Dermatology Foundation Educational Grant Award to Wisconsin Dermatological Society:
Hyperhidrosis Management

Dee Anna Glaser, MD
Hyperhidrosis: Optimizing Treatment

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Primary Focal Hyperhidrosis: Definition and Diagnosis

- Excessive sweating, beyond physiological needs
- Focal, visible, excessive sweating of at least 6 months duration without apparent cause with at least 2 of the following characteristics
  - Bilateral and relatively symmetric
  - Impairment in daily activities
  - Frequency of at least 1 episode per week
  - Age of onset less than 25 years
  - Positive family history
  - Cessation of focal sweating during sleep


Anatomy of Thermoregulation

- Eccrine/apo-eccrine sweat glands
- 1.6 to 4 million glands distributed over body
- Average density varies
  - Back 64 glands/cm²
  - Forehead 181 glands/cm²
  - Palms/soles 700 glands/cm²


Anatomy and Physiology of Sweating

- Thermoregulatory control
  - Preoptic area/anterior hypothalamus
  - Sympathetic nervous system
  - Sympathetic activity in eccrine sweat glands is transmitted by acetylcholine
  - Electrolyte balance
  - Varyed activation stimuli
    - Heat
    - Emotional stimuli
    - Pain
    - Dietary stimuli


Etiology of Primary, Focal Hyperhidrosis

- Etiology unknown
- Genetic component
  - Positive family history in 30%-65% of patients
- Normal sweat glands
- Nervous system dysfunction
  - Sympathetic nervous system
  - Hypothalamus


Disclosure Statement

I, Dee Anna Glaser, M.D., do have a relevant financial interest or other relationship with a commercial entity producing health-care related product and or services:

<table>
<thead>
<tr>
<th>Affiliation/Financial Interest</th>
<th>Name of Corporate Organization(s)</th>
</tr>
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<tbody>
<tr>
<td>Grant/Research Support</td>
<td>Allergan, Suneva – all monies to University</td>
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<tr>
<td>Consultant</td>
<td>Allergan, Medicis, Unilever</td>
</tr>
<tr>
<td>Speaker's Bureau</td>
<td>Allergan, Merz</td>
</tr>
<tr>
<td>Major Stock Shareholder</td>
<td>N/A</td>
</tr>
<tr>
<td>Other Financial or Material Support</td>
<td>Allergan and Medicis provide cosmetic products for level grants for resident education, Board member of International Hyperhidrosis Society, UK led cases of therapies</td>
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</tbody>
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**Presentation has been reviewed by CME Committee Representatives for bias.**
Excessive Sweating

- Prevalence 2.8%
- 8-10 million
- Men = women

Patients Seeking Evaluation

<table>
<thead>
<tr>
<th></th>
<th>American</th>
<th>Canadian</th>
<th>Combined</th>
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<tbody>
<tr>
<td></td>
<td>N=242</td>
<td>N=266</td>
<td>N=508</td>
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<tr>
<td>Female</td>
<td>65.3%</td>
<td>60.5%</td>
<td>62.8%</td>
</tr>
<tr>
<td>Male</td>
<td>34.7%</td>
<td>39.5%</td>
<td>37.2%</td>
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<tr>
<td>Axillary</td>
<td>78.5</td>
<td>68.0</td>
<td>73.0</td>
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<tr>
<td>Palms</td>
<td>47.9</td>
<td>44.0</td>
<td>45.9</td>
</tr>
<tr>
<td>Soles</td>
<td>44.6</td>
<td>38.0</td>
<td>41.1</td>
</tr>
<tr>
<td>Face/scalp</td>
<td>23.6</td>
<td>22.9</td>
<td>22.8</td>
</tr>
<tr>
<td>Groin</td>
<td>12.4</td>
<td>6.4</td>
<td>9.3</td>
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</table>


IMPACT OF HYPERHIDROSIS
DERMATOLOGY LIFE QUALITY INDEX

Burden of Axillary Hyperhidrosis
% of Individuals Moderately to Extremely Limited In Various Activities Due to Sweating

Feel unhappy 65%
Feel depressed 36%

Current Treatments for Hyperhidrosis

- Topical agents
- Iontopheresis
- Systemic agents
- Botulinum toxin
- Surgery
  - Sweat gland resection
  - Microwave technology
  - ETS

Hyperhidrosis Disease Severity Scale (HDSS)

“Which best describes the impact of sweating on daily activities?”

1=never noticeable, never interferes
2=tolerable, sometimes interferes
3=barely tolerable, frequently interferes
4=intolerable, always interferes
Goal of Treatment

- Reduce the impact of hyperhidrosis on patient’s lives
  - Reduce HDSS scores from 4 or 3 to 2 or 1

Impact of sweating on daily activities:
- 4=intolerable, always interferes
- 3=barely tolerable, frequently interferes
- 2=tolerable, sometimes interferes
- 1=never noticeable, never interferes

Over-the-Counter Antiperspirants

- First-line therapy for axillary hyperhidrosis
- Useful for a limited number of individuals
- 87% of 265 patients with axillary HH rated over-the-counter antiperspirants as ineffective
- Aluminium Chloride, Zirconium, Aluminum Zirconium Trichlorohydrex

Mechanism of Action

Anti-perspirants form follicular plugs via this general chemical reaction:

\[ M^{n+} Cl^- + n \text{ moles Base} \rightarrow M(\text{Base})_3 \text{ ppt} + n\text{HCl} \]

Base can be OH$^-$ from Water, Lactate, or Protein

Aluminum Chloride 10-35%

- Topical therapy applied at night, washed off in the morning
- Effective for some patients
- Associated with concentration-related skin irritation and itching, particularly in the axillae
- Long-term use has been associated with atrophy of the eccrine glands in the axillae

New Topical Options

- 15% AC in 2% salicylic acid gel base (Hydrosal®) axillary HH
- HDSS 3 or 4
- Measurements: HDSS, HHIQ, Irritation scale
- N=30
  - 29 (97%) completed through week 4
  - 25 (83.3%) completed through week 12
- Nightly application X 1 week
- Then twice weekly as tolerated
- Baseline, week 4, week 12

References:
- Glanz
Mean HDSS Score at Week 4

- Mean HDSS score decreased from 3.3 at baseline to 2.0 at Week 4 in subjects using 15% AC in 2% salicylic acid gel base two to three times per week.

New Topical Options

- Responders (HDSS ≤ 2)
  - Week 4, 21 of 29 (72%)
  - Week 12, 18 of 25 (72%)
- In subjects who had previously failed 20% AC in AA, 77% and 86% of these subjects were Responders at week 4 and week 12 respectively.

Adverse Events Week 4

<table>
<thead>
<tr>
<th></th>
<th>Redness</th>
<th>Stinging</th>
<th>Itching</th>
<th>Fissuring</th>
<th>Pain</th>
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</thead>
<tbody>
<tr>
<td>Mild or Absent</td>
<td>85.7%</td>
<td>71.5%</td>
<td>71.4%</td>
<td>100%</td>
<td>92.9%</td>
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<tr>
<td>Moderate</td>
<td>10.7%</td>
<td>17.9%*</td>
<td>17.9%</td>
<td>---</td>
<td>7.1%</td>
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<tr>
<td>Severe</td>
<td>3.6%</td>
<td>10.7%*</td>
<td>10.7%</td>
<td>---</td>
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</table>

* p<.05 compared with baseline

Adverse Events at Week 12

<table>
<thead>
<tr>
<th></th>
<th>Redness</th>
<th>Stinging</th>
<th>Itching</th>
<th>Fissuring</th>
<th>Pain</th>
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</thead>
<tbody>
<tr>
<td>Absent or Mild</td>
<td>96%</td>
<td>92%*</td>
<td>84%</td>
<td>---</td>
<td>94%</td>
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<tr>
<td>Moderate</td>
<td>4%</td>
<td>---</td>
<td>8%</td>
<td>---</td>
<td>6%</td>
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<tr>
<td>Severe</td>
<td>---</td>
<td>---</td>
<td>8%</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

* p<.05 compared with week 4

Topicals

- Use Aluminum Chloride product night time
- Apply to dry area
- Wash off in morning
- Alternate with OTC
  - Clinical Strength formulations
- First line for most body sites

Tap Water Iontophoresis

- Introduction of an ionized substance through intact skin by direct current
- Palmar & plantar HH uses
- Can be labor intensive
  - Usually 3-4 treatments per week, 20-30 minutes each;
  - 6-10 treatments usually needed to achieve euhidrosis;
  - weekly to monthly treatments needed to maintain benefit
- May cause skin irritation and transient paresthesia

Flanagan KH, Glaser DA. An open-label trial of the efficacy of 15% aluminum chloride in 2% salicylic acid gel base in the treatment of moderate-to-severe primary axillary hyperhidrosis. J Drugs Derm May, 2009

Glaser

Flanagan KH, Glaser DA. An open-label trial of the efficacy of 15% aluminum chloride in 2% salicylic acid gel base in the treatment of moderate-to-severe primary axillary hyperhidrosis. J Drugs Derm May, 2009

10 minutes anode
10 minutes cathode
10-15 mAmp

Protect skin with petroleum

Excellent results
Patient education and instruction is important
Time intensive initially

Contra-indications
- Pregnancy
- Pacemaker
- Orthopedic hardware at treatment site

Systemic Therapy

- Anticholinergics
- Benzodiazepines
- Beta-blocker
- Diltiazem
- Clonidine
- Indomethacin

- Limited applications
- Off-label
- No data for efficacy or long-term safety

Anticholinergic Agents

- Atropine
- Glycopyrrolate (Robinul)
- Propantheline (Pro-Banthine)
- Benztropine
- Oxybutynin (Ditropan)
- Tolterodine (Detrol)
- Flavoxate (Urispas)

Anticholinergic Side Effects

- GI
  - Dry mouth
  - Reduced gastric secretions
  - Acid, pepsin, mucus
  - Requires high doses
- Ocular
  - Mydriasis
  - Cycloplegia
  - Dry or "sandy" eyes
- Respiratory
  - Bronchodilatation
  - Reduced Secretions

- GU
  - Relax smooth muscle of ureters & bladder wall;
  - Slow voiding
  - Urinary retention, especially elderly men
  - Cardiac arrhythmias
  - Bradycardia at low doses
  - Tachycardia at higher doses
  - Suppresses thermoregulatory sweating

Anticholinergic Agents: Contraindications

- Glaucoma
  - Especially narrow-angle
- Impaired gastric emptying
- History or symptoms of urinary retention

References:

**Who Do I Treat With An Oral Anticholinergic?**

**Possible patients**
- Multiple areas of involvement
- Generalized HH
- Craniofacial
- Failed other first-line therapies

**Think twice**
- Athletes
- School sports
- Construction workers & other outdoor-based occupations
- Children

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**Clinical Application**

- Why glycopyrrolate?
  - Quaternary amine
  - Decreased lipid solubility
  - Poorly taken up by the brain/free CNS effects
- 1mg and 2mg tablets
- Start 1mg BID
- Increase by 1mg ~2 weeks depending on clinical effects and side effects

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**Beta Blocker: Propranolol**

- Highly lipophilic
- B1 and β2 receptors with equal affinity
- HTN, angina, arrhythmias, MI, pheochromocytoma, migraine, anxiety
- Peak concentration 1-1.5 hours post ingestion
- Food may delay peak concentration

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**Clinical Use of Propranolol**

- Propranolol 5-10mg
- Patients with known anxiety-evoked sweat
  - Giving a presentation
  - Job interviews
- Test dose
  - Patient monitors for CNS effects, hypotension, poor performance
- Take 30-60 minutes before “event”

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**Propranolol Contraindications**

- Bradycardia*
- AV block*
- Asthma
- COPD
- Depression
- Diabetes mellitus
- Heart failure
- Hepatic disease

- Hypotension
- Hypoglycemia
- Cerebrovascular disease
- Myasthenia gravis
- Psoriasis
- Renal disease
- Thyroid disease
- Elderly
- Driving or operating machinery

* Absolute contraindication

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**Oral Therapies**

- Anticholinergics
- Benzodiazepines¹
- Beta-blocker
- Diltiazem²
- Clonidine³
- Indomethacin⁴

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Botulinum Toxins

- BoNT-A
  - OnabotulinumtoxinA
  - AbobotulinumtoxinA
  - IncobotulinumtoxinA
- BoNT-B
- Onabotulinumtoxin FDA approved-axillary

BTX Usage: Principles of Therapy

- Identify area starch iodine test
- Deep dermal
  - ~2-5 units/1-2cm
- Reconstitute 4 cc saline/100u vial
  - 30 gauge 1/2 inch needle
  - Leur lock syringe

Negative Starch Iodine Test

- Treat the hair-bearing axilla
- Re-evaluate in 2-4 weeks

Injection Sites

- 10 - 15 intradermal injection sites within defined area using 1.5-2 cm grid spacing of injections

<table>
<thead>
<tr>
<th>Dilation/Vial</th>
<th>4.0 ml</th>
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<tbody>
<tr>
<td>Total Volume/Axilla</td>
<td>2.0 ml</td>
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<tr>
<td>Volume/Injection Site</td>
<td>0.13-0.2</td>
</tr>
<tr>
<td>Units/Injection Site</td>
<td>3-3.5 U</td>
</tr>
<tr>
<td>Total Dose/Axilla</td>
<td>50 U</td>
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</table>

Onabotulinum Axillary Injections

- Reconstitute 4 cc saline
- Needle 30 gauge
- Injections deep dermal 1.5 cm intervals
- Dose 50 units/axilla

If you miss an area, you can inject it on follow-up ~3-5 units per 1-2 cm

**Palmar Hyperhidrosis: OnabotulinumtoxinA**

- **Dosing**
  - 2-3 units
  - 100-200 u/hand
  - Ulnar side
- **Duration**
- **Muscle weakness**
- **Off-label**

**Pain Control: Palmar Injections**

- Topical anesthesia
- Nerve blocks
- Beir Block
- Cold anesthesia
- Vibration
- General / IV sedation anesthesia
- Grin and Bear It

**Facial and Scalp**

- Variable patterns
  - Forehead
  - Ophiasis pattern
  - Global
  - Facial
- Dosing
- Anesthesia
- Off label usage

**Facial and Scalp**

- 2-5 units
- 1-2 cm
- Deep dermal or superficial SQ
- Expect muscle effect

Consider oral agents as well
Microwave Thermolysis

- New technology
- Microwave device*
- FDA-cleared for axillary HH
- 2 treatment sessions
- Local anesthetic
- Results expected to be long lasting

*miraDry

Human histology data

Baseline 11 Days Post Treatment 6 Months Post Treatment

Photos courtesy of Dr. Nobuharu Kushikata

“*The ontogeny of sweat glands is only in the embryonic period, so no new sweat glands are regenerated after birth.” – Li HH et al, J Cutan Pathol 2009; 36: 318-324.

Microwave procedure

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Procedure</th>
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<tbody>
<tr>
<td>Mark customized treatment area</td>
<td>Treat with System</td>
</tr>
<tr>
<td>Administer local anesthetic</td>
<td></td>
</tr>
</tbody>
</table>

* Procedure typically lasts 60 – 75 minutes, depending on the size of treatment area
* Two procedures (spread 3 months apart) required for best results and duration

Active group long-term efficacy

Active group long-term efficacy

Efficacy results for active group

*Kilmer S, et al. Presented at ASLMS 2011, Grapevine, TX

Hyperhidrosis

- Prevalence ~3%
- Quality of life significantly impaired
- Several effective treatments
  - Topical anti-perspirants
  - Iontophoresis
  - Oral medications
  - Local surgical approaches
  - Botulinum toxin type A
  - ETS
- Combination therapies
- High patient satisfaction

Coding

<table>
<thead>
<tr>
<th>Diagnosis / ICD-9</th>
<th>Procedure / CPT</th>
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<tr>
<td>780.8</td>
<td>J0585: BoNT-A units</td>
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<tr>
<td>Diaphoresis</td>
<td>64650: Chemodenervation eccrine units axilla, bilateral</td>
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<tr>
<td>Excessive sweating</td>
<td>64653: Craniofacial</td>
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<tr>
<td>705.21</td>
<td>64699: Chemodenervation eccrine, NOS</td>
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<tr>
<td>Primary focal hyperhidrosis</td>
<td>97033: Iontophoresis, each 15 minutes</td>
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