Asthma Management Updates: A Focus on Long-acting Muscarinic Antagonists and Intermittent Inhaled Corticosteroid Dosing

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Assistant Professor
University of Connecticut School of Pharmacy

Disclosures

- I have been contracted with AHRQ through the EPC program, including sponsorship through the NHLBI
- I have a current contract with AHRQ through the EPC program
- I have been funded through grants from Merck, Pfizer, The Intersocietal Accreditation Commission and The American Pharmacists Association
- I will be speaking of off label indications today
Learning Objectives

- Explain the efficacy of long-acting intermittent muscarinic antagonists (LAMA) and intermittent inhaled corticosteroids (ICS) on health outcomes associated with asthma
- Recognize the asthma “step” in which LAMA or intermittent ICS therapy may be appropriate
- Describe key counseling points for the Respimat delivery device

Question 1

The concept of SMART therapy in asthma is described as
a. Providing adherence monitoring for inhalers to assure optimal compliance
b. Delivery of ICS and LABA simultaneously as rescue and controller medication
c. Self adjusted dosing of maintenance asthma medications at home
d. Immunotherapy for concurrent asthma and allergic rhinitis
Question 2

LAMA are currently recommended by guidelines for which patients:

a. Persistent asthmatics 12y and older as add-on to standard of care
b. COPD only, they are not indicated in asthma
c. Patients 6 years of age and older with persistent asthma
d. As a substitute for LABA in patients with persistent asthma already on ICS

Question 3

All of the following are true regarding Respimat except

a. The device self-locks after designated doses are actuated
b. There is no need for hand eye coordination
c. Tiotropium is available through this delivery device
d. Preparing the inhaler requires some level of strength to insert the canister
Guidelines for Asthma Management

  - Expect an update within the next year regarding four core topics: LAMA, intermittent ICS, FeNO and immunotherapy
- Global Initiative for Asthma (2017)

Pathophysiology

- Asthma is a **chronic inflammatory** disorder of the airway in which many cells and cellular elements play a role
- Variable and recurring symptoms of wheezing, cough, breathlessness, and chest tightness that are **reversible**
- Caused by airflow obstruction from
  - **Underlying inflammation**
  - Bronchial hyper-responsiveness
  - Bronchoconstriction
  - Airway edema and remodeling
Long-Term Goals of Care

● Reduce impairment
  • Prevent chronic and troublesome symptoms
  • Require SABA use ≤2d/week for quick relief, excluding prevention of exercise-induced asthma
  • Maintain near normal pulmonary function and activities of daily living
  • Meet parent’s and families expectations

● Reduce risk
  • Prevent exacerbations and need for ER visits or hospitalizations
  • Prevent loss of lung function and in children, growth
  • Optimize pharmacotherapy while reducing adverse events

Pharmacologic Management Options

- **Initial Controller**
  - ICS
  - LABA, LAMA
  - Montelukast, theophylline

- **Reliever/Rescue**
  - SABA

- **Severe Asthma**
  - Biologics
  - Oral steroids
Inhaled Corticosteroids (ICS)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Brand</th>
<th>Dosage forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate</td>
<td>QVAR</td>
<td>MDI</td>
</tr>
<tr>
<td>Budesonide</td>
<td>Pulmicort Flexhaler Generic</td>
<td>DPI, NEB</td>
</tr>
<tr>
<td>Ciclesonide</td>
<td>Alvesco</td>
<td>MDI</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>Aerospan</td>
<td>MDI</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>Flovent HFA</td>
<td>MDI</td>
</tr>
<tr>
<td></td>
<td>Flovent Diskus</td>
<td>DPI</td>
</tr>
<tr>
<td>Mometasone</td>
<td>Asmanex Twisthaler</td>
<td>DPI</td>
</tr>
</tbody>
</table>

ICS Indications in Asthma

- Reduce asthma symptoms, increase lung function, improve QOL, reduce risk of exacerbations, asthma related hospitalizations and death
- Traditionally dosed on a scheduled, daily basis in addition to a SABA prn as the rescue medication

<table>
<thead>
<tr>
<th>EPR-3</th>
<th>GINA</th>
</tr>
</thead>
</table>
| Persistent asthma defined as SABA use or daytime symptoms ≥2 days/w, 2 or more nighttime awakenings per month, interference with ADLs, reduced FEV1 predicted ≥2/y | Symptoms or SABA ≥2 times/m  
- Waking due to asthma >1 time/m  
- Symptoms plus risk factors for exacerbations including low lung function, exacerbation requiring steroids, ICS for asthma |


### EPR-3 Stepwise Approach for Managing Asthma ≥12y

**Controller**
- **Step 1:** Preferred: None
  - Alternative: Cromolyn, LTRA or Theophylline

**Step 2**
- Preferred: Low dose ICS
  - Alternative: Low dose ICS + LABA

**Step 3**
- Preferred: Medium dose ICS
  - Alternative: Low dose ICS + LABA

**Step 4**
- Preferred: High dose ICS + LABA
  - OR
  - Medium dose ICS

**Step 5**
- Preferred: High dose ICS + LABA
  - OR
  - Medium dose ICS + either LTRA, Theophylline or Zileuton

**Step 6**
- Preferred: High dose ICS + LABA
  - OR
  - Oral corticosteroids + Consider omalizumab

**Reliever**
- **PRN SABA**

### GINA Stepwise Approach for Managing Asthma ≥12y

**Controller**
- **Step 1:** Preferred: None
  - Other: Low-dose ICS

**Step 2**
- Preferred: Low dose ICS

**Step 3**
- Preferred: Medium dose ICS + LABA
  - Other: Medium dose ICS + either LTRA, Theophylline or Zileuton

**Step 4**
- Preferred: High dose ICS + LABA
  - Other: High dose ICS + either LTRA, Theophylline or Zileuton

**Step 5**
- Preferred: Refer for add-on therapy (i.e. tiotropium, anti-IL5, anti-IgE)

**Reliever**
- **PRN SABA or low dose ICS/formoterol**

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*GINA Stepwise Approach for Managing Asthma ≥12y*

Single Maintenance and Reliever Therapy (SMART) or Single Inhaler Therapy (SIT)

- Use of an inhaler containing both an ICS and the LABA formoterol to be used as the controller and reliever inhaler
  - Dulera (mometasone and formoterol) MDI
  - Symbicort (budesonide and formoterol) MDI
  - Neither are currently licensed in the US for this indication

- Formoterol has an onset similar to salbutamol and duration similar to salmeterol
- To provide quick symptom relief when needed, but also quickly increase maintenance medication doses upon symptom deterioration (when albuterol would otherwise be used by the patient)


Does Symbicort DPI vs. MDI matter?

Symbicort DPI vs. MDI

Table 2. Therapeutic equivalence of budesonide/formoterol DPI and budesonide/formoterol pMDI

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Morning PEF (l/min)</th>
<th>Adjusted mean difference</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide/formoterol pMDI vs. budesonide/formoterol DPI</td>
<td>−2.8</td>
<td>−10.4 to 4.9*</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>Budesonide/formoterol pMDI vs. budesonide pMDI</td>
<td>28.6</td>
<td>20.9–36.4</td>
<td>&lt; 0.001</td>
<td></td>
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<td>Budesonide/formoterol DPI vs. budesonide pMDI</td>
<td>31.4</td>
<td>23.7–39.2</td>
<td>&lt; 0.001</td>
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*Therapeutic equivalence was defined as a 95% CI for the difference in morning PEF between budesonide/formoterol pMDI and budesonide/formoterol DPI within the range −15 to +15 l/min. CI, confidence interval; DPI, dry powder inhaler; PEF, peak expiratory flow; pMDI, powder metered-dose inhaler.

Symbicort DPI vs. MDI

![Graph showing clinical outcomes](image_url)

Symbicort DPI vs. MDI


A Summary of SMART Trial Characteristics

<table>
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<tr>
<th>Characteristics</th>
<th>Summary</th>
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| **Population**  | • Mostly ≥12y of age with uncontrolled (symptomatic), persistent asthma taking daily ICS (moderate to high doses) ± LABA  
• Run in periods to assure symptomatic  
• FEV1 ~70-80%  
• Many trials required ≥1 exacerbation in the prior year for enrollment |
| **Intervention** | • Exclusive to budesonide/formoterol 200/6 mcg DPI combination as controller and reliever  
• Generally use max of 12 puffs in one day |
| **Comparator**  | • Budesonide with SABA prn at an equivalent or higher ICS dose  
• Budesonide/formoterol with SABA prn at an equivalent or higher ICS dose  
• Little data reflecting other ICS or ICS/LABA combinations |
| **Outcomes**    | • Mainly focused on composite exacerbation outcomes and death  
• Less evaluation of asthma symptom scores, spirometry, quality of life  
• Serious ADRs |
### Evidence for SMART Compared to ICS+LABA Maintenance

#### SMART vs. ICS and LABA Controller (Same Dose)

<table>
<thead>
<tr>
<th>Study</th>
<th>Controller+Quick Relief</th>
<th>Controller+LABA</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
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<tr>
<td>Vogelmeier, 2005</td>
<td>132 1067</td>
<td>167 1076</td>
<td>0.80 [0.64; 0.99]</td>
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<td>Bousquet, 2007</td>
<td>108 1153</td>
<td>130 1153</td>
<td>0.69 [0.59; 0.80]</td>
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<tr>
<td>Kuna, 2007a</td>
<td>54 1107</td>
<td>91 1138</td>
<td>0.75 [0.58; 0.94]</td>
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**Random effects model** 4226 4257 0.69 [0.66; 0.76]

#### SMART vs. ICS and LABA Controller (Higher Dose)

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<th>Controller+Quick Relief</th>
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**Random effects model** 3371 3371 0.76 [0.65; 0.86]

Exacerbations Composite

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Exacerbation Requiring ER or Hospitalization
Evidence for SMART Compared to ICS Maintenance

- Much less studied than in comparison to ICS+LABA
- Similar trends in data suggesting that SMART
  - Reduces the risk of exacerbations compared to ICS alone at the same or higher dose
  - Does not impact mortality rate differently than ICS

Safety of SMART

- Overall ICS exposure in some studies is higher with SMART but with the trade off of lower systemic exposure for exacerbations
- Adverse events frequencies in individual trials is similar between SMART and control groups

Cates et al. Cochrane Database of Systematic Reviews 2016; Kaw et al. Cochrane Database of Systematic Reviews 2013
GINA Recommendations for SMART ≥12y

- **Controller**
  - Preferred: Low dose ICS
  - Other: LTRA or Theophylline

- **Reliever**
  - PRN SABA
  - PRN SABA or low dose ICS/formoterol

- **Step 1**
  - Preferred: None
  - Other: Low dose ICS

- **Step 2**
  - Preferred: Low dose ICS
  - Other: LTRA or Theophylline

- **Step 3**
  - Preferred: Medium or high dose ICS + LABA
  - Other: Add LTRA or theophylline

- **Step 4**
  - Preferred: Refer for add-on treatment (i.e., Tiotropium, anti-IL5, anti-IgE)
  - Medium or high dose ICS + LABA

- **Step 5**
  - Preferred: Low dose ICS + LABA
  - Other: Add LTRA or theophylline

Assess control


LAMA and Asthma

- LAMA provide bronchodilation through an alternative mechanism of action compared to standard of care treatments
- Tiotropium was FDA approved for asthma maintenance therapy in patients 12y and older in 2015, the indication was for the SMI expanded to 6y and older in 2017

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<tr>
<td>Tiotropium</td>
<td>Spiriva Respinat 1.25mcg</td>
<td>SMI</td>
</tr>
<tr>
<td></td>
<td>Spiriva 18mcg</td>
<td>DPI</td>
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<td><strong>Population</strong></td>
<td>Uncontrolled, persistent asthma taking ICS maintenance therapy Most data is in adults (≥18y), few studies evaluate adolescents (12-17y)</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Tiotropium SMI as add-on to ICS or ICS+LABA (triple therapy)</td>
</tr>
<tr>
<td><strong>Comparator</strong></td>
<td>Placebo or LABA as add-on to ICS, few studies evaluate other controllers</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Exacerbations, spirometry, asthma control, quality of life, rescue medication use</td>
</tr>
</tbody>
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Add-on LAMA- Evidence in Adults

---

A

**Study** | **LAMA vs. placebo vs add-on to ICS** | **Control** | **RRI** | **95% CI** |
--- | --- | --- | --- | --- |
Bekman, 2012 | 16 | 123 | 17 | 120 | 0.80 (0.56; 1.15) |
Pepegno, 2014 | 7 | 139 | 4 | 135 | 0.58 (0.29; 1.15) |
Kangas, 2015 | 52 | 1023 | 46 | 1137 | 0.48 (0.24; 0.95) |
Kameras, 2016 | 286 | 494 | 284 | 507 | 0.55 (0.40; 0.76) |

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B
Add-on LAMA-Evidence in Adults

- **Adolescents 12-17y**
  - Moderate, uncontrolled asthma: Improved FEV1 and trends towards improved symptom control and QOL at 48w when tiotropium was added to ICS vs. placebo; no difference in exacerbations
  - Severe, uncontrolled asthma: Positive trends in improved lung function and asthma symptoms at 12w when tiotropium was added to ICS + another controller vs. placebo; no difference in exacerbations

- **Children 6-11y**
  - Moderate, uncontrolled asthma: Improved spirometry at 24w when tiotropium was added to ICS with or without another controller

- **Children 1-5y**
  - Safety profile is consistent with all older patients

Hamelmann et al. J Allergy Clin Immunol 2016;138:441-450
Rasyi HH. Paediatr Drugs 2017;19:533-38
GINA Recommendations for LAMA ≥12y

Assess control

Step 1
Preferred: None
Other: Low dose ICS

Step 2
Preferred: Low dose ICS
Other: LAMA or Theophylline

Step 3
Preferred: Medium or high dose ICS + LABA
Other: Add Azithromycin

Step 4
Preferred: Refer for add-on treatment (i.e. tiotropium, anti-IL5, anti-IgE)

Step 5
Preferred: Refer for add-on treatment (i.e. tiotropium, anti-IL5, anti-IgE)

Controller

Reliever

PRN SABA

PRN SABA or low dose ICS/formoterol

Respimat Delivery Device

<table>
<thead>
<tr>
<th>Product</th>
<th>Ingredients</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stiolto</td>
<td>Tiotropium/olodaterol</td>
<td>COPD</td>
</tr>
<tr>
<td>Spiriva</td>
<td>Tiotropium</td>
<td>COPD and Asthma</td>
</tr>
<tr>
<td>Combivent</td>
<td>Ipratropium/albuterol</td>
<td>COPD</td>
</tr>
<tr>
<td>Striverdi</td>
<td>Olodaterol</td>
<td>COPD</td>
</tr>
</tbody>
</table>
Example of Respimat Inhaler

Respimat Counseling- Steps Prior to First Use
Respimat Counseling- Daily Use – T.O.P

TURN
OPEN
PRESS

Summary

- Current GINA guidelines recommend SMART therapy as equally preferred option to ICS+LABA and SABA PRN in step 3 or 4 asthma in patients 12y and older
  - Will EPR-3 update adopt these similar recommendations?
- Current GINA guidelines recommend LAMA as add-on therapy to ICS and LABA in patients 12y and older
  - EPR-3 update may include suggestions as alternate to LABA?
  - Will the guidelines adopt use in younger patients?
- More drugs are becoming available with Respimat technology
  - Offers advantages of soft mist and lock out mechanism
  - Still requires coordination of breathing
Question 1

The concept of SMART therapy in asthma is described as
a. Providing adherence monitoring for inhalers to assure optimal compliance
b. Delivery of ICS and LABA simultaneously as rescue and controller medication
c. Self-adjusted dosing of maintenance asthma medications at home
d. Immunotherapy for concurrent asthma and allergic rhinitis

Question 2

LAMA are currently recommended by guidelines for which patients:
a. Persistent asthmatics 12y and older as add-on to standard of care
b. COPD only, they are not indicated in asthma
c. Patients 6 years of age and older with persistent asthma
d. As a substitute for LABA in patients with persistent asthma already on ICS
Question 3

All of the following are true regarding Respimat except
a. The device self-locks after designated doses are actuated
b. There is no need for hand eye coordination
c. Tiotropium is available through this delivery device
d. Preparing the inhaler requires some level of strength to insert the canister

Thank you for your attention!