What's Trending in New Inhalers?

Respiratory Drug Update

Idaho Academy of Family Physicians
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Roger Hefflinger, Pharm.D.
Family Medicine Residency of Idaho
Clinical Associate Professor
Idaho State University
College of Pharmacy
roger@ots.isu.edu

Financial Disclosure:

• I am not receiving financial reimbursement from any of the manufacturers of medications that I will be discussing.

Objectives:

• List the agents in each class utilized as bronchodilators.
• Discuss the quick relief medications
• Categorize various long term control medications and long acting bronchodilators
• Identify newer approved options of therapy
Governing Agencies for Asthma/COPD
Guideine Recommendations

- Global Initiative for Asthma Management and Prevention (GINA)
  - Newest: 2014
- NHLBI
- National Asthma Education and Prevention Program
- Expert Panel 3
  - Newest: 2007
- Global Obstructive Lung Disease (GOLD)
  - Online yearly update

Asthma vs COPD

<table>
<thead>
<tr>
<th>Differentiating Asthma From COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asthma</strong></td>
</tr>
<tr>
<td>Age at onset</td>
</tr>
<tr>
<td>Family history</td>
</tr>
<tr>
<td>Evening peak symptoms</td>
</tr>
<tr>
<td>History of allergies</td>
</tr>
<tr>
<td>Recent exacerbations</td>
</tr>
<tr>
<td>Triggers (deterioration)</td>
</tr>
<tr>
<td>Pulmonary function test (FEV1)</td>
</tr>
<tr>
<td>Symptoms (except cough)</td>
</tr>
<tr>
<td>Reversibility of symptoms</td>
</tr>
</tbody>
</table>

How to help make initial determination:

Examples of Common Office Spirometers
Upper Airway Allergies Triggering Lower Airway Bronchoconstriction:

- This is a high risk patient
  - Spring: Grasses
  - Summer: Grasses, Pollen
  - Fall: Sage, Ragweed
  - Winter: Wood smoke, Cold

- Optimize Antihistamines and Nasal Steroids:

“Non-Sedating” Antihistamines:

- Loratidine: Gen
  - Claritin®, Alavert® 10 mg OTC, Liq, RediTab
  - Claritin-D 12 h, 24 h

- Desloratidine: Gen
  - Clarinex® 5 mg RX
  - Generic

- Fexofenadine: Gen
  - Allegra® 60 BID, 180 QD
  - Allegra-D BID

- Cetirizine: OTC 2/08, gen
  - Zyrtec® 5 mg, 10 mg, Liq
  - Zyrtec-D BID

- Levocetirizine: (2007)
  - Xyzal® 5 mg QD
  - Generic

How do we Determine EFFICACY?

- Dose response curves of histamine in the human skin. Peripheral inhibition of histamine-induced weal by loratadine (L; 10, 20, 40 mg) and cetirizine (C; 2.5, 5, 10 mg) 8 hours after drug. (From De Vos C: Clin Exper Allergy 19:503-507, 1989.)
Nasal Antihistamines:

- Azelastin HCL 137 mcg
  - 1 or 2 sprays each nostril
  - BID
  - Generic available
- Astepro 0.15% Brand
  - 2 sprays each nostril
  - ONCE a day
  - "About 2 months"
  - 200 sprays
- Olopatadine Patanase®
  - 1 spray per nostril BID
  - 240 sprays/bottle
  - 2 month supply
  - Brand Only
  - Combo
  - Fluticasone/Azelastin
  - Dymista®

Corticosteroids: Topical= Nasal

- Most effective for treatment of just nasal symptoms of allergy:
- With continued use block the hypersensitivity of the nasal mucosa. Decreasing symptoms and congestion
- Drying: added to moisturizing additives
- Bad taste, 2.5-3 dollars/day

"Quick Relief" Medications
Short Acting Beta Agonist (SABA) Pharmacology

- "Must Know Physiologic Cascade Number 1"
- Beta-2 = Bronchial smooth muscle relaxation
Of course it can’t be that simple!

Short Acting Beta Agonists:

- **Albuterol**
  - MDI:
    - Proair HFA®
    - Ventolin HFA®
    - Proventil HFA®
  - Solution for Nebulizer:
    - 2.5 mg/3 mL
    - 1.25 mg/3 mL, gen Accuneb®
    - 0.625 mg/3 mL, gen Accuneb®

- **Levalbuterol**
  - MDI:
    - Xopenex®
  - Solution for Nebulizer:
    - Xopenex®

How To Use an HFA MDI?

- Remove dust cap
- Shake well
- Exhale SLOWLY
- Place in mouth
- Or 3 fingers breadths?
- Begin SLOW DEEP inhalation
- Press canister
- Continue inhalation to max
- Hold breath
  - 10 seconds (comfort)
- Exhale SLOWLY
- Wait 30 seconds repeat
  - 1-10 minutes?
Most common SABA Question

What about the HR differences?

• Theory Racemic SR Albuterol equal parts
• R albuterol (Levalbuterol) 100 x more potent on beta receptors
• S albuterol cause more beta-1 tachycardia?

Table 3: Mean Changes from Baseline in Heart Rate at 15 Minutes and in Glucose and Potassium at 1 Hour after First Dose (Day 3)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Heart Rate (beat)</th>
<th>Glucose (mg/dl)</th>
<th>Potassium (mEq/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xopenair 0.63 mg, n=72</td>
<td>2 +/- 0.5</td>
<td>103 +/- 4.3</td>
<td>0.2 +/- 0.3</td>
</tr>
<tr>
<td>Xopenair 1.26 mg, n=73</td>
<td>6.8 +/- 0.3</td>
<td>103 +/- 4.3</td>
<td>0.3 +/- 0.3</td>
</tr>
<tr>
<td>Racemic albuterol 2.5 mg, n=74</td>
<td>5.7 +/- 0.3</td>
<td>103 +/- 4.3</td>
<td>0.3 +/- 0.3</td>
</tr>
<tr>
<td>Metabo, n=75</td>
<td>&lt;2.0 +/- 0.2</td>
<td>-0.2 +/- 0.2</td>
<td>-0.2 +/- 0.2</td>
</tr>
</tbody>
</table>

Levalbuterol Heart Rate Studies

Table 2: Effects of Levalbuterol and Racemic Albuterol on Change in Heart Rate (n=25)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>LEV</th>
<th>RAC</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (range) of largest percentage of change in HR (%)</td>
<td>7 (1.8-8.7)</td>
<td>5.0 (1.9-7.8)</td>
<td>NS</td>
</tr>
</tbody>
</table>

* A 1% change in HR was selected as a clinically relevant intervention change in heart rate.

"Overall, 75% (106/142) in the racemic albuterol group received 2.5 mg (1.25 mg R-albuterol) and 55% (22/40) in the levalbuterol group received 0.63 mg"
Quick Relief Medications: Short Acting Muscarinic Antagonists (SAMA) Pharmacology

- **Ipratropium**
  - Short Acting: 4-6 hours
  - Atrovent® HFA
  - Soln for Nebulization
- **Combinations**
  - Combivent® (Plus Albuterol)
  - Duoneb® Soln for Neb

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When to escalate therapy

- **Asthma:**
  - “Long Term Control Medications”
  - Inhaled corticosteroids
    - Dose?, Dose?, Dose
  - Long Acting Beta Agonists
  - Leukotriene receptor antagonists
  - Phosphodiesterase inhibitors

- **COPD:**
  - “Long Acting Bronchodilators”
  - Long Acting Muscarinic Antagonists
  - Long Acting Beta Agonists
  - Medium Dose ICS
  - Phosphodiesterase inhibitors

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When to escalate therapy ASTHMA

<table>
<thead>
<tr>
<th>Components of Severity</th>
<th>Classification of Asthma Severity</th>
<th>≤5 years of age</th>
<th>5-12 years of age</th>
<th>13 years and older</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate Asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild Asthma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Recommended Step by Step Treatment Plan (from “Respiratory Approach for Managing Asthma in Children”)

Step 1: **Inhaled Corticosteroids**
- Step 2: **Long-Acting Beta 2 Agonists (LABA)**
- Step 3: **Combination Therapy**

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When to escalate therapy COPD

- **Asthma:**
  - “Long Term Control Medications”
  - Inhaled corticosteroids
    - Dose?, Dose?, Dose
  - Long Acting Beta Agonists
  - Leukotriene receptor antagonists
  - Phosphodiesterase inhibitors

- **COPD:**
  - “Long Acting Bronchodilators”
  - Long Acting Muscarinic Antagonists
  - Long Acting Beta Agonists
  - Medium Dose ICS
  - Phosphodiesterase inhibitors
COPD adds Symptoms, Risk to FEV1

Table 1. Stages and Severity of COPD according to the Global Initiative for Chronic Obstructive Lung Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>FEV1 (% of predicted)</th>
<th>FEV1/FVC</th>
<th>BMI</th>
<th>Dyspnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild</td>
<td>&gt;80%</td>
<td>&gt;70%</td>
<td>&lt;25</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>50-80%</td>
<td>&gt;50%</td>
<td>&gt;25</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
<td>≤50%</td>
<td>&lt;50%</td>
<td>&gt;25</td>
<td>Severe</td>
</tr>
<tr>
<td>4</td>
<td>Very Severe</td>
<td>≤30%</td>
<td>&lt;30%</td>
<td>&gt;25</td>
<td>Extreme</td>
</tr>
</tbody>
</table>

Adapted from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.

Table 2. Combined Assessment of COPD

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1/FVC</td>
<td>&lt;70%</td>
<td>Referral to specialist</td>
</tr>
<tr>
<td>BMI</td>
<td>&gt;30</td>
<td>Weight management</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Severe</td>
<td>Hospitalization</td>
</tr>
</tbody>
</table>

Graph 1: Persistent Asthma: Daily Medication

- Persistent Asthma: Daily Medication
- Consult with asthma specialist if FEV1/FVC is lower or symptoms worsen.
- Consider escalation at step 3.

Graph 2: Steps in the Management of Asthma

- Each step: Prevent exacerbation, medication management.

Graph 3: Asthma Pathology

- Normal Lung
- Asthma Lung

List of Key Points:

1. COPD symptoms include chronic cough, phlegm production, and shortness of breath.
2. Risk factors for COPD include smoking, air pollution, and genetic predisposition.
3. Early diagnosis and treatment can improve outcomes and quality of life.
Long Term Control Medications:
Corticosteroids

- Preferred agents to decrease the airway remodeling and hypertrophy secondary to long standing over active inflammatory cascade.

Inhaled Corticosteroids

- **MDI: HFA**
  - Flunisolide
    - **Aerolizer®**: 80 mcg puff
  - **Aeroneb®**: 20 mcg puff

- **DPI**
  - Beclomethasone
    - **QVAR®**: 40 mcg 1-2 puffs BID, 80 mcg 1-2 BID
    - **Flovent®**: 50 mcg 1-2 BID
  - Fluticasone
    - **Flovent®**: 50 mcg 1-4 BID
  - Budesonide
    - **Pulmicort®**: 90 mcg puff
  - **Mometasone Nafathaler**
    - **Asmanex®**: 220 mcg
  - **Ciclesonide**
    - **Alvesco®**: 80, 160 mcg

Inhaled Equipotent Doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Low Daily Dose (µg)</th>
<th>Medium Daily Dose (µg)</th>
<th>High Daily Dose (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide</td>
<td>100 - 200</td>
<td>&gt;200 - 400</td>
<td>&gt;400</td>
</tr>
<tr>
<td>Budesonide</td>
<td>100 - 200</td>
<td>&gt;200 - 400</td>
<td>&gt;400</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>80 - 160</td>
<td>&gt;140 - 320</td>
<td>&gt;320</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>500 - 750</td>
<td>&gt;750 - 1200</td>
<td>&gt;1200</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>100 - 200</td>
<td>&gt;200 - 400</td>
<td>&gt;400</td>
</tr>
<tr>
<td>Mometasone Nafathaler</td>
<td>105 - 220</td>
<td>&gt;220 - 400</td>
<td>&gt;400</td>
</tr>
<tr>
<td>Mometasone Nafathaler</td>
<td>105 - 220</td>
<td>&gt;220 - 400</td>
<td>&gt;400</td>
</tr>
<tr>
<td>Formoterol/Fluticaose</td>
<td>400 - 800</td>
<td>&gt;800 - 1200</td>
<td>&gt;1200</td>
</tr>
</tbody>
</table>

*GINA asthma guidelines 2002-2003*
Step 2/3 Asthma:

- Low dose inhaled corticosteroids
- Cromolyn
- Nedocromil
- No longer USA
- Theophylline

Medium Dose ICS

Step 2
1. Preferred: Low-dose ICS
2. Alternative: Cromolyn, Nedocromil, or Theophylline

Step 3
1. Preferred: Low-dose ICS + LABA
2. Alternative: Medium-dose ICS + either LTRA, Theophylline, or Zirabloc

Leukotriene Receptor Antagonists?

- Montelukast 4 mg Granules 6-23 months
- Montelukast 4 mg chew or granule 2-5 years
- Montelukast 5 mg 6 years to 15 years
- Montelukast 10 mg q day 15 and older

Leukotriene Receptor Antagonists?

<table>
<thead>
<tr>
<th>Treatment Group (dose)</th>
<th>Baseline FEV1 (L)</th>
<th>FEV1 Change from Baseline (L)</th>
<th>Zyrtec/Desloratadine (60mg/60mg, 120mg/120mg)</th>
<th>Zyrtec/Desloratadine (60mg/60mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montelukast 10 mg (oral)</td>
<td>2.09</td>
<td>-0.29</td>
<td>-0.17 (-0.41, -0.08)</td>
<td>N/A</td>
</tr>
<tr>
<td>Placebo (200mg)</td>
<td>2.15</td>
<td>-0.20</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Montelukast 10 mg (oral)</td>
<td>2.09</td>
<td>-0.40</td>
<td>-0.34 (-0.51, -0.17)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* Values are median of individual scores. *Montelukast* dose AUC was assessed by physicians using an endpoint of 5-0 categorical scale. *Zyrtec* dose AUC was assessed by physicians using an endpoint of 5-0 categorical scale.

Long Acting Beta Agonists

Only used as second line long term control

- Salmeterol
  - Serevent Diskus® 50 mcg/puff
  - Powder for inhalation
  - 12-hour DOA
  - Never for quick action
    - Onset 10-15 minutes
- Formoterol
  - Foradil®
  - Dry powder for inh (DPI)
  - 12 mcg/puff
  - Soln for nebulization
    - Perforomist® 20 mcg
- Arformoterol
  - Brovana® 15 mcg/2ml
  - Soln for nebulization
- Indacaterol
  - Arcapect® Neohaler®
  - 75mcg Inhal q day
  - COPD Only at this time
- Olodaterol Striverdi®
  - Salmeterol
  - Serevent Diskus® 50 mcg/puff
  - Powder for inhalation
  - 12-hour DOA
  - Soln for nebulization
    - 20 mcg/puff

Never by themselves in asthmatics
Warning Long Acting Beta Agonists

FDA ALERT [1348]: In some patients with asthma, treatment with long-acting beta-agonists (LABA) may increase the chance of death from asthma-related causes. ETS has asked companies that make products containing long-acting beta agonists, including ICS, to give special warnings to healthcare professionals and patients about these products.

- Long-acting beta agonists, such as SEREVENT DISKUS, may increase the chance of asthma death in some people.
- It should not be the first medicine prescribed for new patients.
- It should not be the only medicine prescribed for your asthma.
- It should only be used with controller medications, and only after other controller medications, such as a long-acting inhaled corticosteroid, have not controlled your asthma (see Warnings).

This information reflects FDA’s current analysis of data available at the time of this writing. FDA intends to update this page upon additional information or analysis when available.

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Step 4 and 5 Asthma

- Step 4: Preferred: Med-high dose ICS + LABA
  - Alternative: Med-high dose ICS + either LTRA, Theophylline, or Zileuton

- Step 5: Preferred: High-dose ICS + LABA
  - Consider Omalizumab for patients who have allergies

If continuing to exacerbate:
- Systemic Corticosteroids
- Above "stress physiologic doses"
- IV no faster than PO
- Pulse vs Taper
  - Look at previous number of exposures to systemic corticosteroids
  - More: Taper
Hyperactive Airway Syndrome (HASS) vs the equivalent... Anything above is Pharmacology

<table>
<thead>
<tr>
<th>Glucocorticoid</th>
<th>Dosage &amp; Pharmacokinetics</th>
<th>Side Effects</th>
<th>Dosage</th>
<th>Unit</th>
<th>Status</th>
<th>Dose</th>
<th>PO?</th>
<th>IV?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-Acting:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coriolone:</td>
<td>20-40 mg/day</td>
<td></td>
<td>1000</td>
<td>1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydrocortisone:</td>
<td>20-60 mg/day</td>
<td></td>
<td>1000</td>
<td>1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate-Acting:</td>
<td>12-24 hours</td>
<td></td>
<td>1000</td>
<td>1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone:</td>
<td>1-4 mg/kg</td>
<td></td>
<td>1000</td>
<td>1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone:</td>
<td>4-16 mg/kg</td>
<td></td>
<td>1000</td>
<td>1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-Acting:</td>
<td>16-36 hours</td>
<td></td>
<td>1000</td>
<td>1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexamethasone:</td>
<td>0.75 (1) mg/kg</td>
<td></td>
<td>1000</td>
<td>1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Betamethasone:</td>
<td>6.6 mg/kg</td>
<td></td>
<td>1000</td>
<td>1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone Furoate:</td>
<td>1.25 mg/kg</td>
<td></td>
<td>1000</td>
<td>1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Modified from Goodman and Gilman's

**HPA Suppression and Tapers:**

- PO as effective as IV
- Use 1 mg/kg prednisone
- NAEPP says 2 mg/kg not to exceed 60 mg
- Burst vs Taper
- Taper?
  - Naïve: not necessary
  - Short course
    - 60, 60, 50, 50, 40, 40, 30, 30, 20, 20, 10, 10 off 120 mg tabs #42
  - Dependent: Gradually
- COPD Studies = 40 mg Prednisone!

**Combination Steroids/LABA**

- Fluticasone + Salmeterol =
  - Advair® Diskus:
    - 100/50 (green), 250/50 (yellow), 500/50 (red)
  - Advair HFA:
    - 45/21 (green), 115/21 (yellow), 230/21 (red) BID
- Budesonide + Formoterol =
  - Symbicort® 80/4.5 (Green), 160/4.5 (Blue)
- Mometasone + Formoterol =
  - Dulera® 100/5 (Yellow), 200/5 (Purple)
  - Fluticasone + Vilanterol =
    - Breo Ellipta® 100/25

Remember where steroid dependent patients can get into trouble!
Combos are going to work

• Don’t go to a Step 3 therapy from the start
• Can’t escalate steroid dose without increasing LABA dose
• All are expensive

Long Acting Muscarinic Antagonists (LAMA)

• Tiotropium—
  — Spiriva Handihaler® 18 MCG capsule Q Day
  — Spiriva Respimat® 5 mcgQD COPD, 2.5 mcg QD Asthma
• Aclidinium—Tudorza®
  — 400 mcg BID
• Umclidinium—Incruse Ellipta®
  — 1 Inhalation (62.5 mcg) QD
• Glycopyrolate SeeBri Neohaler®
  — 1 capsule (15.6 mcg) BID

Aclidinium BID vs Tiotropium QD

COPD. 2013;10:511-522
Newer Long Acting Beta Agonists
COPD

- Salmeterol- Serevent®
- Formoterol- Foradil®
- Arformoterol- Brovana®
- Indacaterol- Arcapta®
- Olodaterol- Striverdi®
- Vilanterol?- Soon?

Once Daily Olodaterol vs Twice Daily Formoterol

Newer Combo Products COPD
Corticosteroids/LABA

- Fluticasone/Salmeterol: Advair®
- Budesonide/Formoterol: Symbicort®
- Mometasone/Formoterol: Dulera®
- Fluticasone Furoate/Vilanterol: Breo Ellipta®
Breo Ellipta®

Combo Products COPD
LAMA/LABA
- Anoro Ellipta®
- Umeclidinium/Vilanterol 62.5 mcg/25 mcg
- 1 puff Q Day COPD

ANORO Package Insert

Combo Products COPD
LAMA/LABA #2 and #3
- Tiotropium/Olodaterol
  - Stiolo Respimat®
    - 2 inhalations once daily COPD
- Glycopyrolate/Indacaterol
  - Utibron Neohaler®
    - 1 capsule (indacaterol 27.5 mcg/glycopyrrolate 15.6 mcg) inhaled twice daily COPD
**ASTHMA Immune Modulators**

- **Omalizumab**: Xolair®
  - Doses and dosing frequency are determined by serum total immunoglobulin E (IgE) level, measured before the start of treatment, and body weight
  - Q 2-4 weeks
- **Mepolizumab**: Nucala®
  - 11/2015
  - 100 mg Q 4 weeks
- **Reslizumab**: Cinqair®
  - 1/2016

**Phosphodiesterase Inhibitors**

- **Theophylline**
  - Been around many years
  - Adults: 300 BID
  - Therapeutic level: 8-20
  - Lots drug interactions
  - Inexpensive

- **Roflumilast (Daliresp)**
  - 500mcg po daily
  - Selective for PDE4
  - Increases intracellular cAMP in lung cells
  - No direct bronchodilator effects
  - Improves FEV1 in those on bronchodilators

**Summary:**

- **Asthma and COPD**: Need to have and know how to use quick relief medication
- **Asthma**
  - Low dose ICS, Medium dose ICS, LABA, High dose ICS, Leukotriene receptor antagonist, Theophylline
- **COPD**
  - LAMA, LABA, Medium dose ICS, Theophylline