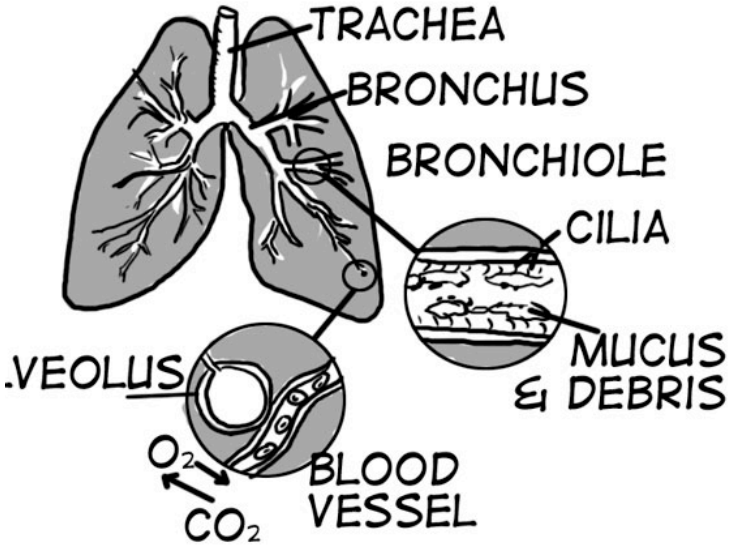
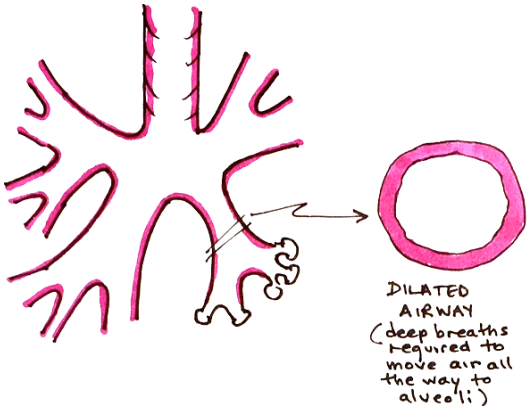
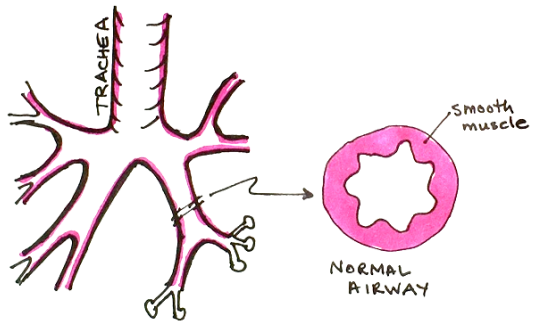
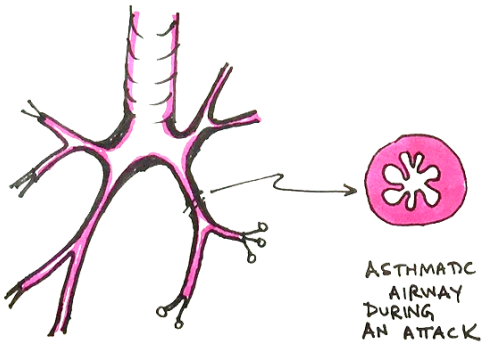
DRUGS FOR ASTHMA
with a few comments about COPD

Important anatomy & physiology:
Air flows into the nose and mouth, down into the trachea, and through a series of branching tubes (bronchi and **bronchiole**s) until the air reaches tiny sacs called alveoli.









At the **alveoli**, nearby blood capillaries drop off used carbon dioxide (CO2) and pick up new oxygen (O2). Oxygen, the gas, dissolves into the cell membrane and then into your bloodstream. Carbon dioxide comes out of solution and turns back into gas. Pretty cool.

Since every breath you take contains all sorts of debris and dust, the lung is constantly cleaning itself out. This debris is trapped in **mucus** produced by the goblet cells lining the bronchioles and tiny beating hair-like brooms (**cilia**) move the dirty mucus up the trachea and into the back of the throat where it gets swallowed. *Ew*.

When you need extra air (for instance, when you are being chased by a bear) the bronchioles expand (dilate) so that more air can move in and out more quickly. Bronchioles are normally dilated by the sympathetic nervous system via beta-2 receptors. But you must take deep strong breaths to get the fresh oxygen all the way to your alveoli at the end of the air passages.

When you need less air moving through your lungs, like when you are at rest, the bronchioles are at a mid-diameter.

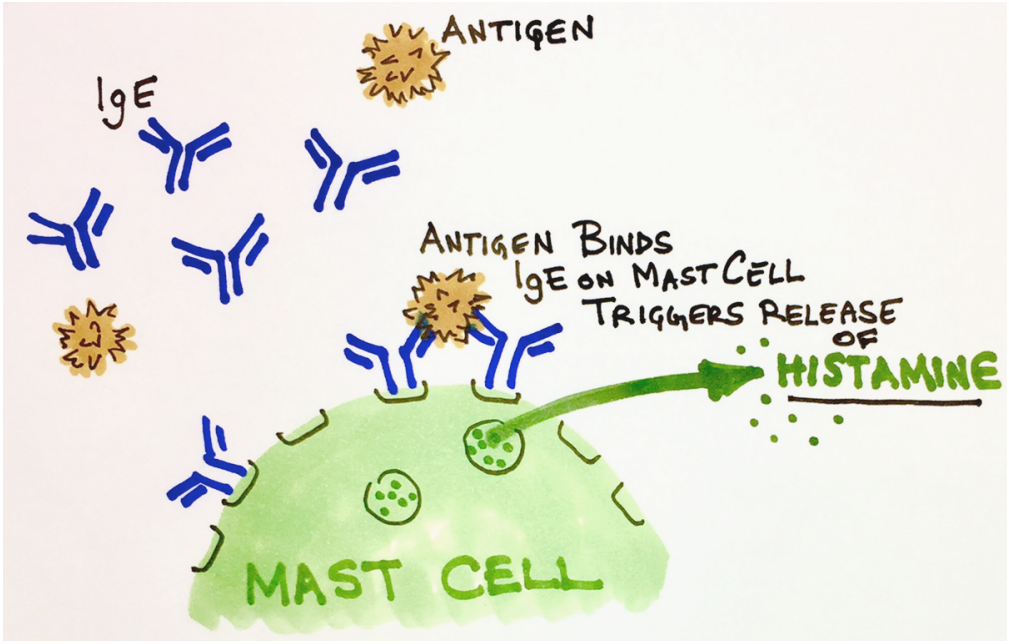
If your body wants even less air moving through your lungs (for instance, if you are in a house fire filled with toxic smoke) the bronchioles will constrict dramatically and extra mucus will form to get rid of the smoke and poison.

In an asthma attack, the bronchioles convert to that most extremely constricted state, causing difficulty breathing, and in the worst case, death.

In Reactive Airway Disease **(Asthma**), the lungs become abnormally sensitive to stimulants such as dust, molds, chemicals, exercise, cold, animal dander, etc. These cause **bronchoconstriction, mucus production, inflammation, and swelling**. Patients cough and wheeze because the air can't get through the tight airways.

Acute attacks can be fatal if severe enough (so-called ***status asthmaticus***). So **with asthmatics you are treating not only inflammation and constriction but you *may* also be treating allergies** that trigger attacks.

Exercise and cold are thought to trigger attacks via direct irritation of the inner surfaces of the bronchi. (Rapid breathing in exercise dries those tissues out.) But the allergic response is mediated through IgE antibodies that are activated by binding the triggering antigens. That turns on **mast cells** that then release histamine. Mast cells are located in areas of the body most likely to come across a new molecule such as skin or the inner surface of the GI tract.



Remember: Histamine binds H2 receptors in the stomach to make acid, and the heart to increase heart rate. For lower respiratory (lungs) or upper respiratory (sinuses) problems, we are talking about H1 histamine receptors.

<u>Actions of Histamine (Binding H1 Receptors)</u>

Histamine binds H1 receptors to cause:

skin: dilation of blood vessels (**redness**)
irritation of nerves (**itching**)
blood vessels: dilation and **drop in blood pressure**
leakage of fluid into tissue to cause **swelling** (edema)
nasal mucosa: dilation of blood vessels and leakage leading to runny nose
lungs: **constricted bronchioles** (asthmatic attack)
swelling of tissue and increased fluid and mucus

In severe allergy (peanuts, bee stings, other) drop in blood pressure, arrhythmias and bronchiole constriction leads to shock and death.

Bronchioles constrict in response to many processes in the body:

1.The parasympathetic (cholinergic) nervous system via the **vagus nerve**.
2. **Histamine** (Acting via H1-receptors)
3. Other inflammatory **chemical mediators** (example: **leukotrienes_**

So, most **lower** respiratory (lung) problems that we deal with in medicine all really come down to doing what we can to improve breathing and air exchange by:

Dilating bronchioles
Reducing inflammation (and therefore scarring and swelling)
Reducing abnormally thick or high amounts of mucus and secretions

Before we proceed, it's important to note that the lungs are unusual in that they are internal organs but **we can apply medication to the lungs topically via inhalation**. This means we can give the patient a far lower dose of the drug and target it to the lung, making the drug less likely to have side effect. **Lower dose = fewer side effects.**

Right? RIGHT?! *(If you are confused about this, review the first handout and perhaps the X-Men worksheet?)*

Note: Remember there are a lot of drugs that can be inhaled for which the target organ is not the lungs. For example, a form of fast-acting **insulin *Afrezza*** is available as an inhaled MDI formulation; it is used by diabetics right before a meal and is especially useful when a patient has an unexpected snack (birthday cake at the office?). *Afrezza* is not considered "topical" because it is absorbed through lungs into the bloodstream, distributes throughout the body and to work throughout the body. In contrast, a drug like **albuterol** is inhaled and its site of action is the spot at which it is inhaled, namely the lungs. So in this case, **albuterol is administered like a topical drug**. **So the total dose of albuterol is TINY**. This is extremely important!

INHALED DRUG DELIVERY SYSTEMS (demonstration in class)

Metered Dose Inhalers (MDIs): deliver a set dose with each trigger of the spray
Breath Activated Inhalers: Taking in the breath triggers drug delivery
Dry Powder Inhalers (DPIs)
Nebulizers: deliver the dose in a soothing, moist mist

All of these delivery systems work to apply the respiratory drug to the inner lung surfaces. Between 10-50% of each dose gets to the lung; the rest ends up being swallowed. **The dose is STILL TINY.**

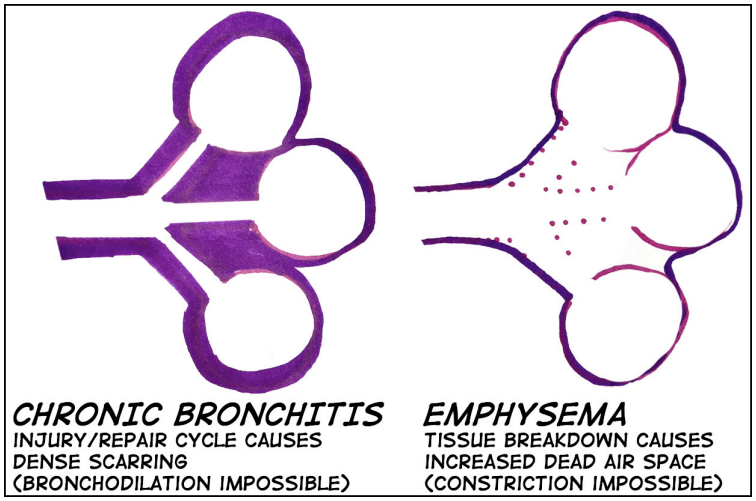
NOTE: Nasal Sprays are either:
low-dose topical for upper respiratory problems like runny nose
examples. **phenylephrine** *short-term* for runny nose
fluticasone *(Flonase):* preventative corticosteroid for allergies

OR normal dose systemic drug delivery (ex. insulin or midazolam)
examples: **midazolam**: a short-acting benzodiazepine (the one that causes anterograde amnesia)
used nasally as a very short-acting sedative or anti-convulsant
naloxone: blocks opioid receptors; used to reverse life-threatening opioid overdose
Currently seeking approval (as of 4/2019): nasal glucagon for hypoglycemia, nasal insulin for early Alzheimer's (hey, the brain is weird)

A brief note about Chronic Obstructive Pulmonary Diseases (**COPD**)
Usually related to smoking.

Chronic Bronchitis: chronic irritation (smoking or other) leads to thick mucus, recurrent
infections and scarring so the air exchange is bad.

Emphysema: Alveolar walls scar and break down -> big dead pockets of air in the lungs.



Treatment of Asthma:

Since COPD is due to long-term injury, scarring and/or tissue breakdown, drug for COPD mostly just help symptoms a little. They don't help treat the problem or prevent death**. In contrast, asthma drugs prevent or stop attacks and reduce mortality.**

First line treatment for asthma rescue is a short-acting **beta-agonist (SABA)** MDI/DPI LOE A
used as a bronchodilator to break an attack or to prevent exercise-induced asthma
Use alone only for the **most mild asthma**, where patient has only occasional attacks

Second line: Add an **anti-inflammatory**/preventative drug such as an **Inhaled Corticosteroid (ICS**)
(work better than LTRAs) LOE A

BRONCHODILATORS (AKA"**rescue therapy**" because it stops an attack rather than preventing it)

1. Beta-2 selective agonists: drugs of choice for asthma, also used for COPD
Shorter acting (**SABA**): **albuterol** *(Ventolin) MDI, HFA, nebulizer, PO*
Acts to dilate bronchioles in asthma & prevent bronchospasm
Side effect: tachycardia (why?), tremor & anxiety (via CNS)
MDI version works in 5-15 minutes, lasts 4 hours. PO versions work in about 30 minutes

Longer-acting: (**LABAs**) arfomoterol *(Brovana)*, formoterol *(Forodil)* or **salmeterol** (*Serevent*) for COPD
SMART Trial showed increased mortality with salmeterol when used alone for asthma so
LABAs are given in combo with a corticosteroid (black box warning removed 2017)
Many **LABA/ICS** (Inhaled CorticoSteroid) combo drugs available:
e.g. **salmeterol + fluticasone** *(Advair, Seretide)*
formoterol + budesonide *(Symbicort)*
formoterol + mometasone *(Dulera)*

Really fast-acting: Remember, for severely ***allergic*** patients with severe acute attacks
Epinephrine is used as a SQ injectable form, as we've discussed before

2. Anticholinergic drugs: Used more for COPD or anesthesia, not asthma
Low inhaled doses work on lungs without affecting heart, bladder and lung secretions
Use **cautiously in patients with glaucoma** or big prostates. *(Why?)*
Ipratropium *(Atrovent):* Inhaled as MDI or DPI, nasal spray
Long-acting **tiotropium** *(Spiriva)* inhaled used in **COPD** patients
Nov 20, 2009: FDA announces **no increased risk of stroke** so safe to use
Takes 1-2 weeks to really start working well
Shorter-acting aclidinium *(Tudorza)* COPD only

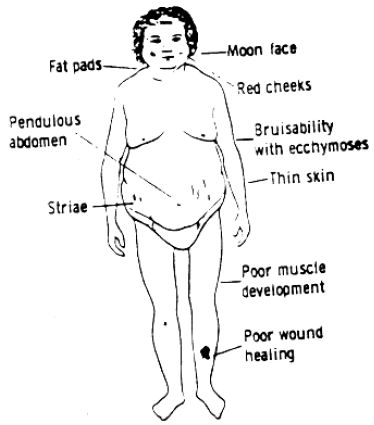
Just to keep it interesting: Albuterol + Ipratropium for COPD patients, inhaled or MDI, is also available

3. Methylxanthenes: family of drugs derived from plants such as coffee, tea, cocoa (caffeine is one).
theophylline: slow-release used for treatment-resistant asthma
IV version used for acute exacerbations
- **has a low TI** *(what does that mean in terms of treatment?)*
- inhibits phosphodiesterase which then affects the levels of inflammatory mediators
- also causes bronchodilation by relaxing bronchial smooth muscle
- antagonizes adenosine (like caffeine)

Theophylline side effects include increase in heart rate, nausea, vomiting, a slight increase in wakefulness, irritability (in kids) and an increase in digestive secretions (think caffeine).
Toxic levels: arrhythmias and seizures
Blood levels increased by caffeine (in coffee, chocolate, tea, etc)
Blood levels ironically decreased by smoking (increases the speed kidney excretes it)
(even more reason not to smoke!!!)
But wait! (I hear you saying*) If theophylline is so much like caffeine, is caffeine good for asthma?*
Excellent question! (I respond): *Caffeine has been shown to improve results on lung function testing. However, studies so far show that to relieve symptoms the dose has to be quite high.*

ANTI-INFLAMMATORY DRUGS:
Remember that *preventative* drugs have worse patient compliance

1. **Corticosteroids** (a.k.a. glucocorticoids)
Cortisol is body's natural anti-inflammatory made by the adrenal gland, and thus corticosteroids are wonderful drugs but **horrible** side effects when used PO or IV. They're also so good at repressing inflammation **they can make infections much worse.** Always be sure there is no untreated infection before prescribing of any kind. That includes **bacterial, viral, yeast, fungal... any kind of infection!**



CUSHING'S SYNDROME

When corticosteroids are used systemically (IV or PO) you can have **SEVERE side effects** such as: **psychosis**, **hip necrosis**, **diabetes**, glaucoma, **osteoporosis**, cataract formation, facial changes consistent with Cushing's disease, and many others, some of which can happen overnight. **GAH! See last page of this handout for a fun list!**

However, corticosteroids used as an MDI or nasal spray have virtually NO systemic side effects because the dose is so small.

Example inhaled steroid: **fluticasone** (*Flonase*) **MDI:** used chronically reduces frequency of attacks.
Takes 1-2 weeks to start working
Weird side effect of MDI: "Thrush": fungal mouth infection, prevent by rinsing mouth after
More commonly seen in immunocompromised patients (AIDS/cancer)
Other inhaled steroids: beclomethasone *(Beclovent, Qvar),* triamcinolone *(Azmacort)*

Oral (systemic) corticosteroids (i.e. **prednisone** or methylprednisolone) are used (lungs):
1. for **severe attacks of asthma** or for **end-stage COPD**
2. for **inflammatory or autoimmune diseases**

Even a short-course (7-10 days) of steroid is often dispensed in a blister pack because the **dose must be tapered.** If steroids are used more than a week or two, the body stops making its own corticosteroids and cannot respond to stress, which can lead to **death** *(Addison's disease).*

Note that in athletes with asthma, several types of steroid inhalers are permitted. **Corticosteroids are not anabolic steroids,** and are thus **not** banned from competitive sports. (Special paperwork is usually required)

Systemic steroids have a LOT of bad side effects. A few examples:

psychosis/agitation	**severe glaucoma**	**breakdown of skin**/connective tissue.
hyperglycemia levels	**aseptic hip necrosis**	
GI ulcers/bleeding	**Cushing's syndrome**	**bone fractures**
(Why?)	Change in appearance	**easy bruising**

Also note that some corticosteroids **also act as weak aldosterone agonists**. *What side effects might you see in that situation? What effect will there be on K+ levels in the bloodstream?*

Corticosteroids are also classified as glucocorticosteroids, that is, they **increase glucose** levels in the bloodstream. *What disease might be a contraindication to corticosteroid use?*

Other glucocorticoids: prednisone, methylprednisolone, cortisone, hydrocortisone, prednisiolone, triamcinolone, dexamethasone, betamethasone.

The first-line asthma *rescue* drug should be *inhaled* **albuterol.**
The first-line asthma *preventative* drug should be an *inhaled* **corticosteroid.**
If there are multiple attacks per week, then a combo ***inhaled*** **LABA/ICS** is next to try

2. **Leukotriene Pathway Inhibitors:**
Inflammatory cells produce leukotrienes which then attract other inflammatory cells to the site of infection, injury or allergy. In asthma leukotrienes cause bronchoconstriction, edema and mucus production.

These drugs are taken PO and are generally preventative.
Nowadays usually prescribed if inhaled steroid didn't do the job.
Ex.: **montelukast** *(Singulair),* zafirlukast *(Accolate)*
QD (once-a-day) dosing in *Singulair* (the name tells you, get it? *Singul*... single dosing.... *air*... because breathing!)

ANTI-HISTAMINES & ANTI-ALLERGY DRUGS

1. Mast cell inhibitors: example: **cromolyn sodium** *(Intal)*, nedocromil *(Tilade)*
Cromolyn acts to prevent mast cells from releasing histamine. (This action is referred to as "anti-allergy" in your book.)
This works well but **only if the patient takes it every day, qid** even when they feel fine and it takes a month to start working.
Usually used as inhaler (*Intal*), nasal spray (*Nasalcrom)* or eyedrops (PO not absorbed well)
Can also be used to prevent exercise-induced-asthma.

2. Antihistamines: See Table 31:3 for a big list if you are really bored
These drugs bind histamine receptors and prevent their action as listed on page 2.
Often cause dry mouth (and sinuses).
The centrally-acting (1st gen) drugs cause sedation & are good for nausea.
"1st Generation" Antihistamines:
Work at Central and Peripheral H1 receptors, so they can be **sedating**.
Can paradoxically stimulate the elderly.
Diphenhydramine *(Benedryl)* is still drug used most often in mild allergic attacks.
available in PO, IV and topical formulations

"2nd Generation" Antihistamines: don't act centrally so they **are designed to be non-sedating**
fexofenadine *(Allegra)*
loratidine *(Claritin)*
cetirizine *(Zyrtec)* ← *about 6% of people taking Zyrtec report the drug makes them sleepy anyway!*

Miscellaneous drugs with antihistamine properties:
promethazine (*Phenergan*): this drug has a structure of a **phenothiazine**,
but works better to block H1 receptors than to block dopamine receptors.

3. Anti-IgE Monoclonal Antibody: **Omalizumab** (*Xolair*) SQ dosing

These are artificially produced antibodies against human IgE… so they're antibodies against anti- bodies! They work by preventing the patient's IgE from binding at its receptor site at the mast cell.
Black box warning: might cause anaphylactic attack up to a year of use
(insert sad trombone sound here)

MISCELLANEOUS OTHER PULMONARY DRUG TYPES

1. **Mucolytics** (ex. **N-acetylcysteine** a.k.a *Mucomyst, inhaled*)
These are drugs intended to **make mucus more watery** and easier to cough up.
Used for COPD, pneumonia, Cystic Fibrosis, TB etc
N-acteylcysteine given PO is also (strangely) a treatment for Tylenol or cisplatin poisoning

2. **Expectorants** (ex. **guaifenesin**)
These drugs actually **increase all of the lung secretions** to help clear away irritants and debris and **help to make a more productive cough.** Used in COPD, Cystic Fibrosis, tuberculosis, pneumonia

3. **Surfactants:**
These are **given to prematurely born infants** who may not have developed their own natural surfactant yet. Surfactant is a fluid in the alveoli which coats the inner surface and helps it stay open. It keeps the walls of the little air sacs from sticking together.

4. Enzymes (ex. DNAase)
Patients with the disease Cystic Fibrosis have unusually thick mucus in the lungs for a number of reasons, one of which is that there is random broken DNA lying around in the bronchioles left over from dead inflammatory cells. The "DNAase" enzyme chops up the useless DNA; this helps to clean up and liquefy the mucus.

5. **Antitussives:** Drugs that **block the cough** reflex
dextromethorphan *(DM)*: an opiate
diphenhydramine (*Benedryl*): What are you kidding me? Yes, diphenhydramine can **also** be used as a cough suppressant. Best OTC drug ever!
benzonatate (*Tessalon Perles®):* acts as a local anesthetic to bronchial stretch receptors

6. **Decongestants:** These act predominantly on the UPPER respiratory system (nose, sinuses) to decrease blood flow via vasoconstriction and therefore overproduction of secretions.
phenylephrine (*Sudafed-PE)* – an alpha-1 sympathetic agonist
- review ANS handout for indications, contraindications and side effects
pseudophedrine *(Sudafed)*

SOME PULMONARY DRUGS in table form yay.

	Albuterol *(Ventolin-MDI)*	**Theophylline** *(Theo-Dur)*	**Ipratropium** *(Atrovent-MDI)*
Class	**Bronchodilator**	**Bronchodilator**	**Bronchodilator**
Mechanism of Action	**Beta-2 agonist**	**Methyxanthine**	Anti-muscarinic (**Anticholinergic)**
Indication	Acute asthma and to prevent exercise-induced **asthma**	Maintenance therapy or in **acute attack if other drugs fail**	Bronchospasm in **COPD**, **asthma**
Contraindication		Epilepsy, Peptic Ulcer or heart disease	**Glaucoma, BPH** (Benign Prostatic Hypertrophy)
Side Effects	**Tachycardia, tremor**	nausea, irritability, headache, insomnia, arrhythmias seizures	few
Pharmacokinetics	**Inhaled**: onset 15min, dur 4h PO: onset 30 min Dur 8 h	PO/PR IV form *must infuse slowly* peak effect in 2 h	**Inhaled,** nasal spray onset 15-30 min
Drug Interactions	MAOI, TCA	**MANY**	**Additive with adrenergic drugs so add to albuterol in severe attack**
Special Note	In severe attacks use 4 puffs q20 minutes for an hour and then continue as travel to the ER	**Very low TI**, so if patient doubles a dose they could end up in the ER	This anticholinergic doesn't dry out lung secretions much when used as an inhaler.

	Montelukast *(Singulair)*	**Cromolyn Sodium** *(Intal)*	**fluticasone** *(Flonase)*	**Prednisone**
Class	**Anti-Inflammatory** & inhibits bronchoconstriction	**Anti-Inflammatory** (Inflammatory Cell Stabilizer)	**Anti-Inflammatory**	**Anti-Inflammatory**
Mechanism of Action	**Leukotriene Receptor Antagonist**	**Prevents release of histamine** from mast cells and other inflammatory cells	**Corticosteroid** (inhaled or nasal) **NOT helpful in an acute attack**	**Corticosteroid** (systemic) PO or IV **CAN be helpful to shorten recovery time from an acute attack**
Indication	**Prevention** of episodes and **chronic asthma** treatment	**Prevention** of asthma attacks or **allergy**	Inhaled: **prevention** of bronchospasm in **asthma or COPD or allergy**	Systemic: **Severe asthma** or **acute** asthmatic episode, MANY other indications
Contraindication	-	-	infection	Fungal infection (cancer, AIDS patients)
Side Effects	Headache, GI distress	Throat irritation	Inhaled: **Rarely: "Thrush"**	**MANY** fluctuating glucose levels, osteoporosis, bone necrosis, psychosis, anxiety, glaucoma, etc
Pharmacokinetics	PO	Inhaled, PO, eye drops, nasal Effect takes 2-3 weeks to work	Inhaled: Inactivated in lungs. Peak effect in 1-2 weeks	PO
Drug Interactions	It is less effective when taken with theophylline, erythromycin or phenobarbital	-	Inhaled form: very few	**Many**
Special Note	Has to be used every day when patient feels fine.	Takes a few weeks to start working. Has to be used every day.	Use every day Also in combination with salmeterol in *"Advair"*	**Must taper dose** **Do not use in a diabetic** *(raises glucose)*