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REVIEW

Hyperhidrosis: A Review of Recent Advances in Treatment with Topical Anticholinergics

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ABSTRACT

Background: Topical anticholinergics have been reported to be effective in managing hyperhidrosis (HH) given the recent approval of glycopyrronium tosylate.
Objective: This review aimed to examine the effectiveness of emerging topical anticholinergic treatments for HH and their associated adverse effects in comparison to current treatment options.
Methods: We conducted a search within the PubMed and Embase databases for current and emerging topical anticholinergic treatments for primary HH.
Results: The topical anticholinergics that have been recently investigated for use in HH include glycopyrrolate, oxybutynin, sofpironium bromide, and umeclidinium. The only agent currently FDA approved is glycopyrrolate.
Conclusion: Knowledge of topical anticholinergic treatment options is important for patient care when managing HH. This review shows that while available safety data thus far are limited, emerging topical anticholinergics pose minimal known human risks.

Keywords: Hyperhidrosis; Topical anticholinergics; Oxybutynin; Sofpironium bromide; Umeclidinium

Key Summary Points

Hyperhidrosis (HH) is a chronic condition that has potential for a debilitating course.

Current treatment modalities for HH are limited with varying side effects.

Systemic anticholinergics have shown benefit in reducing sweat production in HH; however, the associated side effects are limiting factors for use.

Currently, the only approved topical anticholinergic for use in HH is glycopyrronium tosylate.

Topical anticholinergics currently under investigation include oxybutynin, sofpironium bromide, and umeclidinium, each of which has shown a reduction in sweat and anticholinergic-related side effects.

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INTRODUCTION

Primary hyperhidrosis (HH) is the presence of increased sweating in the absence of a physiological trigger or underlying identifiable pathological cause. It is due to the over activity of the reflex circuits stimulating the eccrine glands [1]. There is no increase in the number of eccrine glands as once speculated [2]. Excessive sweating is primarily found in focal body regions such as the palms, axilla, soles of feet, or craniofacial region [3]. HH is often a disregarded condition that can have a significant debilitating impact on patients' psychosocial functioning owing to its persistent nature [4]. It can cause limitations to work, social interactions, relationships, and quality of life. In addition to discomfort, skin maceration from persistent moisture can lead to bacterial and/or fungal overgrowth. Treatment options are based on anatomic location and severity of HH. It ranges from topical and systemic treatments, botulinum toxin, iontophoresis, radiofrequency microneedling, microwave thermolysis, and surgical procedures [5]. Topical anticholinergics are useful medications in the treatment of HH and are often favored given the decreased risk of anticholinergic effects compared with oral anticholinergics. Anticholinergic agents work by inhibiting the acetylcholine-induced activation of eccrine sweat glands [6]. Glycopyrronium tosylate (GT) 2.4%, a quaternary amine, is a towelette premoistened with glycopyrronium that is applied topically and is currently the only topical anticholinergic approved in the USA for primary axillary HH [7].

However, even with the range of available therapies, patients are often recalcitrant to treatment and/or discontinue treatment owing to unpleasant side effects. The formulation of topical anticholinergics is expected to minimize the unpleasant side effects associated with systemic anticholinergics. This review aimed to investigate the data available on the effectiveness of emerging topical anticholinergic treatments for HH and the extent of associated side effects.

MATERIALS AND METHODS

A literature search was performed using the PubMed database with the keywords "primary hyperhidrosis" and "topical anticholinergics." The specifics of article selection and exclusion criteria are detailed in Fig. 1. Primary outcomes focused on safety and tolerability. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Forty articles met the inclusion criteria of topical anticholinergics as a treatment for primary HH in the adult population and were included in the review.

Hyperhidrosis Treatment

Topical Anticholinergics

Topical anticholinergics are useful medications in the treatment of HH and are often favored given the decreased risk of anticholinergic effects compared with oral anticholinergics. GT 2.4%, a quaternary amine, is a topical premoistened towelette and is currently the only topical anticholinergic approved in the USA for primary axillary HH [7]. Although approved for primary axillary HH, studies have also been performed to assess its efficacy in facial HH [8]. Two well-known randomized, double-blind, vehicle-controlled phase III trials, ATMOS-1 and ATMOS-2, demonstrated high efficacy and safety profile of GT [9]. The adverse effects reported throughout the trial were deemed to be an acceptable level [10]. Overall, the anticholinergic-related adverse events were mild to moderate with most side effects occurring early on and resolving without need for interruption or withdrawal of GT [11]. Glaser et al. demonstrated a $\geq$ 50% reduction in baseline axillary sweat production by week 4 of topical application (Table 1) [12]. A long-term open label extension study further examined the effectiveness of GT with continued long-term use in

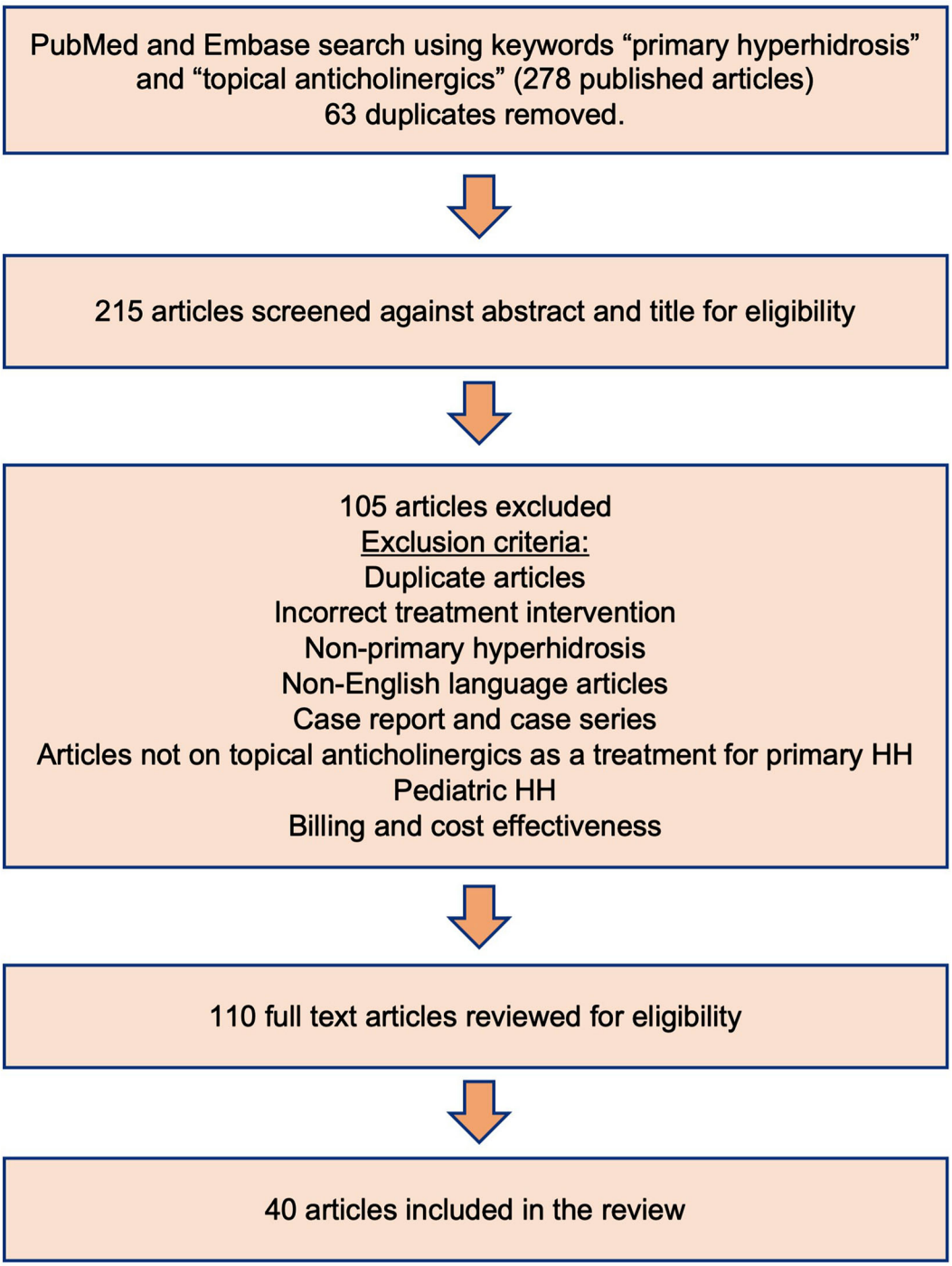

Fig. 1 The specifics of article selection and exclusion criteria

which positive clinical response remained throughout [13, 14]. It was also noted that systemic absorption with GT was significantly lower when compared with oral glycopyrrolate in addition to decreased risk of anticholinergic effects [15].

Overall, GT was well tolerated, though the most reported adverse events included dry

Table 1 Topical anticholinergics for treatment of hyperhidrosis

Agent	Mechanism of action	HH location	Key results/findings
Glycopyrronium tosylate (GT)	Competitively inhibits acetylcholine receptors found on peripheral tissues (including sweat glands) [16]	Axillary	GT demonstrated a significant reduction in the severity of sweat production over the course of 4 weeks with once-daily application. [12] Anticholinergic effects were mild or moderate and transient leading to discontinuation only infrequently [12]
Oxybutynin	Inhibits M1, M2, and M3 muscarinic acetylcholine receptors, M3 receptors are present on sweat glands [32]	Axillary, palmar, plantar	47.8% of patients with axillary HH reported erythema and pruritus upon application. [24] 50% of patients with plantar HH reported that oxybutynin was "sticky" and unpleasant to use. Twice-daily application of 10% oxybutynin gel resulted in a significant reduction in HDSS [24]
Sofpironium bromide	Inhibits muscarinic receptors in eccrine glands. [25]	Axillary	$\geq$ 1 or 2 points improvement in HDSM-Ax from baseline and a 50% or more reduction in total gravimetric weight of sweat. [33] Side effects were typical of anticholinergic symptoms in addition to dermatitis and irritant reactions [26]
Umeclidinium (UMEC)	Long-acting muscarinic antagonist, reducing the overproduction of perspiration. [28]	Axillary, palmar	A decrease in sweat was noted from day 3 of application and the HDSS. [34] The most common reported side effects were application site reactions. [28] Greater absorption through the axillae than the palm

mouth, application site pain, and mydriasis [16]. To further decrease the risk of anticholinergic effects, it is recommended that patients wash their hands immediately with soap and water. Contraindications to use include patients with medical conditions that can be worsened by the anticholinergic effects of GT, including but not limited to glaucoma, paralytic ileus, myasthenia gravis, Sjögren's syndrome, and toxic megacolon complicating ulcerative colitis [16]. Although GT is recommended for use once daily, it is expensive when compared with topical aluminum chloride hexahydrate therapies [17]. Once-daily topical application of GT has the potential to reduce the disease burden in patients with axillary HH.

A study compared topical glycopyrrolate 2% to botulinum toxin A, a commonly used treatment for facial HH, and it was found to have comparable positive results [18]. More recently, glycopyrronium bromide 1% cream was evaluated for the safety and efficacy in patients with primary axillary HH in a randomized controlled trial over the course of 4 weeks [19]. It was found to be both efficacious and safe, with the most commonly reported side effect being dry

Table 2 Clinical properties of topical anticholinergics

Agent	Clinical properties	Absorption	Long-term use concern	Trials assessing concern
Glycopyrronium tosylate (GT)	Permanently charged quaternary amine therefore minimizes oral bioavailability and blood–brain barrier permeability. [35] The diffusion of the active drug is insufficient for the induction of the systemic response, which significantly reduces the possible adverse reactions. [9] In particular, CNS-related adverse effects [36]	Minimal	None	A safety analysis showed no phototoxic, genotoxic, or carcinogenic effect [9]
Oxybutynin	Tertiary amine structure provides ability to cross the blood–brain barrier given its lipophilic nature [34]	Moderate	Neurotoxicity (dementia should be considered)	None
Sofpironium bromide	Similar in chemical structure to glycopyrronium bromide. It has a high binding affinity for the M3 cholinergic receptor at the local site of administration, but is hydrolyzed at the ester linkage to less active metabolites upon entry into blood [31]	Minimal	Unknown	Phase II and III studies completed, currently approved in Japan
Umeclidinium (UMEC)	Long-acting muscarinic antagonist with minimal ability to cross the blood–brain barrier	Minimal	Unknown	Limited studies, one phase II and III study

mouth. Therefore, both the gel and cream formulation appear to be efficacious in treating HH.

Topical oxybutynin gel is currently approved for the treatment of an overactive bladder in adults [20]. It is a small tertiary amine molecule with a 62–84 h half-life when applied topically to the abdomen, upper arm/shoulder, or thigh (Table 2) [21]. Given its long half-life, it is a superior option over other topical HH therapies such as aluminum chloride (a first-line therapy for HH). In comparison, glycopyrronium has a significantly shorter half-life of 3 h [15]. Nguyen et al. investigated the use of topical oxybutynin 3% gel for the treatment of axillary HH in 10 patients and concluded that HH severity was reduced over a study period of 4 weeks [20]. Three patients reported mild application site irritation that resolved within 2 weeks after stopping application, two patients reported xerostomia that lasted one day, and one patient reported constipation and blurry vision that was temporally associated with opioid use after elective surgery. In comparison to the gel formulation, the cream formulation of oxybutynin was examined in a small number of patients and was found to have good efficacy assessed by a reduction in hyperhidrosis disease severity scale (HDSS) and tolerability [22].

The likely reason that systemic anticholinergic effects were rarely observed is due to the fact that transdermal application of oxybutynin

avoids the hepatic and gastrointestinal first-pass metabolism, reducing the metabolism of its active metabolite, *N*-desethyloxybutynin (*N*-DEO), responsible for anticholinergic side effects [23]. Similarly, another study investigated the use of topical oxybutynin 10% gel in a placebo-controlled split study and concluded that twice daily application showed a significant sweat reduction in primary HH as assessed by the HDSS [24]. HH was assessed in axillae, palmar, and plantar sites. Reported side effects included erythema and pruritus upon application; however, this was attenuated by instructing patients to wait at least 2 days between shaving in addition to application on clean and dry skin at room temperature [24]. In this study, 8/16 (50%) of patients with plantar HH reported that the 10% topical gel was "sticky" and unpleasant to use. As a result, a total of four patients (25%) discontinued use owing to the sticky nature (Table 1) [24]. No systemic anticholinergic side effects were reported. Overall, 74% of patients reported a moderate to high satisfaction rate, with most satisfaction seen in those treated for plantar HH [24].

Sofpironium bromide is an ester analog of glycopyrrolate that inhibits muscarinic receptors in eccrine glands (Table 2) [25]. Although not yet approved in the USA, it was recently approved for primary axillary HH in Japan in 2020 [26]. It is available in a topical gel that has been tested at varying concentrations (5%, 10%, and 15%) with a significant reduction in axillary HH assessed through the hyperhidrosis disease severity measure-axillary (HDSM-Ax) by 1 or 2 points [25]. Reported side effects included those typical of anticholinergic effects (blurred vision, dry mouth, mydriasis, urinary hesitation, constipation, and dry eyes) (Table 1). Sofpironium bromide is contraindicated in angle-closure glaucoma and in patients with dysuria secondary to benign prostatic hyperplasia owing to its anticholinergic effects [27]. Additionally, it is recommended against use on broken skin (atopic dermatitis, wounds, etc.) owing to an increased risk of absorption leading to anticholinergic side effects. This is helpful in reducing the risk of mydriasis and other associated anticholinergic effects. The unique aspect of sofpironium's application is delivery through a metered pump that allows for a no-touch application [25]. This is helpful in reducing the risk of mydriasis and other associated anticholinergic effects.

Umeclidinium (UMEC) is a long-acting muscarinic antagonist that is currently used as a bronchodilator for respiratory conditions. It was investigated as a topical dermal formulation for use in HH [16]. UMEC has a similar potency to topical glycopyorrolate [28]. The proposed mechanism of action in HH is the blockage of muscarinic receptor stimulation by acetylcholine, therefore reducing the overproduction of perspiration [28]. Although not currently approved for use in HH, its efficacy was evaluated through topical administration on humans. The most common reported adverse events were mild application site reactions (28% of patients) [29]. Anticholinergic-related side effects included headache, dizziness, syncope, abnormal sensation in the eye, and bronchitis. Notably, urinary hesitancy was reported in one patient that started 3 days after the first application and lasted in duration for 13 days [28]. Authors concluded that this adverse reaction was directly related to UMEC application. The phase II study showed that UMEC was systemically absorbed at a slow rate after topical administration and significantly reduced sweat production comparable to the control (Table 1) [28]. Additionally, the gravimetric scale and total HDSS score both displayed maximum reduction at the end of the treatment period [28]. Therefore, the study suggested that UMEC has potential for clinical use in the treatment of HH but would require further evaluation for systemic absorption.

Another study that investigated the pharmacokinetics of UMEC displayed greater absorption through the axilla than the palm [30]. More recently, a phase III 52 week study conducted in Japan assessed the safety and tolerability with long-term use in patients with primary axillary HH. The incidence of AEs was 80.9% in the group that started off receiving the vehicle and switched to sofpironium midway, and 83.5% in group that received sofpironium from day one [31]. Anticholinergic AEs included headache, mydriasis, dysuria, dry mouth, vision

blurred, thirst, constipation, insomnia, and nausea.

Other Treatments

Historically, the current approach for management of primary HH includes first-line therapy of topical antiperspirants (aluminum chloride hexahydrate or other aluminum salts) and/or lifestyle modifications [5]. Aluminum chloride works through the production of its metal salts that interact with sweat mucopolysaccharides forming precipitates that block the eccrine sweat gland duct lumen [37]. Lifestyle modifications include avoiding HH triggers such as spicy foods, alcohol, crowded areas, and emotional arousal [37]. Tight clothing and occlusive footwear can also worsen symptoms and therefore avoidance is recommended. Another treatment, iontophoresis, is a long-term treatment for palmar and plantar HH. Iontophoresis involves placing the affected area in tap water while delivering an electrical current through intact skin [5]. This treatment has been speculated to inhibit sympathetic nerve transmission, obstruct sweat glands by ions, and cause dysfunction of eccrine gland secondary pH alterations [38].

Procedural therapeutic options generally range from less invasive to more invasive options, such as botulinum toxin A (BTX) injections, surgical curettage, and, for severe refractory cases, endoscopic sympathectomy [34]. BTX inhibits acetylcholine release and works by temporarily blocking eccrine sweat gland function. However, the significant pain associated with injections is often a limiting factor. Nasser et al. investigated modalities to relieve pain associated with BTX injections and concluded that nerve blocks, intravenous regional anesthesia, and needle-free anesthesia are great options for anesthesia [39]. The issue is that these options required specialized training and equipment. Alternative less effective options for pain control include ice application, topical anesthesia, vibration, and cryoanalgesia [39]. Originally, it was once thought that topical anticholinergics should be considered when a patient has failed all other nonsurgical treatments [40]. However, currently in many countries, the initial treatment for HH in clinical practice is oral oxybutynin. More recently, systemic anticholinergic agents such as oral oxybutynin and glycopyrrolate have been shown to be beneficial; however, there is an increased risk of systemic adverse effects [34]. Those symptoms include dry mouth, blurred vision, headache, dizziness, and gastrointestinal complaints. Therefore, new topical anticholinergics have been studied and were found to provide comparable efficacy with a reduction in unpleasant side effects [34].

DISCUSSION

The treatment of HH ranges from topical therapies to injections and surgical options. While varying treatments are available, patient satisfaction is often a limiting factor. The emergence of additional formulations of topical anticholinergics has provided patients and providers with equally effective options with fewer side effects as compared with oral anticholinergics. We reviewed the topical anticholinergics in comparison to other available treatment options for HH and concluded that topical anticholinergics are an effective treatment option for the management of HH. There is an increase in the convenience of use without any painful associations in comparison to BTX or surgical options. In particular, although topical oxybutynin and UMEC are not currently approved for use in HH, both showed a reduction in HH when compared with presently approved HH treatments. It should be noted that the anticholinergic-related side effects are not completely absent with the use of a topical over oral agent; however, it is reduced. While new topical anticholinergics seem like a promising approach to treating HH, the concern remains for possible systemic absorption (Table 2). The use of topical anticholinergic agents for HH may also be limited by local side effects of irritation, redness, and itching. Furthermore, the feel of the formulation itself may be unpleasant for the patient and limit use. For example, half of plantar HH patients using oxybutynin 10% gel reported having a “sticky”

sensation and unpleasant feeling [24]. Further studies should assess the extent of systemic absorption associated with topical anticholinergics and possibly compare the efficacy of oral anticholinergics compared with topical anticholinergics.

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Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

REFERENCES

1. Baker LB. Physiology of sweat gland function: the roles of sweating and sweat composition in human health. Temp Multidiscip Biomed J. 2019;6(3):211–59. https://doi.org/10.1080/23328940.2019.1632145.

2. Smith FCT. Hyperhidrosis. Surgery. 2013;31(5):251–5. https://doi.org/10.1016/j.mpsur.2013.03.005.

3. Walling HW, Swick BL. Treatment options for hyperhidrosis. Am J Clin Dermatol. 2011;12(5):285–95. https://doi.org/10.2165/11587870-000000000-00000.

4. Stashak AB, Brewer JD. Management of hyperhidrosis. Clin Cosmet Investig Dermatol. 2014;7:285–99. https://doi.org/10.2147/CCID.S53119.

5. Liu V, Farshchian M, Potts GA. Management of primary focal hyperhidrosis: an algorithmic approach. J Drugs Dermatol. 2021;20(5):523–8. https://doi.org/10.36849/JDD.5774.

6. Kurta AO, Glaser DA. Emerging nonsurgical treatments for hyperhidrosis. Thorac Surg Clin. 2016;26(4):395–402. https://doi.org/10.1016/j.thorsurg.2016.06.003.

7. Hebert AA, Glaser DA, Green L, et al. Long-term efficacy and safety of topical glycopyrronium tosylate for the treatment of primary axillary hyperhidrosis: post hoc pediatric subgroup analysis from a 44-week open-label extension study. Pediatr

Dermatol. 2020;37(3):490–7. https://doi.org/10.1111/pde.14135.

8. Hyun MY, Son IP, Lee Y, et al. Efficacy and safety of topical glycopyrrolate in patients with facial hyperhidrosis: a randomized, multicentre, double-blinded, placebo-controlled, split-face study. J Eur Acad Dermatol Venereol. 2015;29(2):278–82. https://doi.org/10.1111/jdv.12518.

9. Kisielnicka A, Szczerkowska-Dobosz A, Purzycka-Bohdan D, Nowicki RJ. Hyperhidrosis: disease aetiology, classification and management in the light of modern treatment modalities. Postepy Dermatol Alergol. 2022;39(2):251–7. https://doi.org/10.5114/ada.2022.115887.

10. Pariser R, Hebert A, Nast A, et al. DRM04 for the treatment of primary axillary hyperhidrosis: primary results from the ATMOS-1 and ATMOS-2 phase 3 randomized controlled trials. J Am Acad Dermatol. 2017;76(6):AB105. https://doi.org/10.1016/j.jaad.2017.04.419.

11. Pariser D, Gopalan R, Drew J, Green L. Clinical management of anticholinergic adverse events with topical glycopyrronium tosylate, a treatment for primary axillary hyperhidrosis. J Clin Aesthetic Dermatol. 2019;12(5):S19.

12. Glaser DA, Hebert AA, Nast A, et al. Topical glycopyrronium tosylate for the treatment of primary axillary hyperhidrosis: results from the ATMOS-1 and ATMOS-2 phase 3 randomized controlled trials. J Am Acad Dermatol. 2019;80(1):128-138.e2. https://doi.org/10.1016/j.jaad.2018.07.002.

13. Lain EL, Glaser DA, Gopalan R, Yan V, Drew J, Pariser DM. Long-term efficacy of glycopyrronium cloth in patients with primary axillary hyperhidrosis. J Am Acad Dermatol. 2019;81(4):AB234. https://doi.org/10.1016/j.jaad.2019.06.1049.

14. Glaser DA, Hebert A, Gopalan R, Drew J, Pariser D. Short- and long-term efficacy and safety of glycopyrronium cloth for the treatment of primary axillary hyperhidrosis. J Dermatol Nurses Assoc. 2020;12(2). https://www.embase.com/search/results?subaction=viewrecord&id=L634427626&from=export

15. Pariser DM, Lain EL, Mamelok RD, Drew J, Mould DR. Limited systemic exposure with topical glycopyrronium tosylate in primary axillary hyperhidrosis. Clin Pharmacokinet. 2021;60(5):665–76. https://doi.org/10.1007/s40262-020-00975-y.

16. Lamb YN. Topical glycopyrronium tosylate in primary axillary hyperhidrosis: a profile of its use. Clin Drug Investig. 2019;39(11):1141–7. https://doi.org/10.1007/s40261-019-00853-x.

17. Arnold MJ, O'Connor C. Glycopyrronium (qbrexza) topical wipes for hyperhidrosis. Am Fam Physician. 2019;100(6):372–3.

18. Nofal E, Salem S, Khashaba SA. Intradermal botulinum toxin a injection versus topical 2% glycopyrrolate for the treatment of primary facial hyperhidrosis: a pilot study and review of literature. Dermatol Surg. 2022;48(8):843–8. https://doi.org/10.1097/DSS.0000000000003490.

19. Abels C, Soeberdt M, Kilic A, et al. A glycopyrronium bromide 1% cream for topical treatment of primary axillary hyperhidrosis: efficacy and safety results from a phase IIIa randomized controlled trial. Br J Dermatol. 2021;185(2):315–22. https://doi.org/10.1111/bjd.19810.

20. Nguyen NV, Gralla J, Abbott J, Bruckner AL. Oxybutynin 3% gel for the treatment of primary focal hyperhidrosis in adolescents and young adults. Pediatr Dermatol. 2018;35(2):208–12. https://doi.org/10.1111/pde.13404.

21. Davila GW. Oxybutynin topical gel in the treatment of overactive bladder. Open Access J Urol. 2010;2:91–8.

22. Kontochristopoulos G, Markantoni V, Agiasofitou E, et al. Treatment of primary axillary hyperhidrosis with a cream formulation of oxybutynin chloride 10%. J Eur Acad Dermatol Venereol. 2021;35(8):e524–6. https://doi.org/10.1111/jdv.17297.

23. Baldwin CM, Keating GM. Transdermal oxybutynin. Drugs. 2009;69(3):327–37. https://doi.org/10.2165/00003495-200969030-00008.

24. Artzi O, Loizides C, Zur E, Sprecher E. Topical oxybutynin 10% gel for the treatment of primary focal hyperhidrosis: a randomized double-blind placebo-controlled split area study. Acta Derm Venereol. 2017;97(9):1120–4. https://doi.org/10.2340/00015555-2731.

25. Kirsch B, Smith S, Cohen J, et al. Efficacy and safety of topical sofpironium bromide gel for the treatment of axillary hyperhidrosis: a phase II, randomized, controlled, double-blinded trial. J Am Acad Dermatol. 2020;82(6):1321–7. https://doi.org/10.1016/j.jaad.2020.02.016.

26. Gregoriou S, Tsiogka A, Kontochristopoulos G, Offidani A, Campanati A. Sofpironium bromide: an investigational agent for the treatment of axillary hyperhidrosis. Expert Opin Investig Drugs. 2022;31(1):15–21. https://doi.org/10.1080/13543784.2022.2017880.

27. Paik J. Sofpironium bromide: first approval. Drugs. 2020;80(18):1981–6. https://doi.org/10.1007/s40265-020-01438-1.

28. Nasir A, Bissonnette R, Maari C, et al. A phase 2a randomized controlled study to evaluate the pharmacokinetic, safety, tolerability and clinical effect of topically applied umeclidinium in subjects with primary axillary hyperhidrosis. J Eur Acad Dermatol Venereol. 2018;32(1):145–51. https://doi.org/10.1111/jdv.14651.

29. Nasir A, Bissonnette R, DuBois J, Maari C, Haddad J, Yamaguchi Y. A phase 2a study to evaluate the safety, tolerability, and clinical effect of topically applied umeclidinium in subjects with primary axillary hyperhidrosis. J Am Acad Dermatol. 2017;76(6):AB20. https://doi.org/10.1016/j.jaad.2017.04.098.

30. Pene Dumitrescu T, Santos LL, Hughes SC, et al. A novel method for studying the pharmacokinetics of [(14) C]umeclidinium after application to the axilla or palm of healthy male subjects. Clin Transl Sci. 2016;9(4):183–91. https://doi.org/10.1111/cts.12406.

31. Fujimoto T, Abe Y, Igarashi M, et al. A phase III, 52-week, open-label study to evaluate the safety and efficacy of 5% sofpironium bromide (BBI-4000) gel in Japanese patients with primary axillary hyperhidrosis. J Dermatol. 2021;48(8):1149–61. https://doi.org/10.1111/1346-8138.15927.

32. Campanati A, Gregoriou S, Kontochristopoulos G, Offidani A. Oxybutynin for the treatment of primary hyperhidrosis: current state of the art. Skin Appendage Disord. 2015;1(1):6–13. https://doi.org/10.1159/000371581.

33. Fujimoto T, Okatsu H, Miyama H. Two-week prospective observational study of 5% sofpironium bromide gel in Japanese patients with primary axillary hyperhidrosis. J Dermatol. 2022;49(6):594–9. https://doi.org/10.1111/1346-8138.16384.

34. Gregoriou S, Campanati A, Rigopoulos D, Maria Offidani A, Stratigos A, Kontochristoulos G. Investigational topical anticholinergics in clinical development for the treatment of hyperhidrosis. Expert Opin Investig Drugs. 2021;30(5):479–82. https://doi.org/10.1080/13543784.2021.1900114.

35. Chabicovsky M, Winkler S, Soeberdt M, Kilic A, Masur C, Abels C. Pharmacology, toxicology and clinical safety of glycopyrrolate. Toxicol Appl Pharmacol. 2019;370:154–69. https://doi.org/10.1016/j.taap.2019.03.016.

36. Pariser DM, Lain EL, Mamelok R, Aurora B, Mould DR. 26301 Pharmacokinetic analyses show limited systemic exposure with topical glycopyrronium tosylate. J Am Acad Dermatol. 2021;85(3):AB96. https://doi.org/10.1016/j.jaad.2021.06.405.

37. Nawrocki S, Cha J. The etiology, diagnosis, and management of hyperhidrosis: a comprehensive review: therapeutic options. J Am Acad Dermatol. 2019;81(3):669–80. https://doi.org/10.1016/j.jaad.2018.11.066.

38. Grabell DA, Hebert AA. Current and emerging medical therapies for primary hyperhidrosis. Dermatol Ther. 2016;7(1):25–36. https://doi.org/10.1007/s13555-016-0148-z.

39. Nasser S, Farshchian M, Kimyai-Asadi A, Potts GA. Techniques to relieve pain associated with botulinum injections for palmar and plantar hyperhidrosis. Dermatol Surg. 2021;47(12):1566–71. https://doi.org/10.1097/DSS.0000000000003182.

40. Reisfeld R, Berliner KI. Evidence-based review of the nonsurgical management of hyperhidrosis. Thorac Surg Clin. 2008;18(2):157–66. https://doi.org/10.1016/j.thorsurg.2008.01.004.