ANTIHISTAMINES

Histamine (physiologic substance produced by body)

- Chemical mediator found in all body cells
- Released into bloodstream by mast cells in response to allergens, antigens or trauma
- Response to histamine release is generally detrimental and/or physiologically undesirable
  - Pain - itching
  - Increase secretion of bodily fluids - gastric, intestinal, bronchial, salivary
  - Smooth muscle contraction - significant for bronchial constriction
  - Cerebral blood vessel dilation
  - Vasodilation -> flushing, hypotension
  - Increased capillary permeability - > edema to nose, eyes and throat
  - Anaphylaxis: systemic response which is life threatening
    - Hypotension, laryngeal edema (respiratory arrest)
    - Generalized hives

Antihistamines (drugs given to counteract histamines)

MECHANISM

- Block action of histamines via competitive inhibition for cell receptor sites
  - Histamine production continues unchanged
  - Antihistamine blocks (sits on) receptor site
  - Occupied receptor site prevents histamine from entering cell
  - Histamine cannot exert its detrimental effects because it cannot enter cell

INDICATIONS

- Allergic disorders: seasonal, or acute allergen contact (food, plants, animal dander, etc.)
- Parkinson’s disease

- Motion sickness and antiemetic
  Meclizine (Antivert), Diphenhydramine (Benadryl), dimenhydrinate (Dramamine), prochlorperazine (Compazine)

OTHER DRUG CLASSES - used for motion sickness/antiemesis

Anticholinergics: scopolamine (Transcop) - probably the most common
Phenothiazine:
  promethazine (Phenergan)
  Chlorpromazine (Thorazine), perphenazine (Trilafon)
Cannabinoid: dronabinol (Marinol)
Antidopaminergic: metoclopramide (Reglan)
Trimethobenzamide (Tigan)
Selective 5HT3: Ondansetron (Zofran), granisetron (Kytril)

- OTC hypnotics (Unisom, others) - this use is not widely endorsed by professionals
- Anxiolytic - only hydroxyzine (Atarax, Vistaril)
CLASSIFICATION

1ST Generation: **Sedating** - Cross **blood-brain barrier** - older agents
2nd Generation: **Non-sedating** or less sedating - do not cross **blood-brain barrier**

Intranasal agents: local treatment of allergic rhinitis - can cause drowsiness

RECEPTOR BLOCKADE TYPE

**H1 receptors**: selectively block H1 receptors - treat allergic reactions
- **H1 located throughout body**: dermatitis, rhinitis, conjunctivitis, anaphylaxis, etc.
- Includes 1st generation and second generation agents

**H2 receptors**: selectively block H2 receptors - used to suppress peptic acid
- H2 receptors primarily **located in GI tract** (gastric acid)
- Includes GI agents for peptic acid e.g. ranitidine (Zantac)

**H3 receptors**: presynaptic receptors located on nerve terminals
- H3 activation inhibits release of histamine and other neurotransmitters

<table>
<thead>
<tr>
<th>COMMON ANTIHISTAMINES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H1 AGENTS</strong></td>
</tr>
<tr>
<td>1ST Generation</td>
</tr>
<tr>
<td>diphenhydramine (Benadryl)</td>
</tr>
<tr>
<td>chlorpheniramine (Chlor-Trimeton, others)</td>
</tr>
<tr>
<td>meclizine (Antivert)</td>
</tr>
<tr>
<td>hydroxyzine (Vistaril, Atarax)</td>
</tr>
<tr>
<td>dimenhydrinate (Dramamine)</td>
</tr>
<tr>
<td>2nd Generation</td>
</tr>
<tr>
<td>fexofenadine (Allegra)</td>
</tr>
<tr>
<td>loratadine (Claritin)</td>
</tr>
<tr>
<td>cetirizine (Zyrtec)</td>
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<tr>
<td>desloratadine (Clarinex)</td>
</tr>
<tr>
<td><strong>Discontinued agents</strong></td>
</tr>
<tr>
<td>terfenadine (Seldane)</td>
</tr>
<tr>
<td>astemizole (Hismanal)</td>
</tr>
<tr>
<td>Intranasal agents: Azelastine (Astelin)</td>
</tr>
<tr>
<td><strong>H2 AGENTS</strong> - GI tract agents to suppress peptic acid</td>
</tr>
<tr>
<td>cimetidine (Tigan), ranitidine (Zantac), nizatidine (Axid), famotidine (Pepcid)</td>
</tr>
</tbody>
</table>
SIDE EFFECTS

Problem exists with OTC self-medication of antihistamine, decongestant, antitussive and expectorants

**Sedation** esp with 1st generation - major problem
Patients must not drive or operate machinery

**Anticholinergic effects:**
- **Dry mouth**, drying of secretions (nasal, oral, etc.)
- **Urinary retention** (contraindicated BPH, other bladder neck obstruction)
- **Increased intraocular pressure** (contraindicated with glaucoma)

Hematologic (rare): hemolytic anemia, pancytopenia

**Contraindicated with BPH, urinary retention, glaucoma**
- Many OTC preparations contain antihistamines
- Ill-advised for the elderly
- OTC products advertise "senior cough syrup" (free of antihistamines/decongestants)

DECONGESTANTS

- Most preps can be purchased OTC resulting in potential for interactions and adverse effects
- Many clients do not "count" OTC meds when asked re medications
- Many falsely assume that OTC meds are benign and without potential for problems
- Health care provider must establish RX and OTC meds when taking history
- Combinations with antihistamine and/or decongestants, antipyretics are common
- Avoid in the elderly esp those with hypertension

- Some decongestant preps are available as RX - usually in combo with other agents

**Mechanism:** sympathomimetics - "mimic" the sympathetic NS ("flight or flight") response
Accounts for many of the side effects: hypertension, tachycardia, etc.
Accounts for the therapeutic effects
- **Constriction of arterioles in nasal passage** -> reduce edema
- **Dilate bronchioles** - help to clear secretions which are causing coughing

**Indications**
- Nasal congestion (rhinitis, sinusitis, URI)
- Ocular congestion (vernal conjunctivitis, “red eyes”)

**Cautious/Contraindications:**

- **Cautious use:** hypertension, hyperthyroidism
  - Sympathomimetic effect will raise further raise BP and increase HR
  - Limited use in well controlled hypertension may be appropriate
- **Contraindicated:** narrow-angle glaucoma, MAO-inhibitor or tricyclic therapy

**Side effects**
- CNS: headache, nervousness, tremors, blurred vision
- CV: tachycardia, palpitations, hypertension, arrhythmias
- ENT: nasal irritation and/or dryness, sneezing, rebound nasal congestion

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Rebound nasal congestion with prolonged use (> 3 days) - rhinitis medicamentosa
- Rebound (greater than original) congestion of nasal vessels
- Users can become “addicted” to decongestants -> require constant use to relieve congestion

REVIEW OF AUTONOMIC NERVOUS SYSTEM

SYMPATHETIC NS - Fight or Flight

- Increase BP and HR
- Mobilize energy stores
- Increase blood flow to skeletal muscle
- Divert blood flow away from skin and internal organs
- Dilation of pupils and bronchiole

PARASYMPATHETIC NS - Rest and Digest

- “Vegetative” functions
- Digestion, elimination, urination, defecation
- Acts to balance/oppose sympathetic NS
- Essential to maintain life

COMMON DECONGESTANTS

pseudoephedrine Hcl (Sudafed)
oxymetazoline Hcl (Afrin)
phenylephrine Hcl (Neo-Synephrine)
tetrahydrozoline (Visine, Murine) *
phenylpropanolamine (Entex) - withdrawn

note: many OTC combination products contain decongestants e.g. Dimetane, Robitussin CF, Contact, NyQuil, etc

* ocular decongestant (vernal conjunctivitis, “red eyes”)
ANTITUSSIVES

- Indicated to suppress cough reflex
- Particularly appropriate in when cough is excessive or nonproductive or where results in excessive fatigue or interrupts sleep
- Both narcotic and non-narcotic preparations are available
- Avoid with productive cough which clears secretions

- Mechanism: varies with agent
  - Centrally acting: inhibit cough reflex in medulla (opiates, DM)
  - Locally acting: inhibit cough receptors in throat, trachea: (benzoates)

- Available as both OTC and RX products
  - OTC most commonly in combination with other agents (decongestants, expectorants)
  - RX: preparations contain either opiates or DM, often in combo with other agents

- Dextromethorphan (DM) - now target of teenage drug abuse
  - Non-opioid cough suppressant
  - Chemically related to opioids but does not cross blood-brain barrier in normal dosing
  - Can cause CNS effects in high dosing - newer source of drug abuse
  - Common agents: Robitussin DM, Benylin DM, Delsym, Vicks Formula 44

Narcotic cough suppressants commonly prescribed
- Very effective; nonaddictive for short-term use; relatively low abuse potential
- Cause significant sedation and drowsiness - no driving or machine operation
- Potentiate sedation with other sedating agents - synergistic effect
  - Alcohol, barbiturates, hypnotics, sedatives, TCA, phenothiazine
  - Concomitant use can result in excessive sedation
- Constipation can be side-effect

<table>
<thead>
<tr>
<th>COMMON NARCOTIC COUGH SUPPRESSANTS</th>
</tr>
</thead>
</table>

**Codeine:** (as codeine phosphate) direct depressant on cough center of medulla
- Onset 15-30 min; duration 3-4 hrs
- Robitussin A-C, Dimetane DC, Phenergan with Codeine, others
- Metabolized liver; excreted urine
- S/E: lightheadedness, dizziness sedation, sweating, nausea and constipation

**Hydrocodone**
- Usually in combo with other ingredients
- Tussionex, Entuss-D, Hycomine, Hycodan, Vicodin Tuss
- Weak analgesic and strong antitussive
**COMMON NON-NARCOTIC COUGH SUPPRESSANTS**

**Dextromethorphan HBr**
- Most frequently used cough suppressant
- Robitussin DM, Rondec DM, Humibid DM; many others
- d-isomer of codeine analogue of levorphanol
- Minimal CNS depression; no analgesic
- No constipation or habituation
- Frequent combo with other products
- 30 mg dose equals 15 mg codeine
- Mechanism: unclear, probably depresses cough center medulla

**Benzonatate (Tessalon Perles)**
- Structurally related to tetracaine
- Exerts local anesthetic action on stretch receptors thus dampens cough
  - Respiratory passages
  - Lungs pleural
- Does not alter respiratory center at recommended dosages

**SIDE EFFECTS**
- Sedation, dizziness, nasal congestion, constipation, nausea, GI upset
- Pruritus, skin eruptions, burning in eyes, "chilly" sensation, numbness in hands
- Large doses: CNS stimulation

**Carbetapentane tannate (Rynatuss and other products by Wallace Pharm)**
- Used to control coughing from colds, allergies
- Infrequently used in cough preps in contrast to DM
- Anticholinergic effects

**EXPECTORANTS:**

- Clinical effects (reportedly)
  - Removes viscous mucus from respiratory tree
  - Stimulates secretions of lubricating fluid

- Efficacy of most non-prescriptive products subject to debate

- Probably no more effective than high fluid intake (6-10 glasses H20) and humidification
- Little evidence to support relief of dry irritative cough via increasing soothing fluid
  - Same effect as cough drop or lozenge
  - Inclusion in preps add little value
- Adverse reactions are rare; few side effects

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COMMON EXPECTORANTS

Guaifenesin (Humibid, Robitussin, many others)
  - Syrup or long acting tablets; no evidence 1 more effective than other
  - Questionably effective; low s/e profile

Iodinated glycerol (Tussi Organidin) - removed from market

Potassium iodide (SSKI)
  - Enhance secretion of respiratory fluid and decrease viscosity and tenacity of mucus.
  - Efficacy not conclusively established
  - Iodinated glycerol off market at request of FDA

Ammonium chloride
  - Used primarily as systemic and urinary acidifier for metabolic alkalosis
    - Correct chloride depletion
    - Assist urinary excretion of certain basic drugs
  - Expectorant in OTC preps; efficacy doubtful
  - Use is discouraged

Terpin hydrate:
  - Liquid form to stimulate respiratory secretions
  - Gastric upset and drowsiness; give with H20

Acetylcysteine (n-acetyl cysteine): Mucomyst, Mucosil
  - Decreases viscosity of pulmonary mucus
  - Face mask or mouth piece; tent or croupette if large quantities
  - Nebulizer may not allow sufficient penetration into obstructed bronchiolar passages
  - Not for routine use in bronchial asthma because irritating and possible reflex bronchospasm.
  - Prompt removal of liquified secretions necessary; mechanical suction prn.
  - Can also be given for OD of acetaminophen - blocks formation of toxic metabolites
**REVIEW OF THE PATHOPHYSIOLOGY OF ASTHMA**

**Clinical Features**
- Airway hyperresponsiveness
- Airway inflammation
- Reversible airway obstruction
- Respiratory muscle spasm
- Thickening of respiratory mucosa related to edema
- Excessive secretion of viscous mucus

**Mechanism**
1. Symptoms result secondary to exposure to provoking factors
   - Trigger substances: dust, pollen, etc.
   - Release of endogenous allergen mediators via antigen-antibody reaction *
     - Histamine - Leukotrienes
     - Eosinophil chemotactic factor  * Release is from mast cells
   - Substances interact w bronchiole smooth muscle to cause contraction
   - Atopic asthma: appears without exposure to provoking agent
     - Associated with other allergic disorders
     - Young persons; progressively severe

2. Activation of parasympathetic reflex pathways
   - Hypersensitive in asthma
   - Reflex parasympathetic response triggers release of acetylcholine (ACh)
   - ACh constricts bronchiole smooth muscles
   - Triggering factors: mast cell allergens, cold, stress, infection, exercise

**Airway inflammation - key role** in asthma treatment
- **Inflammatory** changes trigger hyperresponsiveness-bronchoconstriction
  - Occur in airway walls: mast cell degranulation, lymphocyte infiltration
  - Typified by migration of inflammatory cells and edema

- **Locally-acting antiinflammatory agents reduce airway hyper-responsiveness**
  - Inhaled steroids: triamcinolone (Azmacort), fluticasone (Flovent), others
  - Mast cell stabilizers: Nedocromil (Tilade) - Cromolyn (Intal)
  - Leukotriene inhibitors: montelukast (Singulair), others

- **Acute attack:**
  - Adrenergic bronchodilators: Alupent (Proventil), salmeterol (Serevent), others
  - Epinephrine (SQ or IV ) if severe or life-threatening

**BRONCHODILATORS**
- Several classes of drugs which reverse airway constriction - primarily used to treat **asthma**
- **Sympathomimetic bronchodilators** e.g. epinephrine
- **Anticholinergic agents** e.g. ipratropium bromide (Atrovent)
- **Adrenergic agents** (B2-agonist) - example albuterol (Proventil)
- **Methylxanthines** - example: theophylline (Theodor)
SYMPATHOMIMETIC BRONCHODILATORS used in treatment of bronchial asthma and other COPDs

- **Epinephrine** (parenteral) relieves respiratory distress during an acute asthmatic attack
  - Used *parenterally* (IV or SQ) in severe life-threatening attack
  - Also available as OTC prep: *Primatene Mist*
- **Ephedrine**: less potent bronchodilator with pronounced central excitatory effects

ANTICHOLINERGIC AGENTS

- Commonly used in COPD - **Ipratropium bromide (Atrovent)** - main clinical agent used
- Effective bronchodilators - *most commonly used for COPD*
- Naturally occurring belladonna alkaloids (atropine) used for many years to treat asthma
- **S/E with systemic use limits there usefulness**
- Inhalation therapy with **ipratropium (Atrovent)** used as bronchodilator
  - Quaternary amine
  - Poorly absorbed from bronchial tree thus *local effect*
  - Useful in asthma from irritants, smoking, emotional stress
- **Combivent (ipratropium bromide and albuterol)**
  - Useful in treating bronchitis and emphysema
  - Mechanism: *anticholinergic action on bronchioles*
    - Prevent increase in cyclic guanosine monophosphate (GMP) from parasympathetic nerve activation
    - Blocks activity from increased vagal (parasympathetic) activity
    - Blocks contraction of bronchiolar smooth muscle:
    - Blocks increase in mucus secretion
    - May inhibit acetylcholine-induced release of allergenic mediators from mast-cells

SIDE EFFECTS:
- Exacerbation of symptoms
- Cough, dryness of oropharynx, gastric upset, nervousness, anticholinergic effects
- Also common: dizziness, H/A, palpitations, skin rash, blurred vision

CONTRAINDICATIONS
- Allergy to atropine or its derivatives
- Allergy to soya lecithin, peanut or related foods (inhaler)

PRECAUTIONS
- Not for primary treatment of acute attack
- Avoid eyes
- **Narrow-angle glaucoma, BPH and bladder neck obstruction**
- **Pregnancy category B**: nursing mothers
**XANTHINES:** use is increasingly **less frequently** due to side effect profile

Side effects are significant esp with rapid IV administration - need **slow IV administration**

**SIDE EFFECTS**

**Tachycardia, palpitations, cardiac arrhythmias,** dizziness, angina-like pain, hyperventilation, hypotension, **CNS excitation,** headache, nausea, vomiting, **tremors,** seizure (rare)

- Weaker bronchodilator vs B2 agonists
  - Less effective vs B2 agonist
  - More toxic thus less frequently used
- Available in time-released oral form
- Can measure **blood levels:**
  - **Narrow therapeutic window** - potential for **toxicity**
  - Should **wean off** gradually to avoid withdrawal symptoms
    - Withdrawal is similar to **caffeine** (related compound)
    - **Headaches** including migraine

**ADRENERGIC AGENTS (B2-AGONIST)**

**B-adrenergic agonists** (aka **beta-agonists** or **B2-agonists**)

Most commonly used of the various types of bronchodilators

Stimulate **beta 2 receptors** found most in the lung (“flight or flight” response) resulting in **bronchodilation**

Previously was mainstay of asthma treatment; - **no longer first line therapy** *
**Inhaled steroids** are considered first line agents.

**SIDE EFFECTS**

- **Side effects due to non-selectivity**
  - Affects not only lungs but other organs as well
  - Nonselective effects increase at higher doses

  **Tachycardia, jitteriness, cardiac stimulation,** palpitations, tremor, nervousness, headache, excitement

---

**ADRENERGIC ANTAGONISTS**

Beta-adrenergic blockers
- **B1** - cardioselective
- **B2** - nonselective

Alpha 1 adrenergic blockers
- Alpha 1 antagonist (eg prazosin)
- Nonselective (phenoxybenzamine)

**XANTHINE BRONCHODILATORS**

**aminophyllin** (Phyllocontin, Truphylline)
**dyphylline** (Dilor, Dyflex, Lufyllin, Neothylline)
**oxtriphylline** (Choledyl)
**theophylline** (Theo-Dur, Slo-Phyllin)
**SELECTIVE B2 ADRENERGIC BRONCHODILATORS**

- **Albuterol** (Proventil, Ventolin, Volmax)
- **Metaproterenol** (Alupent, Metaprel)
- **Pirbuterol** (Maxair)
- **Salmeterol** (Serevent)
- **Terbutaline** (Brethaire, Brethine, Bricanyl) *
- **Bitolterol** (Tornalate)
- **Isoetharine** (Arm-a-Med Isoetharine, Beta-2, Bronkosol)
- **Isoproterenol** (Isuprel) **

* used for **preterm labor** since it nonselectively affects smooth muscle
** potent but less used due to high side effect profile

* Mounting evidence that chronic use of inhaled **adrenergic bronchodilator** may be associated with **increased mortality and morbidity**. Inhaled steroids to prevent inflammatory process is encouraged as first-line approach

** Nebulized inhalation **treatments** with a face mask often used routinely for **children too young to use inhalers**. Inhalation therapy used in adults in emergency (ER, office visit) setting for **acute exacerbation** and also **inpatient settings** where more **intense therapy** is indicated

- Most agents available as **metered-dose inhalers**
- **Albuterol**: numerous formats including solution for nebulized inhalation treatments **
  Ventolin: syrup, Rotacaps, nebules, solution, metered dose inhaler
  Proventil: syrup, Repetabs, HFA inhaler, solution, metered dose inhaler

**COMMON BETA-2 AGONISTS**

**LONG ACTING B2 AGONISTS**

**salmeterol** (Serevent)
- Not for acute exacerbations
- Not a substitute for inhaled corticosteroids
- Can use for exercise-induced asthma (45 minutes before); school day/gym

**Proventil Repetabs** (extended release albuterol sulfate)

**SHORT ACTING B2 AGONISTS**

**albuterol sulfate** (Proventil)
**bitolterol mesylate** (Tornalate)
**pirbuterol acetate** (Maxair, Maxair Autohaler)
**terbutaline** (Brethaire, Brethine, Bricanyl)

- Provide quick relief; pretreat exercise-induced asthma.
- Patient who needs only 1-2 times per week, needs **antiinflammatory as well**
INHALED CORTICOSTEROIDS

- Synthetic steroids with glucocorticoid activity
- Improve pulmonary function
- **Reduce need for adrenergic bronchodilators** or other antiallemics
- Decrease bronchial reactivity to substances (allergens which cause bronchial constriction)
- **First line therapy for mild asthma** *
  - Inhaled bronchodilators used for acute bronchospastic episodes.
  - Chronic use of B2-agonist can worsen asthmatic symptoms and increase M/M
  - Decrease local inflammatory process
- Inhaled steroids have reduced incidence of adverse effects vs systemic steroids
- Synergistic effects on bronchial smooth muscle when used with other antispasminogenics
- **Effect seen within 2-4 weeks**

- Caution when transferring from systemic to inhaled due to suppression of H-P-A axis
  - Inhaled steroids have little if any systemic absorption - no axis suppression
  - Exogenous PO steroids suppress normal levels for months
  - **PO steroids may be needed** during times of sudden demand on adrenal function during transition period (trauma, stress, surgery, etc.)
- Available in **metered-dose inhalation units** (inhalers)
- Used in combination with B-2 agonist agents (also available as inhalers)
- Combination inhalers available salmeterol and fluticasone (Advair)

* Inflammation of respiratory tree has well established role in increased susceptibility of bronchospasm in response to spasmogens

**SIDE EFFECTS**

- Throat irritation, coughing, dry mouth
- Hoarseness
- Oral and pharyngeal fungal infections
  - Reduced w gargling and mouth rinsing
  - Reduced with use of spacer devices

**LONG-TERM USE INHALED AGENTS**

- Associated with bone demineralization although less so than with systemic steroids *
- Steroid use in children is traditionally avoided due to growth suppression *
- Other side effects of systemic steroids would NOT appear to be a problem with inhaled agents
  - Immunosuppression
  - Fluid retention
  - Suppression of H-P-A axis

* Newer agents (fluticasone) are complete destroyed on first-pass through liver thus may be safer - approved for use in children as young as 2 yrs
NASAL STEROIDS

- Used to control allergic rhinitis: seasonal or perennial
- No systemic absorption - no systemic side effects
- Can be used in combination with inhaled and/or systemic steroids
  - Asthma has high correlation with allergies
- Research suggests agents are effective with onset of use versus delayed benefit

### INTRANASAL STEROIDS

<table>
<thead>
<tr>
<th>Steroid</th>
<th>Formulation</th>
<th>Trade Name</th>
<th>Usage Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate</td>
<td>Aqueous nasal spray</td>
<td>Beconase AQ</td>
<td>1-2 sprays each nostril qd; Allergic and vasomotor rhinitis; prophylaxis of nasal polyp recurrence</td>
</tr>
<tr>
<td>Beclomethasone dipropionate</td>
<td>Nasal spray/inhaler</td>
<td>Beconase</td>
<td>1 spray each nostril bid-qid; Refractory allergic rhinitis; prophylaxis of nasal polyp recurrence</td>
</tr>
<tr>
<td>Beclomethasone dipropionate</td>
<td>Aqueous nasal spray</td>
<td>Vancenase AQ Double Strength</td>
<td>1-2 sprays in each nostril qd; Allergic and vasomotor rhinitis; Prophylaxis of nasal polyp recurrence</td>
</tr>
<tr>
<td>Beclomethasone dipropionate</td>
<td>Nasal inhaler</td>
<td>Vancenase Pockethaler</td>
<td>1 spray each nostril bid-qid; Prophylaxis of nasal polyp recurrence</td>
</tr>
<tr>
<td>Budesonide micronized suspension</td>
<td>Aqueous nasal spray</td>
<td>Rhinocort Aqua</td>
<td>1-2 sprays each nostril qd; Seasonal or perennial allergic rhinitis symptoms in patients 6 years or older</td>
</tr>
<tr>
<td>Budesonide micronized suspension</td>
<td>Nasal spray</td>
<td>Rhinocort</td>
<td>2 sprays each nostril qd; Seasonal or perennial allergic rhinitis in adults and children; non allergic rhinitis in adults</td>
</tr>
<tr>
<td>Flunisolide solution</td>
<td>Nasal spray</td>
<td>Nasalide</td>
<td>2 sprays each nostril bid; Refractory allergic rhinitis</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>Aqueous nasal spray</td>
<td>Nasarel</td>
<td>2 sprays each nostril bid; may increase to 2 tid; Seasonal or perennial rhinitis</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>Aqueous nasal spray</td>
<td>Flonase</td>
<td>2 sprays in each nostril qd or 1 spray in each nostril bid; Seasonal and perennial allergic and nonallergic rhinitis</td>
</tr>
<tr>
<td>Mometasone furoate</td>
<td>Aqueous nasal spray</td>
<td>Nasonex</td>
<td>2 sprays in each nostril qd; Begin 2-4 weeks before pollen season; Seasonal or perennial rhinitis</td>
</tr>
<tr>
<td>Triamcinolone acetate</td>
<td>Aqueous nasal spray</td>
<td>Nasacort AQ</td>
<td>2 sprays in each nostril qd; Seasonal and perennial allergic rhinitis</td>
</tr>
</tbody>
</table>
MAST CELL STABILIZERS

CROMOLYN SODIUM (INTAL)
- Adjuvant antiinflammatory agents for management of bronchial asthma
- Not as potent as inhaled steroids and require more doses per day (compliance issues)
- No intrinsic bronchodilator activity
- Not for acute attacks

- Available as inhalation agent (metered dosing) and as solution for nebulization
- Commonly as used for children to counteract inflammation so as to avoid use of steroids *

* Nebulizer treatments for children, even very young children, frequently involve albuterol solution and cromolyn sodium solution placed into nebulizer and administered via face mask

MECHANISM
- Stabilizes mast cell membrane
- Inhibits release endogenous allergens from mast cells (inflammatory response)
  - Histamines
  - Leukotrienes
- May increase cyclic AMP in bronchioles

DOSING
- Adults and children > 5 yrs: 2 puffs QID or 2 puffs 10-60 min before precipitant
- Children 2-5 yrs: 1 amp in nebulizer QID or 60 min before precipitant

PRECAUTIONS
- Pregnancy class B: approved for use in children 2 yrs and older
- Lactation
- Avoid abrupt cessation of therapy
- Coronary artery disease or arrhythmias (inhaler)
- Discontinue if eosinophilic pneumonia occurs

AVAILABLE MODALITIES
- Solution (2 ml amps) for use with nebulizer
- Metered dose inhaler: 8.1 g (112 inhalations); 14.2 gm (200 inhalations)
- Intranasal spray - see below

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INTRANASAL CROMOLYN (NASALCROM)

- Indicated for **allergic rhinitis**
- 1 spray each nostril 3-6 times per day
- Side effects are rare; drug is well tolerated
- Effects apparent within several weeks
- Use antihistamines or decongestants initially

**ADVERSE REACTIONS**

Bronchospasm, throat irritation, bad taste, cough, wheezing, nasal congestion, anaphylaxis

NEDOCROMIL (TILADE)

- **Inhaled anti-inflammatory** similar to cromolyn
- Maintenance therapy of mild to moderate bronchial asthma
- **No intrinsic bronchodilator effects; not for acute attacks**
- **Bad taste** can be a problem with compliance
- **QID dosing** - compliance issues

**MECHANISM:** 

inhibits bronchoconstrictor response to **mast cell allergens**

**MODALITIES:**

- **Tilade Metered Dose Inhaler** (16.2 gm - 104 sprays)
- **Tilade Nebulizer Solution** 0.5% (2 ml amps)

**DOSING**

- Inhaler: 2 sprays QID - adults and children > 6 yrs
- Nebulizer solution:
  - Under 2 years not recommended
  - 2 yrs and older; adult 1 amp by nebulizer QID
  - 2-5 yrs w mild asthma 1 amp by nebulizer TID

**PRECAUTIONS**

- Monitor when reducing systemic or inhaled steroids
- Cough, bronchospasm
- Pregnancy category B; nursing mothers

**ADVERSE REACTIONS**

- **Unpleasant taste**
- Dysgeusia
- Upper respiratory symptoms
- GI upset
LEUKOTRIENE ANTAGONISTS

AGENTS: Zafirlukast (Accolate), zileuton (Zyflo), montelukast (Singular)

- Not for use with acute attacks
- Antiinflammatory effect is less potent than inhaled corticosteroids
- May be more convenient for mild persistent vs inhaler
- May reduce quantity of inhaled/PO steroids for severe patients
- Good for ASA-induced asthma

Protects against environmental substances to which ASA-sensitive patients have cross-reactions

MECHANISM

- Competitive leukotriene D4 and E4: components slow-reacting substance anaphylaxis
- Cysteinyl leukotriene production and receptor occupation correlated with asthma pathophysiology
  - Airway edema
  - Smooth muscle
  - Altered cellular activity associated with inflammatory process

COMPARISON OF AGENTS

Zileuton (Zyflo):
Zafirlukast (Accolate)
Montelukast (Singular)

LEUKOTRIENE ANTAGONISTS

Zileuton (Zyflo):
Hepatotoxic - requires qid dosing
- Evaluate liver function before and during therapy
- Caution with ETOH consumption
- Discontinue with signs of liver disease

Interactions
- Must reduce dosing of theophylline 50%
- Can increase PT with anticoagulation therapy
- Potentiates warfarin, theophylline
- Monitor with drugs metabolized by CYP3A4

- Adverse reactions: dyspepsia, pain, nausea, asthenia, H/A, myalgia, others
- Not indicated for use with children, pregnancy category C; not for lactation
**Zafirlukast (Accolade)** - 20 mg BID (empty stomach)

- **Children’s dosing**: 7-11 yrs 10 mg bid; 12+ years: dose as adult
- Can increases PT with anticoagulation therapy
- Bid dosing - take on empty stomach (1 h before; 2 h after meals)
- Few cases of Churg-Strauss syndrome
- Decreased levels with erythromycin and theophylline; increased levels w ASA
- Potentiates warfarin, may increase theophylline levels
- Caution with drugs which are metabolized by elements of cytochrome system
  - CYP2C9: tolbutamide, phenytoin, carbamazepine
  - CYP34A: dihydropridine Ca agonists, cyclosporine, cisapride
- Adverse reactions
  - H/A, infections (respiratory tract), GI upset, pain, fever
  - Elevated liver enzymes (rare: follow up if occurs)
- Indicated for children 7 yrs and older; pregnancy category B
- Not recommended for use with nursing mothers
- Caution when withdrawing from oral steroids

**Montelukast (Singular)** - 10 mg QD HS - most commonly used agent

- Once daily (qd) dosing
- **Children’s dosing**: chew tabs
  - 2-5 yrs: one 4 mg chew tab in pm
  - 6-14 yrs: one 5 mg chew tab in pm
  - 15 years or older: dose as adult
- Relatively clean side effect profile
  - Adults: H/A, asthenia/fatigue, fever, GI disturbances
  - Children: flu/cold symptoms, ear/leg pain, thirst, urticaria
- Monitor with drugs that induce CYP450 (phenobarbital, rifampin)
- Indicated for children 2 years and older, pregnancy category B
- Caution when withdrawing from oral steroids
- Caution with nursing mothers