Evidence Supporting the Efficacy of Oral Phenylephrine and Its Role in U.S. Healthcare

September 11-12, 2023

U.S. Food and Drug Administration

Nonprescription Drugs Advisory Committee

Member Companies of the
Consumer Healthcare Products Association (CHPA)

Introduction

Marcia D. Howard, Ph.D., CAE

Vice President, Regulatory & Scientific Affairs

CHPA

9 Member Companies Comprise CHPA Phenylephrine (PE) Task Group

Oral Phenylephrine 10 mg Approved for Temporary Relief of Nasal Congestion

KEEP OUTER PACKAGE FOR COMPLETE PRODUCT INFORMATION

Drug Facts

Active ingredient (in each tablet) **Purpose**

Phenylephrine HCl 10 mg ..... Nasal decongestant

Uses

When using this product do not exceed recommended dosage.

Stop use and ask a doctor if

- nervousness, dizziness, or sleeplessness occur
- symptoms do not improve within 7 days or occur with fever

Drug Facts (continued)

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- adults and children 12 years and over: take 1 tablet every 4 hours. Do not take more than 6 tablets in 24 hours.
- children under 12 years: ask a doctor

Other information

- **TAMPER EVIDENT: DO NOT USE IF OUTER PACKAGE IS OPENED OR BLISTER IS TORN OR BROKEN**
- store at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F)
- see end flap for expiration date and lot number

Inactive ingredients croscarmellose sodium, dextrose monohydrate, dibasic calcium phosphate dihydrate, FD&C red #40, lecithin, magnesium stearate, maltodextrin, microcrystalline cellulose, silicon dioxide, sodium carboxymethylcellulose, sodium citrate dihydrate, titanium dioxide

Questions or comments? 1-888-287-1915

Active Ingredient (in each tablet) Purpose

Phenylephrine 10 mg ..... Nasal decongestant

Uses

- temporarily relieves nasal congestion due to the common cold, hay fever or other upper respiratory allergies
- temporarily relieves sinus congestion and pressure

Current OTC Treatment Landscape for Nasal Decongestion

Active Ingredient	Oral Route of Administration	Sold OTC Without Restriction	Sold in Combinations	Dosing Duration
Phenylephrine*	✓	✓	✓	≤ 7 days
Pseudoephedrine	✓	**	✓	≤ 7 days
Xylometazoline nasal		✓		≤ 3 days
Oxymetazoline nasal		✓		≤ 3 days
Propylhexedrine inhaler		✓		≤ 3 days
Naphazoline nasal		✓		≤ 3 days

Consumers prefer oral formulations over intranasal 3 to 1***

*Phenylephrine also sold as intranasal formulation; **Sold OTC “behind-the-counter”; *** Nielsen xAOC, from July 1st 2022 – June 30th 2023

Background: Pathways for OTC Marketing Status

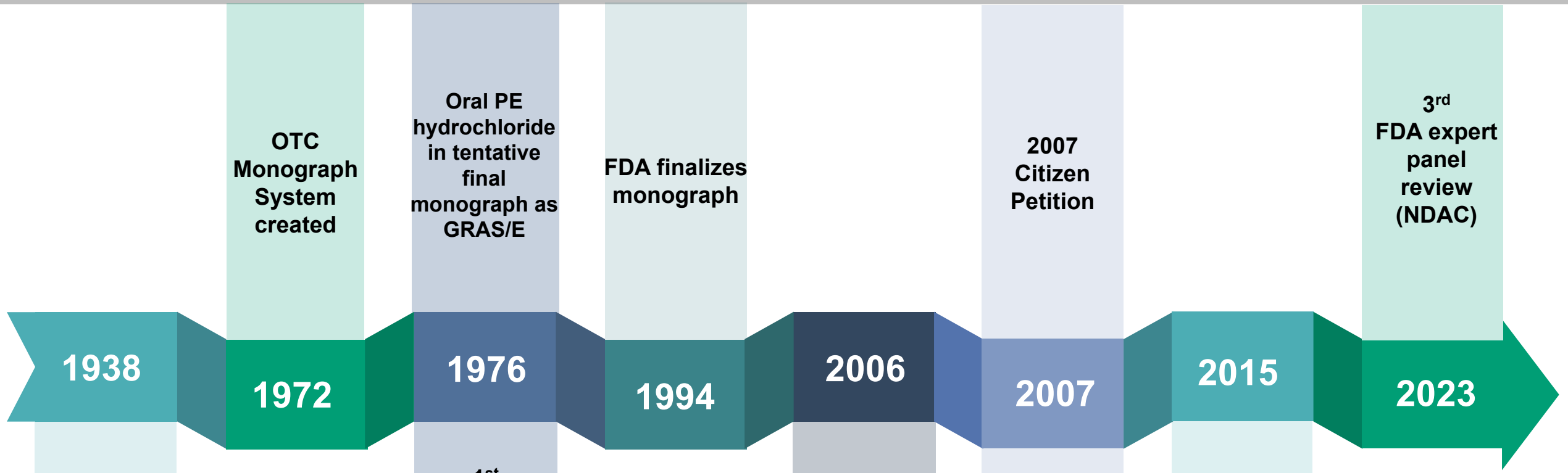
1 **New Drug Application**

2 **OTC Monograph System**

- Methodical, scientific process to systematically review data on established ingredients
- “Rule book” on ingredients, indications, doses, etc.
- Includes ingredients = **G**enerally **R**ecognized **A**s **S**afe and **E**ffective (GRAS/E)

~100,000 OTC medicines in U.S. (Monograph & NDA). GAO 2020 [https://www.gao.gov/products/gao-20-572]

Timeline of FDA Advisory Panel Reviews for Oral Phenylephrine



OTC Oral Phenylephrine Has Important Role in Consumer Self-Treatment of Nasal Congestion

- Only available oral nonprescription medicine for nasal congestion sold without restrictions

- Brand-name & store-brand products
- Treats bothersome symptom
- High consumer satisfaction[1]
  - 50% of sampled households purchased oral PE last year
    - 68% repurchased oral PE
- Available in U.S. and globally
- Wide margin of safety

1. Circana (formerly IRI); all outlets, all doses; 52-week data April 2022 to April 2023

Voice of the Consumer: Survey of American Adults on Oral Phenylephrine

- American adults repeatedly rely on oral PE
  - Effectiveness as a nasal decongestant
  - Physical and personal benefits when they use it
    - Especially true among older adults and people living in rural communities
- Significant burden to consumers and healthcare system if oral PE were not available OTC

National Consumer Survey on Phenylephrine, The Bullfinch Group for CHPA, July 24-28, 2023
[https://www.chpa.org/sites/default/files/media/docs/2023-08/2023-PE-Survey.pdf]

- **1,200 adults (age 21+) reporting use of any OTC medicine with oral PE in past 12 months**
- **Margin of error +/- 2.83, 95% confidence level**
- **Over-sampling: ages 50+ and rural areas**

Consumers Say Phenylephrine Helps Relieve Congestion, Has Meaningful Impact on Daily Activity

83%	*"Medicines with PE help relieve my nasal congestion"*
66%	*"PE helps me get through my day because it relieves my nasal congestion"*
78%	*"Sometimes I need relief from mild/moderate symptoms"*
69%	*"Mild/moderate congestion has a negative effect on my daily activities, sleep, and work"*

National Consumer Survey on Phenylephrine. Conducted by The Bullfinch Group, 2023

Removal of Oral Phenylephrine Would Burden Consumers and the Healthcare System

"If* [oral PE] *were no longer available, what would you do instead if you had nasal or sinus congestion?"

42%	*"I would seek a behind-the-counter decongestant"*
39%	*"I would make an appointment with a doctor"*
26%	*"I would go to a clinic or urgent care"*
14%	*"I would go without treatment"*

Additional burden on the consumer and a burden on the healthcare system

National Consumer Survey on Phenylephrine. Conducted by The Bullfinch Group, 2023

Voice of Consumer Underscores Unintended Consequences of Oral Phenylephrine Removal

- > 50% of American households rely on oral phenylephrine
- Challenges with pseudoephedrine availability*
  - Impacts on manufacturing, retailers, and consumers
- Unequal burden on consumers
- Impact on the healthcare system
- Potential of worsened clinical outcomes due to lack of treatment

*Combat Methamphetamine Epidemic Act of 2005 [https://www.deadiversion.usdoj.gov/meth/pl109_177.pdf]

Addressing Issues Cited in FDA Briefing Materials and Misconceptions About Phenylephrine

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Change in GRAS/E status will have significant unintended consequences	✓ Removal would mean increased demand for PSE; shortage of FDA-approved, on-shelf products; supply chain implications; burden on consumers and healthcare system

Agenda

Assessment of Nasal Congestion	**Howard M. Druce, M.D.** Clinical Professor of Medicine Rutgers New Jersey Medical School
Clinical Pharmacology of Phenylephrine	**Cathy K. Gelotte, Ph.D.** Clinical Pharmacology Consultant
Efficacy	**Howard M. Druce, M.D.**
Discussion and Comparison of Meta-Analyses	**Chris M. Mullin, M.S.** Director, Global Strategy Services NAMSA
Benefit-Risk Profile	**Marcia D. Howard, Ph.D., CAE** Vice President, Regulatory & Scientific Affairs CHPA

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CHPA

Assessment of Nasal Congestion

Howard M. Druce, M.D.

Clinical Professor of Medicine

Division of Allergy, Immunology and Rheumatology

Department of Medicine

Rutgers New Jersey Medical School, Newark, NJ

Sufferers of Upper Respiratory Allergies and Common Cold Self-Manage Symptoms

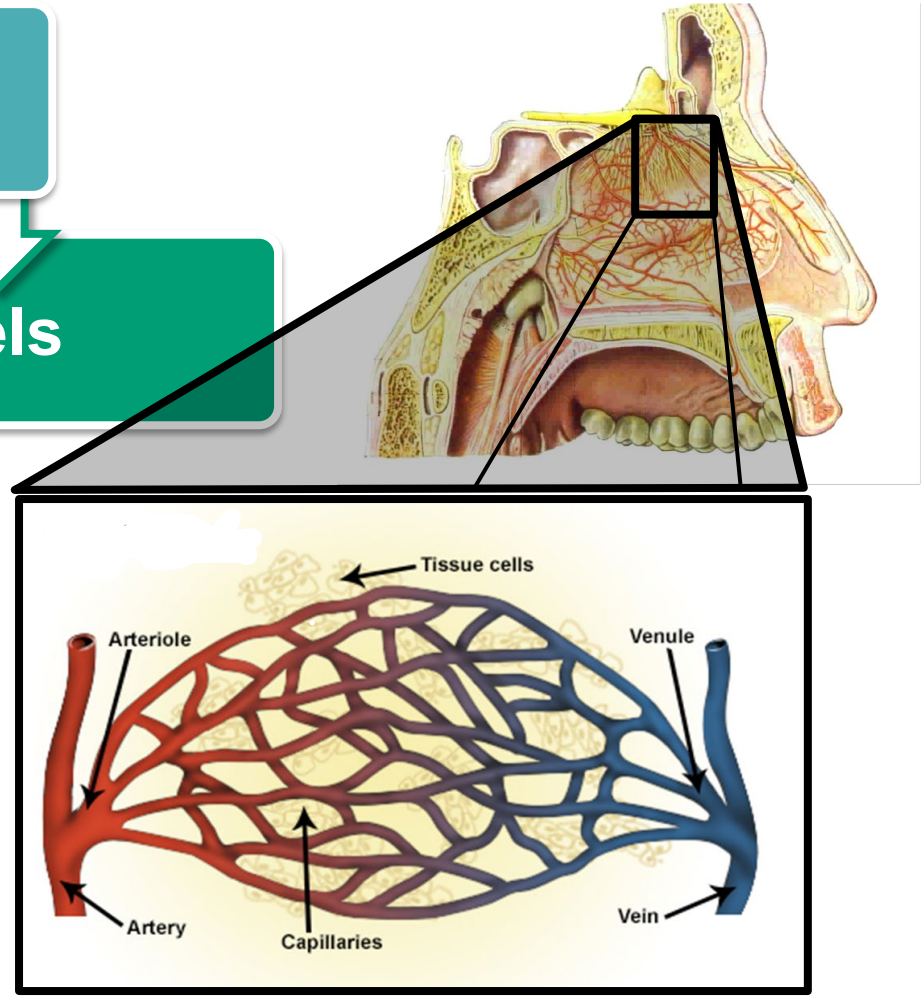
- Majority of sufferers of upper respiratory allergies self-manage condition, do not seek medical intervention
  - Symptoms limited or transient
- Proportion of self-management higher in common cold

Oral phenylephrine 10 mg is labeled to provide *temporary* relief of nasal congestion

Pathogenesis of Temporary Nasal Congestion

Common cold, hay fever, or upper respiratory allergies

Dilatation of nasal blood vessels



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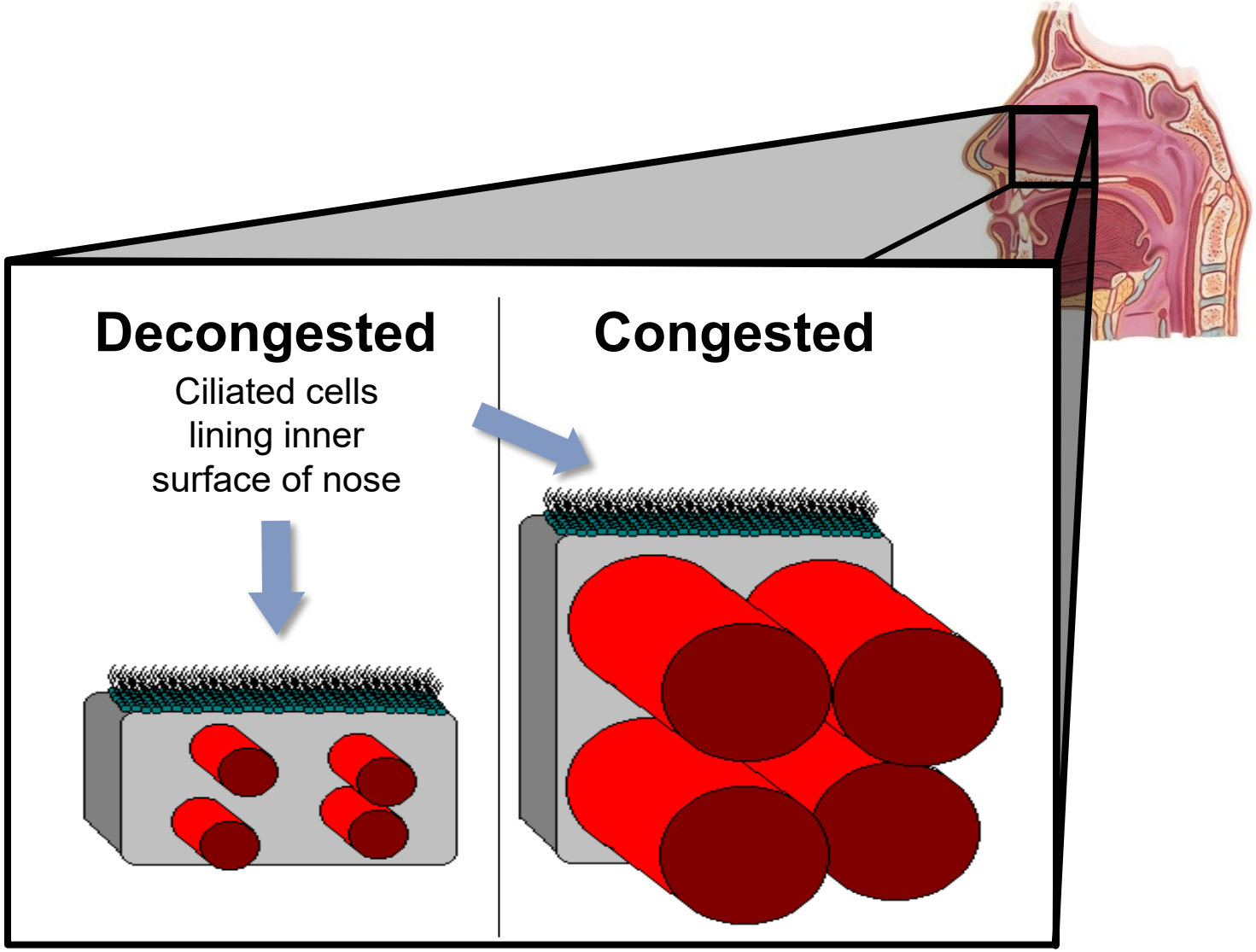
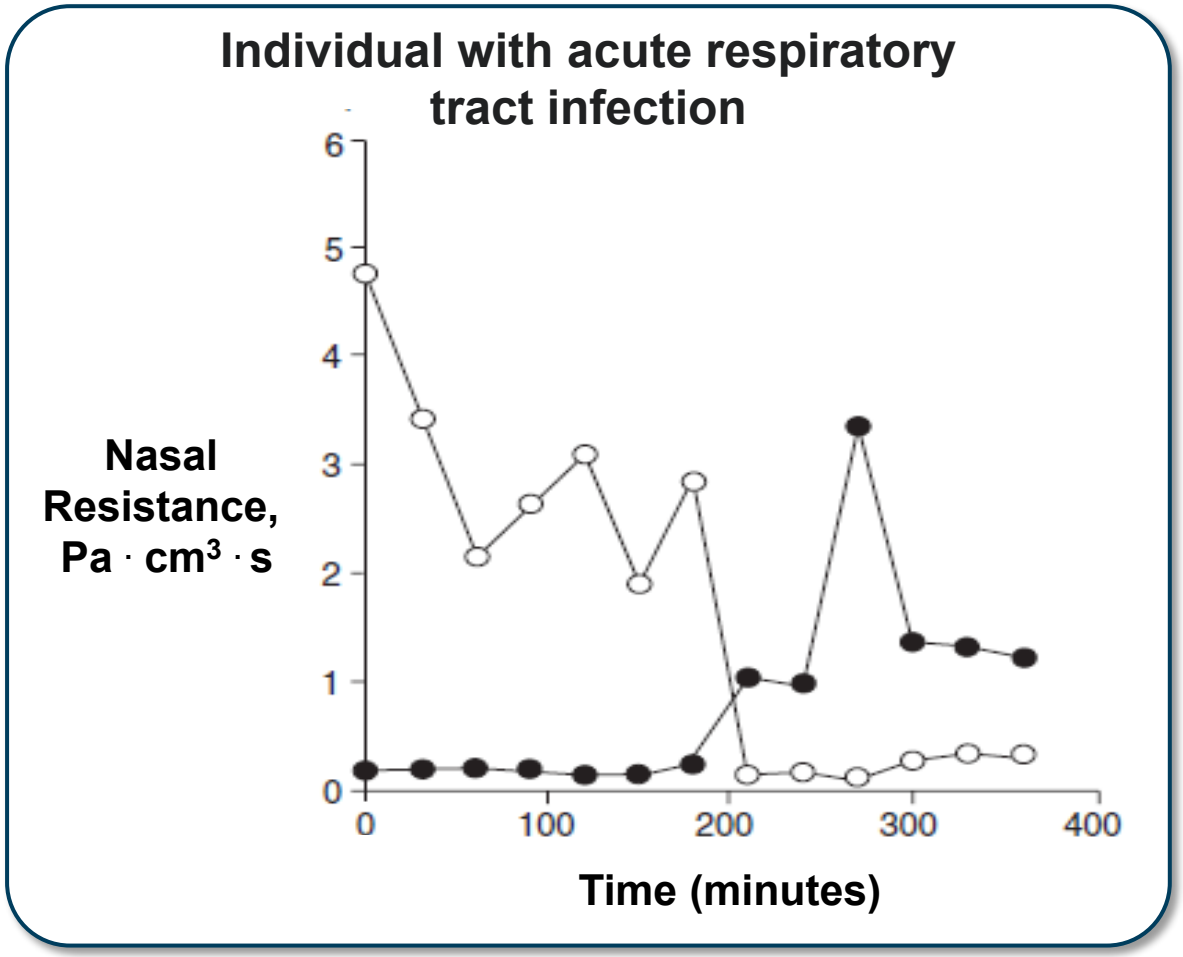
NIH: Classification & Structure of Blood Vessels

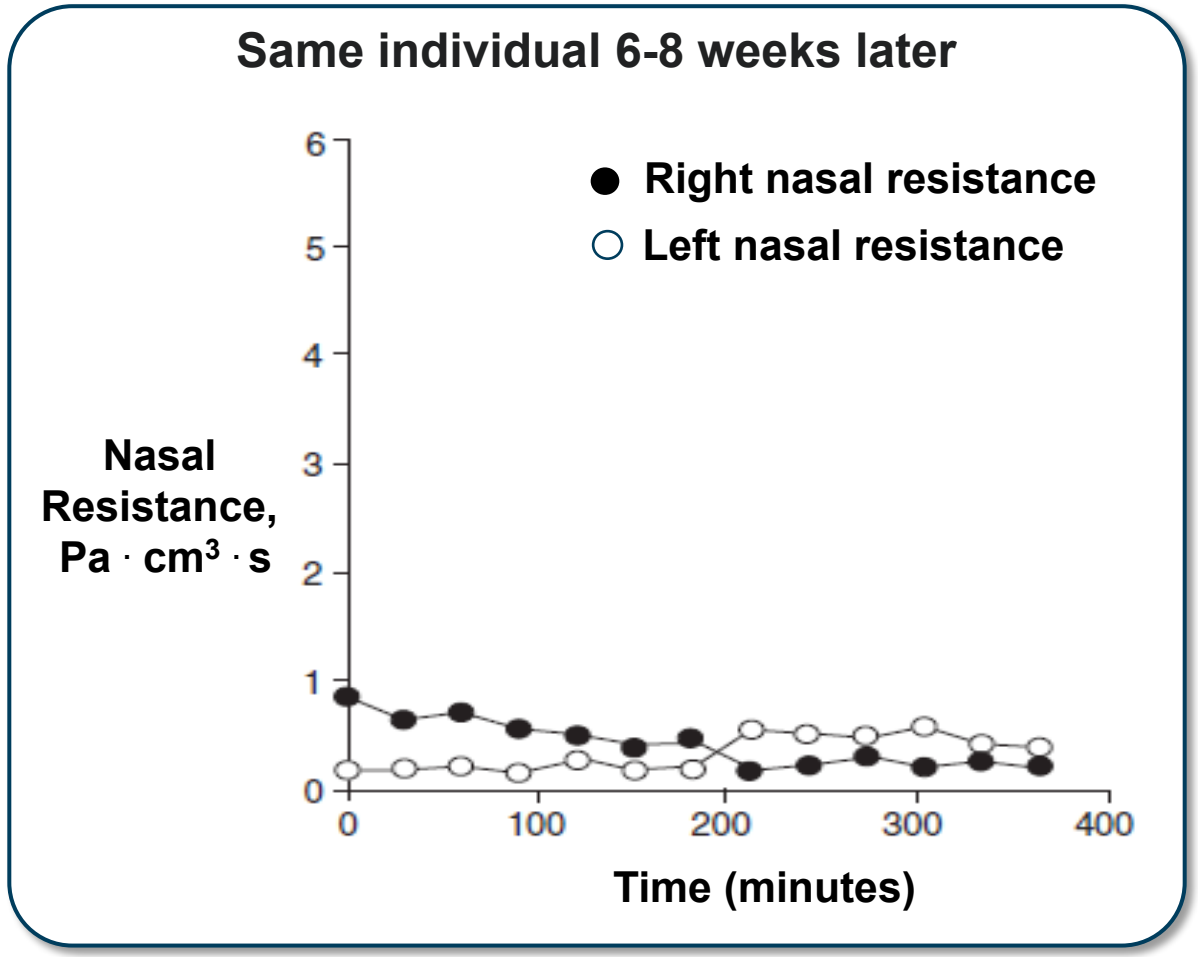
Nasal Anatomy and Function: Capillary Sinusoids Inside Nasal Turbinate Mucosa

- Capillary sinusoids: blood vessels that make up bulk of nasal turbinate mucosal vascular supply
- Turbinate mucosa containing sinusoids: major site of action for nasal decongestants



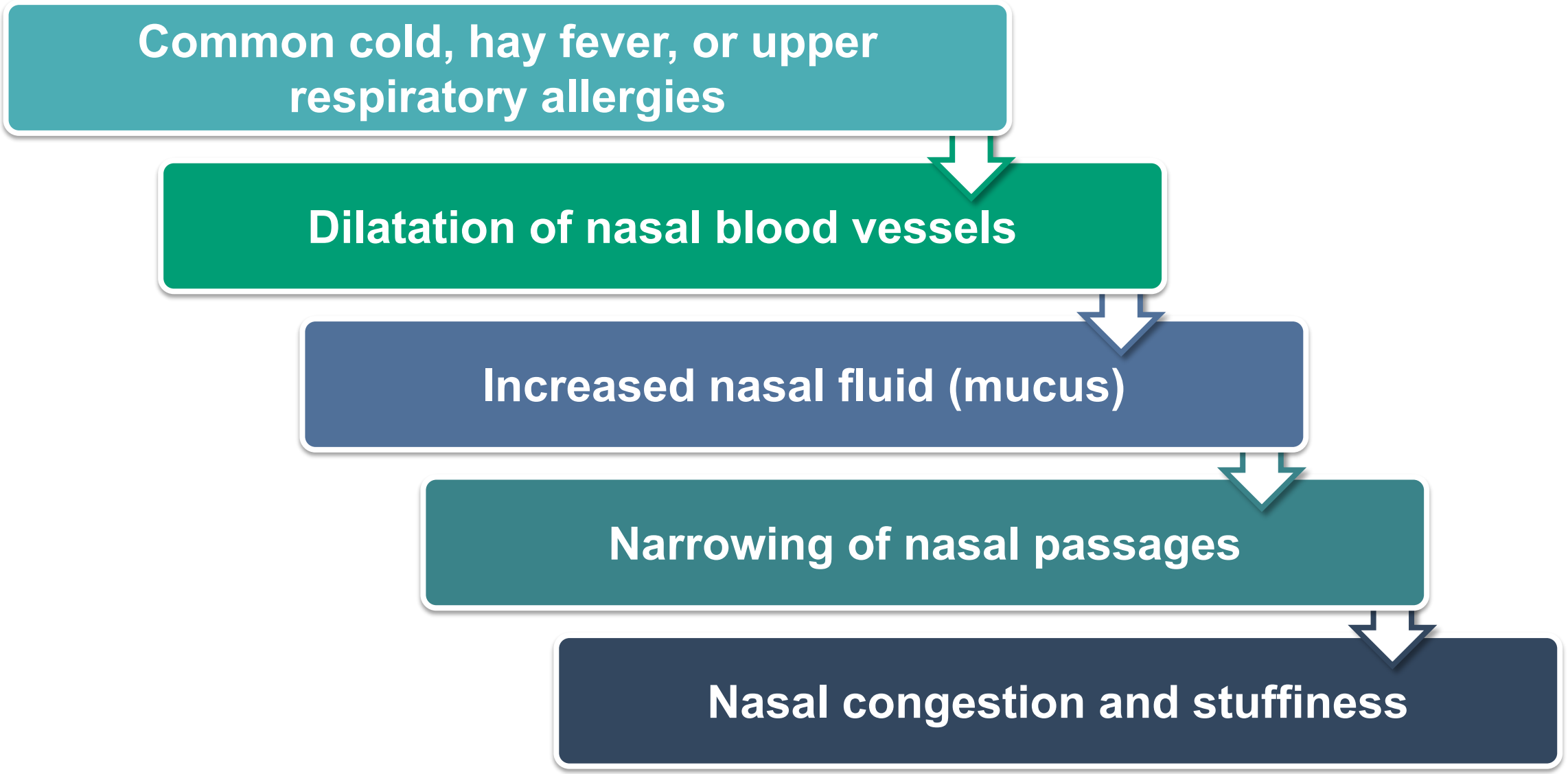
Extreme Congestion Perceived When Nasal Cycle Disrupted





Eccles 1996 *Eur Resp J* 9(2):371-6

Dilatation of Blood Vessels Within the Turbinates Is Major Feature of Temporary Nasal Congestion

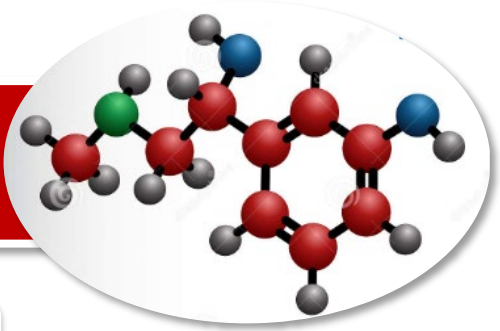


Pathogenesis of Temporary Nasal Congestion

Common cold, hay fever, or upper respiratory allergies

Dilation of nasal blood vessels

Reverse dilatation



Increased nasal fluid (mucus)

Narrowing of nasal passages

Nasal congestion and stuffiness

Mechanism by Which Decongestants Relieve Temporary Nasal Congestion

- Activation of alpha receptors
  - Direct binding of sympathomimetic agent to binding site of receptor or
  - Enhanced release of norepinephrine produces vasoconstriction
- Vasoconstriction decreases blood flow through nasal mucosa and results in shrinkage of tissue
- Nasal congestion: most bothersome symptom of common cold and upper respiratory allergies

Common Cold and Seasonal Allergic Rhinitis (SAR) Are Different Conditions

- Different etiology, pathophysiology, time course, and response to medications
- However, the mechanism of vasoconstriction is the same in both conditions
- In SAR
  - Inflammatory IgE-mediated hypersensitivity response may affect overall tissue recoil in the nasal turbinate mucosa
  - Vasoconstrictors alone may not remediate nasal congestion

Both acute conditions are self-diagnosable and self-treatable by the vast majority of consumers using OTCs without a healthcare professional

Different Histopathology but No Known Differences in Blood Vessels

Common Cold[1]

- Sloughing of epithelial cells in nose with completely intact epithelial lining
- Early neutrophil migration (2nd day) in disease
  - No involvement of mast cells or other cells

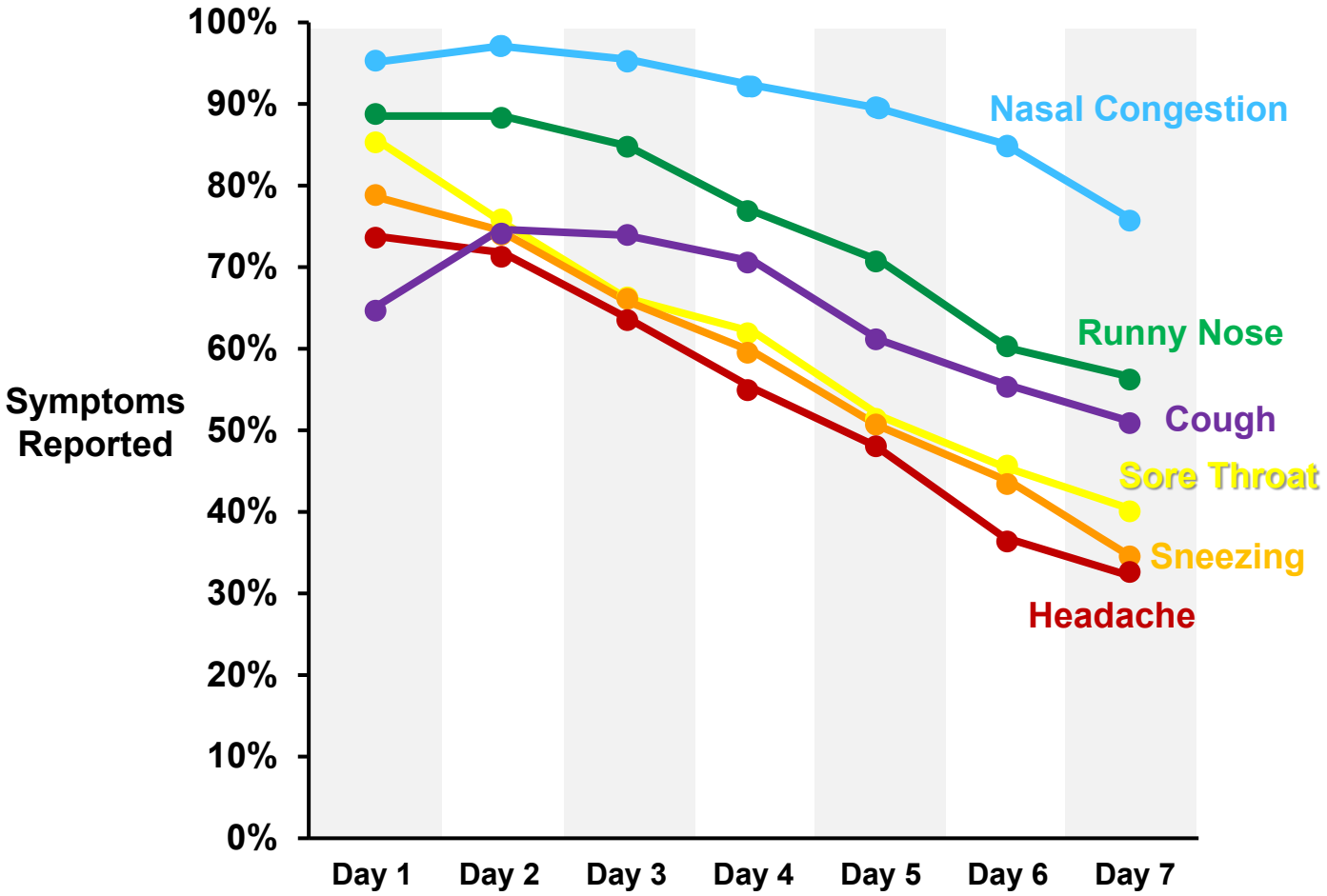
Allergic Rhinitis[2]

- Thickening of basement membrane, goblet cells, and squamous metaplasia
- Increased number of mast cells
- Eosinophilia may be present
- Stromal markers showed edema and fibrosis which characterize remodeling and consequent turbinate hypertrophy

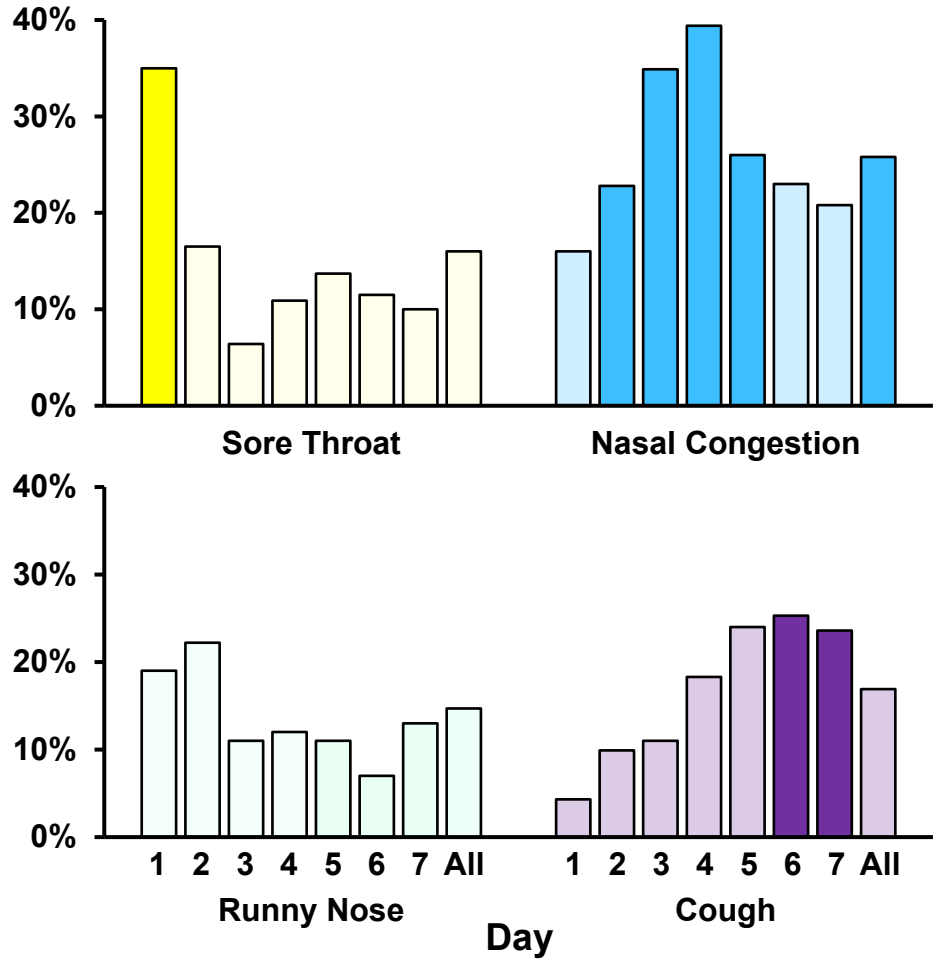
1. Winther et al. 1984 *Acta Otolaryngol* 97(3-4):309-18; 2. Rios-Deidan et al. 2023 *Ind J Otolaryn Head Neck Surg* DOI: 10.1007/s12070-023-03922-y

Nasal Congestion Most Frequent and Most Bothersome Symptom of Common Cold

Overall Daily Cold Symptoms Reported[a]



Single Most Bothersome Symptom During a Cold



Pharmacy Times: Feb 2016 [https://www.pharmacytimes.com/view/r743_february2016]

[a]Symptoms reported by 104 patients throughout the day (assessed at 9 am, 3 pm, and 9 pm) over 226 cold episodes

Nasal Congestion in Common Cold: Importance of Phenylephrine Combination Products

- Phenylephrine in most combination products
  - Treat concurrent nasopharyngeal symptoms such as sneezing, runny and itchy nose, sore throat, and sinus pressure
- Combination products containing decongestant can provide more complete and clinically meaningful benefit

Davis and Eccles 2004, *Clin Otolaryngol All Sci* 29(6):659-66

Upper Respiratory Allergies: An Important Distinction

Upper Respiratory Allergies

Sufferers with allergies that last for few hours or days

- Majority self-manage symptoms
  - Adequate symptom relief by avoiding allergy triggers, OTC H1-antihistamines, OTC decongestants
  - Symptoms typically transient, occur more frequently on peak allergy days

Patients diagnosed as having seasonal allergic rhinitis

- May choose temporary decongestant
- Other symptoms may require additional treatment

Summary: The Science of Congestion

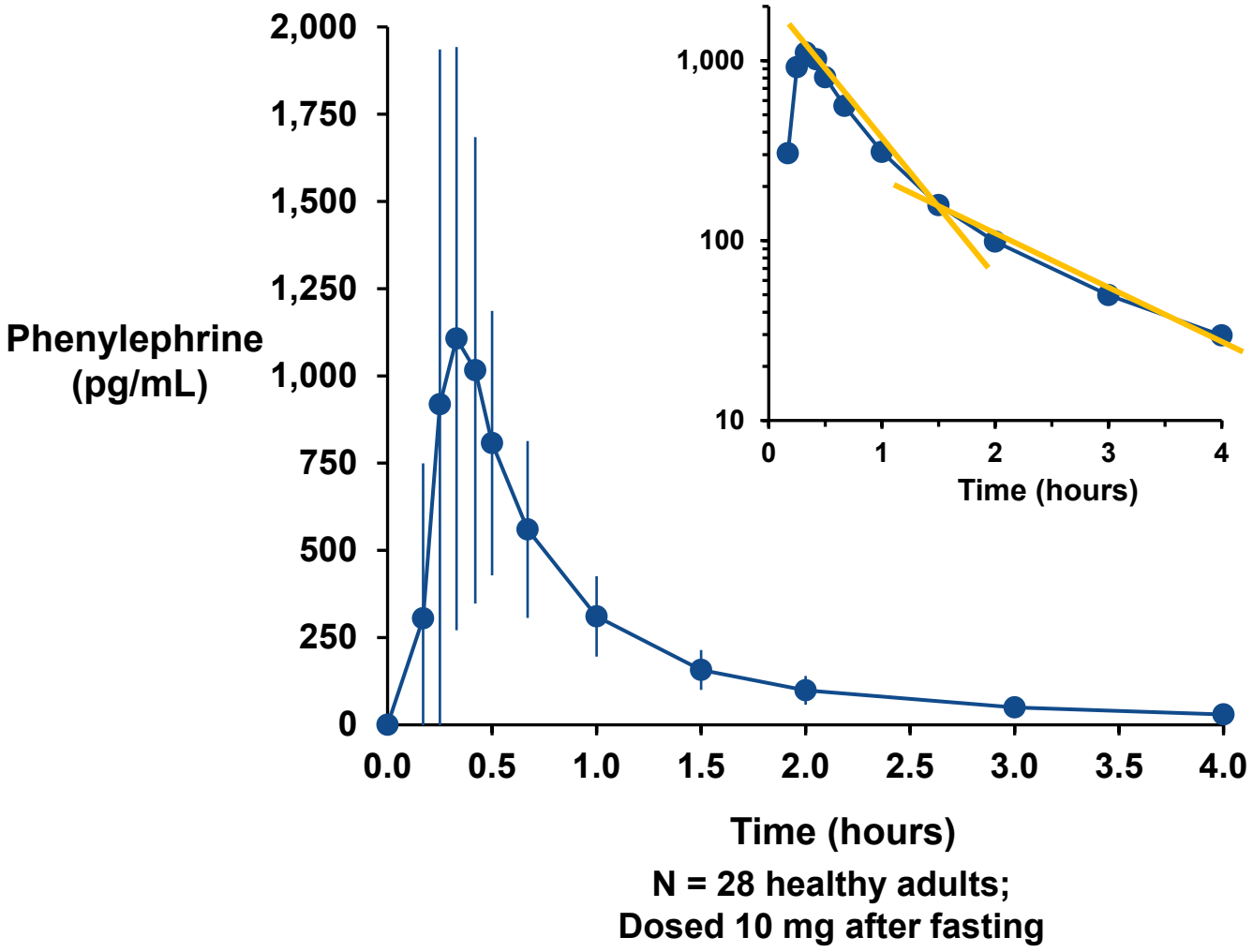
- Upper respiratory viral infections and upper respiratory allergies are different conditions with different pathophysiology
- Scientific literature review showed no difference in blood vessels or mechanism of congestion / decongestion
- More difficult to detect evidence of decongestion in established and persistent seasonal allergic conditions
  - Appropriate clinical trial endpoint critical

Clinical Pharmacology of Phenylephrine

Cathy K. Gelotte, Ph.D.

Clinical Pharmacology Consultant

Pharmacokinetics of 10 mg Phenylephrine



N = 28 healthy adults;
Dosed 10 mg after fasting

- High first-pass metabolism
  - Sulfate conjugation
- Rapid distribution phase
- t½ (h) = 1.9 ± 0.8
- Volume distribution (Vd/F) = 24.8 ± 10.2 (x 10^3 L)
- Absolute bioavailability (F)[1] ~ 38%

1. Hengstmann et al. 1982, *Eur J Clin Pharmacol* 21(4):335-41; F not confirmed with other IV and oral data using contemporary analytical methods

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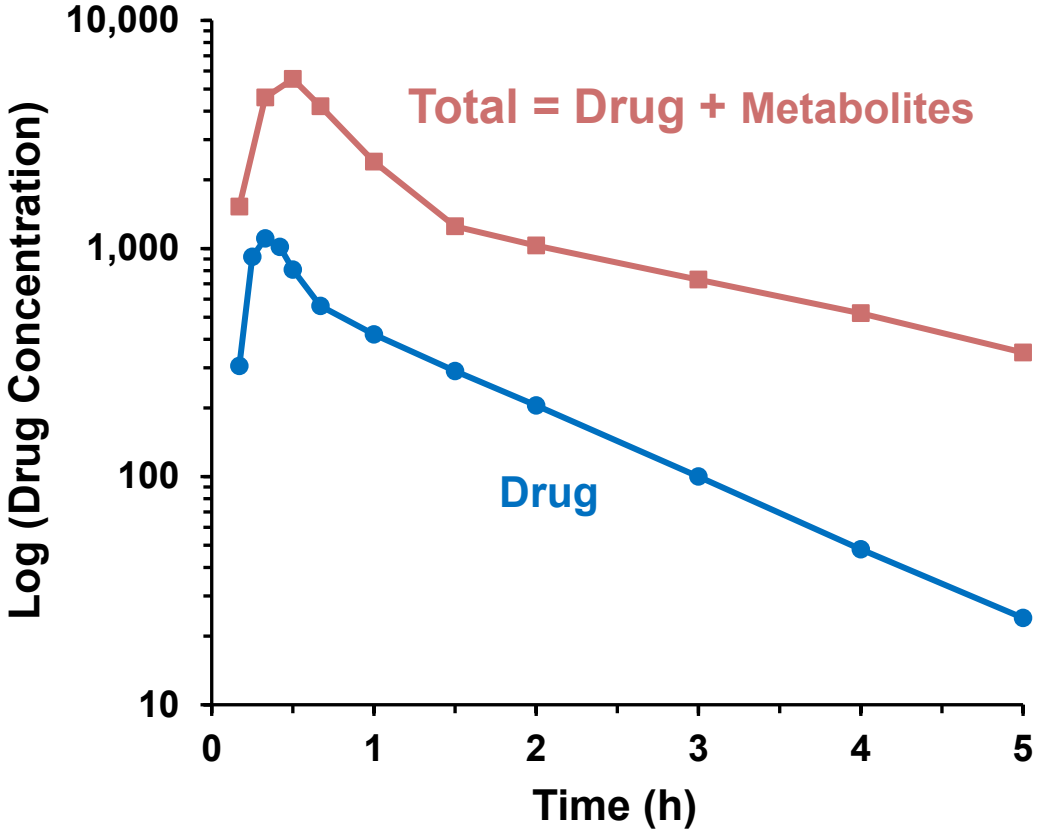
Absolute Bioavailability of Phenylephrine Not Confirmed; Other Estimations Violate Basic Principles

- Estimated from concentrations of *"active moiety* in pharmaceutical equivalents or pharmaceutical alternatives when administered at the same molar dose."*



$$F_{relative} = \left(\frac{AUC\ PE\ (ng \cdot h/mL)}{AUC\ Total\ PE\ (ng \cdot h/mL)} \right)$$

- "Total PE" AUC includes inactive moieties (metabolites)
- Each metabolite has different volume of distribution and elimination rate
- Clinical plasma concentrations (ng/mL) of each moiety must be corrected for differences in molar mass

*21 Code of Federal Regulations § 314.3 "Bioavailability"

Low Bioavailability (BA) Does Not Mean a Medicine Lacks Efficacy

- Other key factors in determining efficacy
  - Receptor density
  - Effect site concentrations
  - Drug potency
  - Intracellular mediators

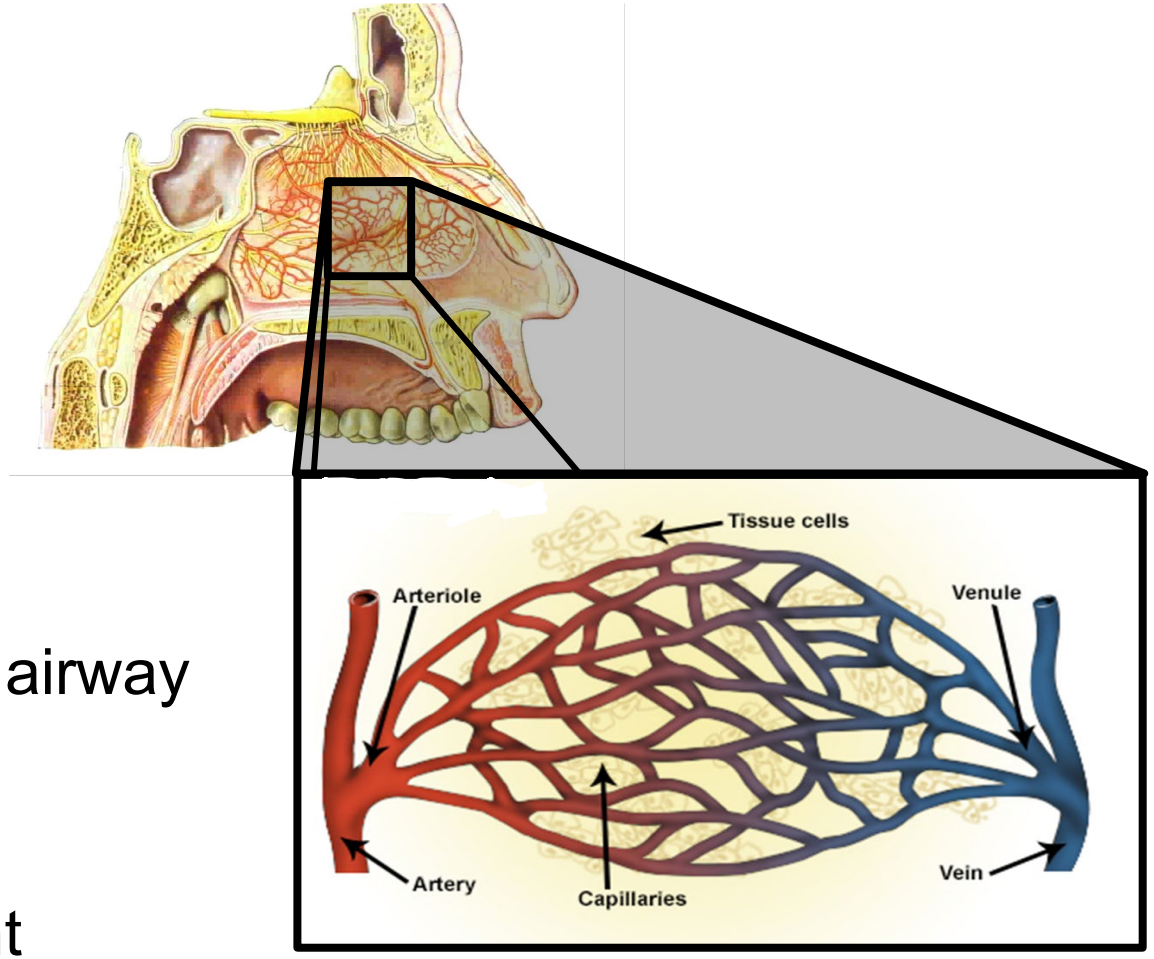
Drug	% BA	Therapeutic Indication
Desmopressin	0.08-0.16	Central diabetes insipidus
Pamidronate	0.31-0.48	Paget's Disease
Risedronate	0.6	Osteoporosis
Alendronate	0.76	Osteoporosis
Zanamivir	2-2.5	Acute influenza A and B
Saquinavir	4	HIV/AIDS
Sumatriptan	15	Migraine
Phenylephrine	38* (?)	Nasal congestion
Loratadine	40	Allergy symptoms
Chlorpheniramine	40.8	Allergy symptoms

Therapeutic effects demonstrated in clinical studies at oral doses tested

***Hengstmann et al. 1982, *Eur J Clin Pharmacol* 21(4):335-41; F is not confirmed with other IV and oral data using with contemporary analytical methods**

Phenylephrine's Mechanism of Action: α1 Adrenergic Receptor Agonist

- Decongestion from constriction of local arterioles that lead to capillaries
- Arteriole constriction
  - Decreases fluid entering densely packed capillary beds
  - Promotes shrinking of swollen turbinates
- Easier breathing due to diminished nasal airway resistance, decreased stuffiness
- Minimal adverse pressor effects at 10 mg
  - Much higher oral doses for significant constriction of peripheral blood vessels



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Potency Is Just One Contributory Factor of Clinical Efficacy

Potency

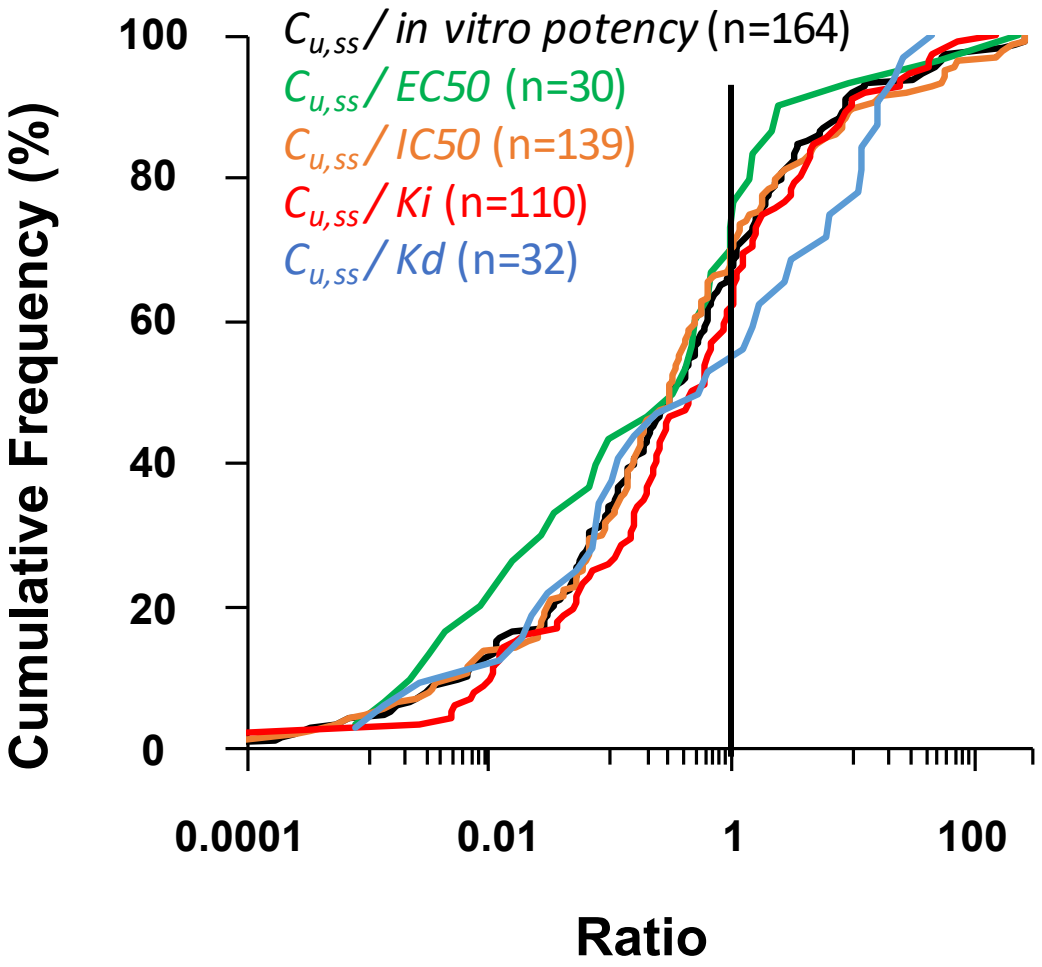
- Drug concentration needed to produce a certain response
- *In vitro* bioassays for drug screening (closed systems)
- Dependencies
  - Rates of drug-receptor binding / release
  - Receptor affinity

Efficacy

- Ability of a drug to elicit a physiologic response when interacting with receptors
- Dependencies
  - Effect site concentrations
  - Number of receptors - expressed differently among tissues; mediate different levels of response
  - Disease states - may alter drug pharmacokinetics or receptor numbers
  - Potency

For example: *in vitro* potency of PE (EC50 = 2.3 and 16.9 ng/mL) for α1-adrenergic agonism using calcium flux response assay > clinical plasma concentrations (0.4 to 2.3 ng/mL)

Many Drugs Have Clinically Effective Concentrations that Are Lower than *in Vitro* Potency Values



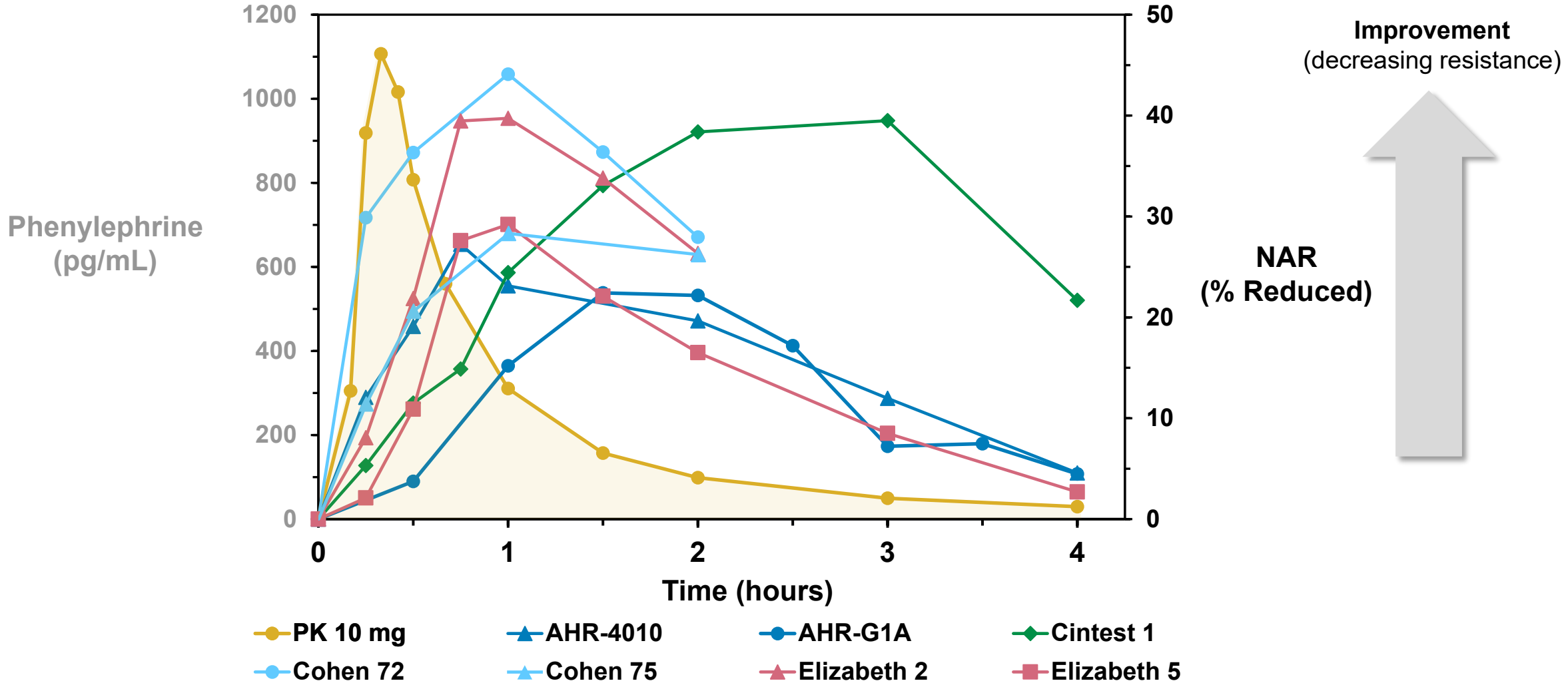
Compound	Receptor	*In Vivo* C_{ss} (nM)	*In Vivo* $C_{u,ss}$ (nM)	Ratio = $C_{u,ss}$ / *in vitro* potency
Montelukast	Leukotriene	153.5	0.31	0.039
Diphenhydramine	Histamine H1	344.0	5.16	0.088
Phenylephrine*	α1-Adrenergic	1.33	1.29	0.094
Cetirizine	Histamine H1	252.7	17.7	0.582
Chlorpheniramine	Histamine H1	52.0	36.4	3.277

C_{ss} = plasma concentration at steady state; $C_{u,ss}$ = unbound C_{ss}

Jansson-Löfmark et al. 2020, *Clin Pharmacol Ther* 108(2):298-305

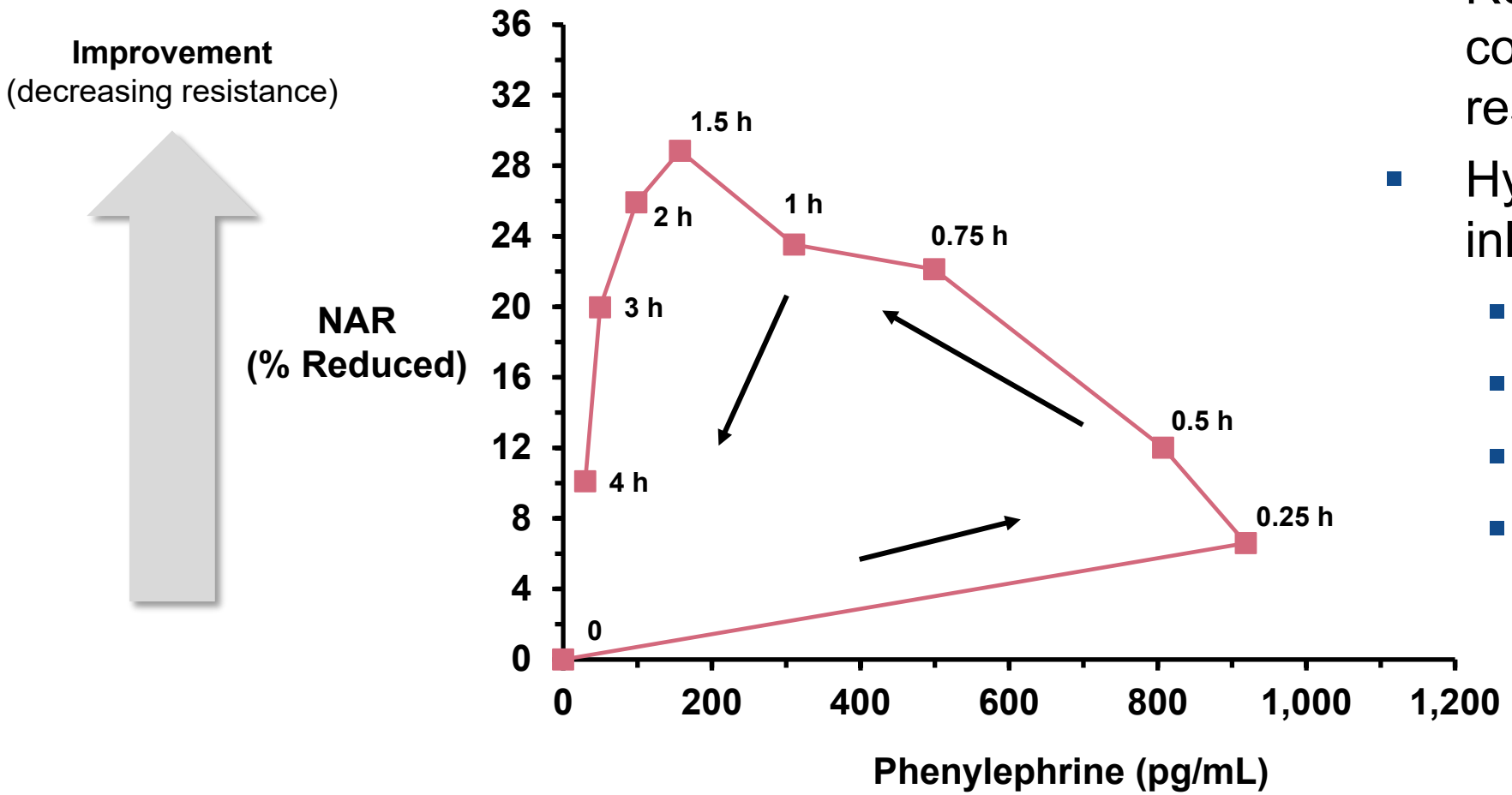
*Human PK data 10 mg dose from Gelotte and Zimmerman 2015 *Clin Drug Invest* 35(9):547-58; EC50 data from Schering-Plough Corp slides (2007 NDAC Meeting)

Relationship Between PE Concentration and % Change in Nasal Airway Resistance Shows Duration of Action



NAR = Nasal airway resistance

Cross-Study PK-PD Relationship Shows Counterclockwise Hysteresis for Oral PE 10 mg



- Relationship between PE concentrations and NAR response is not direct
- Hysteresis loops imply inherent time delay
  - Distribution kinetics
  - Uptake into active site
  - Slow receptor kinetics
  - Tolerance (clockwise)

Studies: PK - Gelotte and Zimmerman 2015, *Clin Drug Investig* 35(9):547-58; NAR - Monograph Studies AHR-4010, AHR-G1A, Cintest #1, and Elizabeth #5

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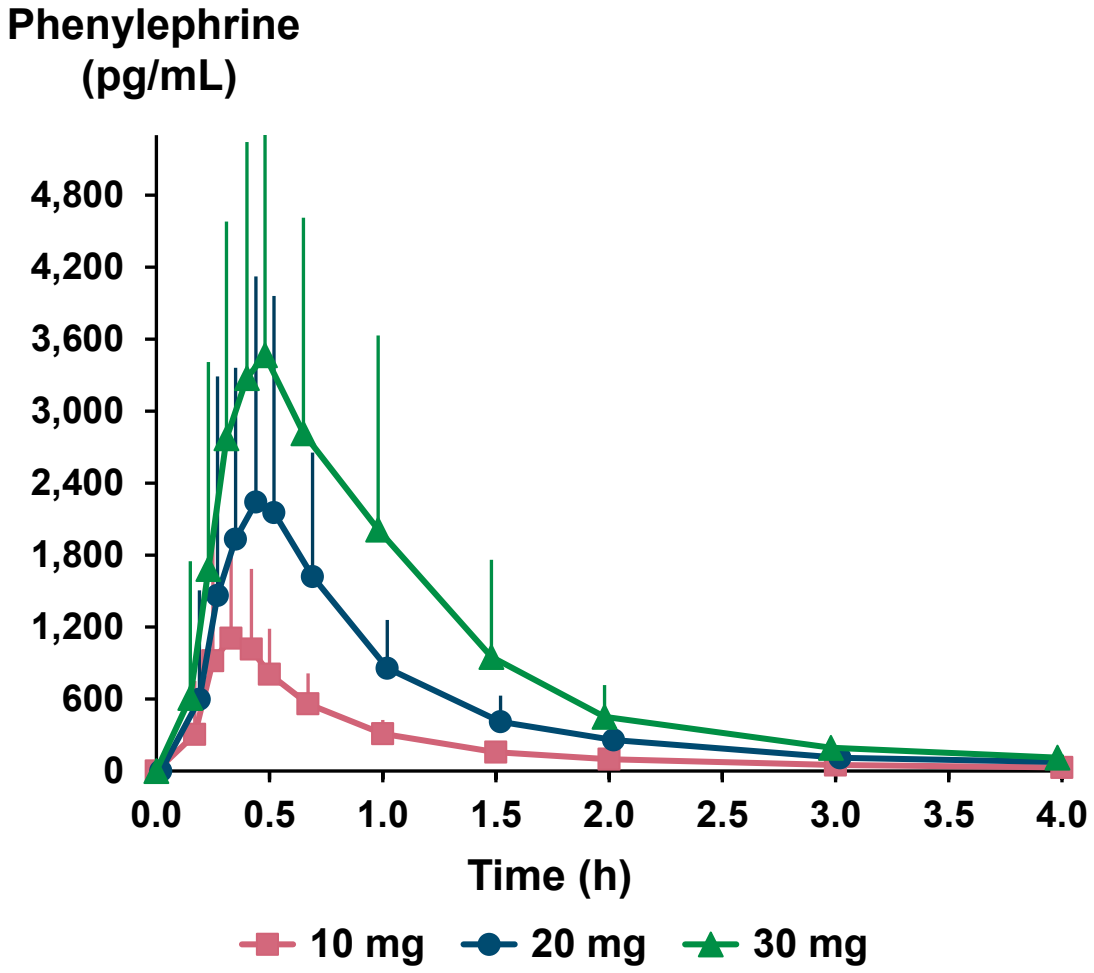
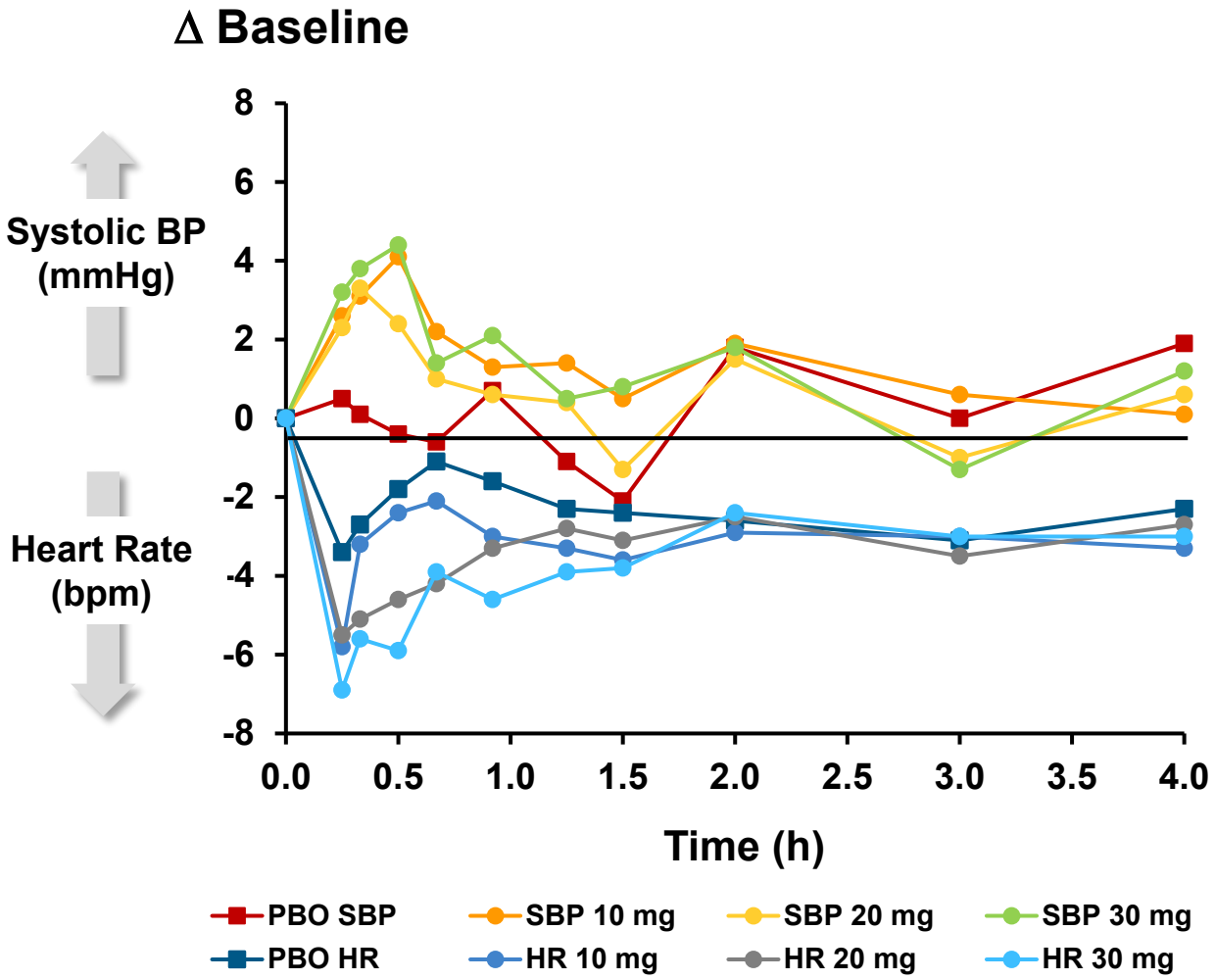
Differential Decongestion and Hemodynamic Responses of Oral Phenylephrine

- Direct stimulation of nasal and peripheral vasculature with phenylephrine results in vasoconstriction
- Responsiveness in various tissues varies quantitatively
  - Differences in distribution of receptors
  - Differences in concentrations at effect sites
  - Reflex changes in heart rate due to stimulation of baroreceptors that diminish pressor response

Homeostasis of Peripheral Blood Pressure Through Reflex Bradycardia Results in Diminished Responses



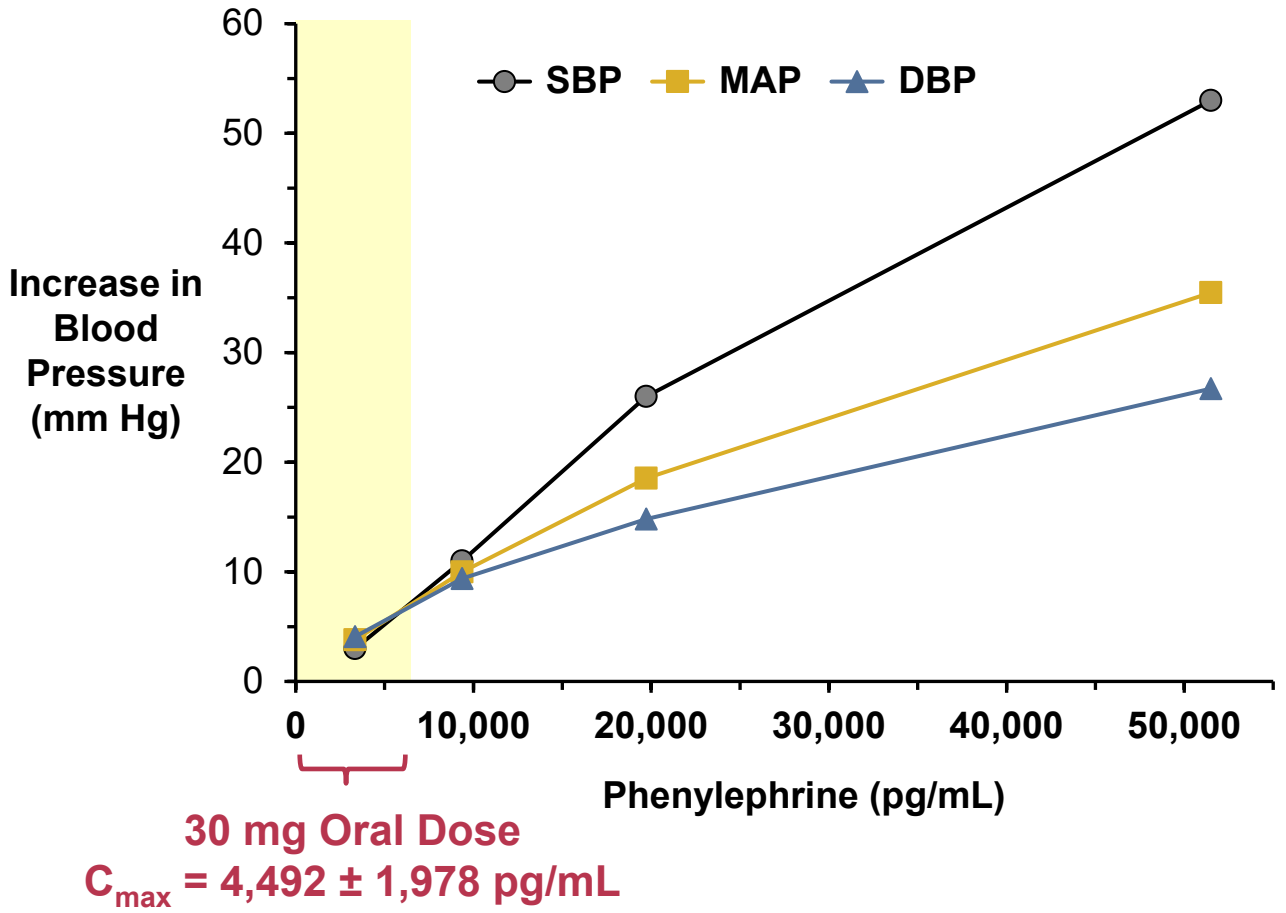
Single-dose study of three PE doses and placebo in 28 adults
Gelotte and Zimmerman 2015, *Clin Drug Invest* 35(9):547-58



HR = heart rate; PBO = placebo; SBP = systolic blood pressure

Minimal Adverse Effects on Blood Pressure Does Not Mean Lack of Decongestant Effects on Nasal Mucosa

- Having minimal pressor effects in clinical studies reinforces PE's favorable safety profile
- Martinsson study[1]
  - Healthy adults (7M/2F)
  - Infused 4 doses of phenylephrine
  - Evaluated pressor effects



1. Martinsson et al. 1986, *Eur J Clin Pharmacol* 30(4):427-31

SBP = systolic blood pressure; MAP = mean arterial pressure; DBP = diastolic blood pressure

Summary: Clinical Pharmacology

- Concentration-time profile of phenylephrine
  - Shows rapid distribution to site of action
  - Supports labeled 4-hour dosing interval
- Clinical concentrations are consistent with oral PE 10 mg being effective
  - Therapeutic effects (e.g., decreased NAR) demonstrated in clinical studies at doses evaluated
- Baroreflex response to PE diminishes increases in blood pressure at doses from 10 to 30 mg

Efficacy

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Clinical Professor of Medicine

Division of Allergy, Immunology and Rheumatology

Department of Medicine

Rutgers New Jersey Medical School, Newark, NJ

Addressing Issues Cited in FDA Briefing Materials and Misconceptions About Phenylephrine

Issues and Misconceptions	CHPA's Position
Removal of oral PE from final monograph	Totality of evidence supports efficacy ✓ No safety signals identified Consumer repurchase data indicate high consumer satisfaction
Low bioavailability indicates lack of efficacy	Multiple interacting factors determine efficacy: concentration at active site, drug potency, receptor sensitivity, and intracellular mediators
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Lack of adverse pressor effects at labeled dose indicates lack of efficacy	Homeostatic mechanism likely has a role in diminished pressor effects Reinforces safety profile
Nasal airway resistance no longer used	✓ Appropriate objective measurement of temporary nasal congestion
Monograph studies do not support GRAS/E	*Scientific basis and measurements still appropriate and relevant*
Post-2007 studies do not support efficacy	Post-2007 studies all have methodology limitations Post-2007 studies do not negate previous findings of efficacy and safety
2007 meta-analyses were inconclusive	Kollar meta-analysis used more relevant endpoint, individual patient data, well-accepted statistical methods
Change in GRAS/E status will have significant unintended consequences	Removal would mean increased demand for PSE; shortage of FDA-approved, on-shelf products; supply chain implications; burden on consumers and healthcare system

Both Objective and Subjective Measurements Provide Valuable Information

Primary Objective Endpoint

Most critical to capture short-term decongestant changes typical of drugs like phenylephrine

Nasal Airway Resistance (NAR): An Objective Measurement of Nasal Congestion

- Most appropriate clinical endpoint to assess temporary decongestion of oral PE 10 mg as labeled
- Subjective measurements of nasal congestion will be lost in 12-hr or 24-hr scoring, especially a 12-hr morning reflective score
  - Dosing interval for oral PE 10 mg is up to 4 hours to provide temporary relief

Objective Measurement of Nasal Congestion

- Multiple techniques (anterior, posterior, acoustic rhinometry, peak nasal inspiratory flow)[1,2]
  - Anterior rhinometry: most widely used technology for clinical trials; can measure flow through each nostril separately

Rhinostat Labs

- Operator-dependent, but accurate and standardized[2] in small studies
- No recent submissions (as mentioned in FDA's briefing materials) using an objective measurement as a primary endpoint

1. Clement et al. 1984, *Rhinology* 22(3):151-5; 2. Demirbas et al. 2011, *Expert Rev Med Devices* 8(6):769-77

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Challenges in Studying Effects of Nasal Congestion: Clinical Trial Design and Populations

Assess severity via objective or subjective measures	**Objective**	▪ Nasal airway resistance (NAR)
	Subjective	▪ Symptom diary scores (descriptors or visual analog scale/VAS)
Varied methodology	**Studies performed after 2007**	▪ Randomized, controlled, parallel-group studies ▪ Allergen chamber studies for patients with established allergic rhinitis ▪ Open-label studies
Patient selection	**Nasal congestion typically self-managed**	▪ Inclusion criteria: studies tend to enroll patients with > severity

Efficacy of Oral PE 10 mg Accepted by FDA (1976) and Re-Affirmed by NDAC (2007)

14 Monograph studies — Studies evaluating oral PE 10 mg conducted prior to 2007

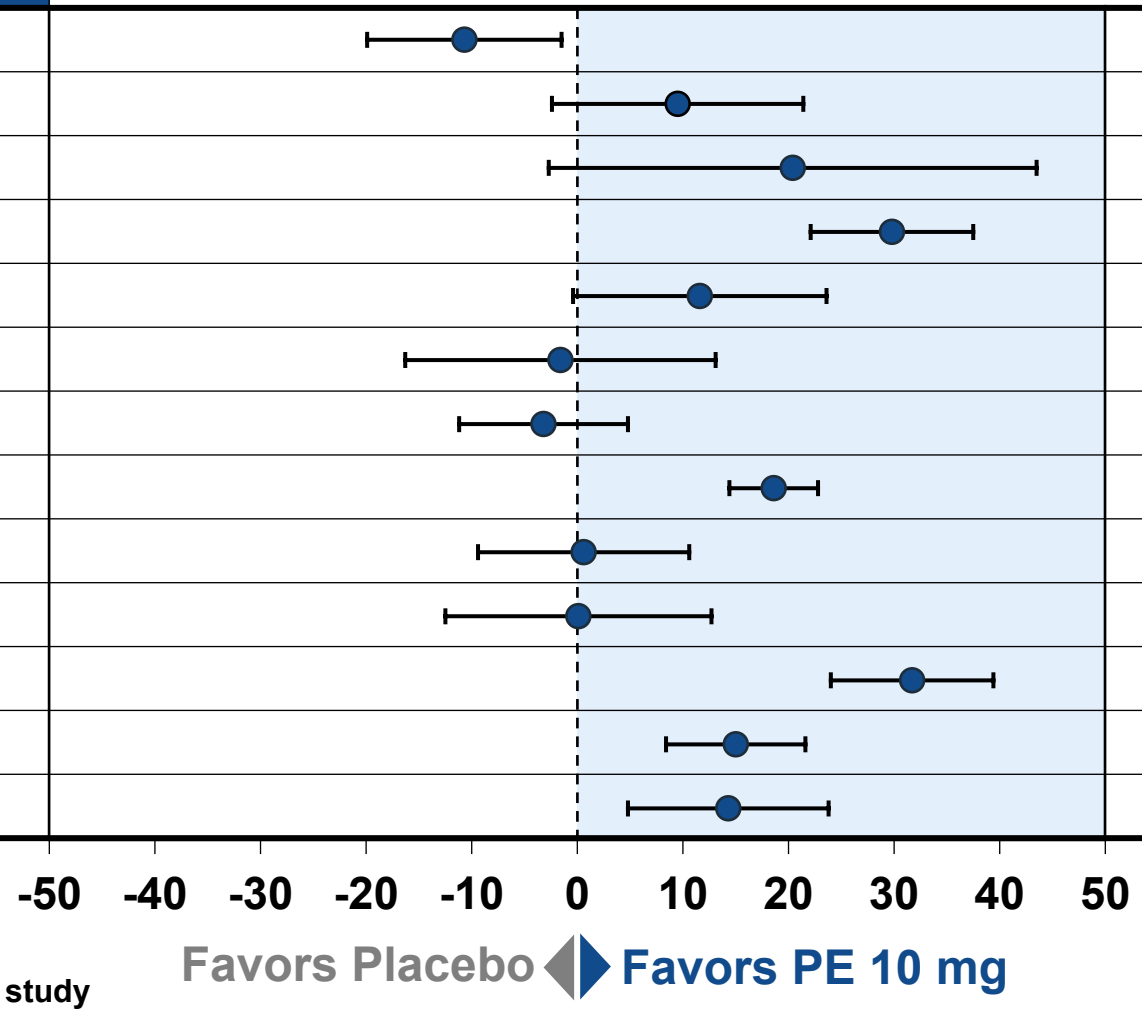
7 — Studies demonstrated statistically significant effect on NAR

5 of 7 — Demonstrated statistically significant efficacy based on subjective endpoints

Totality of evidence met regulatory standard determined by FDA to demonstrate efficacy

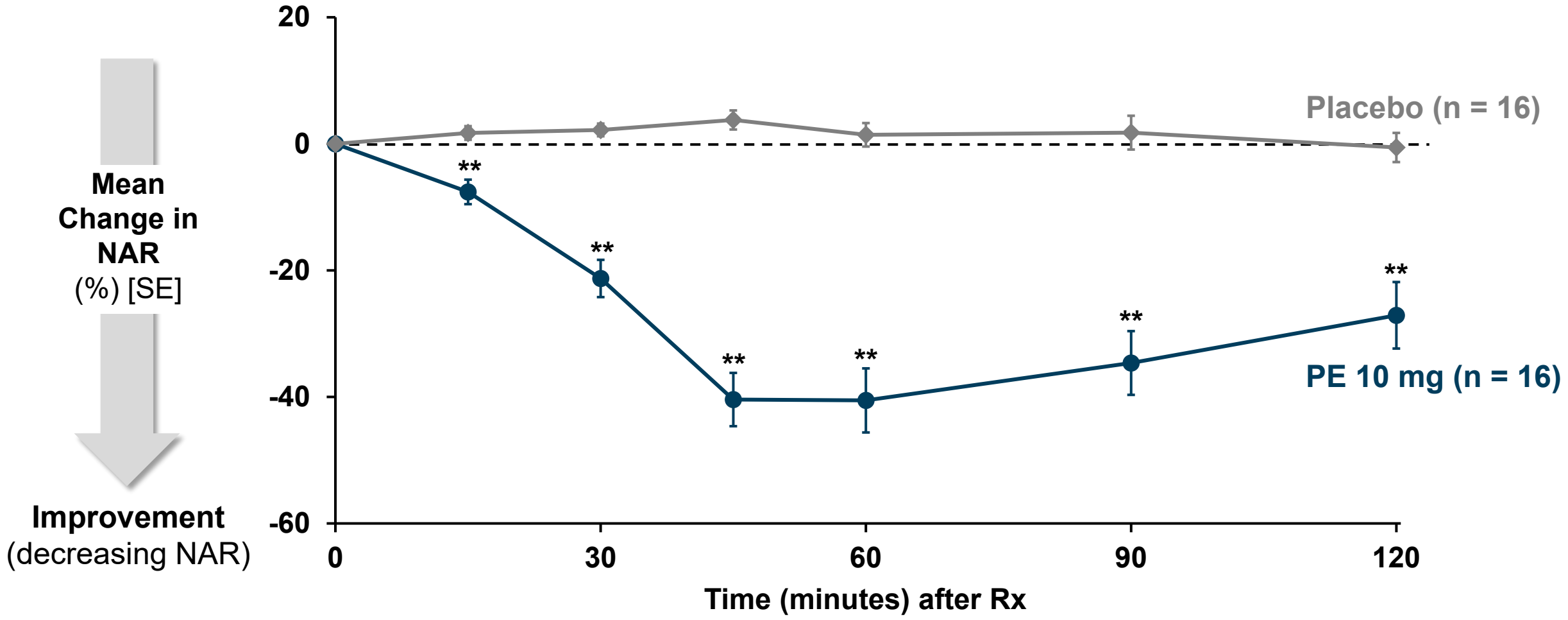
Oral PE 10 mg Shows Consistent Benefit vs Placebo, Measured by NAR, and Considered Effective in FDA Monograph Review

Studies prior to 2007	PE 10 mg (N)	Treatment Difference (95% CI)
Lands (1959)	**15**	**-10.7** (-19.9, -1.5)
McLaurin (1961)	**88**	**9.5** (-2.4, 21.4)
AHR 7032 (1967)	**8**	**20.4** (-2.7, 43.5)
Elizabeth #2 (1968)	**16**	**29.8** (22.1, 37.5)
Cintest #1 (1969)	**16**	**11.6** (-0.4, 23.6)
Huntingdon #1 (1969)	**16**	**-1.6** (-16.3, 13.1)
Huntingdon #2 (1969)	**25**	**-3.2** (-11.2, 4.8)
Elizabeth #5 (1970)	**10**	**18.6** (14.4, 22.8)
Cintest #2 (1970)	**15**	**0.6** (-9.4, 10.6)
Cintest #3 (1970)	**15**	**0.1** (-12.5, 12.7)
Cohen 72 (1972)	**16**	**31.7** (24.0, 39.4)
Cohen 75 (1975)	**25***	**15.0** (8.4, 21.6)
AHR 4010-3 (1983)	**12***	**14.3** (4.8, 23.8)



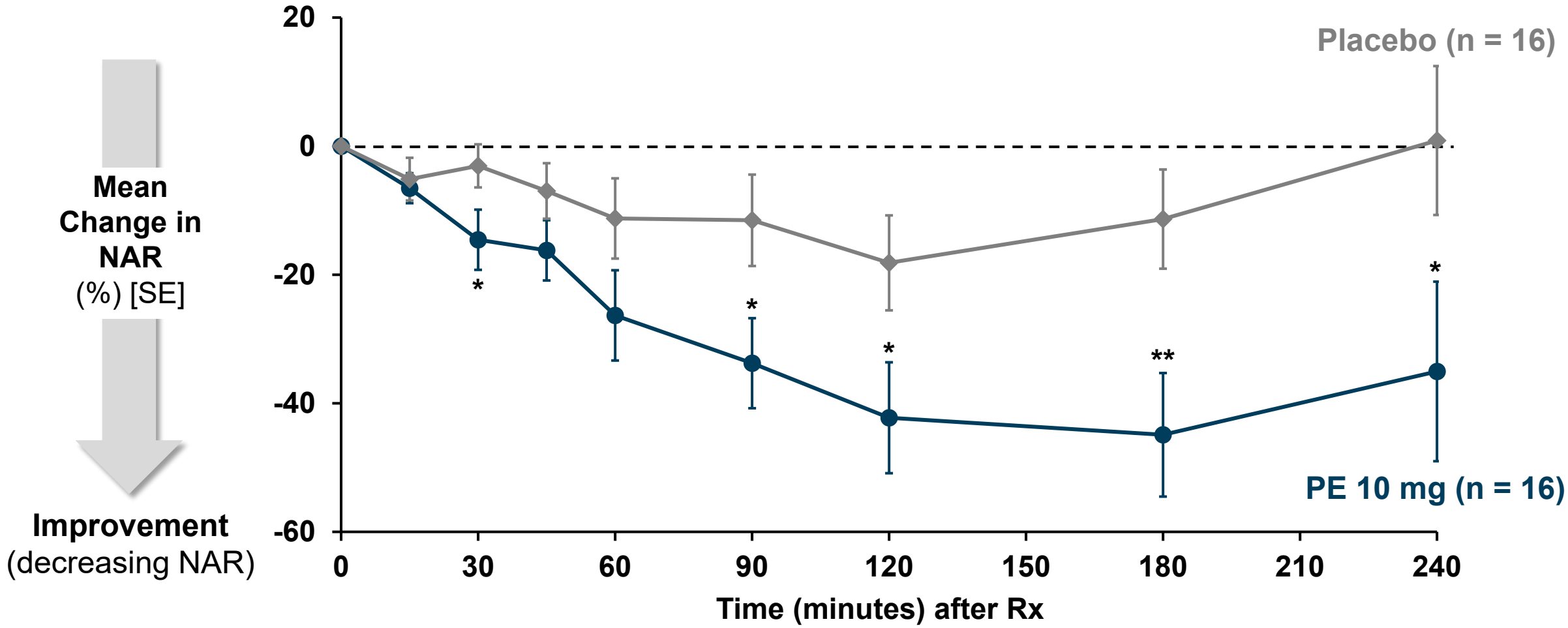
*Parallel study, same number of subjects both groups
AHR-G1A not included since not a placebo-controlled study

Elizabeth #2: One of Multiple Studies to Demonstrate Effectiveness of PE 10 mg in Common Cold



*p < 0.05; **p < 0.01 vs placebo

Cintest #1: One of Multiple Studies to Demonstrate Effectiveness of PE 10 mg in Common Cold

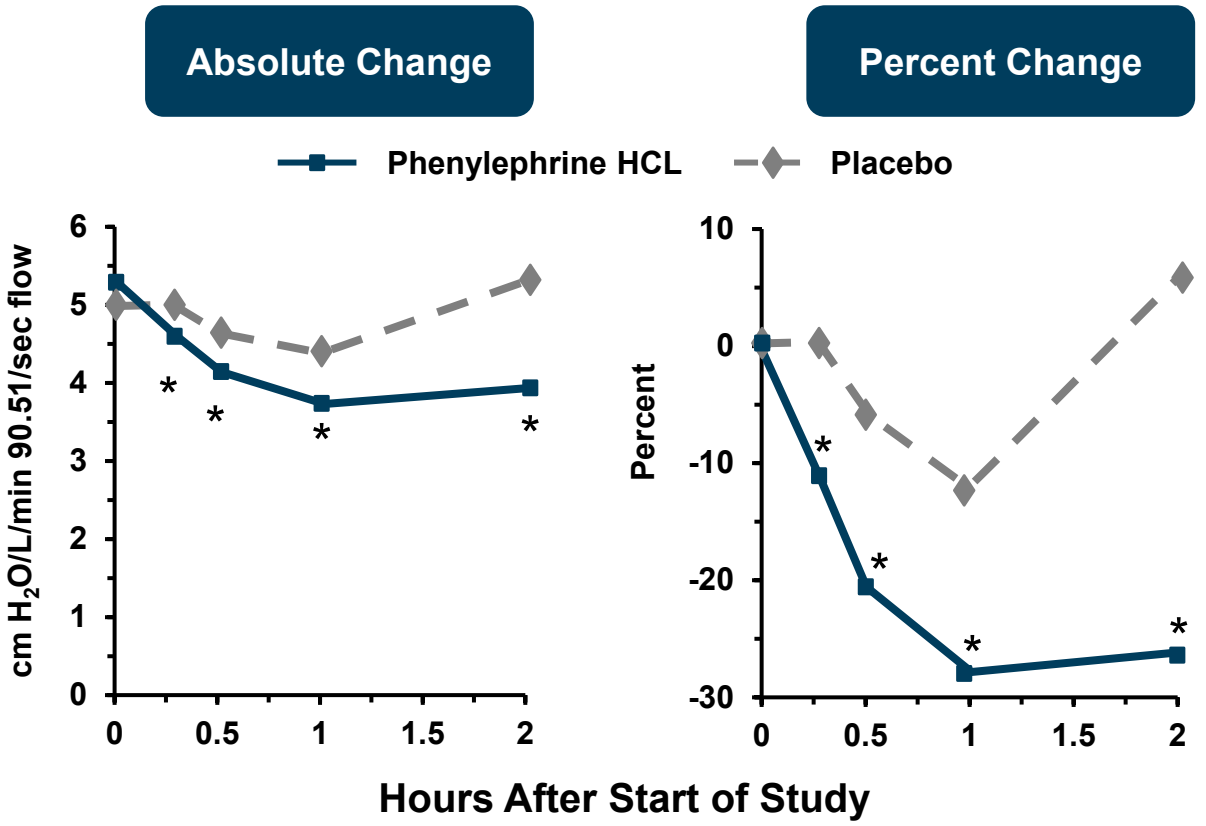


*p < 0.05; **p < 0.01 vs placebo

Cohen 75 (Whitehall Labs Study BEI-1025): Efficacy Shown Soon After Taking PE 10 mg in Common Cold

Large Double-Blind Randomized, Placebo-Controlled Study (N = 200)

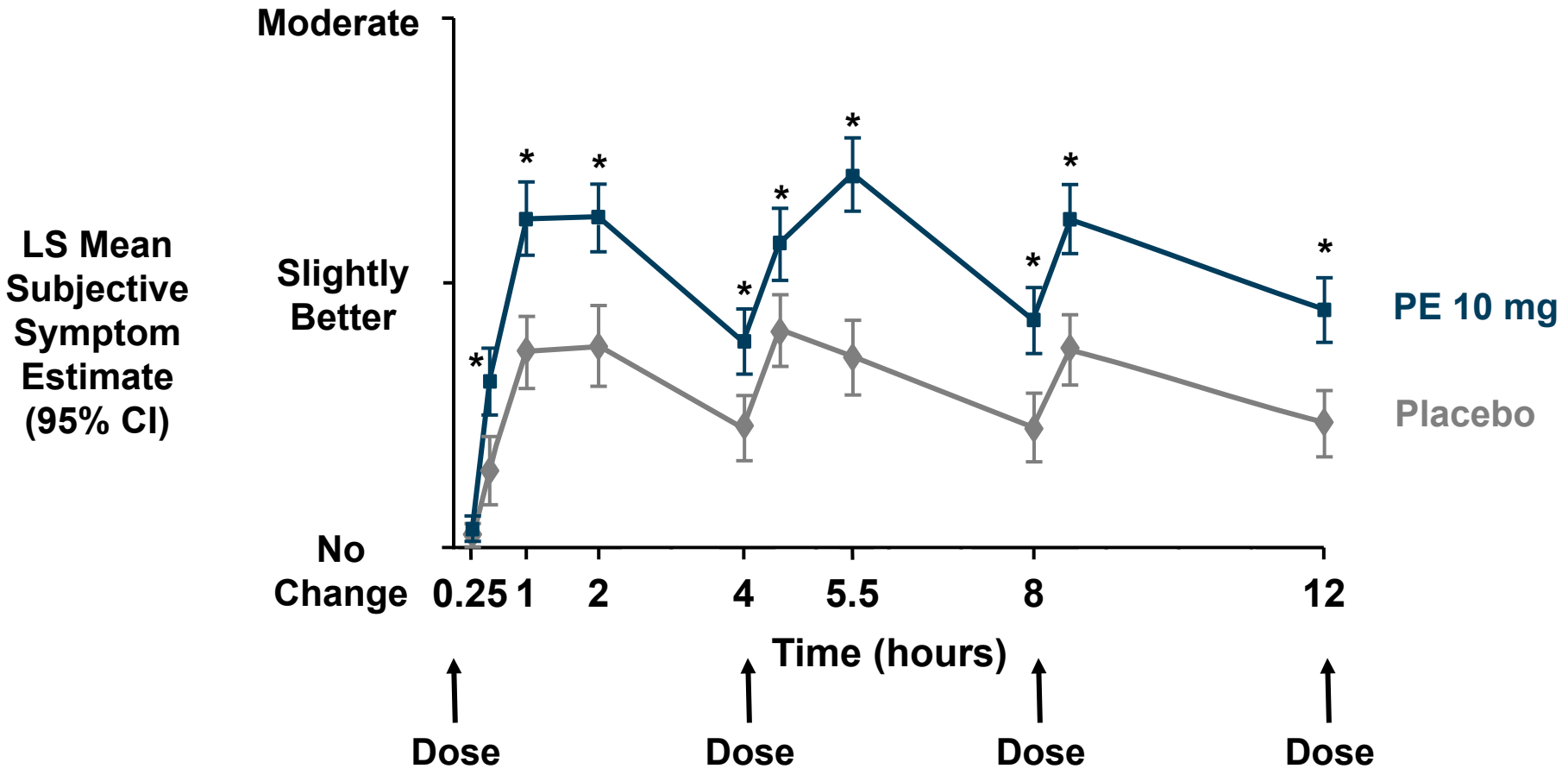
- Effectiveness of phenylephrine HCl in cold
- 200 volunteers ≥ 18 years
  - Both objective measurements and subjective assessment (N = 50 patients)
  - Subjective assessment only (N = 150 patients)
- Phenylephrine HCl 10 mg sustained for up to 12 hours with repeat dosing



*p < 0.05 vs placebo; information received via Freedom of Information Act (FOIA); OTC Volume 040288B, June 1975

Cohen 75 (Whitehall Labs Study BEI-1025): Subjective Endpoint Demonstrated Statistically Significant Benefit Compared to Placebo

Large Double-Blind Randomized, Placebo-Controlled Study (N = 200)



*p ≤ 0.001 vs placebo from an analysis of covariance model by timepoint with baseline as covariate; adapted with statistical analysis for error bars

Cohen 75 (Whitehall Labs Study BEI 1025): Merits of Largest Cold Study Comparing PE 10 mg to Placebo

"The twelfth study, and the seventh positive study, was a relatively large, double-blind, placebo-controlled, parallel-group study (BEI 1025 and 1025a) that had been conducted for Whitehall Laboratories in 200 adults with nasal congestion associated with the "common cold" (100 per group) who were administered four doses of either PEH 10 mg or placebo at 4-hour intervals over 12 hours. Because of the way it is described in the ANPR (as a full paragraph that is last in the efficacy section), it is likely that this particular study pushed the Panel in favor of a positive recommendation for oral PE." (emphasis added)

- FDA Briefing Book Section 2.1.2.4 (2023)

Substantial evidence of statistically significant and clinically meaningful results at all timepoints after 15 minutes

Clinical Relevance of Subjective Assessments in Study Cohen 1975 (Whitehall Labs BEI-1025)

	Adjusted Mean (SE)		Treatment Difference		Clinical Meaningful Techniques (3 Options)		
Timepoint	PE 10 mg N = 100	Placebo N = 100	Adjusted Mean (SE)	p-value	Norman et al 2003/2004 (Anchor)[1]	Barnes et al 2010 (Anchor)[2]	Barnes et al 2010 (Distribution)[3]
15 minutes	**0.04** (0.033)	**0.00** (0.033)	**0.04** (0.047)	**0.4150**	No	No	Small effect
30 minutes	**0.63** (0.065)	**0.29** (0.065)	**0.34** (0.092)	**0.0003**	Yes	Yes	Medium effect
1 hour	**1.24** (0.07)	**0.74** (0.07)	**0.50** (0.099)	**<0.0001**	Yes	Yes	Large effect
2 hour	**1.25** (0.068)	**0.76** (0.078)	**0.49** (0.103)	**<0.0001**	Yes	Yes	Large effect
4 hour	**0.78** (0.062)	**0.45** (0.062)	**0.33** (0.088)	**0.0002**	Yes	Yes	Medium effect
4.5 hour	**1.15** (0.07)	**0.82** (0.07)	**0.33** (0.099)	**0.0011**	No	Yes	Medium effect
5.5 hour	**1.41** (0.071)	**0.72** (0.071)	**0.69** (0.101)	**<0.0001**	Yes	Yes	Large effect
8 hour	**0.86** (0.064)	**0.46** (0.064)	**0.40** (0.091)	**<0.0001**	Yes	Yes	Large effect
8.5 hour	**1.24** (0.068)	**0.75** (0.068)	**0.49** (0.096)	**<0.0001**	Yes	Yes	Large effect
12 hour	**0.90** (0.063)	**0.47** (0.063)	**0.43** (0.089)	**<0.0001**	Yes	Yes	Large effect

1. Norman has shown via 2 publications that minimal important difference (MID) determined by anchor-based approaches are consistently ½ SD. Conservatively used t-test SD vs smaller ANCOVA modeled estimates. [*Med Care* 41(5):582-92; *Exp Rev Pharmacoecon Outcomes Res* 4(5):581-5]
2. Barnes et al. 2010 [*Clin Exp* Allergy 40(2):242-50] has shown anchor-based models to determine MID thresholds for AR (BEI 1025 scale is 9 pt vs 12 pt in pub but conservatively used pub metrics)
3. Barnes et al. 2010 also showed a distribution-based method for MID using Hedges G

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These Post-2007 Clinical Studies of SAR Patients Do Not Invalidate Demonstrated Efficacy of PE in Common Cold

- Horak et al. 2009[1]
- Day et al. 2009[2]
- Meltzer et al. 2015[3]
- Meltzer et al. 2016[4]

Differing methodologies

No clinical endpoint appropriately addressed labeled indication of oral PE 10 mg

1. Horak et al. 2009, *Ann Allergy Asthma Immunol* 102(2):116-20; 2. Day et al. 2009, *Ann Allerg Asthma Immunol* 102(4):328-38

3. Meltzer et al. 2015, *J Allergy Clin Immunol Pract* 3(5):702-8; 4. Meltzer et al. 2016, *Ann Allerg Asthma Immunol* 116(1):66-71

Design of New Clinical Studies Not Relevant to Evaluating Short-Acting Oral Decongestants

Methodological Limitations with SAR Studies	Horak 2009 Chamber Study	Day 2009 Chamber Study	Meltzer 2015 Clinical Study	Meltzer 2016 Clinical Study
Inappropriate study population	✓	✓	✓	✓
Inadequate blinding	✓*		✓*	
Possible recall bias due to crossover design	✓			
Insufficient PE dose for 6-hour endpoint	✓	✓		
Concomitant use of loratadine			✓*	✓*
Reflective 12-hour endpoints not appropriate			✓	
Inclusion criteria permitted nasal congestion scores of “mild” severity				✓*

*Does not conform to FDA Guidance - Allergic Rhinitis: Developing Drug Products for Treatment; Sept 2018

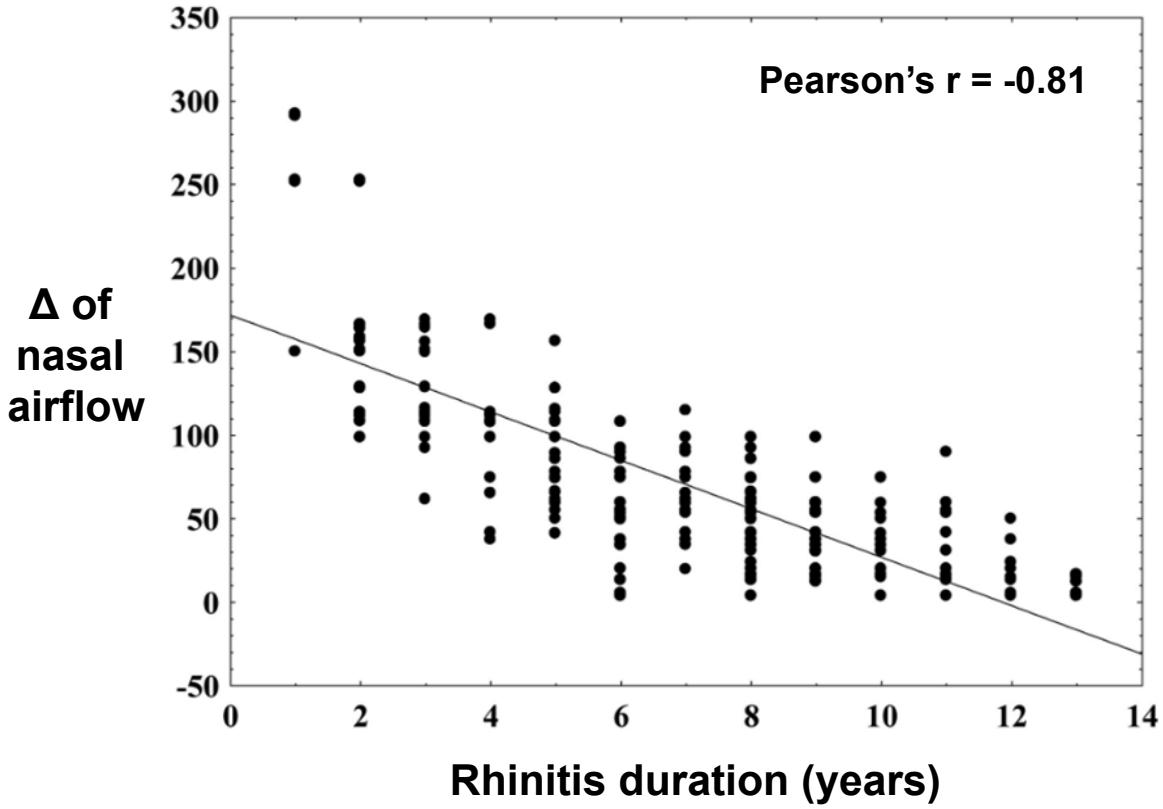
Subjects Not Representative of Population with Intermittent* Allergic Rhinitis Choosing Self-Care

Eligibility of Subjects	Horak 2009 Chamber Study	Day 2009 Chamber Study	Meltzer 2015 Clinical Study	Meltzer 2016 Clinical Study
Severity of nasal congestion symptom	≥ Moderate	≥ Moderate	≥ Moderate	≥ Mild
History of seasonal allergy	≥ 2 seasons	ragweed for ≥ 2 seasons	within last 4 y; symptomatic ≥ last 2 y	within last 4 y; symptomatic ≥ last 2 y
Positive skin testing to allergens or *in vitro* test for specific IgE	(+) grass pollen	(+) ragweed pollen	spring pollen test within last 4 y	fall pollen test within last 4 y
Have used systemic, nasal, ocular corticosteroids (after 30-day washout)	NR	NR	✓	✓
Have started allergen immunotherapy (longer than 1 month before study start)	NR	NR	✓	✓
History of mild intermittent asthma (not symptomatic at entry)	NR	12%	✓	✓

*Intermittent rhinitis = symptoms present for < 4 days / week or < 4 weeks in duration; NR = not reported in publication

Patients with Allergic Rhinitis May Be Less Responsive to Decongestants

- Prospective study[1] of 312 adults with moderate-to-severe persistent allergic rhinitis
  - Nasal airflow measured by anterior rhinomanometry (both nostrils)
  - Measured before and after decongestant test with naphazoline nasal spray
- Responses to nasal decongestion test decrease with rhinitis duration



Therefore, study populations in 4 new allergy studies <u>not appropriate</u> to evaluate temporary decongestant effect of oral phenylephrine

1. Ciprandi et al. 2008, *Laryngoscope* 118(7):1139-41

Horak 2009: Vienna Challenge Chamber - Subjective Assessments by Study Subjects

Crossover Design

Commercial products used in study

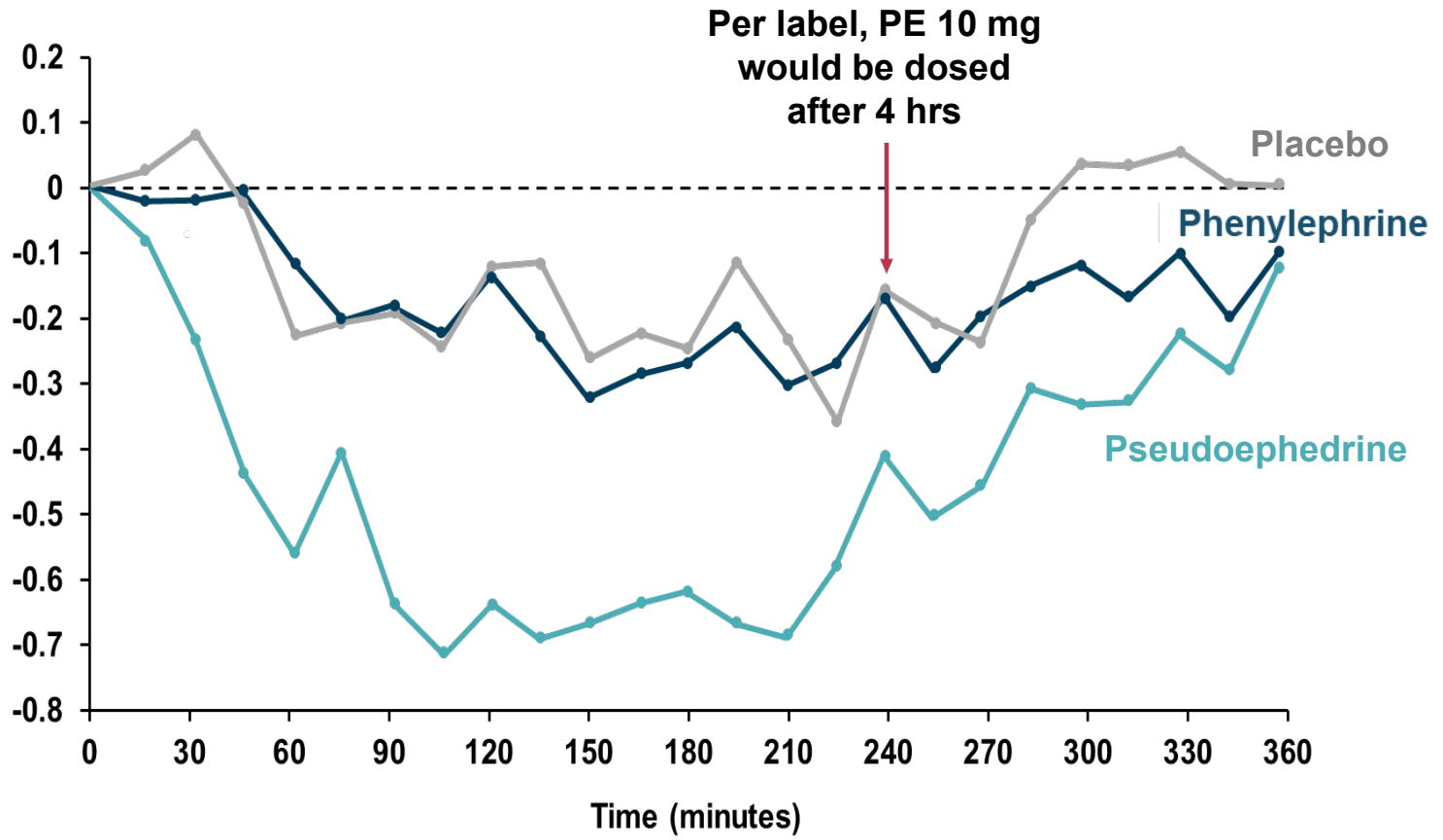
PE 10 mg

PSE 60 mg

Placebo provided by Sponsor

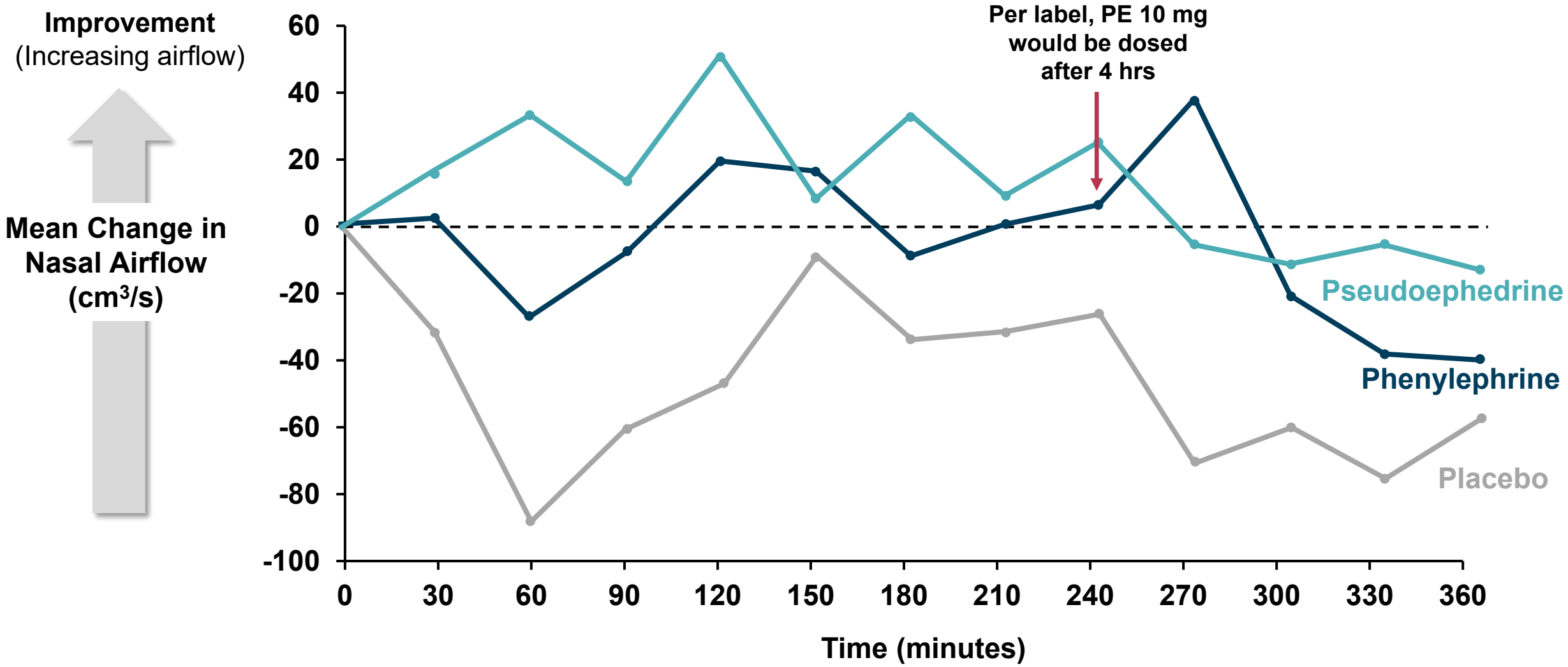
Placebo

"…the patients knew that they took either a tablet or a capsule".



No variability measures provided in published study

Horak 2009: Vienna Challenge Chamber - Objective Rhinomanometry Measurements by Investigator



No variability measures provided in published study

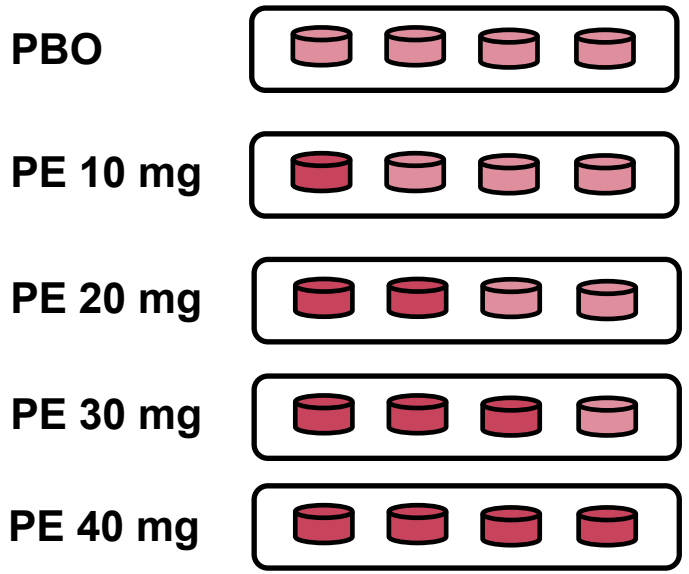
Meltzer 2015: Every Patient Given Loratadine, Complicating the Evaluation of Phenylephrine

Study Design

- Based on draft FDA guidance for allergic rhinitis trials
- Daily treatment with loratadine throughout study
- Study reported as open-label
- Primary endpoint - daily reflective congestion scores

Participants

- Documented seasonal allergic rhinitis for ≥ 2 seasons with positive allergy tests
- Continued nasal congestion after washout period
- Minimum congestion score for entry was ≥ moderate



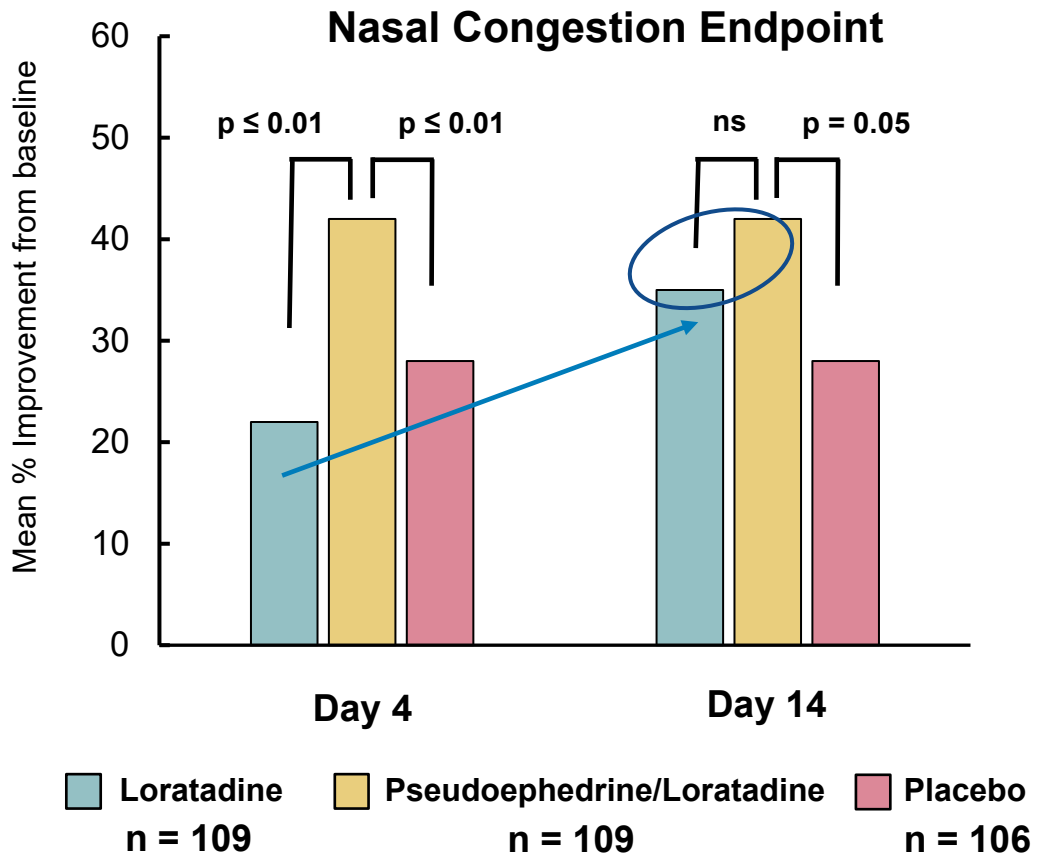
"Commercial PE10-mg tablets were used. Both PE 10-mg and placebo tablets were red and concave, but not exactly matching."

Meltzer et al. 2015, *J Allerg Clin Immunol Pract* 3(5):702-8

Daily Antihistamine Decreases Sensitivity of Clinical Model by "Halo Effect" on Nasal Congestion Scoring

- Meltzer 2015 dose-ranging study required daily loratadine use with phenylephrine doses
- Concomitant use of loratadine, an antihistamine
  - Provides "halo effect": subjects' reduced perception of severity of other rhinitis symptoms biases scoring of nasal congestion[1]

Example of "halo effect"
Storms et al. 1989[2]



1. Greiner et al. 2006, *J Allergy Clin Immunol* 118(5):985-98
2. Storms et al. 1989, *J Allergy Clin Immunol* 83(6):1083-90
ns = not significant; variability of means not reported

Meltzer 2015: Primary Endpoint Comprised of 12-Hour Reflective Scores Problematic for Evaluating Short-Acting PE

Primary Endpoint

- Mean change from baseline over 7 days in daily reflective nasal congestion scores
  - Daily scores = average of morning and evening scores reflected over previous 12 hours

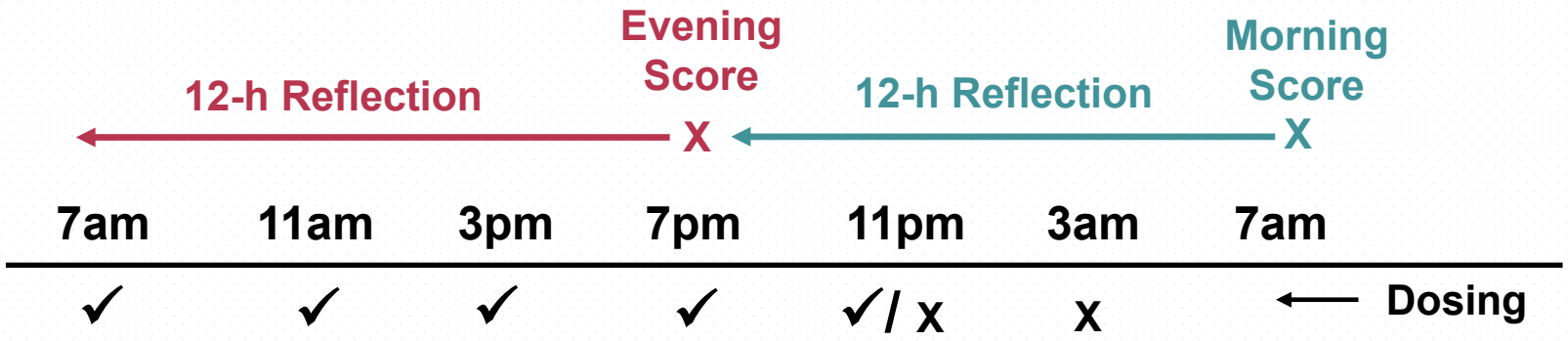
SAR Dosing

- Evaluated once or twice daily treatments for seasonal allergies

OTC Dosing

- Oral phenylephrine 10 mg dosed every 4 hours for temporary relief

- Low compliance, especially overnight (mean = 4.5 doses per day)



Meltzer 2016: Diminished Sensitivity of Clinical Model

Study Design

- Compared experimental **modified-release PE tablet**, 30 mg with placebo for 7 days
- Daily use of loratadine permitted as needed for other allergic symptoms

Participants

- Documented seasonal allergic rhinitis for ≥ 2 seasons with positive allergy tests
- Nasal congestion score was at least **"mild"** for randomization

Mean loratadine exposure:

3.8 ± 2.4 days out of 7 days for both PE-MR and placebo

Nasal congestion scores:

0 = none, 1 = mild, 2 = moderate, 3 = severe

Without an active control, these changes in the model can not be interpreted

J&J Phase 2 Study* (NCT03339726) of Experimental Extended-Release PE 30 mg Tablets in Common Cold (Canada)

- Placebo-controlled, noninferiority study of extended-release PE 30 mg (2 doses of one tablet 12 hours apart) compared with immediate release PE 12 mg (4 doses of one capsule 4 hours apart)
- Common cold symptoms for up to 72 hours before entry
- Various subjective endpoints - instantaneous and reflective symptom scores over 12 hours
- Study terminated at 43% enrollment due to inability to recruit planned sample size after cold season ended

Inferences may be made from incomplete data in proof-of-concept studies but should not be considered definitive

*Sponsored by Johnson & Johnson Consumer, Inc.

Conclusion: Oral PE 10 mg Provides Temporary Relief of Nasal Congestion

- Oral PE 10 mg indicated for temporary relief of nasal congestion
  - Clinical evidence justifies labeled indication based mostly on common cold model, which led to OTC regulatory status as GRAS/E
  - Monograph studies methodologically sound; still relevant to support GRAS/E status
- New data not compelling to challenge earlier efficacy data

No novel technology or clinical trial design endpoint has emerged to negate established data or warrant re-investigation of phenylephrine for its labeled indication

Discussion and Comparison of Meta-Analyses

Chris M. Mullin, M.S.

Director, Global Strategy Services

NAMSA

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Hatton et al 2007 Meta-Analysis Overview

Sources

- Cochrane Review, MEDLINE, EMBASE, International Pharmaceutical Abstracts, *Federal Register*, Web of Science

Selection Criteria

- Randomized, placebo-controlled clinical trials, single ingredient oral PE (10 mg) in patients with acute nasal congestion due to common cold

Analysis

- Endpoint: % maximum reduction in NAR over 120 minutes
- Random effects model based on summary study data

Conclusion

- Insufficient evidence that oral phenylephrine is effective

Kollar et al 2007 Meta-Analysis Overview

Sources

- Cochrane Review, MEDLINE, EMBASE, International Pharmaceutical Abstracts, *Federal Register*, Web of Science

Selection Criteria

- Randomized, placebo-controlled clinical trials, single ingredient oral PE (10 mg) in patients with acute nasal congestion due to common cold

Analysis

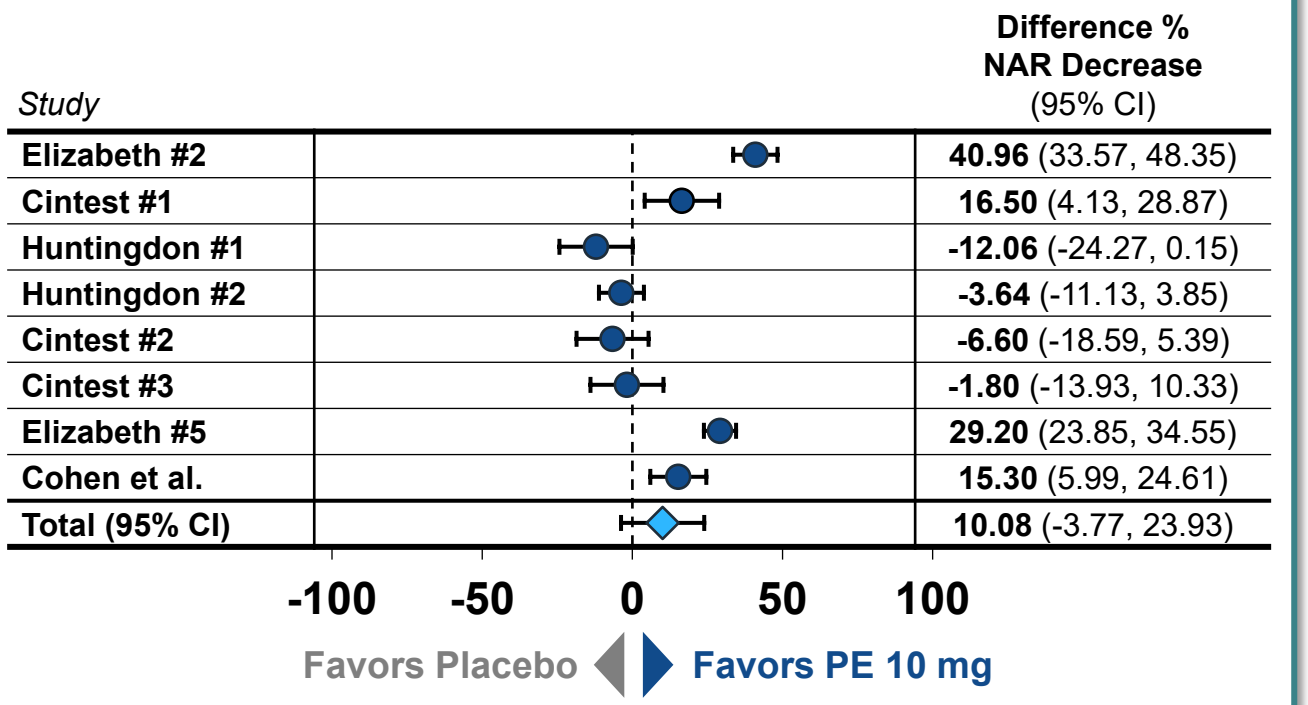
- Endpoint: treatment differences in NAR from baseline at all available time points up to 240 minutes
- Random effects model based on individual participant data

Conclusion

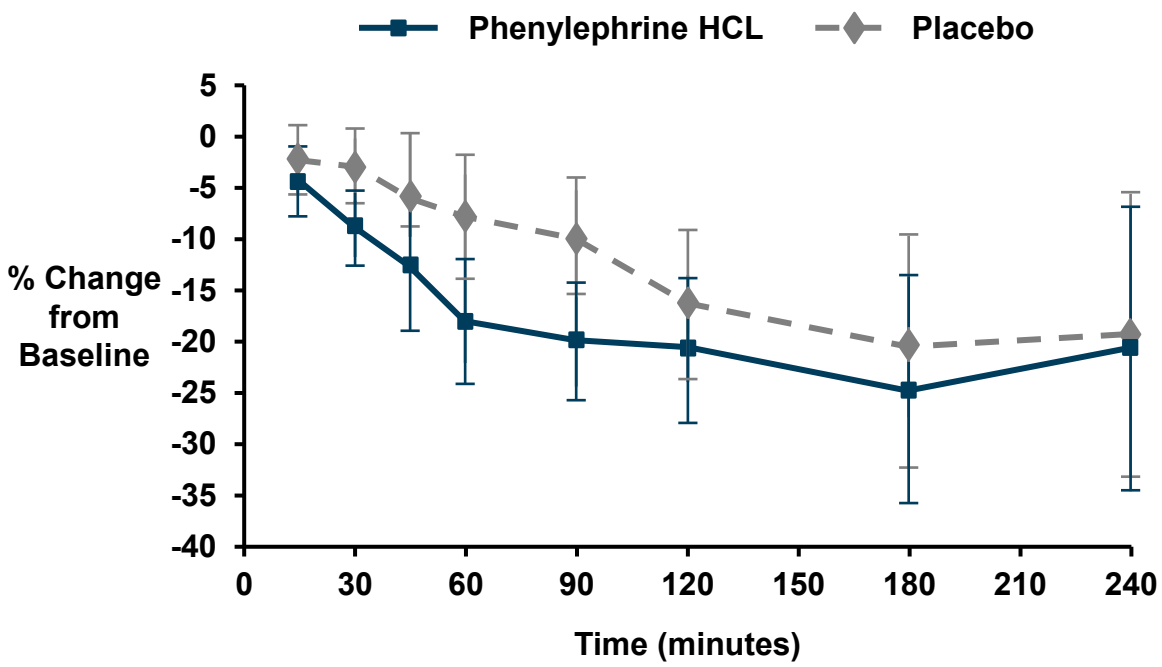
- Oral phenylephrine (10 mg) is effective

Hatton[1] and Kollar[2] Produced Similar Effect Estimate

Hatton



Kollar



Hatton estimated treatment effect ~ 10%

Kollar estimated treatment effect ~ 10% at 60 or 90 minutes

1. Hatton et al. 2007, *Ann Pharmacother* 41(3):381-90

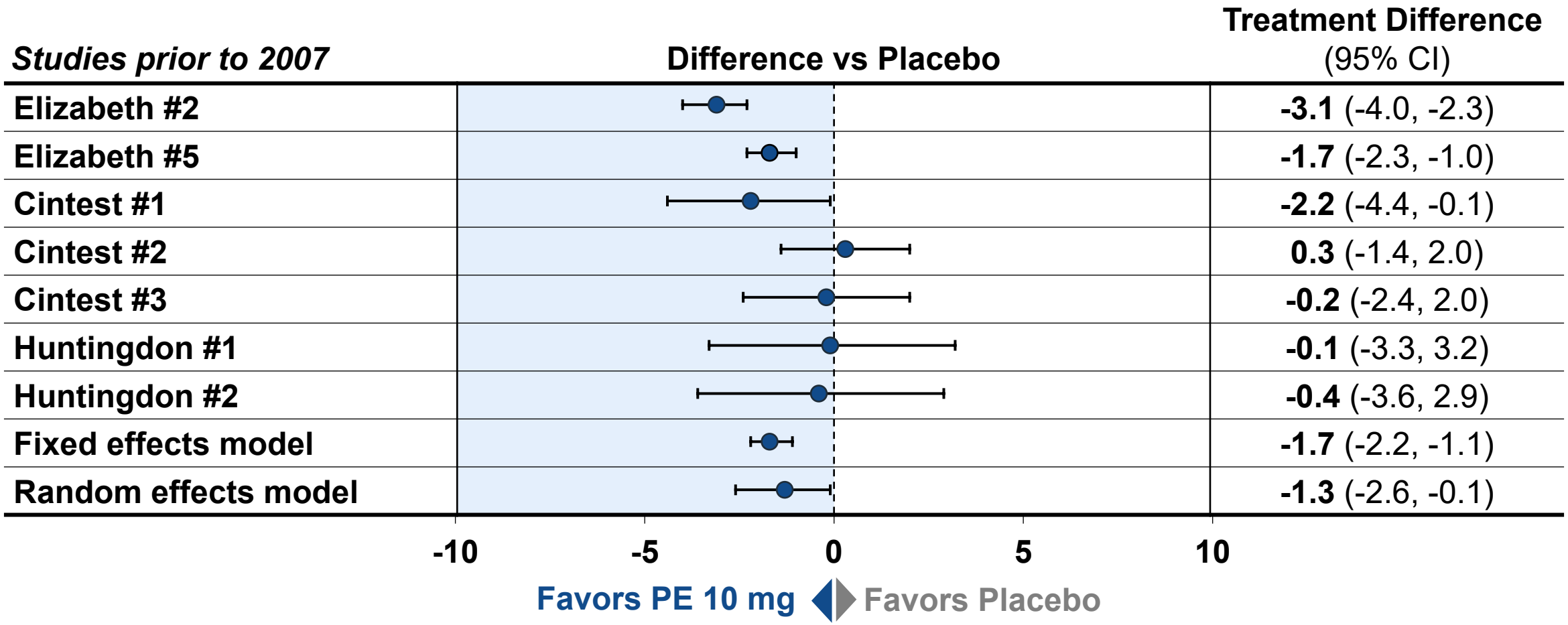
2. Kollar et al 2007, *Clin Ther 29*(6):1057-70

Kollar Conclusions Based on Multiple Studies

Model / Statistic	Time After Dosing (minutes) 15	30	45	60	90	120	180	240
2b Treatment Difference (95% CI)	**-0.27** (-0.61, 0.08)	**-1.68** (-2.23, -1.14)*	**-2.71** (-3.57, -1.85)*	**-3.68** (-4.39, -2.97)*	**-2.80** (-3.54, -2.06)*	**-2.02** (-2.67, -1.37)*	**-1.09** (-1.61, -0.58)*	**-0.33** (-1.21, 0.55)
3 Treatment Difference (95% CI)	**-0.41** (-1.18, 0.36)	**-1.32** (-2.56, -0.09)*	**-1.38** (-3.51, 0.74)	**-2.30** (-4.34, -0.26)*	**-2.24** (-4.17, -0.31)*	**-1.01** (-3.42, 1.40)	**-0.95** (-4.85, 2.96)	**-0.32** (-1.21, 0.57)
8 (Parallel group) Treatment Difference (95% CI)	**-0.60** (-1.14, -0.07)*	**-0.67** (-1.23, -0.11)*	**NA**	**-0.68** (-1.28, -0.09)*	**NA**	**-0.96** (-1.48, -0.44)*	**NA**	**NA**

*p ≤ 0.05

Kollar Conclusions Based on Multiple Studies



“Negative" Studies Have Issues that Call into Question Individual Conclusions

1. Study included positive control but failed to show significant benefit of positive control over placebo

2. Other studies did not include positive control group at all

3 of 4 negative studies did not demonstrate assay sensitivity

Kollar meta-analysis provides conservative estimate of benefit

Criticisms of Elizabeth Biochemical Laboratory (EBL) Studies

Specific concern about data came
2 years after 2007 advisory committee meeting

Criticisms based on post-hoc data analysis susceptible to selection bias

Terminal digit preference known phenomenon[1]: random rounding error would affect heterogeneity, not introduce bias

1. Hessel 1986, *Int J Epidemiol* 15(1):122-5

Relevant Elizabeth Labs Studies

Product / Dose / Lab	Time Point (minutes) and SD								
	0	15	30	45	60	90	120	180	240
PPA 50 mg									
Elizabeth	1.3	0.7	0.9	0.9	1.5	1.8	2.1	2.6	2.3
Cintest	4.1	12	13	18	20	17	18	23	45
Huntingdon	6.5	27	20	16	25	37	36	38	38
Neo-Synephrine 10 mg									
Cintest	7.3	12	14	16	21	21	23	27	42
Huntingdon	7.7	12	18	18	28	22	58	79	166
Neo-Synephrine 25 mg									
Cintest	5.4	14	22	23	21	22	22	22	30
Huntingdon	10	22	29	32	38	44	45	35	44
Neo-Synephrine 15 mg									
Elizabeth	0.8	0.3	1.0	1.7	2.1	1.5	1.5	1.4	2.3

Reproduced from Table 12, FDA Briefing Document; original source: Huntingdon #1 study report, ANPR Reference 20, Table II; PPA: phenylpropanolamine

"Small Study Effect": Well-Known Phenomenon, Many Possible Explanations

- Effect size may be truly larger in smaller studies
- Smaller studies may be better designed, investigators more skilled[1]
- *"Small studies cannot be said to inappropriately bias the mean effect upward any more than the large studies can be said to inappropriately bias the mean effect downward"* [2]

1. Waksman 2010, *Stat Med* 29(12):1268-9; 2. Borenstein, Hedges, Higgins and Rothstein, Introduction to Meta Analysis, 2021

J&J Phase 2 Study (NCT03339726) Cannot be Considered a Negative Study; Does Not Support Conclusion that PE Is Ineffective (1/2)

- Not powered or designed for PE comparison to placebo
- FDA: *"appears to have been designed as a Phase 3 study to support approval of an extended-release PE product to be marketed outside the United States."*
  - However, protocol states: "*This is a Phase II POC [proof-of-concept] study"*
- Lacked a positive control
- Study terminated after cold season ended due to inability to recruit planned number of subjects; smaller sample size reduces power regardless of objective

J&J Phase 2 Study (NCT03339726) Cannot be Considered a Negative Study; Does Not Support Conclusion that PE Is Ineffective (2/2)

Parameter	Placebo N = 64	PE-IR 12 mg N = 66	PE-ER 30 mg N = 63
Baseline	**NA**	**NA**	**NA**
Mean change (SE) over 12 hours	**1.80 (0.156)**	**2.03 (0.1540)**	**1.93 (0.158)**
Mean difference vs placebo (95% CI)		**0.23** (-0.205, 0.662)	**0.13** (-0.311, 0.564)
p-value vs placebo		**0.300**	**0.569**

Primary efficacy endpoint: change from baseline (score improvement) in nasal congestion severity score (NCSS) averaged over assessments at 2, 4, 6, 8, 10, and 12 hours on Day 1

Subsequent Studies Not Appropriate for Inclusion in Meta-Analysis

Study	Formulation Studied	
Horak et al. 2009	Vienna Chamber model / SAR, possible carryover bias identified by authors	Differing methodologies
Day et al. 2009	Quick dissolving strip	
Meltzer et al. 2015	Included loratadine; results not applicable to PE alone	
Meltzer et al. 2016	30 mg modified-release	

Meta-Analyses Criticisms and New Studies Do Not Change Confidence in Effectiveness of Oral Phenylephrine

- Both Kollar and Hatton meta-analyses included similar studies and produced similar estimates
  - Superficial differences regarding statistical conclusions can be explained by methodology differences
- Several small crossover monograph studies show significant results
  - Size of effects themselves and small degree of variability may simply demonstrate well-conducted, highly-controlled studies
- Several “negative studies” not free from limitations, specifically a lack of demonstration of assay sensitivity
- New studies also with flaws
  - Do not address current labeling for PE 10 mg nor indication for relieving nasal congestion due to common cold
  - Results do not contradict monograph study results

Benefit-Risk Profile

Marcia D. Howard, Ph.D., CAE

Vice President, Regulatory & Scientific Affairs

CHPA

Benefit-Risk of Oral Phenylephrine Remains Favorable

Benefit Considerations

Consumer satisfaction with treatment results highlighted by purchase / repurchase data

Efficacy supported by 2 FDA advisory panels

- Established by 7 monograph studies
- Confirmed by meta-analysis

- Convenient availability of medication on retail shelves / online, without restriction
- Oral formulation preferred by consumers

Risk Considerations

Removal would negatively impact consumers' ability to access self-treatment

- Other oral OTC (PSE) has sales restrictions and DEA quotas, and is not equally available to consumers

- Favorable safety profile
- Large margin of safety

- Untreated congestion could lead to worsened outcomes

Conclusion: PE Task Group Perspective on Key Issues

1. Clinical data support efficacy
2. No scientific rationale to negate established data
3. Low bioavailability and lack of significant adverse pressor effects do not mean poor efficacy
4. Kollar meta-analysis supports efficacy and uses more clinically relevant endpoint, well-accepted statistical methodology
5. Removal of oral phenylephrine from monograph would have negative unintended consequences on American consumers

Evidence Supporting the Efficacy of Oral Phenylephrine and Its Role in U.S. Healthcare

September 11-12, 2023

U.S. Food and Drug Administration

Nonprescription Drugs Advisory Committee

Member Companies of the
Consumer Healthcare Products Association (CHPA)

AA-95

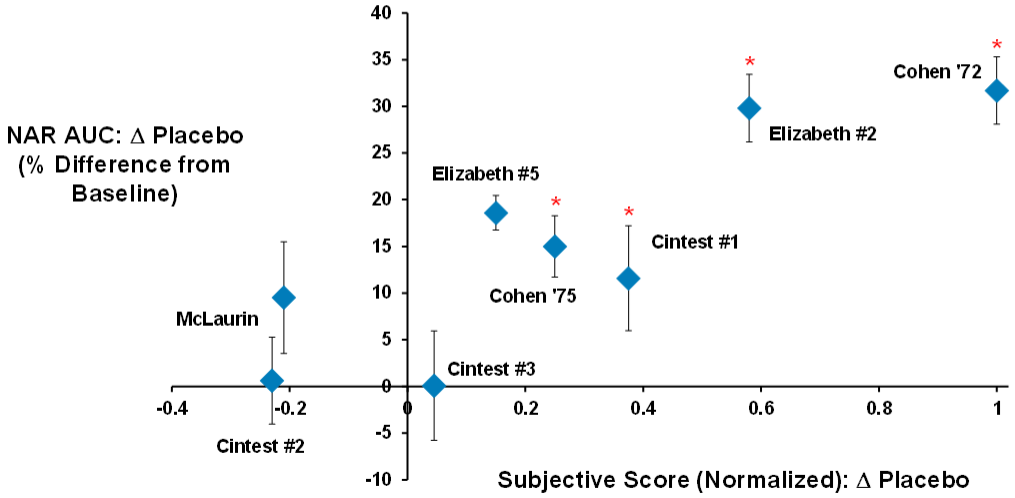
Day 1

Back-up Slides Shown On-Screen

95

AA-8

Correlation of Subjective and NAR Assessments for PE 10 mg Across Studies



* p-value ≤ 0.05 vs placebo

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AA-97

Day 2 (September 12, 2023)

Slides Shown On-Screen

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