How to Meet the Challenges of Hyperhidrosis

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Dr. Bhatia’s Disclosures:

- Affiliations with Brickell Biotech, Dermira
- Some slides from industry and www.sweathelp.org were borrowed for explanation of data and scientific background, not for promotion; Off-label discussion is likely
- Copies of pdf or questions: bhatiaharbor@gmail.com
- Several slides borrowed from Seemal Desai, MD
Learning Objectives

- After participating in this activity, learners will be better able to:
  - Review the impact of HH on patient’s QOL
  - Use appropriate tools and scales to assess severity of HH
  - Understand the most commonly used and latest treatment approaches
  - Discuss strategies to personalize treatment approaches
  - Recognize the urgency of prompt treatment of HH
Why do we need to sweat?

- Perspiration allows for thermal regulation
  - 2 to 4 million sweat glands
  - Temperature rises → Sweating maintains cooling

- Physiological Triggers of Sweat:
  - Emotions—anger, fear, anxiety
  - Stimulants—exercise, alcohol, drugs, sex, caffeine, spicy food
  - Stressors—Pain, Fever, Illness, Cardiac, Neurogenic

- Hyperhidrosis vs. Excessive Sweating
  - Some physiologically sweat more often with triggers and stop
  - Hyperhidrosis is a faucet that does not turn off

Doolittle et al, Arch Dermatol Res, 2016; 308(10); 743-9
Primary Focal Hyperhidrosis

- Visible and excessive sweating, >6 months duration
  - No clear trigger or cause
  - >70% sweat from more than one area—axillary, acral, etc.

- At least 2 of these criteria:
  - Bilateral and relatively symmetric
  - Impairs daily activities
  - Age of onset less than 25 years
  - Positive family history
  - Cessation of sweating during sleep

- Reality—85% of pts wait >3 years to get evaluated
  - 50% wait 10+ years
  - 30% pts are not diagnosed


Glaser et al, “Understanding Patient Experience with Hyperhidrosis…” J Drugs Dermatol, 2018; (17(4);392-396
Generalized Hyperhidrosis

- Generalized Secondary Hyperhidrosis involves sweating on larger surfaces or diffusely over the body.
- Sweating often while sleeping.
- Age of onset:
  - Generalized hyperhidrosis often starts in adulthood.
  - Primary hyperhidrosis usually starts in childhood or adolescence.
Quality of Life

- Published surveys: multifocal hyperhidrosis is more common than singular focal hyperhidrosis
  - 81% of patients reported 3 or more focal hyperhidrotic sites
- Symptom severity does not improve with age
  - Stays the same or gets worse without seasonal variation

Hyperhidrosis Clinical Trials Endpoints

- **Subjective measuring scales:**
  - Hyperhidrosis Disease Severity Score (HDSS): severity rating
  - Hyperhidrosis Disease Severity Measure Axillary (HDSM-Ax)
    - Subjective outcome, symptom overview, and disease impact

- **Primary endpoints:**
  - Dose-related 2-grade improvement in HDSS
  - Statistically significant 1- and 2-grade improvement in the HDSM-Ax
  - Safety and Tolerability at all concentrations

- **Adverse Events of Special Interest (AESI):**
  - Urinary Retention, Mydriasis, Arrhythmias, Xerostomia, CNS Stimulation

Courtesy Dee Anna Glaser, MD
Current and Future Treatments

Medical

- Topical
  - Antiperspirants
  - Glycopyrrolate cloths
  - Sofpironium gel

- Systemic
  - Glycopyrrolate
  - Oxybutynin
  - Beta blockers

- Iontophoresis

Procedural

- Minimally invasive
  - Neuromodulator injections
  - Microwave Thermolysis
    - Destruction of axillary glands

- Surgical
  - Excision of axillary glands
  - Thoracic Sympathectomy
Antiperspirants 101

- Aluminum Chloride MOA: aluminum salt blockage of the distal acrosyringium
  - Leads to functional and structural degeneration of the eccrine acini
- Aluminum Zirconium Trichlorohydrex
  - Less irritating than aluminum chloride
- Antiperspirant soft-solid formula
- Apply bid and qHS with gentle massaging into dry skin
  - Increased irritation if skin is wet
  - No benefit to occlusion

Courtesy David Pariser MD
Glycopyrronium Tosylate: Mechanism of Action

- Inhibits sweat gland activation by blocking acetylcholine receptor$^1$
  - Glycopyrronium tosylate (GT) acts as a cholinergic receptor antagonist
  - GT inhibits interaction between acetylcholine and cholinergic receptors responsible for sweat gland activation and sweat production

ATMOS-1 and ATMOS-2 were Phase 3, randomized, double-blind, vehicle-controlled trials

Patients aged ≥29 years with PAHH:
- ≥6 months duration
- Sweat production of ≥50 mg/5 min in each axilla
- ASDD item #2 score ≥4
- HDSS grade 3 or 4

Key exclusion criteria:
- Known causes of secondary hyperhidrosis
- Certain prior procedures or treatments

Coprimary efficacy endpoints at Week 4:
- ASDD/ASDD-C Item #2 responder rate (≥4-point improvement)
- Absolute change in axillary sweat production

Secondary efficacy endpoints at Week 4:
- HDSS responder rate (≥2-grade improvement)
- Sweat production response rate (≥50% reduction)

Other efficacy analyses at Week 4:
- Change from Baseline in DLQI
- Patient Global Impression of Change (PGIC)
<table>
<thead>
<tr>
<th></th>
<th>Vehicle N=115</th>
<th>GT N=229</th>
<th></th>
<th>Vehicle N=119</th>
<th>GT N=234</th>
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<tbody>
<tr>
<td>Discontinued</td>
<td>3</td>
<td>21</td>
<td>Discontinued</td>
<td>6</td>
<td>16</td>
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<td>Adverse event</td>
<td>1</td>
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<td>9</td>
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<tr>
<td>Withdrew consent</td>
<td>1</td>
<td>6</td>
<td>Withdrew consent</td>
<td>0</td>
<td>5</td>
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<tr>
<td>Lost to follow-up</td>
<td>1</td>
<td>5</td>
<td>Lost to follow-up</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Noncompliance</td>
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<td>Noncompliance</td>
<td>0</td>
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<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>1</td>
<td>Other</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Completed study</td>
<td>N=112 (97.4%)</td>
<td>N=208 (90.8%)</td>
<td>Completed study</td>
<td>N=113 (95.0%)</td>
<td>N=218 (93.2%)</td>
</tr>
</tbody>
</table>

GT – glycopyronium tosylate.
Median Reduction in Sweat Production

Pooled ATMOS-1 and ATMOS-2

Median Sweat Production
Baseline to Week 4

<table>
<thead>
<tr>
<th>Week</th>
<th>GT (N=463)</th>
<th>Vehicle (N=234)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>124.6</td>
<td>114.8</td>
</tr>
<tr>
<td>Week 1</td>
<td>73.3</td>
<td>36.5</td>
</tr>
<tr>
<td>Week 2</td>
<td>64.7</td>
<td>34.6</td>
</tr>
<tr>
<td>Week 3</td>
<td>59.7</td>
<td>34.8</td>
</tr>
<tr>
<td>Week 4</td>
<td>57.0</td>
<td>32.8</td>
</tr>
</tbody>
</table>

Reduction in Sweat Production
Percent Change Baseline to Week 4

- Median Reduction from Baseline Sweat Production, %
- GT: 74%
- Vehicle: 54%

Post hoc analysis. Intent-to-treat (ITT) population, MCMC multiple imputation.

Gravimetrically-measured average from the left and right axillae.

Vehicle-treated patients interquartile range (IQR): 25th percentile: 33.8 mg/min; 75th percentile: 105.9 mg/min.

GT-treated patients IQR: 25th percentile: 15.3 mg/min; 75th percentile: 75.0 mg/min.

Grav – gravimetric measurement of sweat production; GT – glycopyrronium tosylate; MCMC – Markov chain Monte Carlo; min – minutes.

### Common TEAEs Reported in ≥5% of Patients\(^1,2a\)

**Safety Population**

<table>
<thead>
<tr>
<th>Common TEAEs, n (%)</th>
<th>Vehicle N=114</th>
<th>GT N=227</th>
<th>Vehicle N=118</th>
<th>GT N=232</th>
<th>Vehicle N=232</th>
<th>GT N=459</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>4 (3.5)</td>
<td>43 (18.9)</td>
<td>9 (7.6)</td>
<td>68 (29.3)</td>
<td>13 (5.6)</td>
<td>111 (24.2)</td>
</tr>
<tr>
<td>Application site pain</td>
<td>11 (9.6)</td>
<td>20 (8.8)</td>
<td>11 (9.3)</td>
<td>20 (8.6)</td>
<td>22 (9.5)</td>
<td>40 (8.7)</td>
</tr>
<tr>
<td>Mydriasis</td>
<td>0</td>
<td>15 (6.6)</td>
<td>0</td>
<td>16 (6.9)</td>
<td>0</td>
<td>31 (6.8)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>2 (1.8)</td>
<td>9 (4.0)</td>
<td>1 (0.8)</td>
<td>17 (7.3)</td>
<td>3 (1.3)</td>
<td>26 (5.7)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (2.6)</td>
<td>10 (4.4)</td>
<td>2 (1.7)</td>
<td>13 (5.6)</td>
<td>5 (2.2)</td>
<td>23 (5.0)</td>
</tr>
</tbody>
</table>

- Commonly reported TEAEs in the GT group included some events associated with anticholinergic activity (dry mouth, mydriasis)

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\(^a\)≥5% in either treatment arm in pooled ATMOS population.

GT – glycopyrronium tosylate; TEAE – treatment emergent adverse event.
Sofpironium Bromide
Brickell Biotech, Inc: BBI-4000

- Soft drugs
  - active isosteric–isoelectronic analogues of a lead compound deactivated after achieving their therapeutic peak
  - designed to be rapidly metabolized into inactive species

- Sofpironium Bromide
  - “soft glycopyrrolate” analog (anti-cholinergic) active only at the local site of administration, hydrolyzed upon reaching the systemic circulation
  - Inhibits binding of neurotransmitter acetylcholine to cholinergic receptor
  - Proposed to suppress eccrine sweat stimulation
Sofpironium Bromide
Proposed Mechanism of Action

M3 AC receptors

Sofpironium bromide

One step (hydrolytic) metabolic deactivation

Sofpironium bromide metabolite

Designed to create fast elimination

Systemic AC receptors

Sofpironium bromide metabolite

Reduced binding affinity

AC

Skin

Sweat gland

Hair

Being Investigated to Inhibit Sweat Production

Acetylcholine (AC) binds to M3 AC receptors in sweat glands inducing sweat production.

Sofpironium bromide, an investigational anticholinergic agent, was created to bind selectively to the M3 AC receptors, potentially inhibiting sweat production.
Phase II studies

- 23 sites, n=227, randomized 1:1:1:1 sofpironium bromide gel, 5%, 10%, 15% or vehicle qd to the axillae for 42 days
- Hyperhidrosis Disease Severity Measure-Axillary (HDSM-Ax) scores of 3 or 4 (scale, 0 - 4)
- Combined axillary gravimetric sweat production (GSP) of ≥ 150 mg/5 minutes

- The 15% dose was more efficacious than the other doses, while the 5% dose was better tolerated

Smith, S, Kirsch, B, Walker, P, "A Multicenter, Randomized, Double-Blinded, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of 5%, 10% and 15% Topically Applied Sofpironium Bromide Gel in Subjects with Axillary Hyperhidrosis," Presented at the 76th Annual Meeting of the American Academy of Dermatology, San Diego, CA | Saturday, February 17, 2018
Sofpironium bromide application resulted in statistically significant higher response rates as measured by the HDSM-Ax at end of therapy.

HDSM-Ax ≥ 1-point Reduction from Baseline to End of Treatment

- **Vehicle** (N = 57): 54.4% responders, p = 0.0387
- **5%** (N = 57): 70.2% responders, p = 0.0099
- **15%** (N = 54): 75.9% responders

Smith, S, Kirsch, B, Walker, P. “A Multicenter, Randomized, Double-Blinded, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of 5%, 10% and 15% Topically Applied Sofpironium Bromide Gel in Subjects with Axillary Hyperhidrosis,” Presented at the 76th Annual Meeting of the American Academy of Dermatology, San Diego, CA | Saturday, February 17, 2018
Sofpironium bromide application resulted in significantly higher response rates as measured by the HDSM-Ax as early as Day 8 and sustained over time.

Smith, S, Kirsch, B, Walker, P, "A Multicenter, Randomized, Double-Blinded, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of 5%, 10% and 15% Topically Applied Sofpironium Bromide Gel in Subjects with Axillary Hyperhidrosis," Presented at the 76th Annual Meeting of the American Academy of Dermatology, San Diego, CA | Saturday, February 17, 2018
Dry mouth was the most common anticholinergic dose dependent Treatment-Emergent AE

<table>
<thead>
<tr>
<th>Subjects Reporting at Least One Adverse Event</th>
<th>Vehicle (N=57)</th>
<th>Sofpironium Bromide 5% (N=57)</th>
<th>Sofpironium Bromide 15% (N=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>9 (15.8%)</td>
<td>17 (29.8%)</td>
<td>28 (51.9%)</td>
</tr>
<tr>
<td>Blurred Vision</td>
<td>0 (0.0%)</td>
<td>2 (3.5%)</td>
<td>5 (9.3%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0 (0.0%)</td>
<td>3 (5.3%)</td>
<td>3 (5.6%)</td>
</tr>
<tr>
<td>Urinary Hesitation</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>4 (7.4%)</td>
</tr>
<tr>
<td>Application Site AEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>0 (0.0%)</td>
<td>1 (1.8%)</td>
<td>5 (9.3%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>3 (5.6%)</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>0 (0.0%)</td>
<td>3 (5.3%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

Twelve subjects discontinued from the study due to TEAEs (7 subjects at 15%, 4 subjects at 10%, 1 subject at 5%)
Randomized, Placebo- and Active-Controlled Crossover Study of the Safety and Efficacy of THVD-102, a Fixed-dose Combination of Oxybutynin and Pilocarpine, in Subjects With Primary Focal Hyperhidrosis

David M. Pariser MD FACP FAAD,¹ Janakan Krishnaraja MD,² Thomas M. Tremblay RN,³ R. Michael Rubison PhD,³ Ted W. Love MD,³ and Benjamin F. McGraw III PharmD³

¹Eastern Virginia Medical School and Virginia Clinical Research, Inc., Norfolk, VA
²Linear Clinical Research, Perth, Western Australia
³Flint Hills Consulting, LLC, Lake Forest, IL
⁴TheraVida, Inc., San Mateo, CA

THVD-102
(oxybutynin 7.5mg + pilocarpine 7.5mg)

Oxybutynin 7.5mg
(muscarinic antagonist)

Instant release

Delayed onset, instant release

Pilocarpine 7.5mg
(Muscarinic agonist)
Real World Dosing:
Start 2.5 mg daily then every week to every 2 weeks work up to bid then either stay at 5 mg daily or titrate between 7.5 mg qd or 10 mg po qd
4-6 weeks taper up to maximal dose as tolerated
The combination of oxybutynin and pilocarpine in THVD-102 provides an advantage over oxybutynin alone with respect to less dry mouth, an advantage over botulinum toxin A in that it does not require physician administration and an advantage over sympathectomy in that there is no compensatory sweating. If the results of the present study are supported by larger randomized, placebo-controlled studies with longer treatment duration, THVD-102 may provide an oral treatment option for patients with PFH.
Coding algorithms for Hyperhidrosis

- ICD-10: L74. 510
- CPT Codes for Neuromodulators
  - Face/Head Primary Hyperhidrosis: 64653
  - Plantar and/or Palmar Primary Hyperhidrosis: 64999
    - Axillary Primary Hyperhidrosis: 64650
    - Botulinum toxin: J0585
- CPT Codes for Treatment of Hyperhidrosis with Iontophoresis: for each 15-minute session 97033