging the eccrine sweat glands; another proposes alterations in the electrochemical gradient result from hydrogen ions in tap water, which increases the acidity in the eccrine gland.[17] These changes induce damage to the sweat apparatus with a subsequent decrease in perspiration.[17] Iontophoresis is most often utilized to control primary hyperhidrosis of the palms and soles; however, specialized patches are available to make treatment of the axillae feasible. Tap water alone or with an anticholinergic drug, such as glycopyrronium bromide, is placed in the treatment tray and an electrical current is passed through the water.[17] This technology offers the convenience of in-home use, but the cost of the machine may be prohibitive, insurance coverage may be limited, and long-term adherence is required to maintain results. A 2012 study of tap water iontophoresis in 43 patients younger than 18 years of age found a significant reduction in participant hyperhidrosis disease severity scale (HDSS) comparing pre-treatment scores to post-treatment scores.[17] Participants underwent an average of seven therapy sessions, and 36 participants experienced improvement in their hyperhidrosis symptoms. A majority of study participants (88%) experienced paresthesia as an adverse effect, while a smaller number of participants reported pain, pruritus, erythema, or dryness.[17] Kacar and colleagues performed a retrospective analysis of iontophoresis therapy in adolescent patients and

found improvement in symptoms after 15 sessions of iontophoresis.[18] No statistically significant improvement was noted beyond this treatment timepoint, but 7 of the 19 participants had dryness lasting for three months following their final iontophoresis treatment.[18] A prescription is needed for the purchase of an iontophoresis machine in the United State. Examples of machines approved or cleared by the US FDA are included in Table 1.

Onabotulinum Toxin A

Onabotulinum toxin A (BoNT-A) received FDA approval in 2004 to treat primary axillary hyperhidrosis in adults and may be used off-label for pediatric patients suffering from primary hyperhidrosis.[19] This neurotoxin inhibits the release of acetylcholine from presynaptic neurons at the neuromuscular junction, thereby decreasing stimulation of the eccrine sweat glands.[20] One study of BoNT-A in pediatric patients with axillary hyperhidrosis found a significant reduction in sweat production four weeks after treatment.[19] Using the HDSS to track symptoms, nearly half of study participants experienced a two-point improvement within two treatment cycles spaced 14 days to 8 weeks apart, depending on initial hyperhidrosis severity.[19] The authors reported a median duration of effect of 4.5 months, but suggested this duration may be longer lasting in the adolescent population.[19] Given this potentially longer lasting duration of effect, the intervals between treatments may increase with time and decrease the need for more frequent injections. While this neurotoxin appears to be effective and safe, the use of BoNT-A injections may be limited by cost, lack of insurance coverage, pain, and need for multiple cycles of treatment.

Microwave Thermolysis

Microwave thermolysis is an in-office procedure that utilizes heat to damage the eccrine and apocrine sweat glands. In one study of microwave thermolysis, adult study participants were

treated with two procedures at least two weeks apart, with a third procedure performed within 30 days if the participant's sweating response was inadequate.[21] A majority of patients (80%) had a statistically significant decrease in their sweat severity as measured by a reported HDSS score of 1 or 2 at either the 30-day or six month follow-up.[22] This efficacy was maintained for the active treatment group through one year, which marked the end of the study timeframe. Limitations include a high initial investment, transient changes in sensation, incomplete reduction in sweating and pain after the procedure.[21] One machine, miraDry®, has been approved by the FDA to treat primary axillary hyperhidrosis in patients 18 years of age and older, but this machine has not been studied in the pediatric population. There are no studies currently registered with clinicaltrials.gov examining microwave thermolysis on pediatric subjects.

Ultrasound

Ultrasound has many medical uses in the dermatologic setting, such as the imaging of lymph nodes and subcutaneous masses, and may be used for aesthetic reasons, such as body contouring. VASER Ultrasound is one such device FDA approved for body contouring by using soft tissue emulsification.[23] This technology has not been FDA approved to treat primary hyperhidrosis but has been used off-label for axillary sweating when medical management has failed.[22] Ultrasound can be performed in an outpatient setting with local anesthesia and is a minimally invasive option. Ultrasound has not been studied in the pediatric population.

Liposuction/curettage

Liposuction or curettage removes eccrine glands in the axillae when medical management has failed.[23] This has not yet been studied in the pediatric population, but potential benefits include its minimally invasive nature and a lack of compensatory sweating compared to

sympathectomy.[23] One study in adult patients found it less effective than treatment with BoNT-A injections.[24] Scarring and pain at the treatment site may occur.

Sympathectomy, Sympathicolysis, or Video-Assisted Thoracoscopic Sympathectomy

Sympathectomy, sympathicolysis, or video-assisted thoracoscopic sympathectomy (VATS) are invasive surgical procedures that interrupt the sympathetic chain via various means, such as clipping or cauterizing, between the T2 to T4 level.[25] This is most often pursued to address palmar hyperhidrosis. Regardless of the method, the resultant denervation of the eccrine sweat glands prevents their stimulation and decreases perspiration.[25] Unfortunately, compensatory hyperhidrosis is a unique and well-documented adverse effect that occurs in a majority of patients following the procedure and may expand the burden of sweating to new sites.[25] Additional postoperative risks include gustatory sweating, Horner's Syndrome, or ptosis.[25] The inherent risks of general anesthesia and surgery, combined with the likelihood of compensatory sweating at new sites, warrant a cautious approach to irreversible surgical management.

Emerging Therapies

New treatments are being explored for primary hyperhidrosis, primarily in the arena of topical therapeutics. Novel anticholinergics and antimuscarinics are being evaluated, and new methods of drug delivery are also being explored.

Sofpironium Bromide

Sofpironium bromide is an ester analog of glycopyrrolate and functions as an anticholinergic, inhibiting muscarinic receptors.[26] Topical delivery of this gel solution is thought to decrease systemic side effects, due in part to its formulation, which is designed to become quickly inactivated.[26] As a result, its effects are thought to be felt primarily at the site of

application.[26] A study in adult patients with hyperhidrosis evaluated three strengths of a gel solution and found all to be effective in reducing excessive sweating.[26] However, some systemic effects were still reported, the most common being xerostomia and mydriasis.[26] A US study of 15% sofpironium bromide gel for the treatment of pediatric axillary hyperhidrosis has been registered with clinicaltrials.gov. However, the data have not yet been published. In Japan, the manufacture and marketing of 5% sofpironium bromide gel for the treatment of primary hyperhidrosis was recently approved.[27]

Umeclidinium (UMEC)

Umeclidinium is a long-acting muscarinic antagonist that blocks the action of acetylcholine on its receptors.[28] One recent study of its effectiveness was limited to the axillae with topical application of 2 mg/cm^2 of 1.85% UMEC showing no significant improvement compared to placebo.[28] Side effects included local irritation and pain.[28]

Topical BoNT-A

BoNT-A injections are an effective treatment for primary hyperhidrosis in adults. However, this method of delivery is painful and limits its use in children. Topical delivery vehicles for BoNT-A would be an attractive, seemingly pain-free alternative. A recent study in adults found improvement in hyperhidrosis severity by using a BoNT-A containing liposomal cream.[29] After a week of once daily topical application, patients reported a decrease in sweating, with results lasting up to eight weeks and no reported adverse effects.[29] This topical formulation has not been studied in the pediatric population.

Adjunctive Therapies

In addition to medical management, patients may benefit from exploring adjunctive therapies to improve quality of life. A plethora of products are currently on the market and listed

in Table 2. The International Hyperhidrosis Society (sweathelp.org) maintains a list of resources and provides comprehensive hyperhidrosis information for patients and healthcare providers alike.

Conclusions

Primary hyperhidrosis is a chronic condition that negatively impacts daily living starting in childhood. While no cure exists, there are a wide range of treatment modalities ranging from topical preparations to invasive surgery. Table 3 summarizes current therapeutics for primary hyperhidrosis in the pediatric population.

Many factors influence therapeutic selection, including patient age and affected site(s). Younger children may prefer topical therapies, given ease of administration and avoidance of systemic or painful side effects. The affected site(s) can further drive therapeutic decisions. For axillary hyperhidrosis, treatment can begin with topical therapies, then progress to oral anticholinergics or BoNT-A therapy if sweating is inadequately controlled. For palmoplantar hyperhidrosis, if topical therapies and oral anticholinergics have failed, then iontophoresis or BoNT-A are reasonable next steps. For patients with sweating at multiple anatomic sites, oral anticholinergics are an attractive initial option, as these agents improve sweating at all affected sites. Finally, other factors such as patient preference, insurance coverage, and cost should be considered when developing a treatment plan.

Topical therapies, oral therapies, non-surgical and procedural interventions, and adjunctive therapies are currently available to decrease disease burden, and new options are slowly emerging. Some therapeutics, such as topical sofpironium bromide, are being studied in both children and adults. Others therapies, such as microwave thermolysis, have only been studied in adults, but provide hope for more long-term control. Despite recent advances,

additional studies and treatment options are needed to better address primary hyperhidrosis in the pediatric population.

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