Making Sense of New Inhalers for COPD and Asthma

Eloise Harman MD
Malcom Randall VAMC
Inhaled Drugs for COPD/Asthma

- Beta agonists
- Anticholinergics (anti-muscarinic)
- Corticosteroids
Short Acting Beta Agonists (Rescue)

- Albuterol (Proventil, Ventolin)
- Levalbuterol (Xopenex)
Long Acting Beta-Agonists

Only for COPD unless combined with ICS

- Salmeterol (Serevent-BID)
- Formoterol (Foradil-BID)***
- Indacaterol (Arcapta-QD)
- Olodaterol (Striverdi-QD)
- Arformoterol (Brovana-BID nebulized)
- Vilanterol (only in comb with LAMA or ICS)

***No longer available
Short Acting Anticholinergics

• Ipatropium
Long Acting Anticholinergics

- Tiotropium (Spiriva-QD)
- Aclidinium (Tudorza-BID)
- Umeclidium (Incruse-QD)
- Glycopyrrolate (Seebri-BID)
Inhaled Corticosteroid

- Beclomethasone
- Budesonide
- Ciclesonide
- Flunisolide
- Fluticasone furoate
- Fluticasone propionate
- Mometasone
LABA/LAMA Combinations

Only for COPD
Utibron (indacaterol/glycopyrrolate)
Stiolto (olodanterol/tiotropium)
Anoro (vilanterol/umeclidium)
LABA/ICS

- Budesonide/formoterol (Symbicort)
- Mometasone/formoterol (Dulera)
- Fluticasone/salmeterol (Advair)
- Fluticasone/vilanterol (Breo)
ICS/LABA

- Fixed dose may limit ability to deliver high dose inhaled corticosteroid in patients with severe asthma
- Symbicort is an example where maximum dose of budesonide is 320 mcg BID whereas high dose is considered to be >1200 mcg daily
Types of Inhalers

• Dry powder multidose inhaler (internal blister pack)-Pressair, Ellipta, Discus
• Dry powder capsule with piercing device on inhaler (Neohaler, Handihaler)
• Metered dose inhaler (HFA)
• Soft mist inhaler (Respimat)
MDI

• Require training to optimize technique
• 1/3 impacts the oropharynx even if technique is flawless
• Require slow and deep inhalation
Dry Powder Inhalers

• Breath activated
• Require deep forceful inhalation
• Because of concern that moisture may affect drug delivery, DPI containing internal blister packs should be discarded 6 weeks after opening
FIG. 1. External view of the ELLIPTA inhaler. This figure is copyrighted by GSK, 2014.
FIG. 3. Operation of the ELLIPTA DPI. This figure is copyrighted by GSK, 2014. DPI, dry powder inhaler.
Respimat-soft mist inhaler

• Some experts believe it is the optimal delivery system
• Once training is provided re priming and use, there is excellent lung delivery
Fig. 6. Scintigraphic scans from one individual showing the deposition of radiolabelled aerosol in the lungs immediately after administration of a single dose of 250 μg flunisolide delivered via Respimat® Soft Mist™ Inhaler, pressurised metered dose inhaler (pMDI) or pMDI plus spacer, on each of three study days (Newman et al., 1996).
Safety Concerns: LABA in Asthma

• Studies of LABA in asthma have shown a small but significant increased risk of asthma death with the use of LABAs alone

• FDA comprehensive review in 2010 concluded that the benefit of LABAs outweighs the risks when the drug is used appropriately
Specific Label Changes for Long-Acting Beta-Agonists (LABAs).

1. Contraindicate the use of LABAs for asthma in patients of all ages without concomitant use of an asthma-controller medication such as an inhaled corticosteroid.

2. Stop use of the LABA, if possible, once asthma control is achieved and maintain the use of an asthma-controller medication, such as an inhaled corticosteroid.

3. Recommend against LABA use in patients whose asthma is adequately controlled with a low- or medium-dose inhaled corticosteroid.

4. Recommend that a fixed-dose combination product containing a LABA and an inhaled corticosteroid be used to ensure compliance with concomitant therapy in pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid.
Safety Concerns?

- Some studies have raised concern about increased risk of arrhythmias and death in COPD patients treated with LAMAs.
- Post hoc analysis of 4 trials of Spiriva respimat spanning 6-12 months reported increased risk of death for Respimat vs the Handihaler.
- These concerns were disspleled by the TIOSPIR study reported in 2013.
Tiotropium Respimat Inhaler and the Risk of Death in COPD

Robert A. Wise, M.D., Antonio Anzueto, M.D., Daniel Cotton, M.S., Ronald Dahl, M.D., Theresa Devins, Dr.Ph., Bernd Disse, M.D., Daniel Dusser, M.D., Elizabeth Joseph, M.P.H., Sabine Kattenbeck, Ph.D., Michael Koenen-Bergmann, M.D., Gordon Pledger, Ph.D., and Peter Calverley, D.Sc., for the TIOSPIR Investigators*

*Randomized, double-blind trial comparing Respimat 2.5 and 5 mcg to Handihaler
*17,135 pts were randomized
*Mean follow-up of 2.3 years
*Respimat was non-inferior to Handihaler in terms of risk of death and efficacy
C Death in As-Treated Analysis

D Death in As-Treated Analysis

Hazard Ratio (95% CI)

0.79 0.91 1.06

Tiotropium Respimat 5 μg vs. Tiotropium HandiHaler 18 μg

0.86 1.00 1.16

Tiotropium Respimat 2.5 μg vs. Tiotropium HandiHaler 18 μg

No. at Risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tiotropium Respimat 2.5 μg</td>
<td>5730 5387 5179 5015 4822 4671 4423 3183 385</td>
</tr>
<tr>
<td>Tiotropium Respimat 5 μg</td>
<td>5711 5333 5138 4978 4809 4662 4427 3171 364</td>
</tr>
<tr>
<td>Tiotropium HandiHaler 18 μg</td>
<td>5694 5351 5146 4998 4811 4659 4398 3141 373</td>
</tr>
</tbody>
</table>
Training Improves Effectiveness of All Inhalers
Elements of Training

- Priming inhaler
- Proper technique
- Cleaning
- Recognizing when inhaler is empty
Figure 3. Samples of scintigraphic images from a patient showing deposition pattern from Respimat® Soft Mist™ Inhaler before training (a) and after training (b), and from pMDI before training (c) and after training (d).
MDIs

- HFA inhalers must be primed 3-4 times
- Shake, exhale, slow deep breath, breath hold
- Clean mouthpiece at least once a week
- Determine when empty if it doesn’t have a counter
- Spacer may help
*OptiChamber

AeroChamber
Dry powder inhalers

• Exhale first but not into the inhaler
• Must inhale forcefully (may not be appropriate in certain subgroups of patients)
• Hold inhaler in the proper position
Soft Mist Inhaler

• Must be primed at least 4x
• Exhale first but not into the inhaler
COPD and Inhalers

• Bronchodilators do not alter the natural course of COPD
• No treatment is needed in asymptomatic patients
• Goals of therapy: improved dyspnea, exercise tolerance and quality of life
7 New Inhalers For COPD: 2014-15

• 2015
  Seebri neohaler (glycopyrrolate)-LAMA
  Utibron Neohaler (glyco/indacaterol)LAMA/LABA
  Stiolto Respimat (Tiotropium/olodaterol)

• 2014
  Incruse Ellipta (umeclidium)-LAMA
  Tudorza Pressair (aclidinium)-LAMA
  Striverdi Respimat (olodaterol)-LABA
  Anoro Ellipta (umeclidium/Vilanterol)
Why so many inhalers for COPD

• CDC estimates that 15 million adults are suffering from COPD
• COPD is the 4th leading cause of death in the US
• Use of LABA without ICS not recommended in asthma whereas they can be used in COPD
• Use of LABA/LAMA combinations is recommended only for COPD
Asthma

- Inhaled Corticosteroids
- ICS/LABA combinations
- Discontinue LABA when possible
- Short acting beta-agonist for rescue
- LAMA as add on for severe asthma
COPD

- LAMA
- LABA
- LAMA/LABA combinations
- LABA/ICS
- Short acting beta agonist
- Short acting LAMA
LAMA vs LABA in Older Pts with COPD

- Population-based retrospective cohort study from Canada for COPD pts >66 yo
- 46,406 patients newly prescribed a LABA or LAMA (not both) between 2003-2007
- Mortality was higher in patients initially prescribed LAMA vs LABA
- Rates of hospitalizations and ED visits were higher for those initially prescribed LAMA
Figure. Observed survival, by initial medication prescribed.

![Graph showing survival rates for long-acting β-agonists and long-acting anticholinergics over time from index date. The log-rank P value is less than 0.001.]

At risk, n

| Long-acting anticholinergic | 15 532 | 13 603 | 11 891 | 8401 | 5311 | 2114 |
| Long-acting β-agonist       | 15 532 | 13 780 | 12 245 | 8731 | 5577 | 2095 |

Gershon A. Ann Int Med 2011;154:583-92
LABA alone or LABA/ICS in COPD

- Population-based longitudinal cohort study in Canada in COPD pts over age 66
- 8712 new users of LABA/ICS vs 3160 users of LABA alone followed for 2.5-2.7 years
- New use of LABA/ICS was associated with a moderately reduced risk of death or COPD hospitalizations compared with LABA alone
- Greatest difference was in pts with co-diagnosis of asthma and those not receiving a long acting anticholinergic

Gereshon A. JAMA2014;312:1114-1121
Table 2. Associations of Study Outcomes in New Users of LABA-ICS Combination Therapy Compared With New Users of LABAs Alone After Propensity Score Matching

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>New LABA and ICS Users, No. (%) (n = 8712)</th>
<th>New LABA Alone Users, No. (%) (n = 3160)</th>
<th>Difference in Outcomes at 5 y, % (95% CI)</th>
<th>Propensity Score-Matched Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Had Outcome</td>
<td>Had Outcome at 5 y</td>
<td>Had Outcome</td>
<td>Had Outcome at 5 y</td>
</tr>
<tr>
<td>Death or hospitalization for COPD</td>
<td>5594 (64.2)b</td>
<td>5010 (57.5)</td>
<td>2129 (67.4)c</td>
<td>1933 (61.2)</td>
</tr>
<tr>
<td>Death</td>
<td>4815 (55.3)</td>
<td>4142 (47.5)</td>
<td>1853 (58.6)</td>
<td>1613 (51.0)</td>
</tr>
<tr>
<td>Hospitalization for COPD</td>
<td>2420 (27.8)</td>
<td>2199 (25.2)</td>
<td>950 (30.1)</td>
<td>881 (27.9)</td>
</tr>
<tr>
<td>Hospitalization for pneumonia</td>
<td>2486 (28.5)</td>
<td>2220 (25.5)</td>
<td>894 (28.3)</td>
<td>811 (25.7)</td>
</tr>
<tr>
<td>Hospitalization for fracture of hip, wrist, or vertebrae</td>
<td>495 (5.7)</td>
<td>423 (4.9)</td>
<td>159 (5.0)</td>
<td>145 (4.6)</td>
</tr>
</tbody>
</table>

Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting β-agonist.

* Reflects the risk of outcome in new users of LABAs and ICSs compared with new users of LABAs alone.

Composite end point in the LABA alone group consists of 950 COPD hospitalizations (30.1%) and 1179 deaths (37.3%) that did not have a preceding COPD hospitalization during follow-up.

Composite end point in the LABA-ICS group consists of 2420 COPD hospitalizations (27.8%) and 3174 deaths (36.4%) that did not have a preceding COPD hospitalization during follow-up.

Hospitalization outcomes were modeled using subdistribution proportional hazards models to account for the competing risk of death.
Table 2. Associations of Study Outcomes in New Users of LABA-ICS Combination Therapy Compared With New Users of LABAs Alone After Propensity Score Matching

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>New LABA and ICS Users, No. (%) (n = 8712)</th>
<th>New LABA Alone Users, No. (%) (n = 3160)</th>
<th>Difference in Outcomes at 5 y, % (95% CI)</th>
<th>Propensity Score-Matched Regression Hazard Ratio (95% CI) ^ P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or hospitalization for COPD</td>
<td>5594 (64.2)b</td>
<td>2129 (67.4)c</td>
<td>-3.7 (-5.7 to -1.7)</td>
<td>0.92 (0.88-0.96)</td>
</tr>
<tr>
<td>Death</td>
<td>4815 (55.3)</td>
<td>1853 (58.6)</td>
<td>-3.5 (-5.5 to -1.5)</td>
<td>0.92 (0.87-0.97)</td>
</tr>
<tr>
<td>Hospitalization for COPDd</td>
<td>2420 (27.8)</td>
<td>950 (30.1)</td>
<td>-2.7 (-4.5 to -0.9)</td>
<td>0.91 (0.85-0.98)</td>
</tr>
<tr>
<td>Hospitalization for pneumoniad</td>
<td>2486 (28.5)</td>
<td>894 (28.3)</td>
<td>-0.2 (-2.0 to 1.8)</td>
<td>1.01 (0.93-1.08)</td>
</tr>
<tr>
<td>Hospitalization for fracture of hip,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>wrist, or vertebrae d</td>
<td>495 (5.7)</td>
<td>423 (4.9)</td>
<td>0.3 (-0.6 to 1.2)</td>
<td>1.13 (0.95-1.35)</td>
</tr>
</tbody>
</table>

Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; LABA, long-acting β-agonist.

^ Reflects the risk of outcome in new users of LABAs and ICSs compared with new users of LABAs alone.

Composite end point in the LABA-ICS group consists of 2420 COPD hospitalizations (27.8%) and 3174 deaths (36.4%) that did not have a preceding COPD hospitalization during follow-up.

Composite end point in the LABA alone group consists of 950 COPD hospitalizations (30.1%) and 1179 deaths (37.3%) that did not have a preceding COPD hospitalization during follow-up.

Hospitalization outcomes were modeled using subdistribution proportional hazards models to account for the competing risk of death.
 Choosing An Inhaler

- Efficacy
- Ease of use
- Dosing frequency
- Safety
- Preferred Drug formulary
- Need for high dose ICS
- Cost
The Soaring Cost of a Simple Breath

Robin Levi’s two daughters both have asthma, but they are able to control it thanks to good insurance coverage. Some students Ms. Levi tutors also suffer from asthma but lack the same insurance and medical care.  

High Cost

• In 2008, the FDA banned asthma inhalers containing chlorofluorocarbons because of environmental concerns (ozone depletion)
• Immediately following the ban, the price of beta-agonist inhalers rose from an avg of $13.50 to $25 in 2009
• Prices increased because generic CFC inhalers were replaced with more expensive brand name inhalers carrying HFA (hydrofluoroalkane) or new dry powder delivery systems.
What $250 of Qvar looks like:

United States
2 inhalers

Greece
37 inhalers