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Drug Class Review: Drugs for Hyperhidrosis

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Purpose for Class Review:
To evaluate evidence of efficacy and safety for drugs for hyperhidrosis and develop criteria to support medically appropriate and necessary use of drugs to treat hyperhidrosis. Hyperhidrosis is currently an unfunded condition on the Prioritized List of Health Services.

Plain Language Summary:
- Hyperhidrosis is defined as excessive sweating that makes it difficult to do daily tasks. When hyperhidrosis is caused by another condition such as alcohol use or heart failure, treatment of the underlying condition is recommended. If the cause of hyperhidrosis is unknown, then medicines are available to decrease symptoms.
- The Food and Drug Administration has approved 3 medicines to treat excessive underarm sweating. These medicines are sofpironium, glycopyrronium, and onabotulinumtoxinA. Short-term studies (over 4-16 weeks) show that these medicines can decrease underarm sweating compared to placebo. There are no published studies to determine if any of these medicines decrease sweating more than another or the safety of these medicines.
- We recommend that the Oregon Health Plan only pay for these medicines when providers document severe symptoms and have consulted a dermatologist.

Research Questions:
1. What is the comparative efficacy of drugs (aluminum, sofpironium, glycopyrronium, and botulinum toxins) for treatment of hyperhidrosis?
2. What is the comparative safety of drugs for hyperhidrosis?
3. Are there any subgroups (based on age, gender, race or ethnicity, disease severity, or concomitant treatments) that would benefit or be harmed from topical therapies for hyperhidrosis?

Conclusions:
- There is no direct comparative evidence evaluating efficacy or safety of drugs to treat hyperhidrosis.
- Compared to placebo, sofpironium, glycopyrronium and onabotulinumtoxinA can improve sweating in people with primary focal axillary hyperhidrosis and severe sweating that interferes with daily activities. Topical anticholinergics (sofpironium and glycopyrronium) are applied topically each day, and onabotulinumtoxinA is injected at 10-15 sites in the axilla. In clinical trials, one injection improved sweating over a median of 7 months following botulinum toxin injection before retreatment was needed.[1]
- Response to treatment was evaluated using various criteria including 2-point improvement on the Hyperhidrosis Disease Severity Scale (HDSS) or Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax) scales, 4-point improvement on the Axillary Sweating Daily Diary (ASDD) score, or 50% decrease in sweat production. These thresholds generally represent minimum clinically significant improvements in symptoms.[2-4] Compared to placebo, response to treatment was more common in people who received drug therapy for:

    - sofpironium (17% to 18% difference from placebo; NNT 6; 3 RCTs; low-quality evidence),[5-7]
    - glycopyrronium (25% to 39% difference from placebo; NNT of 3 or 4; 3 RCTs; moderate-quality evidence),[8,9] and
    - onabotulinumtoxinA (49% or 55% difference from placebo; NNT 2 or 3; 2 RCTs; moderate-quality evidence).[1,10]
- Topical anticholinergics (sofpironium and glycopyrronium) are associated with dermatologic reactions (e.g., dermatitis, pruritus, erythema, application site pain) and systemic anticholinergic side effects (e.g., blurred vision, dry mouth).[11,12] Like other anticholinergic drugs, they are contraindicated in people with comorbid conditions that may be worsened by anticholinergic effects (e.g., ulcerative colitis, myasthenia gravis, Sjögren's syndrome, glaucoma, urinary retention).[11,12]
- The most common adverse events associated with onabotulinumtoxinA during trials of axillary hyperhidrosis included injection site pain or bleeding and compensatory, non-axillary sweating.[13]
- There is insufficient evidence to evaluate efficacy in subgroups of people. These therapies have primarily been studied as monotherapy in people with severe axillary hyperhidrosis (HDSS of 3 or 4).
- There are no studies evaluating sofpironium or glycopyrronium for non-axillary hyperhidrosis, and insufficient evidence evaluating onabotulinumtoxinA for non-axillary hyperhidrosis. Studies in non-axillary hyperhidrosis are generally limited by small populations, high risk of bias, and lack of methodological reporting.[14,15] OnabotulinumtoxinA is not FDA-approved for non-axillary hyperhidrosis and includes warnings for serious adverse reactions associated with unapproved uses.[13]

Recommendations:

- Implement prior authorization criteria for topical anticholinergics and onabotulinumtoxinA to limit use to people with:
    - Diagnosis of primary axillary hyperhidrosis
    - Severe symptoms that interfere with daily activities
    - When prescribed by, or in consultation with, a dermatologist
    - When symptoms have failed to respond to non-pharmacologic lifestyle management
- Recommend onabotulinumtoxinA as a preferred option for treatment of hyperhidrosis based on large treatment effect size and relatively long duration of effect. Make topical anticholinergics non-preferred.

Background:

Hyperhidrosis is a condition that causes excessive sweating that can be classified as primary (no known cause) or secondary (caused by an underlying condition or medication). Most (90%) of hyperhidrosis is classified as primary, and about half of people have axillary hyperhidrosis.[16] Hyperhidrosis most commonly affects the underarm (axillary), head (craniofacial), hands (palmar), or feet (plantar). Hyperhidrosis is estimated to affect 1% to 4.8% of people in the United States.[16,17] Excessive sweating can be secondary to a multitude of other conditions including substance use disorders, chronic pulmonary disease, congestive heart failure, endocrine or metabolic disorders (e.g., diabetes, hyperthyroidism), anxiety disorders, neurologic conditions, menopause, pregnancy, malignancy, and medications (e.g., opioids, antidepressants).[16] Diagnosis of primary focal hyperhidrosis is based on presence of excessive sweating for at least 6 months without identification of an underlying medical cause plus at least 2 of the following characteristics: bilateral presentation, impairment of activities of daily living, symptom frequency more than once per week, age of onset less than 25 years old, positive family history, or excessive sweating that does not occur during sleep.[16]

Symptom severity can be defined by the hyperhidrosis disease severity scale (HDSS; range 1-4) where a score of 3-4 points represents severe disease with frequent impacts on quality of life (**Table 1**). Other symptom severity assessments used in clinical trials include the HDSM-Ax score and the ASDD sweating

severity score. Complications of severe hyperhidrosis can include reduced quality of life, interference with participation in social activities (such as sports or employment), and maceration of the skin leading to secondary skin infections.[16]

Table 1. Common Disease Severity Measures for Hyperhidrosis

Symptom scale	Description	MCID
Hyperhidrosis disease severity scale (HDSS)	1 - sweating is never noticeable and never interferes with daily activities 2 - sweating is tolerable, but sometimes interferes with daily activities 3 - sweating is barely tolerable and frequently interferes with daily activities 4 - sweating is intolerable and always interferes with daily activities	1 point change = 50% reduction in sweat production[4] 2 point change = 80% reduction in sweat production[4]
Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax)	Scale includes 7 or 11 questing assessing disease severity (depending on the version of the scale). Each question is assessed on a 5-point scale with 0 representing no symptoms and 4 representing worse symptoms. Total score is reported as an average of all questions from 0 (no sweating) to 4 (worst possible sweating).	1 point average change[2]
Axillary Sweating Daily Diary (ASDD)[3]	Evaluates sweating in the past 24 hours with a variety of questions including a 0 to 10 point assessment of sweating severity. An average 3.8 point change in severity for this item corresponds to a score of moderately better on the 1-7 point patient global impression of change since starting treatment (1 – much better; 2 – moderately better; 3 – a little better; 4 – no difference; 5 – a little worse; 6 – moderately worse; 7 – much worse).	4-point change[3]
Dermatology Life Quality Index (DLQI)	Scale includes 10 questions that assesses symptoms, feelings, daily activities, leisure, work, school, personal relationships, and treatment over the past week. Score ranges from 0 to 30. For inflammatory skin conditions, the Health Evidence Review Commission defines severe symptoms related to functional impairment as scores greater than or equal to 11.	3 to 5 point change depending on the condition and validation method[18]

General recommendations for management of hyperhidrosis include avoidance of triggers and clothing that increases sweating. Triggering events can include spicy foods, alcohol, stressful situations, emotional triggers, and use of antiperspirant spray (rather than deodorant).[16] Wearing loose-fitting clothes, non-occlusive shoes, and dress shields to absorb sweat can also help decrease impact of sweating on daily activities.[16]

Table 2 provides a summary of available drugs for hyperhidrosis. Topical aluminum chloride is included in prescription antiperspirants and is generally recommended as a first-line treatment option for axillary hyperhidrosis.[4,16] Other topical treatments include anticholinergic drugs (sofpironium or glycopyrronium). Botulinum toxin is recommended for more severe axillary symptoms or when topical drugs have not improved axillary hyperhidrosis.[13] There is some evidence for off-label use of botulinum toxin as second-line therapy for palmar or craniofacial hyperhidrosis.[19] However, labeling for botulinum toxins also includes warnings for serious adverse reactions with unapproved use.[13] Weakness of hand muscles and blepharoptosis have been reported in people who receive onabotulinumtoxinA for palmar or facial hyperhidrosis.[13] Off-label oral anticholinergic drugs have evidence for use, but are associated with significant adverse effects and are typically reserved for refractory cases.[16] Non-pharmacologic treatments (such as iontophoresis, microwave thermolysis, and surgery) are also options for patients with refractory symptoms, though evidence is limited by small studies with high risk of bias.[14,15]

Additional information for these drugs is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions.

Table 2. Indications and Dosing of Available Medication Therapy

Generic Name (Brand)	Indication(s)	Strength/Route	Dose and Frequency
Aluminum chloride (DRYSOL, XERAC AC)[20]	Hyperhidrosis	6.25%; 20% topical solution	Apply once daily before bedtime. Leave on the skin for 6-8 hours before washing off.
Glycopyrronium (QBREZXA)[12]	Primary axillary hyperhidrosis in patients 9 years of age and older	2.4% topical cloth	Apply one cloth under both arms once daily.
Sofpironium (SOFDRA)[11]	Primary axillary hyperhidrosis in patients 9 years of age and older	12.45% topical gel	Apply 1 pump underarm once daily at bedtime.
OnabotulinumtoxinA (BOTOX)[13]	Primary axillary hyperhidrosis with severe symptoms inadequately controlled with topical agents in people 18 years of age and older	100, 200 units intradermal injection	Inject a total of 50 units per axilla, distributed into 10-15 sites about 1-2 cm apart. Repeat injections as needed based on symptom recurrence; do not exceed more than 400 units in a 3-month interval.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Canada's Drug Agency (CDA-AMA), Scottish Intercollegiate Guidelines Network (SIGN), and Oregon Mental Health Clinical Advisory Group (MHCAG) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:

A systematic review with high methodologic quality evaluated the efficacy and safety of treatments for primary hyperhidrosis.[14,15] The original publication identified 32 RCTs, 17 non-randomized studies and one case series which were published through July 2016.[15] Most studies were small (<50 participants), had high risk of bias, and poor methodological reporting. Interventions included botulinum toxins (23 studies), anticholinergics (5 studies), iontophoresis (10 studies), curettage (9 studies), and other technologies that damage the sweat gland (3 studies).[15] A updated literature search through 2020 identified an additional 29 studies (10 RCTs, 13 investigational studies, 3 cohort studies, and 3 systematic reviews).[14] However, this new evidence had similar limitations including high risk of bias, small study size, and poor methodological reporting.[14] Most studies were compared to placebo or did not have an active comparator group.[14,15] With the exception of botulinum toxin for axillary hyperhidrosis, authors concluded that evidence for most interventions was of low or very low quality.[14,15] There was insufficient evidence to draw firm conclusions about the relative effectiveness and safety of most interventions for primary hyperhidrosis.[14,15] There was moderate-quality evidence that botulinum toxin injections improve symptoms of axillary hyperhidrosis in the short term (over 16 weeks) compared to placebo.[14,15] Effect sizes generally represented clinically meaningful improvements compared to placebo for HDSS improvement of at least 2 points (relative risk [RR]: 3.30, 95% confidence interval [CI]: 2.46 to 8.32; $p<0.001$, $I^2=0\%$), gravimetric sweat reduction (RR 2.87, 95% CI: 1.94 to 4.26; $p<0.001$, $I^2=48\%$), and quality of life improvements (mean difference [MD]: -4.80, 95% CI: -5.67 to -3.94; $p<0.001$, $I^2=3\%$).[15] The most common adverse events were injection site pain and

compensatory sweating.[15] One small study (n=24) compared onabotulinumtoxinA (50 units per axilla) to rimabotulinumtoxinB (1500 units/axilla) in patients with axillary hyperhidrosis with no differences in efficacy assessments between therapies.[14] While studies of topical and oral anticholinergics did demonstrate improvements in symptoms of hyperhidrosis, evidence was mixed and limited by small study sizes and high risk of bias. Oral anticholinergics improved symptoms of hyperhidrosis in the short-term (low-quality evidence) but were associated with significant rates of adverse events including dry mouth.[14,15]

A second systematic review with adequate methodologic quality evaluated effects of botulinum toxin on primary and secondary hyperhidrosis.[21] The review included RCTs published through August 2020 and included many of the same studies outlined in the systematic review above.[21] Of the 8 studies (n=937) that met inclusion criteria, 6 evaluated axillary hyperhidrosis, one evaluated craniofacial hyperhidrosis, and one evaluated lower-limb hyperhidrosis secondary to amputation.[21] Six studies evaluated primary hyperhidrosis and 2 evaluated secondary hyperhidrosis. Compared to placebo, there was moderate-quality evidence that botulinum toxin improved gravimetric sweat reduction of at least 50% from baseline (risk difference [RD] 0.63, 95% CI 0.51 to 0.77; I^2 = 75%, 7 RCTs), HDSS improvement of at least 2 points (RD: 0.56, 95% CI 0.42 to 0.69; I^2 = 56%, 4 RCTs), and Dermatologic Life Quality Index (MD -5.55, 95% CI -7.11 to - 3.98; I^2 = 70%, 4 RCTs) over 2 to 8 weeks compared to placebo.[21] Trials were limited by lack of reported methodology and evidence for efficacy outcomes were graded as moderate quality.[21] Differences among subgroups based on type of botulinum toxin, cause of hyperhidrosis (e.g., primary vs. secondary), or location (e.g., axillary vs. craniofacial) were not evaluated.

After review, 6 systematic reviews were excluded due to poor quality (e.g., network meta-analyses), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).

Guidelines:

High Quality Guidelines:

No recent high-quality guidelines were identified. Guidelines from the American Academy of Neurology were most recently updated in 2008 and have since been retired.[19]

After review, 2 guidelines were excluded based on methodologic quality.[4,19]

Randomized Controlled Trials:

A total of 203 citations were manually reviewed from the initial literature search. After further review, all citations met exclusion criteria because of wrong study design (e.g., observational), comparator (e.g., no control or non-pharmacologic comparator), or outcome studied (e.g., non-clinical). Because recent high quality systematic reviews and guidelines are limited, the 8 phase 3 trials for available drug treatments are summarized in **Table 3** below. Full abstracts are included in **Appendix 3**.

Table 3. Description of Randomized Phase 3 Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Yokozeki, et al. 2021.[7]	1. Sofpironium 5% gel once daily	Inclusion criteria: - Primary axillary hyperhidrosis - Age ≥ 12 years - HDSS of 3-4	HDSS of 1 or 2 and 50% reduction in total	Primary Outcome: HDSS of 1 or 2 and 50% reduction in sweat production 1. 53.9%	Treatment allocation was conducted using minimization method (methodology is not completely random and is

DB, MC, PC, phase 3 RCT Duration: 6 weeks Japan	2. Placebo-vehicle N=281	- HDSM-Ax ≥2 - Gravimetric weight of sweat ≥ 50 mg - Symptoms for ≥ 6 months - ≥ 2 of the following: ○ Onset at <25 years of age ○ Bilateral symmetrical sweating ○ No sweating during sleep ○ ≥ 1 heavy sweating episode/week ○ Family history of axillary hyperhidrosis ○ Excessive sweating interfering with daily activities <u>Key exclusion criteria:</u> - Secondary hyperhidrosis - Sweating worsened by menopause	gravimetric weight of sweat at 6 weeks	2. 36.4% Difference 17.5% (95% CI 6.02 to 28.93%) <u>Secondary Outcomes:</u> Change in HDSM-Ax from baseline to 6 weeks 1. -1.41 (SD 1.008) 2. -0.93 (SD 0.902) MD -0.48 (95% CI -0.704 to -0.253) Change in DLQI score from baseline to 6 weeks 1. –6.8 (SD 4.94) 2. –4.5 (SD 4.54) MD -2.2 (95% CI -3.36 to -1.13)	intended to balance baseline disease severity characteristics between groups). Potential for unblinding due to application site adverse effects (e.g., dermatitis, erythema, pruritus) which were more frequent with treatment compared to placebo (23.1% vs. 5%). Adverse events were generally mild and did not result in treatment discontinuation. Attrition low and similar between groups. Analysis using ITT population. FDA-approved dose is 15% (or 12.25% base) and this study evaluated a lower dose.
CARDIGAN 2 NCT03948646 [6,11] DB, MC, PC, phase 3 RCT Duration: 11-15 weeks United States	1. Sofpironium 15% gel (n=160) 2. Placebo-vehicle (n=157)	<u>Inclusion criteria:</u> - Primary axillary hyperhidrosis - Age ≥ 9 years - HDSM-Ax 3-4 - Gravimetric weight of sweat ≥ 50 mg in each axilla & combined ≥ 150 mg - Symptoms for ≥ 6 months - ≥ 2 of the following: ○ Onset at <25 years of age ○ Bilateral symmetrical sweating ○ No sweating during sleep ○ ≥ 1 heavy sweating episode/week ○ Family history of axillary hyperhidrosis ○ Excessive sweating interfering with daily activities	Change ≥ 2 points in HDSM-Ax-7 at 6 weeks	<u>Primary Outcome:</u> 1. 108 (64%) 2. 75 (48%) Difference 17% (95% CI 6% to 27%)	Unpublished study and risk of bias cannot be fully assessed. Adverse events occurred in 44% of treated patients compared to 5% of patients in the placebo group. Most common adverse events included: - Blurred vision (11.7% vs. 0.6%), - Dry mouth (17.2% vs. 1.2%) - Application site pain (10% vs. 1.2%) - Erythema (7.8% vs. 0%)

		Key exclusion criteria: - Secondary hyperhidrosis - Use of other anticholinergic or cholinergic drugs - Other chronic conditions that may worsen sweat production with anticholinergics (e.g., diabetes, thyroid disease, renal/hepatic impairment, BPH, neurologic or psychiatric conditions, intestinal mobility disease, myasthenia gravis, Sjögren's syndrome)			
CARDIGAN 1 NCT03836287 [5,11] DB, MC, PC phase 3 RCT Duration: 11-15 weeks United States	1. Sofpironium 15% gel (n=173) 2. Placebo-vehicle (n=177)	Inclusion criteria: - Primary axillary hyperhidrosis - Age ≥ 9 years - HDSM-Ax 3-4 - Gravimetric weight of sweat ≥ 50 mg in each axilla & combined ≥ 150 mg - Symptoms for ≥ 6 months Key exclusion criteria: - Secondary hyperhidrosis - Use of other anticholinergic or cholinergic drugs - Other chronic conditions that may worsen sweat production with anticholinergics (e.g., diabetes, thyroid disease, renal/hepatic impairment, benign prostatic hyperplasia, neurologic or psychiatric conditions, intestinal mobility disease, myasthenia gravis, Sjögren's syndrome)	Change ≥ 2 points in HDSM-Ax-7 at 6 weeks	Primary Outcome: 1. 84 (49%) 2. 54 (29%) Difference 18% (95% CI 8% to 29%)	Unpublished study and risk of bias cannot be fully assessed. Attrition was higher in treatment group (13.3% vs. 8.5%). Adverse events were more common with treatment than placebo (33% vs. 3%). Most common adverse events included: - Dry mouth (11.6% vs. 0%) - Mydriasis (7.5% vs. 0%) - Application site pain (6.4% vs. 0.6%) - Pruritus (6.4% vs. 0.6%) - Dermatitis (5.8% vs. 0.6%) - Erythema (5.2% vs. 0.6%) - Blurred vision (5.2% vs. 0.6%)
Glaser, et al. 2018.[8]	1. Glycopyrronium tosylate 3.75%	Inclusion criteria: - Primary axillary hyperhidrosis - Age ≥ 9 years	Change ≥ 4 points in sweating	Primary outcomes ASDD ≥ 4 point change in sweating severity	Randomized via IVRS but patients in treatment group had more severe HDSS scores (42%

ATMOS-1/ NCT02530281 DB, MC, PC, phase 3, RCT Duration: 4 weeks United States & Germany	(2.4% base) cloth (n=229) 2. Vehicle-placebo (n=115)	- ASDD sweating severity score ≥ 4 - HDSS of 3-4 - Gravimetric weight of sweat ≥ 50 mg in each axilla - Symptoms for ≥ 6 months <u>Key exclusion criteria:</u> - Secondary hyperhidrosis - Other treatments for hyperhidrosis or anticholinergic drugs (e.g., prior surgery, botulinum toxin within 1 year, iontophoresis within 4 weeks).	severity on the ASDD (a 10-point scale) at 4 weeks. Change in gravimetric sweat production at 4 weeks	1. 52.8% 2. 28.3% p<0.001 Sweat production change from baseline over 5 minutes 1. -102 mg (SD 176.1) 2. -100.3 mg (SD 172.3) p=0.065 <u>Secondary outcomes</u> HDSS ≥ 2 point improvement 1. 56.5% 2. 23.7% P<0.001	vs. 27% with grade 4 symptoms) and greater sweat production at baseline (183 vs. 170 mg/5 min) compared to vehicle. Blinded with matched vehicle. Analysis performed in ITT population with multiple imputation for missing data. In a pooled analysis of ATMOS-1 and ATMOS-2, adverse events which were more common with treatment included dry mouth (24.2% vs. 5.6%) and mydriasis (6.8% vs. 0%).
Glaser, et al. 2018.[8] ATMOS-2/ NCT02530294 DB, MC, phase 3, RCT Duration: 4 weeks United States	1. Glycopyrronium tosylate 3.75% (2.4% base) cloth (n=234) 2. Vehicle-placebo (n=119)	<u>Inclusion criteria:</u> - Primary axillary hyperhidrosis - Age ≥ 9 years - ASDD sweating severity score ≥ 4 - HDSS of 3-4 - Gravimetric weight of sweat ≥ 50 mg in each axilla - Symptoms for ≥ 6 months <u>Key exclusion criteria:</u> - Secondary hyperhidrosis - Other treatments for hyperhidrosis or anticholinergic drugs (e.g., prior surgery, botulinum toxin within 1 year, iontophoresis within 4 weeks).	Change ≥ 4 points in sweating severity on the ASDD (a 10 point scale) at 4 weeks. Improvement in gravimetric sweat production at 4 weeks	<u>Primary outcomes</u> ASDD ≥ 4 point change in sweating severity 1. 66.1% 2. 26.9% p<0.001 Sweat production change from baseline over 5 minutes 1. -81.2 mg (SD 66.7) 2. -115.4 mg (SD 66.5) P<0.001 <u>Secondary outcomes</u> HDSS ≥ 2 point improvement 1. 61.6% 2. 27.8% p<0.001	Randomized via IVRS but patients in placebo group had greater sweat production at baseline (181 mg/5 min) compared to treatment (162 mg/5 min). Blinded with matched vehicle. Analysis performed in ITT population with multiple imputation for missing data. In a pooled analysis of ATMOS-1 and ATMOS-2, adverse events which were more common with treatment included dry mouth (24.2% vs. 5.6%) and mydriasis (6.8% vs. 0%).
Yokozeki, et al. 2021.[9]	1. Glycopyrronium tosylate 3.75% (2.4% base) cloth (n=163)	<u>Inclusion criteria:</u> - Primary axillary hyperhidrosis - Age ≥ 9 years - HDSS of 3-4	Change ≥ 2 points in HDSS and ≥50%	HDSS ≥ 2 point change and ≥50% sweat reduction at 4 weeks 1. 83 (51.6%)	Randomized via IVRS with baseline characteristics similar between groups. Method of blinding was not reported.

DB, MC, PC, phase 2/3, RCT Duration: 4 weeks Japan	2. Glycopyrronium tosylate 2.5% cloth (1.6% base) (n=168) 3. Vehicle-placebo (n=166)	- Gravimetric weight of sweat ≥ 50 mg in each axilla - Symptoms for ≥ 6 months <u>Key exclusion criteria:</u> - Use of other anticholinergics, cholinergics, antiperspirants, or clonidine - Other treatments for hyperhidrosis (e.g., prior surgery, botulinum toxin within 1 year, iontophoresis within 4 weeks).	reduction in sweat production from baseline at week 4	2. 69 (41.1%) 3. 27 (16.4%) 1 vs. 3: 35.2% (95% CI 24.8 to 45.1%); p<0.001 2 vs. 3: 24.7% (95% CI 14.0 to 34.8%); p<0.001	Formulation studied in Japan is not the formulation approved by the FDA (e.g., different excipients and ethanol content). Overall rate of AEs was similar between groups and were generally categorized as mild. Events which were more common with treatment included blurred vision/mydriasis (11.2% vs. 7.7% vs. 3.6%) and urinary retention/ dysuria (8.7% vs. 4.8% vs. 5.5%) for glycopyrronium tosylate 3.75%, 2.5% and vehicle groups, respectively.
Naumann, M, et al. 2001.[10] MC, DB, PC, RCT Duration: 16 weeks Belgium, Germany, Switzerland, & the United Kingdom	1. OnabotulinumtoxinA 50 units per axilla (n=242) 2. Placebo (n=78) Administered by 10-15 intradermal injections at randomization.	<u>Inclusion criteria</u> - Primary axillary hyperhidrosis - Interference with daily activity - Age 18-75 years - Gravimetric weight of sweat ≥ 50 mg in each axilla	Change of ≥ 50% in sweat production at 4 weeks	Primary outcome: Sweat reduction of ≥ 50% at 4 weeks 1. 227 (94%) 2. 28 (36%) P<0.001 Sweat reduction ≥ 50% at 16 weeks 1. 198 (82%) 2. 16 (21%) P<0.001	Method of randomization and blinding was not reported increasing risk for selection, performance, and detection bias. Adverse events were generally similar between groups. Increases in non-axillary sweating occurred in 5% of patients (n=11) who received onabotulinumtoxinA compared to 0% in placebo.
Lowe, 2007.[1,13] PC, MC, DB, RCT	1. OnabotulinumtoxinA 75 units per axilla (n=110) 2. OnabotulinumtoxinA 50 units	<u>Inclusion criteria</u> - Primary axillary hyperhidrosis - HDSS of 3-4 - Age ≥ 18 year - Gravimetric weight of sweat ≥ 50 mg in each axilla	Change in HDSS ≥ 2 points at 4 weeks after 2nd dose or did not	Primary outcome: HDSS ≥ 2 point change[13] 1. 54 (49%) 2. 57 (55%) 3. 6 (6%)	Method of randomization and blinding was not reported increasing risk for selection, performance, and detection bias.

Duration: 52 weeks Canada & the United States	per axilla (n=104) 3. Placebo (n=108) Administered by 10-15 intradermal injections at randomization. Patients were re-treated no sooner than 8 weeks if they requalified for disease severity inclusion criteria.	<u>Exclusion criteria:</u> - Secondary hyperhidrosis - Medical conditions that might interfere with botulinum toxin treatment	need re-treatment during the study	1 vs. 3: 43% (95% CI 33.2 to 53.8) 2 vs. 3: 49% (95% CI 38.8 to 59.7)	Overall, 78% of people completed the study, with differential attrition between groups (13% in 75 units, 20% in 50 units, and 32% in placebo). Median duration of effect was 205 days (~7 months) following the first injection. Adverse effects which were more common than placebo included injection site pain, injection site bleeding, and non-axillary sweating.

Abbreviations: AE = adverse events; ASDD = Axillary Sweating Daily Diary; CI = confidence interval; DB = double-blind; DLQI = dermatologic quality of life index; FDA = Food and Drug Administration; HDSS = Hyperhidrosis Disease Severity Scale; HDSM-Ax = Hyperhidrosis Disease Severity Measure-Axillary; ITT = intention to treat; IVRS = interactive voice response system; MC = multicenter; MD = mean difference; mg = milligrams; PC = placebo controlled; RCT = randomized controlled trial; SD = standard deviation

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Appendix 1: Specific Drug Information

Table A1. Clinical Pharmacology and Pharmacokinetics.

Drug Name	Mechanism of Action	Absorption	Metabolism/Excretion	Pharmacokinetics
Aluminum chloride[20]	Antiperspirant	Applied topically; absorption not reported	Not reported	• Not reported
Glycopyrronium[12]	Anticholinergic	Applied topically; no accumulation after topical application for 5 days	Metabolism not characterized	Adults: • Half-life: not reported • C_{max}: mean 0.08 ng/mL (SD 0.04) • AUC $_{0\text{-}24H}$: mean 0.88 h*ng/mL (SD 0.57) • T_{max}: median 1 h
OnabotulinumtoxinA[13]	Acetylcholine release inhibitor and a neuromuscular blocking agent	Not detectible in peripheral blood following intramuscular injection at the recommended doses.	NA	NA
Sofpironium[11]	Anticholinergic	Applied topically; no accumulation after topical application for 21 days	Metabolized by non-enzymatic hydrolysis, CYP2D6 and CYP3A4 mediated-oxidative metabolism, and glycine conjugation.	Adults: • Half-life: not reported • C_{max}: mean 2.71 ng/mL (SD 6.94) • AUC: mean 0.45.1 h*ng/mL (SD 85.1) • T_{max}: mean 5.34 h (SD 5.45)

Abbreviations: AUC = area under the curve; C_{max} = maximum concentration; h = hours; mL = milliliters; NA = not applicable; ng = nanogram; SD = standard deviation; T_{max} = time to maximum concentration

Use in Specific Populations:

- Aluminum chloride: No data available.
- Glycopyrronium has not been studied in people with renal impairment, hepatic impairment, during pregnancy, lactation, or in people over 65 years of age. Elimination of glycopyrronium after IV administration is severely impaired in people with renal failure.
- Sofpironium has not been studied in people with renal impairment, hepatic impairment, during pregnancy, lactation, or in people over 65 years of age. Animal studies indicate sofpironium may be excreted in milk.
- OnabotulinumtoxinA: Safety and efficacy have not been established for hyperhidrosis related to body areas other than axillary. Weakness of hand muscles and blepharoptosis may occur in people who receive onabotulinumtoxin for palmar or facial hyperhidrosis. Evaluate potential causes of secondary hyperhidrosis to avoid symptomatic treatment of hyperhidrosis without treatment of the underlying condition. OnabotulinumtoxinA has not been studied during pregnancy or lactation; animal data indicate risk for adverse effects on fetal growth. OnabotulinumtoxinA has not been studied in pediatric patients with hyperhidrosis.

Drug Safety:

Boxed Warnings:

- Aluminum chloride, glycopyrronium, sofpironium: None
- OnabotulinumtoxinA: Distant spread of toxin effect. Symptoms have been reported hours to weeks after injection and may include life-threatening swallowing and breathing difficulties.

Risk Evaluation Mitigation Strategy Programs: None

Contraindications:

- Aluminum chloride: None
- Glycopyrronium: Conditions exacerbated by anticholinergic side effects (e.g., glaucoma, paralytic ileus, unstable cardiovascular status in acute hemorrhage, ulcerative colitis [severe or complicated by toxic megacolon], myasthenia gravis, Sjögren's syndrome)
- Sofpironium: Conditions exacerbated by anticholinergic side effects (e.g., glaucoma, paralytic ileus, unstable cardiovascular status in acute hemorrhage, ulcerative colitis [severe or complicated by toxic megacolon], myasthenia gravis, Sjögren's syndrome)
- OnabotulinumtoxinA: infection at the proposed injection site; hypersensitivity to botulinum toxin

Table A2. Summary of Warnings and Precautions.

Warning/Precaution	Aluminum chloride[20]	Glycopyrronium[12]	Sofpironium[11]	OnabotulinumtoxinA[13]
Urinary retention		X	X	
Control of body temperature		X	X	
Operating machinery (blurred vision)		X	X	
Risk of accidental exposure. Discard cloth appropriately.		X		
Skin irritation	X			
Spread of toxin effects; swallowing and breathing difficulties may occur				X
Caution in patients with compromised respiratory function. Dysphagia and Breathing difficulties have occurred.				X
Serious adverse reactions with unapproved use				X
Concomitant neuromuscular disorders may worsen adverse effects (e.g., myasthenia gravis, Lambert-Eaton syndrome, amytrophil lateral sclerosis, peripheral motor neuropathic diseases)				X
Hypersensitivity reactions (e.g., anaphylaxis, serum sickness, urticaria, soft tissue edema, dyspnea)				X
Hyman albumin and transmission of viral diseases.				X

Appendix 2: Medline Search Strategy

Ovid MEDLINE(R) ALL 1946 to January 21, 2025

1	exp Hyperhidrosis/	4247
2	exp Botulinum Toxins/	19625
3	exp Glycopyrrolate/	1277
4	sofpironium.mp.	18
5	glycopyrronium.mp.	637
6	exp Aluminum Compounds/	38036
7	exp Cholinergic Antagonists/	87606
8	2 or 3 or 4 or 5 or 6 or 7	144894
9	1 and 8	919
10	limit 9 to (english language and humans)	790
11	limit 10 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	203

Appendix 3: Abstracts of Randomized Controlled Trials.

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.e122.

BACKGROUND: Glycopyrronium tosylate (GT) is a topical anticholinergic developed for once-daily treatment of primary axillary hyperhidrosis.

OBJECTIVE: Assess the efficacy and safety of GT for primary axillary hyperhidrosis.

METHODS: ATMOS-1 and ATMOS-2 were replicate randomized, double-blind, vehicle-controlled, 4-week phase 3 trials. Patients were randomized 2:1 to GT 3.75% or vehicle applied once daily to each axilla for 4 weeks. Coprimary endpoints were responder rate (>=4-point improvement from baseline) on item 2 (severity of sweating) of the Axillary Sweating Daily Diary (ASDD), which is a newly developed patient-reported outcome measure, and absolute change from baseline in axillary gravimetric sweat production at week 4. Safety evaluation included treatment-emergent adverse events.

RESULTS: Pooled data, which are consistent with the individual trial results, show that significantly more GT-treated patients achieved an ASDD-Item 2 response than did those treated with vehicle (59.5% vs 27.6%), and they had reduced sweat production from baseline (-107.6 mg/5 min vs -92.1 mg/5 min) at week 4 ($P < .001$ for both coprimary end points). Most treatment-emergent adverse events were mild or moderate and infrequently led to discontinuation.,

LIMITATIONS: Short trial duration and inherent challenges in gravimetrically assessing sweat production.

CONCLUSIONS: GT applied topically on a daily basis over 4 weeks reduced the severity of sweating as measured by ASDD-Item 2, reduced sweat production as measured gravimetrically, and was generally well tolerated in patients with primary axillary hyperhidrosis.

Yokozeki H, Fujimoto T, Wanatabe S, Ogawa S, Fujii C. Topical glycopyrronium tosylate in Japanese patients with primary axillary hyperhidrosis: A randomized, double-blind, vehicle-controlled study. *The Journal of dermatology.* 2022;49(1):86-94.

Glycopyrronium tosylate cloth, an anticholinergic drug, has been approved for the topical treatment of primary axillary hyperhidrosis in the USA, but its effects in Japanese patients have not been previously investigated. This 4-week, randomized, double-blind, vehicle-controlled, multicenter study was conducted to evaluate the efficacy and safety of glycopyrronium tosylate cloth for primary axillary hyperhidrosis patients in Japan. Eligible patients, who were >=9 years of age and had primary axillary hyperhidrosis >=6 months, with gravimetrically-measured sweat production >=50 mg/5 min, and Hyperhidrosis Disease Severity Scale >=3 (moderate) were randomized 1:1:1 to once daily topical glycopyrronium tosylate 3.75%, 2.5%, or vehicle. Overall, 497 patients (163 in the glycopyrronium tosylate 3.75% group, 168 in the glycopyrronium tosylate 2.5% group, and 166 in the vehicle group, hereinafter in this order) were randomized. Statistically higher proportions of patients in the glycopyrronium tosylate groups achieved >=2-point improvement in Hyperhidrosis Disease Severity Scale and >=50% reduction in sweat production from baseline versus vehicle at week 4 (51.6%, 41.1%, and 16.4%, respectively; $p < 0.001$ in both cases). Higher responder rates in the glycopyrronium tosylate groups compared with the vehicle group occurred as early as week 1. The most common treatment-emergent adverse events in patients treated with glycopyrronium tosylate were photophobia, mydriasis, thirst, and dysuria. Most treatment-emergent adverse events were mild as determined by the investigators. The incidence of treatment-emergent adverse events leading to treatment modification was low in the three groups. The 4-week use of topical glycopyrronium tosylate improved the patient-reported outcome measure Hyperhidrosis Disease Severity Scale and objectively-evaluated sweat production with a favorable benefit/risk profile.

Yokozeki H, Fujimoto T, Abe Y, et al. A phase 3, multicenter, randomized, double-blind, vehicle-controlled, parallel-group study of 5% sofpironium bromide (BBI-4000) gel in Japanese patients with primary axillary hyperhidrosis. *The Journal of dermatology.* 2021;48(3):279-288.

A phase 3 study was conducted to verify the efficacy and safety of 5% sofpironium bromide (BBI-4000) gel (hereinafter referred to as sofpironium) administrated for 6 weeks in Japanese patients with primary axillary hyperhidrosis. The primary efficacy end-point was the proportion of patients who satisfied both criteria of a Hyperhidrosis Disease Severity Score (HDSS) of 1 or 2 at the end of 6-week treatment and a 50% or more reduction in total gravimetric weight of sweat at the end of treatment relative to baseline. A total of 281 patients were randomized to receive 5% sofpironium (141 patients) or vehicle (140 patients), and all patients were included in the full analysis set (FAS). In the FAS, 70.1% of patients were female, and the median age was 35.0 years. The proportion of patients who achieved the primary efficacy end-point was 53.9% in the sofpironium group and 36.4% in the vehicle group, with a statistically significant difference of 17.5% (95% confidence interval, 6.02-28.93) between these two groups ($P = 0.003$). The incidence of adverse events was 44.0% in the sofpironium group and 30.7% in the vehicle group, and the incidence of adverse drug reactions was 16.3% in the sofpironium group and 5.0% in the vehicle group. Reported adverse events were generally mild or moderate in severity. In the sofpironium group, common events (incidence, >=5%) were nasopharyngitis (14.2%) and dermatitis/erythema at the application site (8.5%/5.7%), with no serious adverse events reported. This study demonstrated the efficacy and safety of 5% sofpironium.

Naumann M, Lowe NJ. Botulinum toxin type A in treatment of bilateral primary axillary hyperhidrosis: randomized, parallel group, double blind, placebo-controlled trial. *BMJ (Clinical research ed).* 2001;323(7313):596-599.

OBJECTIVES: To evaluate the safety and efficacy of botulinum toxin type A in the treatment of bilateral primary axillary hyperhidrosis.,

DESIGN: Multicenter, randomized, parallel group, placebo-controlled trial.

SETTING: 17 dermatology and neurology clinics in Belgium, Germany, Switzerland, and the United Kingdom.

PARTICIPANTS: Patients aged 18-75 years with bilateral primary axillary hyperhidrosis sufficient to interfere with daily living. 465 were screened, 320 randomized, and 307 completed the study.

INTERVENTIONS: Patients received either botulinum toxin type A (Botox) 50 U per axilla or placebo by 10-15 intradermal injections evenly distributed within the hyperhydrotic area of each axilla, defined by Minor's iodine starch test.
MAIN OUTCOME MEASURES: Percentage of responders (patients with >/=50% reduction from baseline of spontaneous axillary sweat production) at four weeks, patients' global assessment of treatment satisfaction score, and adverse events.
RESULTS: At four weeks, 94% (227) of the botulinum toxin type A group had responded compared with 36% (28) of the placebo group. By week 16, response rates were 82% (198) and 21% (16), respectively. The results for all other measures of efficacy were significantly better in the botulinum toxin group than the placebo group. Significantly higher patient satisfaction was reported in the botulinum toxin type A group than the placebo group (3.3 v 0.8, P<0.001 at 4 weeks). Adverse events were reported by only 27 patients (11%) in the botulinum toxin group and four (5%) in the placebo group (P>0.05).
CONCLUSION: Botulinum toxin type A is a safe and effective treatment for primary axillary hyperhidrosis and produces high levels of patient satisfaction.

Lowe NJ, Glaser DA, Eadie N, Daggett S, Kowalski JW, Lai P-Y. Botulinum toxin type A in the treatment of primary axillary hyperhidrosis: a 52-week multicenter double-blind, randomized, placebo-controlled study of efficacy and safety. *J Am Acad Dermatol.* 2007;56(4):604-611.

BACKGROUND: The long-term effects of botulinum toxin type A (BoNTA) on the global impairment associated with severe primary axillary hyperhidrosis have not been comprehensively assessed relative to placebo.
OBJECTIVE: To assess the efficacy and safety of 2 dosages of BoNTA compared with placebo in subjects with primary axillary hyperhidrosis.
METHODS: Subjects (N = 322) were randomized to the use of BoNTA (75 U or 50 U/axilla) or placebo in this 52-week, multicenter, double-blind study.
RESULTS: BoNTA treatment significantly reduced daily activity limitations at 4 weeks after injection. A 2-point improvement on the 4-point Hyperhidrosis Disease Severity Scale (HDSS) was reported in 75% of subjects in the 75-U and 50-U BoNTA groups and in 25% of the placebo group (P < .001). Improvements in HDSS scores were corroborated by gravimetric results. The median duration of effect was 197 days, 205 days, and 96 days in the 75-U, 50-U, and placebo groups, respectively. BoNTA was well tolerated.
LIMITATIONS: The effect of total surface area involvement on treatment efficacy was not evaluated.
CONCLUSION: BoNTA treatment effectively reduces the symptoms of primary axillary hyperhidrosis and is well tolerated.

Appendix 4. Key Inclusion Criteria

Population	People with hyperhidrosis
Intervention	Drugs in **Appendix 1**
Comparator	Drugs in **Appendix 1** or placebo
Outcomes	Hyperhidrosis symptoms, quality of life, complications of skin disease
Setting	Outpatient

Topical Anticholinergics for Hyperhidrosis

Goal(s):

- Promote coverage in evidence-supported conditions and in people with severe symptoms that interfere with daily activities.
- Allow case-by-case review for members covered under the EPSDT program.

Length of Authorization:

Up to 12 months

Requires PA:

- Topical anticholinergics (e.g., sofpironium, glycopyrronium)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Topical anticholinergics approved by the FDA

Drug	Age	Indication
Glycopyrronium	≥ 9 years	Primary axillary hyperhidrosis
Sofpironium	≥ 9 years	Primary axillary hyperhidrosis

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** If not eligible for EPSDT review: Pass to RPh. Deny; not funded by the OHP If eligible for EPSDT review: Go to #3.

Approval Criteria		
3. Is this an FDA approved age and indication (**Table 1**)? Note: secondary axillary hyperhidrosis related to comorbid conditions and non-axillary hyperhidrosis are not FDA-approved.	**Yes**: Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the requested product prescribed by, or in consultation with, a dermatologist?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the request for renewal of a product previously approved by FFS?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #6
6. Is there documentation of severe symptoms which interfere with daily activities more than once per week as indicated by one of the following: • Hyperhidrosis Disease Severity Scale (HDSS) ≥ 3 • Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax) ≥ 3 • Axillary Sweating Daily Diary – item 2 (sweating severity) ≥ 4 on a 0-10 point scale Note: these same assessments should be evaluated for continuation of treatment.	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical necessity
7. Is there documentation indicating lack of adequate response with non-pharmacologic lifestyle management (e.g., trigger identification and avoidance, clothing modification, use of topical antiperspirants)?	**Yes**: Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Has the patient had lack of benefit, inadequate response, intolerance or contraindication to preferred therapy options for hyperhidrosis (e.g., botulinum toxins)?	**Yes**: Approve for 3 months	**No:** Pass to RPh. Deny; medical appropriateness

Renewal Criteria		
1. Is there documentation of symptom improvement from baseline as assessed by the prescribing provider? Note: the following are described as clinically relevant responses to therapy: • Total score ≤ 2 on the Hyperhidrosis Disease Severity Scale (HDSS) or Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax) • ≥ 4 point improvement on the Axillary Sweating Daily Diary – item 2 (sweating severity)	**Yes**: Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 4/25 (SS)
Implementation: TBD