Rhinitis – Part 1
Pharmacologic Therapy

Pharmacotherapy II
728-556
2021

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Objectives

Discuss the pharmacist's role in managing patients with rhinitis

- Initiate an appropriate treatment and monitoring plan
- Understanding the effect of treatment
- Optimize therapy
- Propose appropriate preventative measures
- Patient education

As trusted healthcare professionals in the community, and often the initial point of contact for allergic rhinitis, pharmacists are well placed to identify the symptoms of allergic rhinitis and to recommend appropriate treatment by:

- Understanding effect of treatment on rhinitis
- Determine whether pharmacist management is appropriate
- Initiate an appropriate treatment and monitoring plan
  - Adherence and technique
- Propose appropriate preventative measures
- Assess co-morbidities

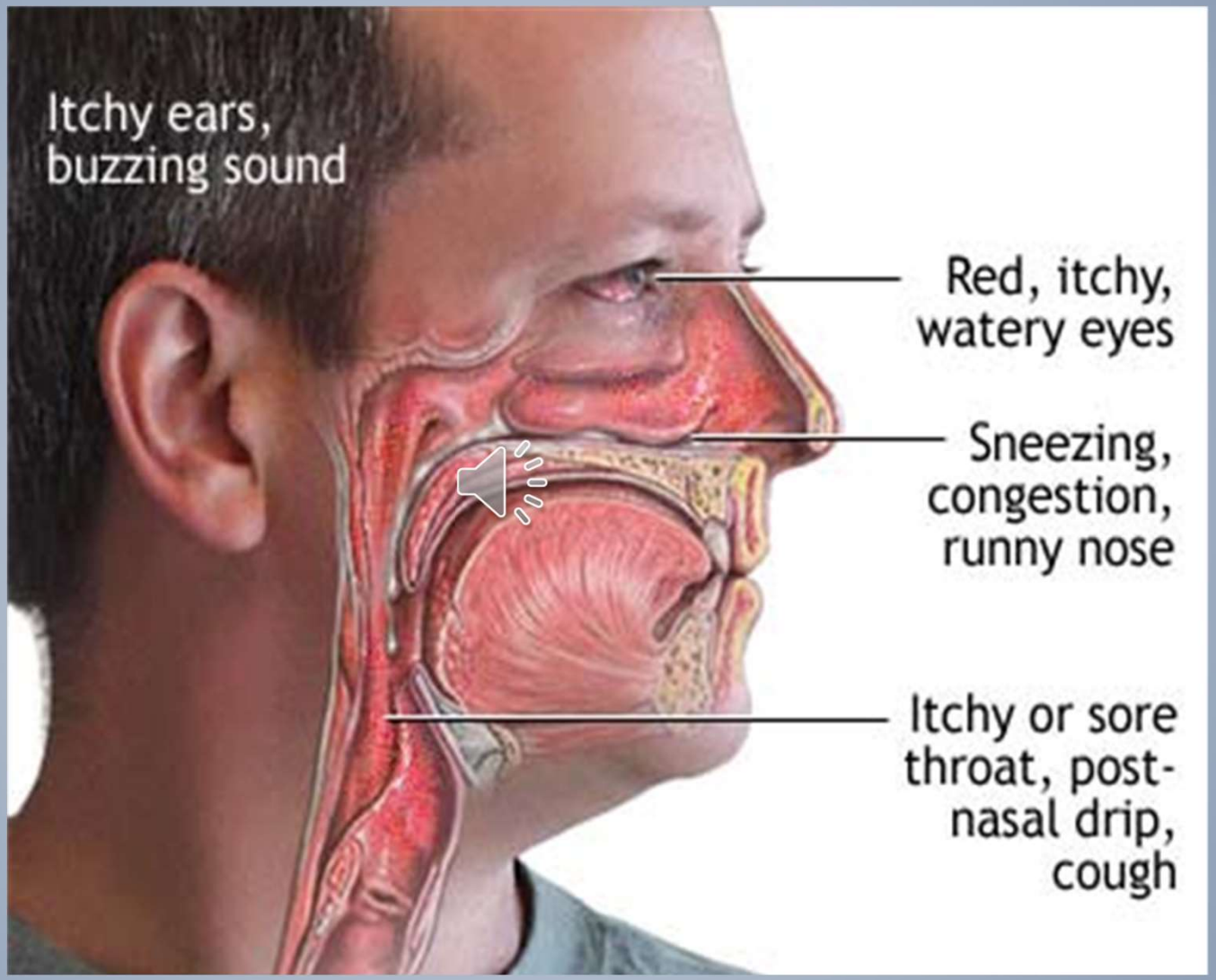
Bousquet J et al. *Allergic Rhinitis and it Impact on Asthma (ARIA) 2008*. Allergy 2008;63:8-160
Bosnic-Anticevich S. et al. *ARIA Pharmacy 2018* doi: 10.1111/all.13701

Domains of Pharmacist Care

- Recognition and classification of rhinitis symptoms
- Identification of rhinitis related comorbidities
- Treatment
- Patient support and monitoring

Rhinitis

- Inflammation of the nasal mucosa
- Symptoms – present for 2 or more consecutive days
  - Nasal obstruction (stuffy nose, congestion)
  - Watery nasal discharge (runny nose)
  - Sneezing
  - Itching
  - Conjunctiva: itching, redness, tearing
- Impact
  - Ability to concentrate
  - Interference with daily activities and sleep
  - Increased risk for the development of asthma


Itchy ears,
buzzing sound
Red, itchy,
watery eyes
Sneezing,
congestion,
runny nose
Itchy or sore
throat, post-
nasal drip,
cough

Treatment Options

- Pharmacologic Therapy
  - Antihistamines – systemic, intranasal
  - Decongestants – systemic, intranasal
  - Mast cell stabilizers
  - Corticosteroids – intranasal, systemic
  - Anticholinergics
  - Leukotriene Receptor Antagonists
  - Saline irrigation
- Allergen Immunotherapy – SCIT, SLIT
- Environmental Control - AVOIDANCE
- Patient Education

Treatment Principles

- Appropriate therapy
  - Maximize benefit
  - Minimize adverse events
  - Stepwise, patient specific
  - Treatment of comorbid conditions

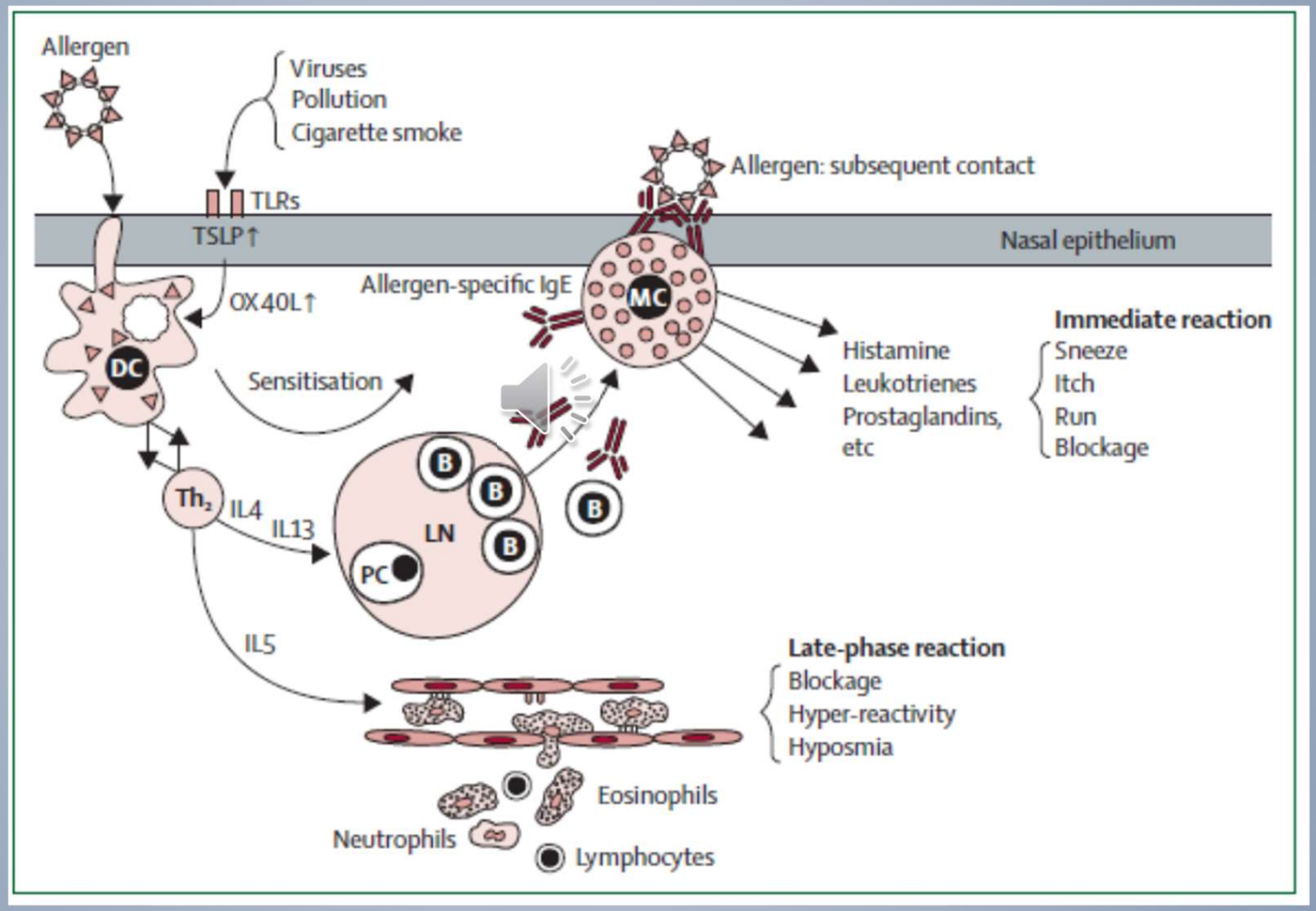
INCS (IntraNasal CorticoSteroids)

- Preferred therapy for treatment of allergic rhinitis
- Dose response studies are lacking
- Topical application may be ineffective for some patients based on device/delivery system
- Mucosal edema/enhanced delivery with use of topical decongestants
- Strongly recommended for patients whose symptoms affect QoL
- May reduce bronchial hyperreactivity and improve asthma control

INCS - MOA

- Modulate pathophysiology of AR
  - Reduction in release of mediators and cytokines
  - Inhibit recruitment of basophils, eosinophils, neutrophils mononuclear cells
  - Reduction of inflammatory cells and cytokines within the nasal mucosa
  - Reduce hyperresponsiveness to antigen challenge
- Onset of action
  - 3-5 hours to 36 hours
- Symptom reduction
  - Sneezing, itching, rhinorrhea, congestion
  - Allergic conjunctivitis
  - Improved QoL, sleep

Pathogenesis of Allergic Rhinitis



Greiner AN, et al. *Lancet* 2011

Medication	Brand Name	Age	Dosing**	
Beclomethasone (AQ)	Beconase AQ	≥ 6-11 y ≥ 12 y	1ppn QD-BID 1-2ppn BID	Rx
Beclomethasone (HFA)	QNASL – 40 QNASL - 80	≥ 4-11 y ≥ 12 y	1ppn QD 2ppn QD	Rx
Budesonide (AQ)	Rhinocort AQ	≥ 6 -11 y ≥ 12 y	2ppn QD 4ppn QD	OTC
Ciclesonide (AQ)*	Omnaris	≥ 6 y	2ppn QD	Rx
Ciclesonide (HFA)*	Zetonna	≥ 12 y	1ppn QD	Rx
Flunisolide (AQ)	Nasalide	≥ 6-14 y > 14 y	1ppn TID or 2ppn BID 2ppn BID - TID	Rx
Fluticasone furoate (AQ)	Flonase Sensimist	≥ 2-11 y ≥ 12 y	1ppn QD 2ppn QD	OTC
Fluticasone propionate (AQ)	Flonase	≥ 4 y ≥ 12 y	1ppn QD 2ppn QD	OTC, Rx
Fluticasone propionate (EDS)	Xhance	≥ 18 y	1-2 ppn BID	Rx
Mometasone (AQ)	Nasonex	≥ 2-11 y ≥ 12 y	1ppn QD 2ppn QD	Rx
Triamcinolone (AQ)	Nasacort	≥ 2-5 y ≥ 6-11 y ≥ 12 y	1ppn QD 1-2ppn QD 2ppn QD	OTC

Systemic Bioavailability

Ciclesonide	≤ 0.1%
Mometasone	≤ 0.1%
Fluticasone furoate	0.55%
Fluticasone proprionate	1-2%
Budesonide	30-40%
Beclomethasone	40-50%
Triamcinolone	40-50%
Flunisolide	50%

Derendorf H and Meltzer EO. *Allergy* 2008

Adverse Effects

- Local
  - Dryness, burning, epistaxis
  - Sneezing
  - HA
  - Nasal septal perforation
- Systemic
  - HPA axis suppression, ocular changes (increased IOP, glaucoma, cataracts)
  - Children 2-11 years
    - Growth rate may be slower
    - Children should use for the shortest amount of time necessary to achieve symptom relief
- ICS - MDI

Systemic Corticosteroids

- Limited role
  - Adverse effects
  - Limited morbidity of rhinitis
- Short course
  - Severe nasal congestion
  - Decreased nasal edema, increased efficacy of topical medication

Antihistamines

- No loss of efficacy over time
- Rapid onset of action
  - Relieve sneezing, itching, rhinorrhea
  - Possible effect on eye, skin symptoms
  - Decrease vascular permeability
- Inverse agonist of histamine at the H_1 receptor
  - Decreased antigen presentation & expression of proinflammatory cytokines
  - Inhibition of mast cell activation and histamine release
  - Down regulation of allergic inflammation
  - Possible binding to dopaminergic, serotinergic and cholinergic receptors

Histamine

- H_1, H_2 receptors
  - Present on endothelial, epithelial and smooth muscle cells
  - Stimulated in both the early and late phase allergic response
    - Increased vascular permeability
    - -edema, erythema, rhinorrhea
  - Stimulation of sensory nerve endings
    - Itching, sneezing
- H_3, H_4 receptors

2nd Generation Oral Antihistamines

Medication		Age/Dose*		AE	
Cetirizine	Zyrtec	6-11 mos 2.5mg QD 12-23mos 2.5mg up to BID 2-5y 2.5mg QD-BID 6-12y 5-10mg QD 12-65y 10mg QD 66-76y 5-10mg QD ≥ 77y 5mg QD	Tab Chew ODT Syrup	Sedation, dry mouth, urinary retention	OTC
Desloratadine	Clarinex	6-11mos 1mg QD 12mo-5y 1.25mg QD 6-11y 2.5mg QD ≥ 12y 5mg QD	Tab ODT Syrup	Sedation	Rx
Fexofenadine	Allegra	2-11y 30mg BID ≥ 12y 60mg BID or 180mg QD	Tab Gelcap OCT Syrup	HA	OTC

Medication		Age/Dose*		AE	
Levocetirizine	Xyzal	6mo-5y 1.25mg QD 6-11y 2.5mg QD ≥ 12y 2.5-5mg QD	Tab ODT Syrup	Sedation, dry mouth, urinary retention	OTC
Loratadine	Claritin Alavert	2-5y 5mg QD ≥ 6y 10mg QD	Tab Cap ODT Chewable Syrup	Sedation	OTC

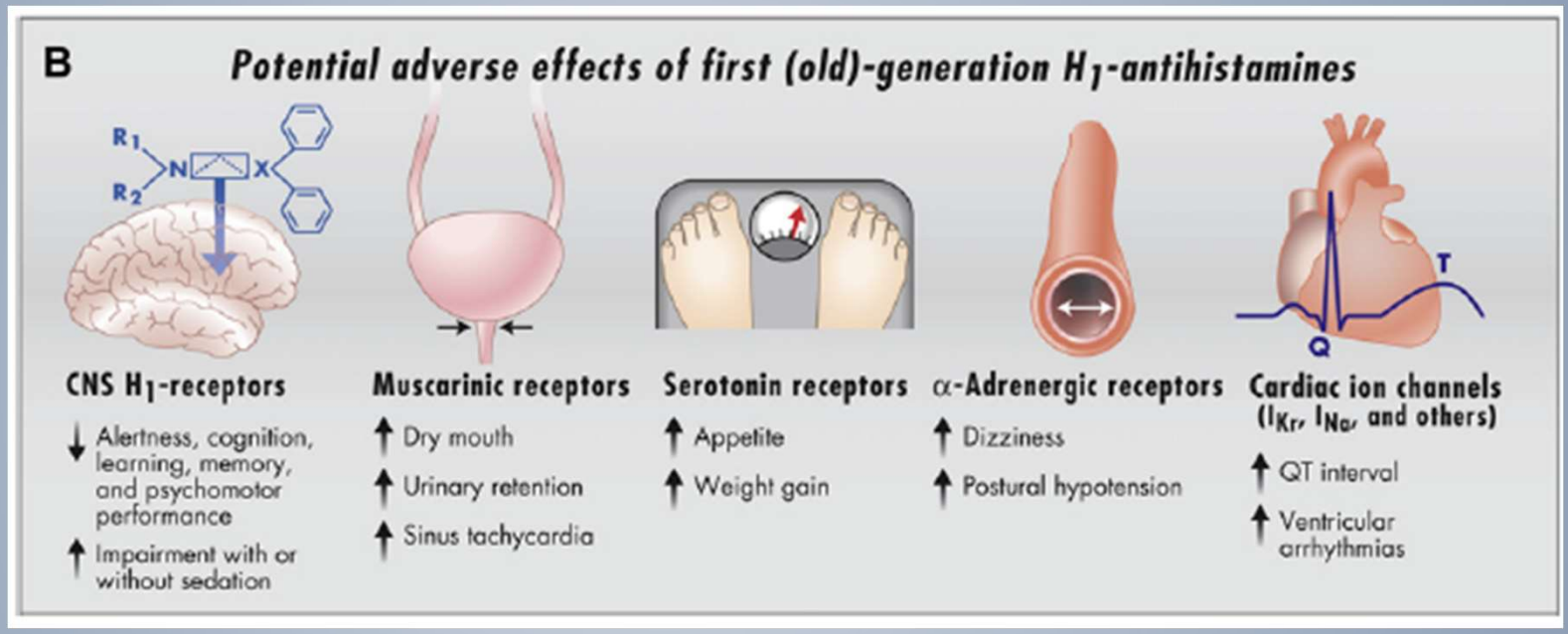
- May be considered first line therapy for treatment of mild to moderate intermittent or mild persistent allergic rhinitis

1st Generation Antihistamines

Medication	Dose (mg)	Dosing Interval	Sedation	Antihistaminic Activity	Anticholinergic Activity
Chlorpheniramine	4	4-6 hrs	+ - ++	++	++
Triprolidine	2.5	4-6 hrs	+ - ++	++	++
Cyproheptadine	4	8 hrs	+	++	++
Promethazine	12.5-25	6-24	+++	++ - +++	++
Clemastine	1	12 hrs	++	+ - ++	+++
Diphenhydramine	25-50	4-6 hrs	+++	+ - ++	+++ - ++++

1st Generation Antihistamines

Medication	Dose (mg)	Dosing Interval	Sedation	Antihistaminic Activity	Anticholinergic Activity
Doxylamine	12.5	4-6	++++	++	++ - +++
Hydroxyzine	25-100	4-8	+++	++ - +++	++
Meclizine	12.5-50	4-8	+++	++ - +++	++



Simons FE, et al. *J Allergy Clin Immunol* 2011;128:1139-50

Proportional Impairment Ratios

Antihistamine	Dose (mg)	PIR
Fexofenadine	80-360	0.00
Cetirizine	2.5-20	0.18
Loratadine	10-40	0.58
Diphenhydramine	25-150	2.05
Promethazine	10-50	3.24

Shamsi Z, Hindmarch I. Sedation and anti-histamines: a review of inter-drug differences using proportional impairment ratios. *Hum Psychopharmacol Clin Exp*. 2000;15:S3-S30.

Topical Antihistamines

- Azelastine
  - Astelin (0.1%)
  - Astepro (0.15%)
- Olopatadine
  - Patanase (0.6%)
- Rapid onset
  - 15-30 minutes
- Symptom relief
  - Rhinorrhea, sneezing, nasal itching
- Adverse Effects
  - Alteration of taste, drowsiness, epistaxis, burning

Topical Antihistamine/INCS

- Dymista™
  - Azelastine (137mcg)/Fluticasone propionate (50mcg)
  - More rapid and complete symptom control
  - AE's
    - Alteration of sense of taste
    - HA
    - Epistaxis, dryness
    - Drowsiness
    - Slowing of growth in children
- Olopatadine (665 mcg) / Mometasone (25 mcg) (Ryaltris)
  - BID dosing
  - AE's
- Future therapies
  - INCS/Anticholinergic combination products

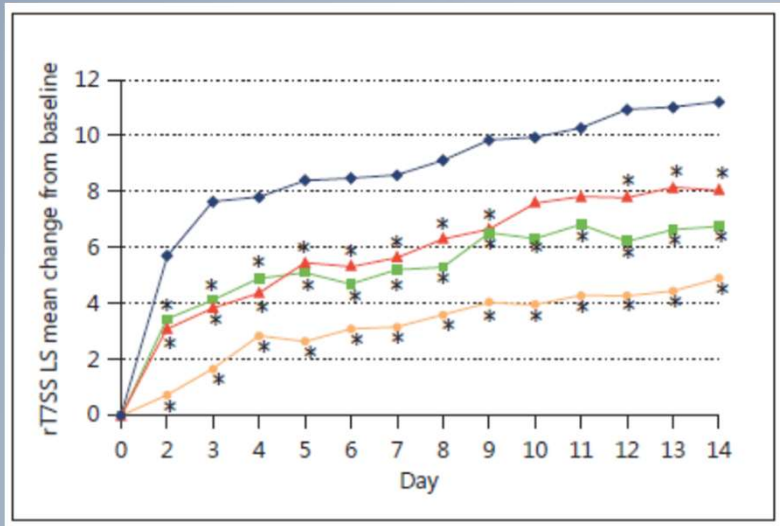
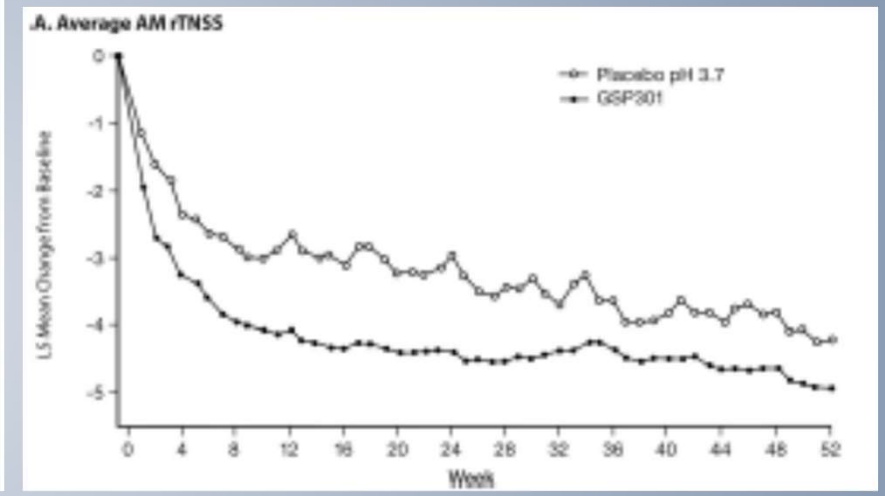


Fig. 1. Effect of MP29-02 (blue), FP (red), AZE (green) and placebo (yellow) on least squares (LS) mean change from baseline in rT7SS by treatment day (numbers and baseline data are provided in online suppl. table 6). * $p \leq 0.0336$ vs. MP29-02.



FP/Azelastine

Olopatadine/Mometasone

Segall, N. et al. *Allergy Asthma Proc* 40:301-310, 2019

INCS versus oral Antihistamines

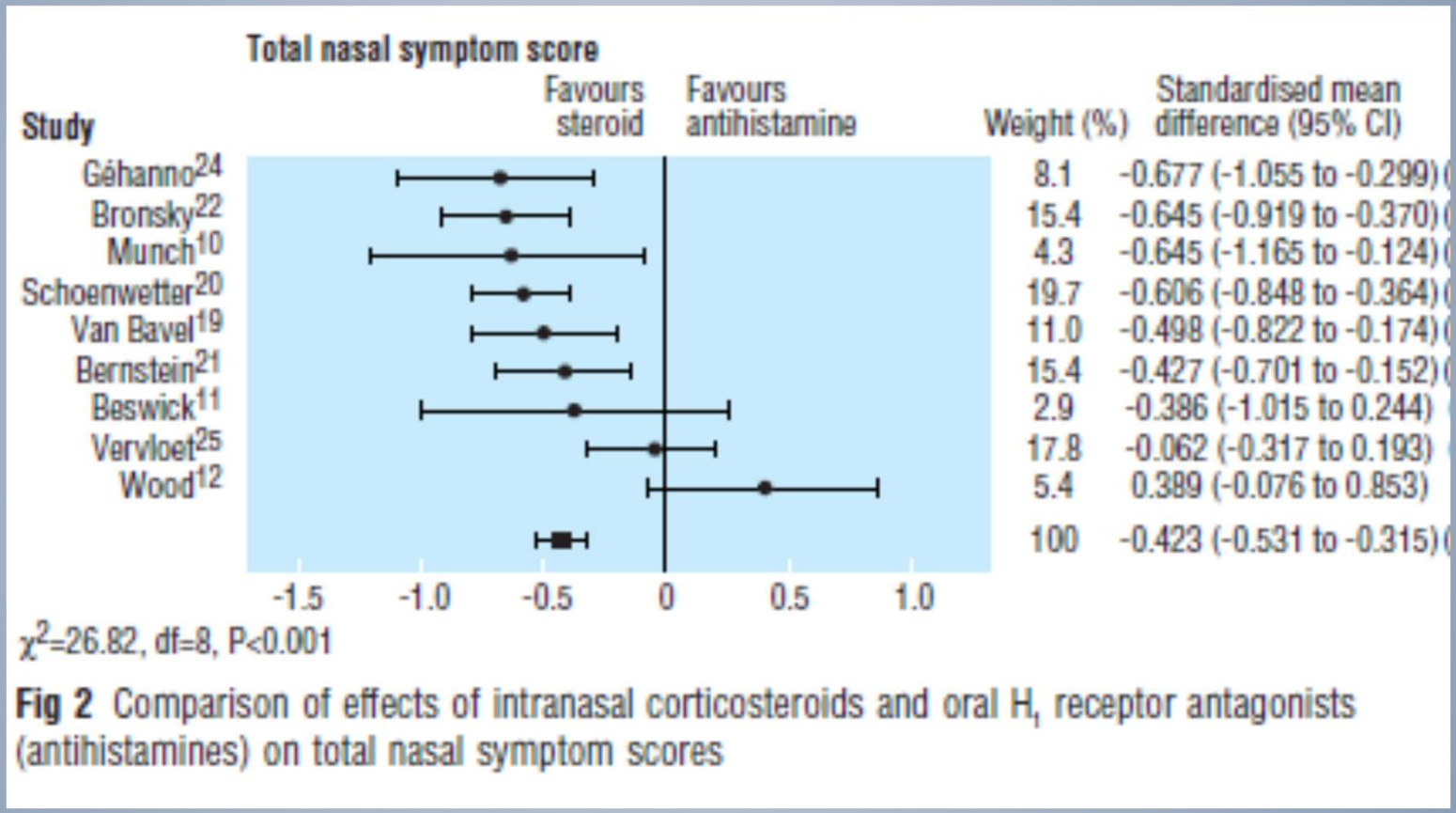


Fig 2 Comparison of effects of intranasal corticosteroids and oral H_1 receptor antagonists (antihistamines) on total nasal symptom scores

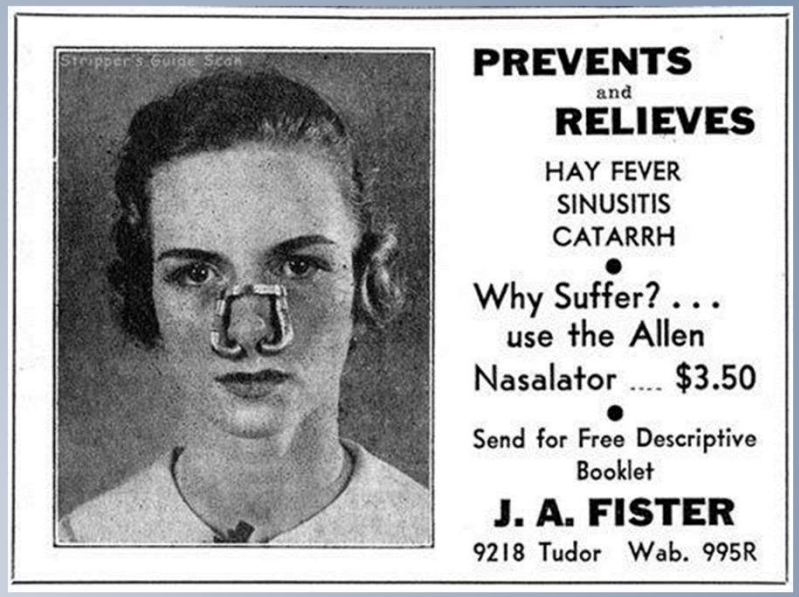
Weiner, J. M et al. BMJ 1998;317:1624-1629

Decongestants

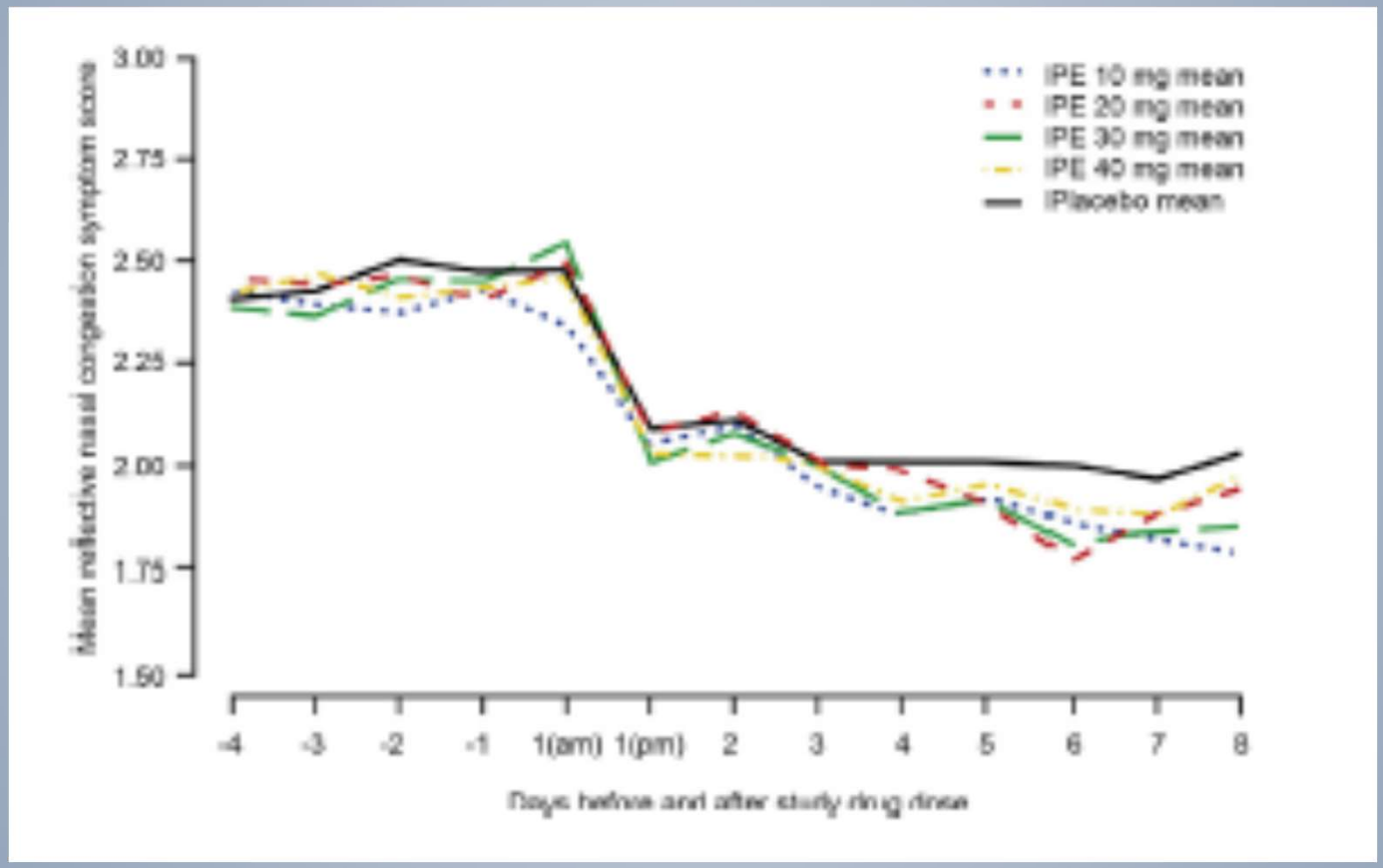
- Sympathomimetic agents
  - α-adrenergic stimulation –
    - Vasoconstriction of vessels in nasal mucosa
    - Reduction of nasal blood supply
- Topical
  - Faster onset
  - With overuse- irreversible tissue hypertrophy, rebound congestion
  - Local irritation, dryness
- Oral
  - Adverse effects
    - Hypertension, decrease in appetite, tremor, insomnia, irritability/agitation, dizziness, HA, tachycardia, rebound congestion, seizures
    - Monitor use in elderly, HTN, hyperthyroidism, prostate hypertrophy, glaucoma, psychiatric disorders, urinary retention, cardiac disease, seizure disorders
    - Pregnancy – vasoconstriction of uterine arteries
    - Contraindication – MAO inhibitor use

Decongestants

- Oral
  - Pseudoephedrine
    - 30-60mg q4-6 hours (Max 240mg/day)
    - Children 6-12 years: 30 mg q4-6 hours
  - Phenylephrine
    - 10-20mg q4 hours
    - Children 6-12 years: 5mg every 4 hours
- Topical
  - Oxymetazoline
    - 2-3 sprays twice daily
  - Phenylephrine
    - 2-3 sprays every 4 hours
    - 12-18 years: 0.25-0.5% - 2-3 sprays every 4 hours
    - 6-12 years: 0.25% - 2-3 sprays every 4 hours
  - Propylhexedrine
    - ≥ 6 years: 2 inhalations prn (no more often than q 2 hours)
    - "new" drug of abuse – stimulant high



Phenylephrine



Meltzer, EO, et al. *J Allergy Clin Immunol Pract* 2015

Anticholingergics

- Ipratropium nasal spray
  - 0.03% and 0.06%
  - Relieves rhinorrhea
- Dosing
  - 2 sprays in each nostril 2-4 times a day
  - Titrate based upon response, symptoms
- Adverse effects
  - Headaches
  - Nasal dryness, epistaxis

Nasal Saline

- Liquefies thick nasal mucus
- Soothes irritated tissues
- Inexpensive
- Safe
- Infants/toddlers: drops, sprays

http://www.youtube.com/watch?v=rsZeILCedRw&feature=related

http://www.neilmed.com/usa/sinusrinse_video.php

Nasal Saline

- Tap water versus “treated” water
  - 48% use tap water
  - Correct: distilled, bottled, filtered, or boiled
- Cleaning rinse bottle
  - Wash daily – hot soapy water, air dry
  - Rinse, shake dry, microwave all pieces for 90-120 seconds

Careful use of neti pot advised after woman contracts rare but fatal brain infection

The woman inhaled a brain-eating amoeba that was not discovered until nearly a year later.

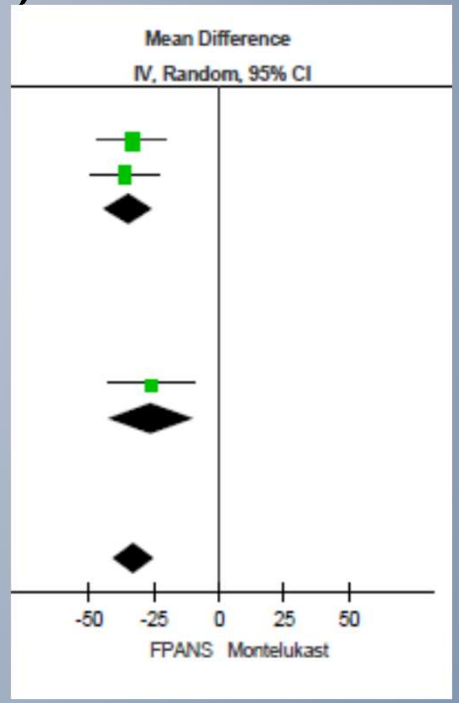
NBC Evening News 12/2018

Buffered Saline Solution

- Premix salt
  - 3 parts **pickling** or **canning** salt
  - 1 part baking soda
- Add ½-1 teaspoonful of salt mix to 1 cup (240ml) of distilled, boiled (and cooled) or filtered/bottled water

Leukotriene Receptor Antagonists (LTRA)

- Inhibit leukotrienes - inflammatory mediators produced by mast cells, eosinophils, basophils, macrophages, and monocytes
- Montelukast
  - Ages ≥ 6 months
- Good safety profile
  - Adverse effects: URI, headache
    - Rare: neuropsychiatric events – aggression, depression, suicidal thoughts and behaviors
- INCS more effective



Dykewicz MS, et al. Treatment of seasonal allergic rhinitis *AnnAllergyAsthma Immunol* (2017)

Montelukast

- Dosing
  - Age > 14 years – 10 mg daily
  - Age 6-14 years – 5mg daily
  - Age 6 months – 5 years – 4mg daily
- Adverse effects
  - Headache, flu-like symptoms
  - Mood and behavioral changes
    - Hallucinations, night terrors, suicidal thoughts
    - Black box

Mast Cell Stabilizers

- Cromolyn 4% nasal spray
- MOA
  - Prevents mast cell degranulation and release of allergic mediators
- 1 spray in each nostril 3-4 times/day
  - Approved in children ≥ 2 years
  - Safe in pregnancy, breast feeding
- Limited efficacy, well tolerated
- Adverse effects
  - Sneezing, nasal irritation/stinging, unpleasant taste, headache

Immunotherapy

- May prevent development of asthma and sensitivity to new allergens in children (disease modifying)
- May improve control of atopic dermatitis
- Curative properties for SAR and PAR
- May decrease long-term asthma medication use, improve QoL
- SCIT, SLIT
- Adverse effects
  - SCIT – localized itching, redness, swelling; anaphylaxis
  - SLIT – localized oral and pharyngeal itching and swelling; throat irritation; anaphylaxis
  - **All** immunotherapy patients MUST have autoinjectable epinephrine

Immunotherapy

- Proven effective in allergic rhinitis
  - Reduces symptoms in about 85% of those treated
- For patients not adequately controlled with maximal medical therapy and demonstrated allergic sensitization
  - Immediate skin hypersensitivity skin testing
  - Laboratory testing to measure the level of antigen-specific IgE antibody
- Benefits seen after 2-12 months
- Duration is 3-5 years to lifetime
  - Weekly first 6-8 months
  - Monthly thereafter
- Contra-indicated
  - Using beta-blockers
  - Severe cardiovascular or pulmonary disease

Sublingual Immunotherapy (SLIT)

- Grass
  - Start ≥ 12 weeks prior to season & throughout the season
  - Grastek (timothy grass) ≥ 5 y.o.
  - Oralair (5 grass mix) ≥ 10 y.o.
- Ragweed
  - Start ≥ 12 weeks prior to season & throughout the season
  - Ragwitek ≥ 18 y.o.
- Dust Mite
  - Odactra ≥ 18 y.o.
- Adverse Effects
  - Throat irritation, itching (mouth, ears), swelling (mouth, lips, tongue), N, taste alteration
- Clinical Pearls
  - Clean, dry hands
  - Allow to slowly dissolve under the tongue
  - No food or beverage for ≥ 5 minutes post dose
  - Wash hands after taking dose

NAEPP: EPR4

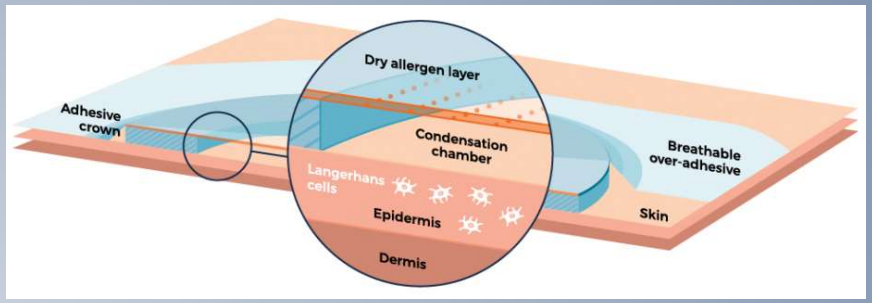
- Role of SCIT vs SLIT
  - SCIT: conditionally recommended for patients ≥ 5 years with mild-moderate allergic asthma as adjunct treatment to standard pharmacotherapy
    - Patients with worsening asthma upon exposure to allergen
    - Patients with not well controlled allergic asthma
    - Patients with well controlled allergic asthma hoping to ↓ med burden
  - SLIT: conditionally recommends against the use of SLIT in asthma treatment
    - Beneficial for patients with rhinoconjunctivitis and comorbid allergic asthma
    - No reduction in asthma symptoms, no improvement in asthma QoL
    - Improvement in disease specific QoL, FEV_1
    - Decreased medication use

J Allergy Clin Immunol. 2020;146:1217-70
AHQR Publication No. 1(18)-EHCO29-EF, March 2018
J Allergy Clin Immunol. 2020;146:1286-1287

Oral Immunotherapy

- Peanut (Palforzia – peanut allergen powder)
  - Patients 4-17 years old
  - Dosing
    - Initial dose escalation – in clinic
    - Up-Dosing (3mg – 300mg)
      - 11 separate 2 week increments, initial up-dose in clinic
    - Maintenance
      - 300mg daily
    - AE
      - Abdominal pain, V, N, oral/ear pruritus, throat irritation, cough, rhinorrhea, sneezing, throat tightness, wheezing, dyspnea, pruritus, urticaria, anaphylaxis
    - Mix contents with food, eat entire amount
    - Take same time of day each day and with a meal
    - Wash hands thoroughly before and after

Epicutaneous



- Peanut Patch
  - Viaskin®
  - Solubilized antigen is captured by Langehans cells in the epidermis
  - 250mcg per patch
  - Escalating “wear” time
    - 6 hours/day week 1
    - 12 hours/day week 2
    - 24 hours/day thereafter
  - Approved for ages 4-18 (Verify)
  - Adverse Effects
    - Skin itching and redness at application site

Adverse effects/Anaphylaxis

- Trouble breathing
- Throat tightness/swelling
- Trouble swallow/speaking
- Dizziness, fainting
- Rapid or weak heartbeat
- Severe stomach cramps/pain, V, D
- Severe flushing or itching of skin
- Sense of doom

Treatment recommendations

- Leukotriene modifiers – as add on therapy only
- Antihistamines – 2nd generation strongly recommended for primary complaints of sneezing and nasal itching
- Immunotherapy – patients who have inadequate relief to pharmacologic therapy
  - In clinical trials
    - Epicutaneous (patch)
    - Oral
    - Intralymphatic

Combination Therapy

- INCS and oral antihistamine
  - No superior clinical benefit
  - May provide additional benefit for specific individuals
  - Monotherapy with INCS preferred
- INCS and INAH
  - May be clinical benefit associated with combination
  - Overall reduction in nasal symptom score
    - Reduced ocular symptoms, increased QoL
  - Increased adverse events
    - Headache, bitter taste, epistaxis, sedation
- INCS and INAH/MCS (Mometasone/Olopatadine-Ryaltris®)
  - May be clinical benefit associated with combination
  - Rapid onset of action (15 minutes)
  - Improvement in symptom scores, QoL

Pharmacist Treatment Algorithm

Symptoms of allergic rhinitis

Mild Intermittent

- Antihistamine
- Decongestant
- Cromolyn
- Nasal Saline

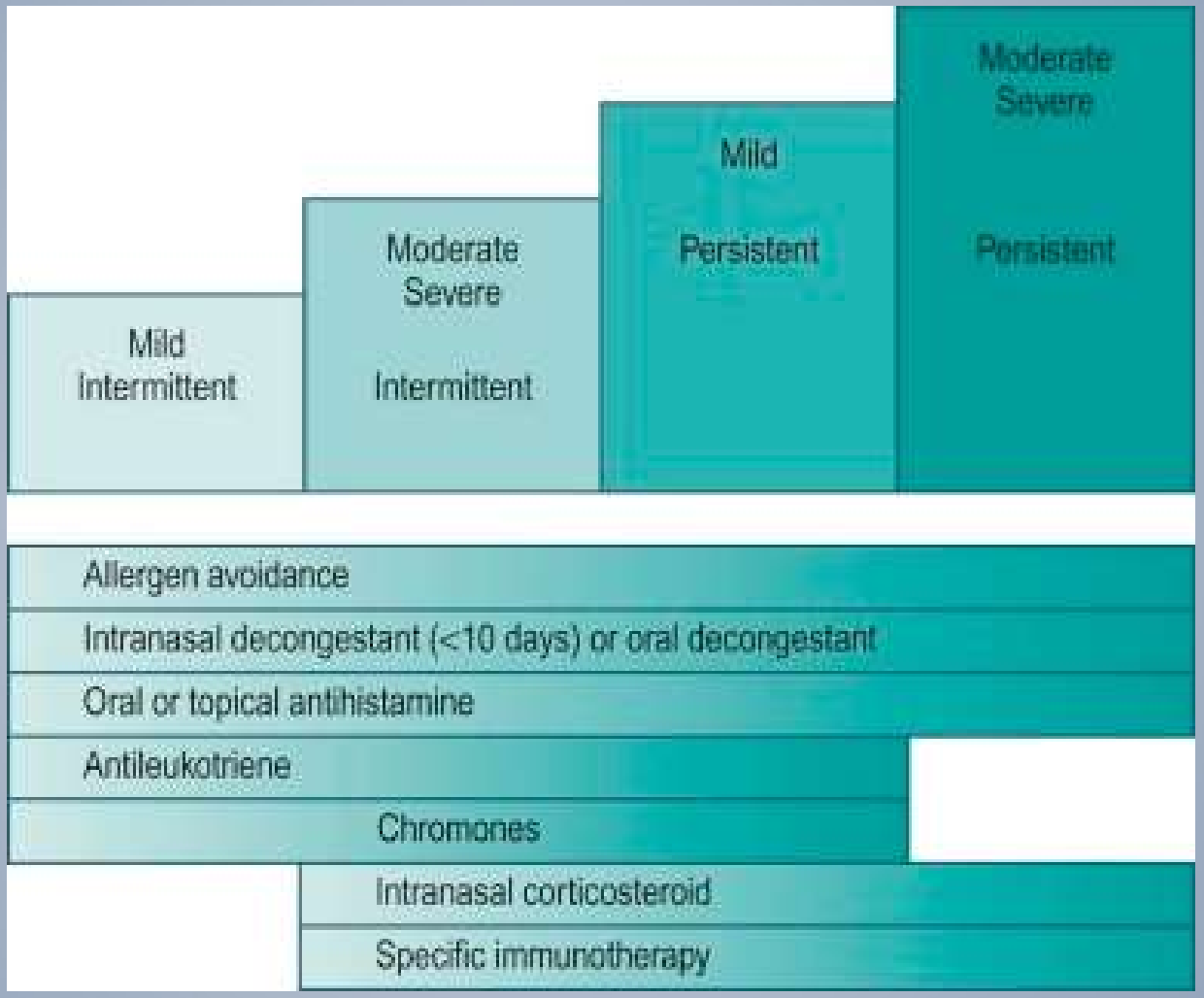
Mild Persistent
Moderate – Severe
Intermittent

- Nasal Steroid
- Antihistamine
- Decongestant
- Cromolyn
- Nasal Saline

If after 7- 15 days – No Improvement

Moderate – Severe
Persistent

Refer to practitioner



Coren J. Middleton's Allergy Essentials. January 1, 2017

Effects of Various Pharmacotherapies

Therapy	Sneezing	Rhinorrhea	Congestion	Nasal itch	Eye symptoms
H_1-antihistamines					
Oral	+ +	+ +	~	+ + +	+ +
Intranasal	+ +	+ +	+/-	+ +	0
Ophthalmic	0	0	0	0	+ + +
Corticosteroids					
Intranasal	+ + +	+ + +	+ + +	+ +	++
Cromolyn sodium					
Intranasal	+	+	+	+	0
Ophthalmic	0	0	0	0	+
Decongestants					
Intranasal	0	0	+ + + +	0	0
Oral	0	0	+	0	0
Anticholinergics	0	+		0	0
Leukotriene Modifiers	+	+		0	+ +
INCS/INAH	+ + +	+ + +	+ + +	+ + +	+ + +

Adapted from van Cauwenberge P, et al. *Allergy*. 2000;55:116-134 and Nayak AS, et al. *Ann Allergy Asthma Immunol*. 2002;88:592-600. Bosnic-Anticevich S. et al. *ARIA Pharmacy 2018* doi: 10.1111/all.13701