

HYPERHIDROSIS: THE PEDIATRIC PERSPECTIVE

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DISCLOSURES

- RESEARCH: ALLERGAN, DEMIRA, BRICKELL, GSK:
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- INTERNATIONAL HYPERHYDROSIS SOCIETY:
 - FOUNDING MEMBER
 - MEMBER OF BOARD OF DIRECTORS

WHY CONSIDER THE PEDIATRIC POPULATION UNIQUE IN THE REALM OF HYPERHIDROSIS?

- AGE OF ONSET
- ANATOMIC DISTRIBUTION OF SWEATING
- IMPACT ON:
 - SCHOOL
 - DEVELOPMENT OF SELF CONFIDENCE
 - LIMITED THERAPIES APPROVED

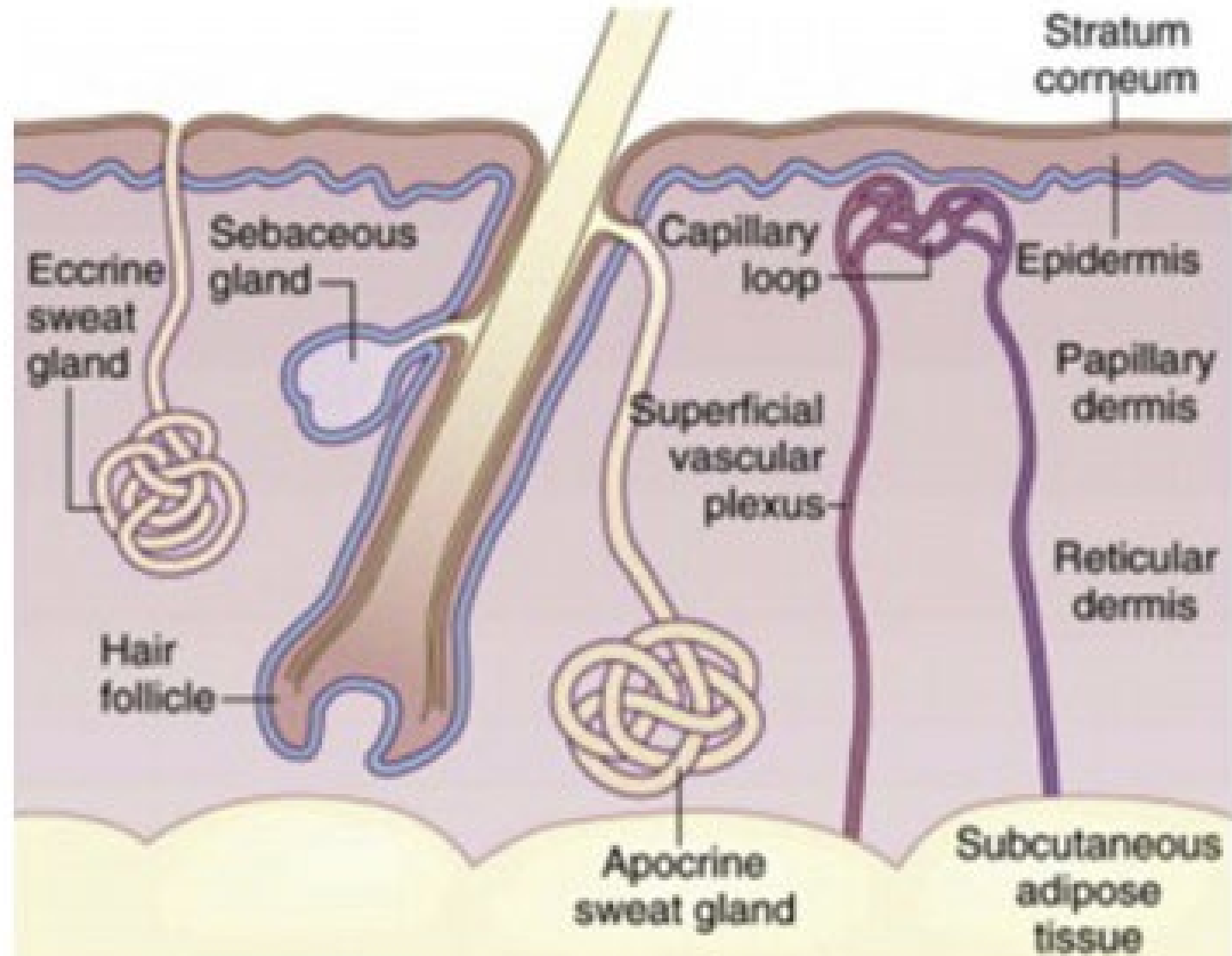
SWEAT GLANDS

- HUMANS HAVE 2 TO 4 MILLION SWEAT GLANDS
- SWEAT GLANDS FOUND ALL OVER THE BODY
- MOST DENSE ON PALMS, SOLES, FOREHEAD, UPPER LIMBS

SWEAT GLANDS

- UP TO 10L/day OF SWEAT PRODUCED ON ACLIMATED INDIVIDUALS
- **ECCRINE**: BEGINNINGS ON FETAL PALMS/SOLES AT 3.5 MONTHS
- **APOCRINE**: LARGELY ON PALMS, AXILLAE
 - DO NOT BECOME FUNCTIONAL UNTIL PUBERTY

FITZPATRICK'S DERMATOLOGY IN GENERAL MEDICINE : EIGHTH EDITION



HYPERHIDROSIS

- SWEAT GLANDS OF NORMAL SIZE, DENSITY, LOCATION, HISTOLOGIC APPEARANCE
- ACETYLCHOLINESTERASE = NORMAL:
 - QUANTITY
 - FUNCTION

HYPERHIDROSIS

AFFECTS:

- 3% OF THE POPULATION OF THE UNITED STATES
- 176 MILLION PEOPLE WORLDWIDE
- 1.6 % OF CHILDREN AND ADOLESCENTS < 18

J AM ACAD DERMATOL 2004:51:241-248

HYPERHIDROSIS ETIOLOGY

GENETIC BASIS

- DISEASE ALLELES PRESENT IN 5% OF POPULATION
- ONE or TWO ALLELES RESULT IN 25% OF HYPERHIDROSIS CASES
- STUDIES IN CHINESE AND JAPANESE POPULATIONS:

GENETIC LOCI ON CHROMOSOMES

- 2q31.1
- 14q11
- 14q13

THE ETIOLOGY, DIAGNOSIS, AND MANAGEMENT OF HYPERHIDROSIS: A COMPREHENSIVE REVIEW

NAWROCKI S, CHA J

JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY

JAN 2019 (19): 3016

HYPERHIDROSIS ETIOLOGY

NEUROLOGIC BASIS:

- More **REGULATORY DYSFUNCTION** than purely over function
- Perceptual abnormalities and exaggerated sudomotor reactions to thermoalgesic stimulation compared with central desensitization of sympathetic circuits
- Hyperexcitability of the somatosympathetic polysynaptic pathway involving sweating

PRIMARY FOCAL HYPERHIDROSIS

DEFINITION:

- FOCAL, VISIBLE, EXCESSIVE SWEATING OF AT LEAST 6 MONTHS DURATION WITHOUT APPARENT CAUSE
- BILATERAL AND RELATIVELY SYMMETRIC
- SWEATING IMPAIRS DAILY ACTIVITIES
- FREQUENCY OF AT LEAST ONE EPISODE PER WEEK

FOCAL HYPERHIDROSIS: GENETIC COMPONENT

- 13/85 (15%) patients with affected parent; 29/85 (34%) with 1 or more affected siblings¹
- 43% (N=80) patients reported a family history of HH²
- 32/49 (65%) patients reported a family history of HH, compared with 0% in the control group³

PRIMARY FOCAL HYPERHIDROSIS

SWEATING:

- OCCURS **ANY TIME** IRRESPECTIVE OF TEMPERATURE, STRESS, PLEASURE
- MAY BE CONTINUOUS OR PHASIC
- PHASIC OUTBURSTS WITH MINOR EMOTIONAL ACTIVITY: EQUAL YEAR ROUND
- **CEASES** UNDER GENERAL ANESTHESIA

FITZPATRICK'S DERMATOLOGY IN GENERAL MEDICINE : EIGHTH EDITION

PRIMARY PEDIATRIC HYPERHIDROSIS: A REVIEW OF CURRENT TREATMENT OPTIONS

GELBARD C, EPSTEIN H, HEBERT AA

PEDIATR DERMATOL 2008; 25 (6):591-8

SPECIAL CONSIDERATIONS FOR CHILDREN WITH HYPERHIDROSIS

Bohaty BR, Hebert AA

Dermatologic Clinics 2014 Oct; 32(4):477-84.

CURRENT AND EMERGING MEDICAL THERAPIES FOR PRIMARY HYPERHIDROSIS

GRABELL, DA, HEBERT AA

DERMATOL THER 2017 MAR;7(1):25-36

HYPERHIDROSIS

- DISORDER THAT OFTEN BEGINS IN CHILDHOOD
- EMBARRASSING
- UNCOMFORTABLE
- ANXIETY INDUCING
- AT TIMES:
 - DISABLING
 - ISOLATING

Focal Hyperhidrosis: Age at Onset—Data From 3 Studies

Age	Herbst ¹ (N=323)	Drott ² (N=850)	Amir ³ (N=48)
Early childhood	61.1%	62%	60.4%
Puberty	30%	33%	39.6%
>18 years	8.9%	5%	0

1. Herbst F et al. *Ann Surg.* 1994;220:86-90. 2. Drott C et al. *J Am Acad Dermatol.* 1995;33:78-81. 3. Amir M et al. *Isr J Psychiatry Relat Sci.* 2000;37:25-31.



Focal Hyperhidrosis: Age at Onset—US National Survey

- Average age of onset: 25 years
 - 13 years for only palmar HH
 - 19 years for only axillary HH
 - 22 years for palmar or axillary HH alone or in combination with at least 1 other location

**Strutton DR et al. Poster presented at: American Academy of Dermatology
61st Annual Meeting; March 21-26, 2003; San Francisco, Calif. Abstract P362**

HYPERHIDROSIS: RECENT SURVEY 2018

USA DATA:

- AVERAGE AGE OF ONSET OF HYPERHIDROSIS WAS 11.3 YEARS OF AGE
- ONE OUT OF SIX US TEENAGERS REPORT HAVING HYPERHIDROSIS

MOST (92%) TEENS WITH HYPERHIDROSIS

- SWEAT FROM 2 + FOCAL AREAS
- AVERAGE NUMBER OF RECORDED AREAS OF FOCAL SWEATING = 5

Diagnostic Work-up

- Depends on clinical presentation
- Idiopathic hyperhidrosis – history and physical examination
 - Focal
 - Classic distribution
 - Characteristic age of onset
 - Bilateral/symmetrical
- All others require additional work-up tailored to the specific clinical presentation

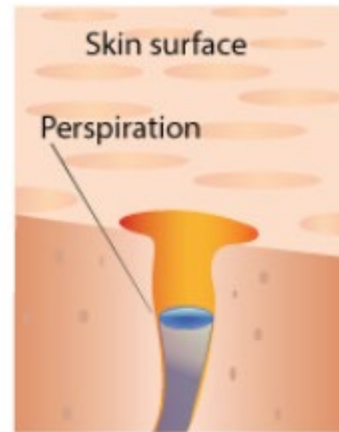
TREATMENT OF HYPERHIDROSIS

- GROWING UP WITHIN THE CONFINEMENT OF THIS SOCIALLY OSTRASIZING DISEASE:
- CAN BE EXTREMELY DETRIMENTAL TO CHILD'S DEVELOPMENT OF CONFIDENCE AND SENSE OF SELF

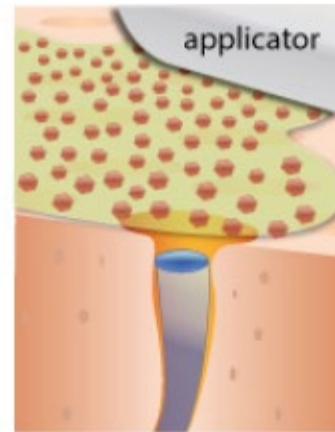
TREATMENT: LIMITED THERAPEUTIC OPTIONS FOR CHILDREN WITH HYPERHIDROSIS

- OVER THE COUNTER:
 - CLINICAL STRENGTH ANTI PERSPIRANTS
 - SHOULD BE APPLIED **BID**

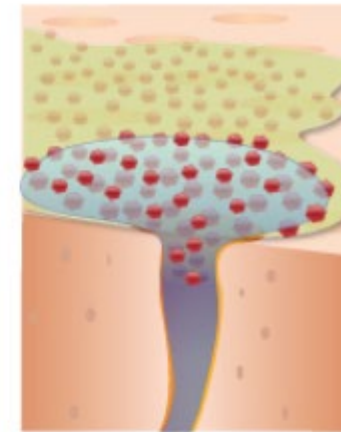
International Hyperhidrosis Society



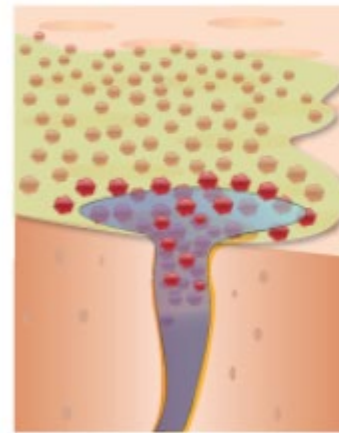
Sweat duct



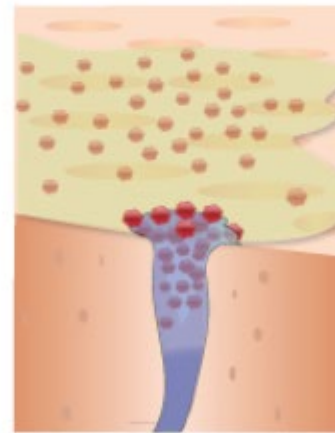
Antiperspirant is applied to skin



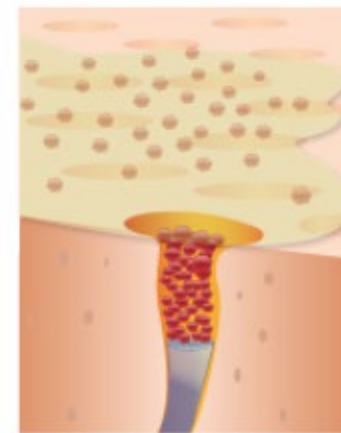
Perspiration mixes with antiperspirant



Antiperspirant mixes with perspiration on skin surface and in sweat duct



Chemical reaction occurs forming precipitate salt



Inside the sweat duct the antiperspirant forms a shallow plug reducing the flow of perspiration

TREATMENT: LIMITED THERAPEUTIC OPTIONS FOR CHILDREN WITH HYPERHIDROSIS

- **RX: NOT FDA APPROVED FOR PEDIATRIC HYPERHIDROSIS**
 - ORAL: OXYBUTININ, GLYCOPYRROLATE
 - TOPICAL: ALUMINUM CHLORIDE 20%

DEVICE: IONTOPHORESIS

- **FDA APPROVED 9 YEARS AND ABOVE:**
 - GLYCOPYRRONIUM TOSYLATE 2.4% CLOTH

OXYBUTYNIN

- MORE COMMONLY USED ANTICHOLINERGIC AGENT FOR CHILDREN FOR ALL INDICATIONS
- < 5 YEARS 0.1 MG / KG / DOSE UP TO TID – COMES AS 5 MG / 5 ML
- > 5 YEARS : 5 MG UP TO TID
- EXTENDED RELEASE FORMS :
 - NOT RECOMMENDED FOR HYPERHIDROSIS THERAPY

PREVIOUS STUDIES

- OXYBUTININ UP TO 10 MG TOTAL/DAY:
 - IMPROVED SYMPTOMS 60 TO 90%
 - SIDE EFFECTS: DRY MOUTH, CONSTIPATION, URINARY RETENTION, TACHCARDIA, BLURRY VISION, DROWSINESS
 - 11% STOP DRUG DUE TO SIDE EFFECTS

GLYCOPYRROLATE

- PEDIATRIC PATIENTS: ORAL THERAPY
 - 90 % EXPERIENCED IMPROVEMENT AT 2MG PER DAY
- SIDE EFFECTS NOTED IN 30%:
- DRY MOUTH
 - DRY EYES

PALLER AS, SHAH PR, SILVERIO AM, WAGNER A, CHAMBLIN SL, MANCINI AJ
J AM ACAD DERMATOL 2012: 67(5): 918 - 923

ORAL GLYCOPYRROLATE FOR REFRACTORY PEDIATRIC AND ADOLESCENT HYPERHIDROSIS

- REVIEW OF 12 CHILDREN PRESCRIBED MEDICATION
- 92% NOTED IMPROVEMENT
- 75% WOULD RECOMMEND MEDICATION TO THEIR FRIENDS

KUMAR MG, FOREMAN RS, BERK DR, BAYLISS SJ

PEDIATR DERMATOL VOL 31 (1), 2014: e28-30

ORAL GLYCOPYRROLATE FOR REFRACTORY PEDIATRIC AND ADOLESCENT HYPERHIDROSIS

- FDA APPROVED LIQUID FOR DROOLING
ASSOCIATED WITH CEREBRAL PALSY
- AGES \geq 3 YEARS

WILEY

PEDIATRIC DERMATOLOGY

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[Pediatr Dermatol.](#) 2019 Jan-Feb; 36(1): 89–99.

PMCID: [PMC6587744](#)

Published online 2018 Nov 19. doi: [10.1111/pde.13723](#)

PMID: [30451318](#)

Glycopyrronium tosylate in pediatric primary axillary hyperhidrosis: Post hoc analysis of efficacy and safety findings by age from two phase three randomized controlled trials

[Adelaide A. Hebert, MD,](#) ¹ [Dee Anna Glaser, MD,](#) ² [Lawrence Green, MD,](#) ³ [William P. Werschler, MD,](#) ⁴
[Douglass W. Forsha, MD,](#) ⁵ [Janice Drew, MPH,](#) ⁶ [Ramanan Gopalan, PhD,](#) ⁶ and [David M. Pariser, MD](#) ⁷

GLYCOPYRRONIUM TOSYLATE CLOTH

- INDICATED FOR AXILLARY HYPERHIDROSIS
- AGES 9 YEARS OF AGE and UP
- CLINICAL TRIAL: 4 WEEKS:
 - SIGNIFICANT IMPROVEMENT IN HYPERHIDROSIS-RELATED QOL vs THOSE RANDOMIZED TO PLACEBO
 - 72 TO 77 % OF PTS ON DRM04 HAD \geq 50% REDUCTION IN MEASURED SWEAT VOLUME COMPARED TO CONTROLS

GLYCOPYRRONIUM TOSYLATE CLOTH

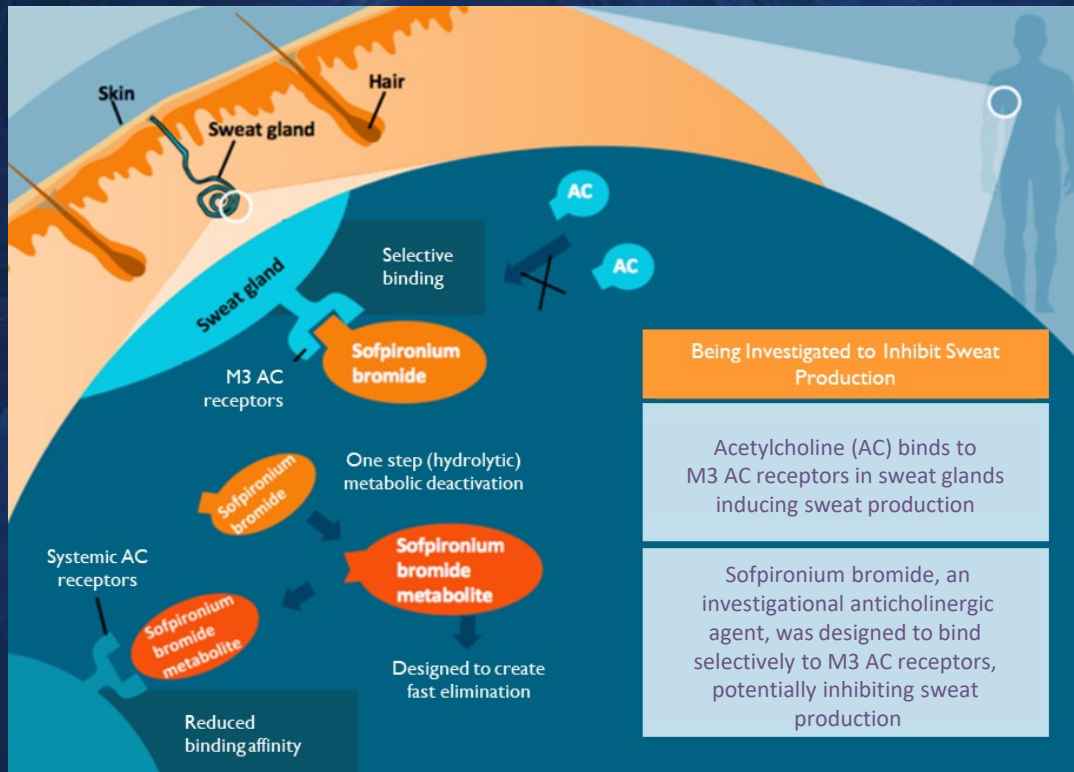
- SYMPTOMS OF SWEATING IMPROVED AS EARLY AS 1 WEEK AFTER STARTING TX
- ADVERSE EVENTS:
 - DRY MOUTH 16.9 TO 24.2%
 - ERYTHEMA/ AREA REDNESS 17%
 - BURNING/STINGING 14.1%

PEDIATRIC PATIENTS ENROLLED

- ONLY ONE PATIENT DROPPED OUT OF THE TRIAL
- THAT PATIENT:
 - HAD ANTICHOLINERGIC SIDE EFFECTS

Sofpironium Bromide: Retrometabolic Anticholinergic Agent

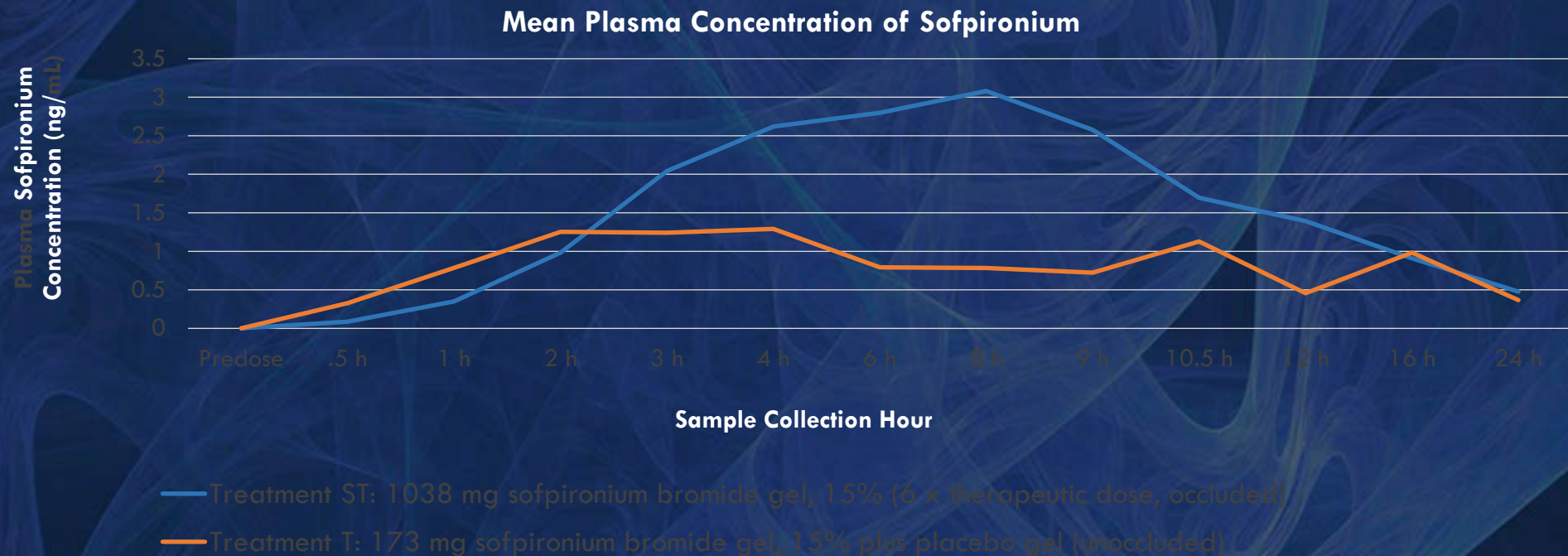
MECHANISM OF ACTION

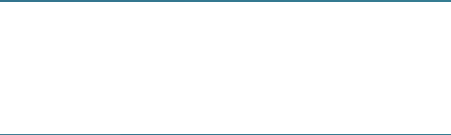


- **Sofpironium bromide** is an analog of glycopyrrolate (an anticholinergic agent)
- **Retrometabolic** molecules are designed such that they undergo rapid metabolism into less active moieties following absorption after topical application and therefore have a short systemic half-life.
- Allows for a potentially **enhanced therapeutic effect** at application sites with **reduced systemic side effects**.

Results for Systemic Absorption

As anticipated, systemic exposure increased more than 3-fold following suprathreshold dosing under occlusion





A Multi-Center, Open-Label Extension Study to Assess the Long-term Safety/Tolerability and Pharmacokinetics, and Explore the Efficacy of Sofpironium Bromide Gel, 15% Applied Topically to Children and Adolescents, 9 to 16 Years of Age, with Primary Axillary Hyperhidrosis

Brandon Kirsch, MD¹, Janet DuBois, MD², Martin N. Zaiac³, Deepak Chadha, MS, MBA, RAC⁴, Sanjeev Ahuja, MD, MBA, FACP⁴

¹Kirsch Dermatology, Naples, FL ²DermResearch Inc., Austin, TX, ³Sweet Hope Research Specialty, Hialeah, FL, ⁴Brickell Biotech, Inc., Boulder, CO

Study Objective & Methods

Objectives:

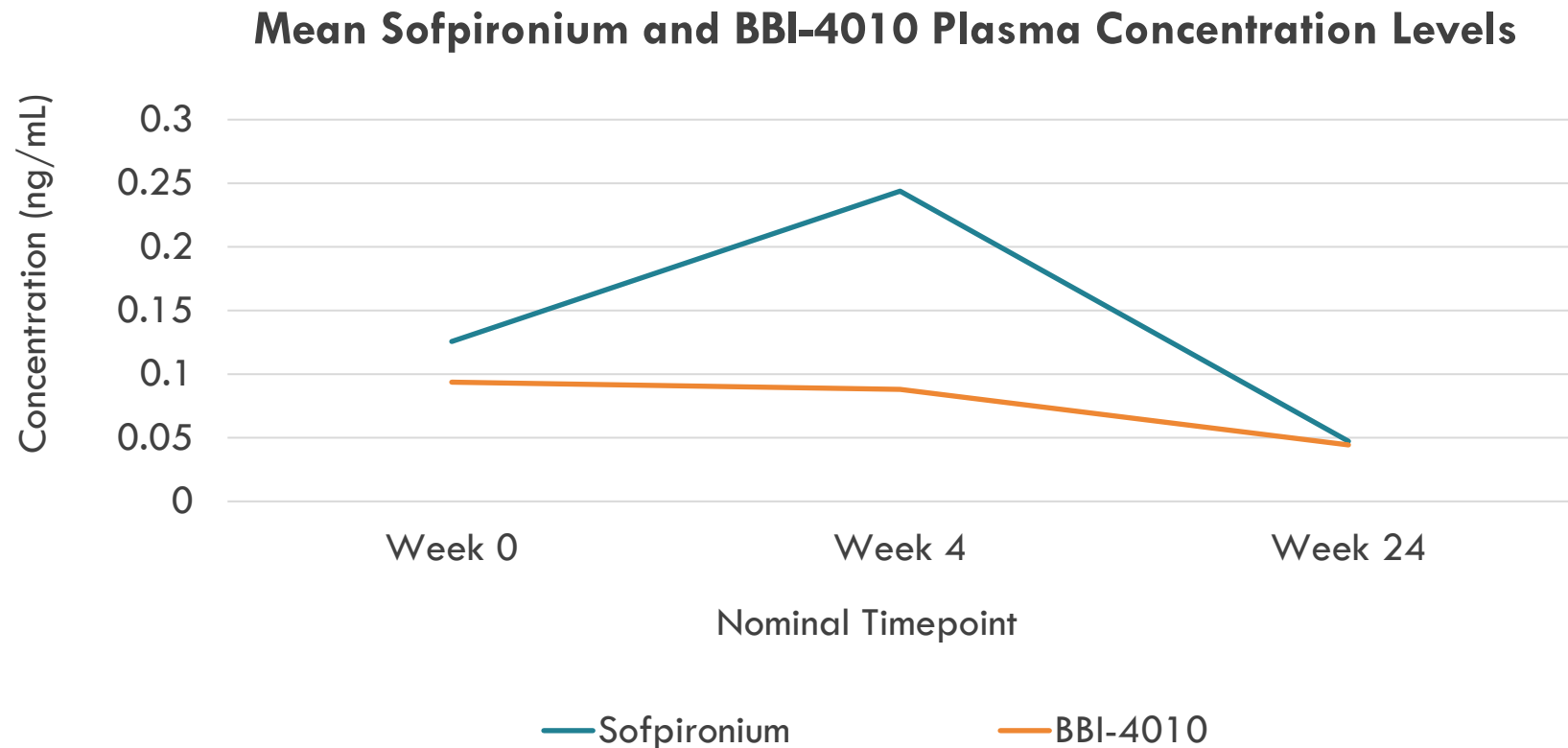
- ▶ Evaluate the long-term safety, tolerability and pharmacokinetics of topically applied sofpironium bromide gel, 15% for the treatment of axillary hyperhidrosis in pediatric subjects, as well as to explore efficacy

Methods:

- ▶ 21 subjects ages ≥ 9 to ≤ 16 with at least 6 months duration of axillary hyperhidrosis who completed a previous 1-week safety and pharmacokinetic study were enrolled
- ▶ Subjects were dosed daily for 24 weeks

Results for Systemic Absorption

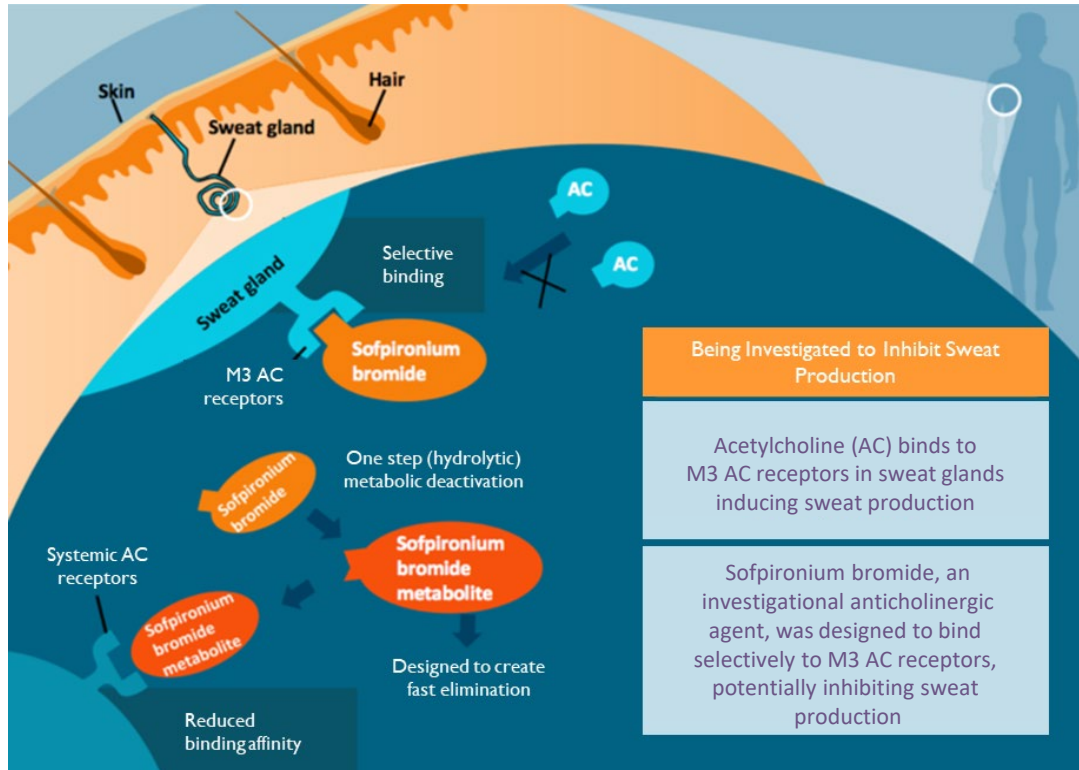
There was minimal systemic exposure and no evidence of accumulation



Note: Plasma concentrations of sofpironium and its primary metabolite (BBI-4010) were detected in 9 subjects and 7 subjects, respectively

Sofpironium Bromide: Retrometabolic Anticholinergic Agent

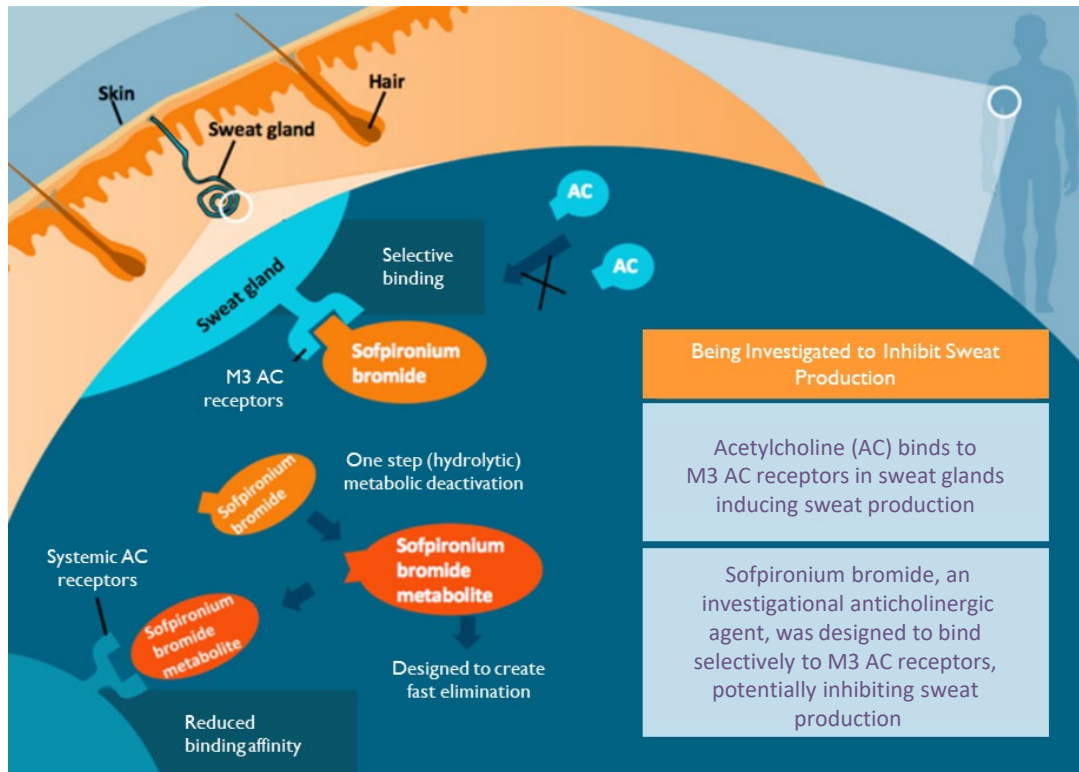
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Sofpironium Bromide: Retrometabolic Anticholinergic Agent

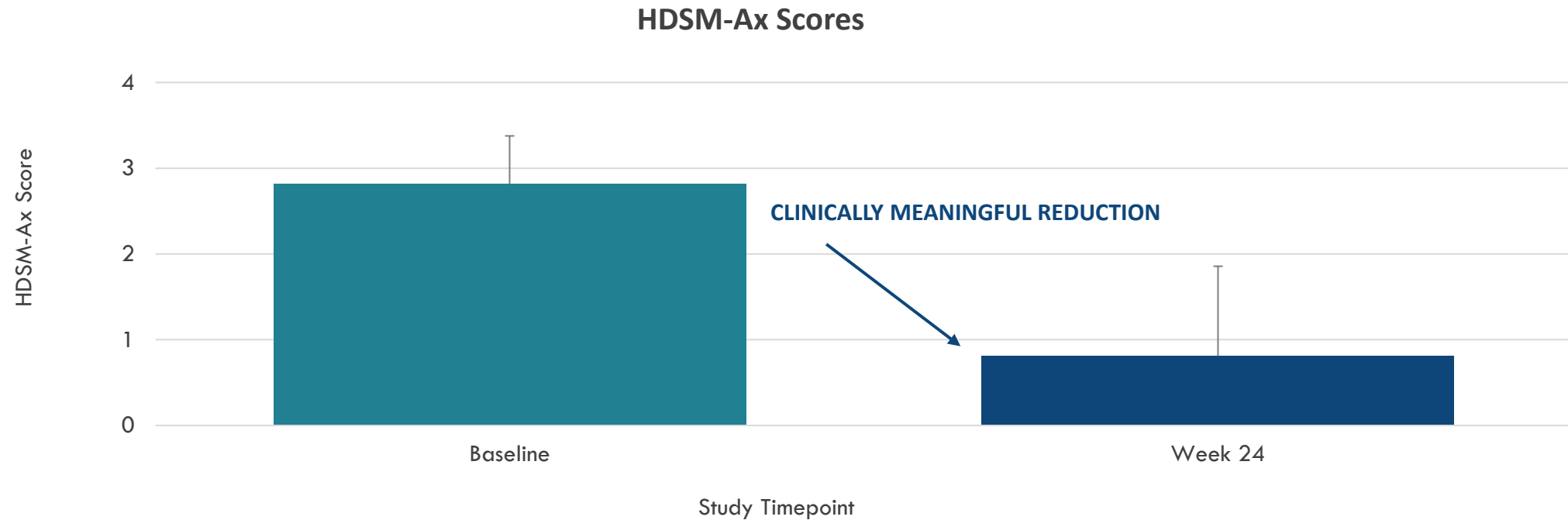
MECHANISM OF ACTION



- **Sofpironium bromide** is an analog of glycopyrrolate (an anticholinergic agent)
- **Retrometabolic** molecules are designed such that they undergo rapid metabolism into less active moieties following absorption after topical application and therefore have a short systemic half-life.
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Results for Efficacy (HDSM-Ax)¹

Clinically meaningful reduction in axillary hyperhidrosis severity



¹The Hyperhidrosis Disease Severity Measure-Axillary© (HDSM-Ax) is a validated 11-item measure of axillary hyperhidrosis severity and frequency with a 5-point scale for each item. A change of -1.00 from the mean baseline score has been defined to represent clinically meaningful improvement.

INTERNATIONAL HYPERHIDROSIS SOCIETY

- [Sweathelp.org](https://www.sweathelp.org)
- GENERAL EDUCATION
- INSURANCE TOOLS
- PODCASTS
- HYPERHIDROSIS TREATMENT MATRIX

INTERNATIONAL HYPERHIDROSIS SOCIETY

- Sweathelp.org
- LIST OF MEDICATIONS THAT CAN CAUSE HYPERHIDROSIS

SPECIAL CONSIDERATIONS

- DYAUTONOMIA
- EHLORS DANLOS

UNIQUE CONSIDERATIONS WITH PATIENTS THAT HAVE HYPERHIDROSIS

- DYSAUTONMIA
- DRUG INDUCED HYPERHIDROSIS
 - LOOK AT SWEAT HELP.ORG WEB SITE:
 - FOR LIST OF MEDICATIONS THAT MAY BE IMPLICATED
 - FOR PRODUCTS, FORMS, INSURANCE INFORMATION

DYSAUTONOMIA

- HYPERHIDROSIS
- FLUSHING
- CYANOSIS
- JOINT HYPERMOBILITY : EHLERS DANLOS
- FAINTING
- LIVEDO RETICULARIS



Dysautonomia and Joint Hypermobility

- Hypermobile-type Ehlers-Danlos Syndrome (EDS) is characterized by generalized joint hypermobility and skin texture abnormalities
- Hypermobile EDS is common among patients with dysautonomia



WHY CONSIDER THE PEDIATRIC POPULATION UNIQUE IN THE REALM OF HYPERHIDROSIS?

- AGE OF ONSET
- ANATOMIC DISTRIBUTION OF SWEATING
- IMPACT ON:
 - SCHOOL
 - DEVELOPMENT OF SELF CONFIDENCE
 - LIMITED THERAPIES APPROVED

Codes for Hyperhidrosis

ICD 10 codes

- Primary focal hyperhidrosis:
 - axillae: L54.510
 - palm: L54.512
 - sole: L54.513
 - unspecified: L54.519
- Secondary hyperhidrosis: L54.52
- Generalized hyperhidrosis: R61

HYPERHIDROSIS

- DISORDER THAT OFTEN BEGINS IN CHILDHOOD
- EMBARRASSING
- UNCOMFORTABLE
- ANXIETY INDUCING
- AT TIMES:
 - DISABLING
 - ISOLATING