Setting the Facts Straight around

Triple Therapy in COPD
Scientific Planning Committee

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- Relationships with financial sponsors: N/A
- Advisory Boards/ Speakers Bureau: N/A
- Grants/Research Support: N/A
- Honoraria: ICEBM
- Consulting Fees: N/A
- Patents: N/A
- Other: N/A
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- Grants/Research: N/A
- Speakers Bureau: N/A
- Honoraria: ICEBM, GlaxoSmithKline, AstraZeneca, BI
- Consulting Fees: N/A
- Patents: N/A
- Other: N/A
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- Potential for conflict(s) of interest:

The sponsor (GlaxoSmithKline) benefits from the sale of a product that will be discussed in this program.
Mitigating Potential Bias

• The content has been developed based on needs assessment results.
• The 5 planning committee members developed the program content independent of the sponsor and ensured that there was equal coverage of relevant therapies.
Learning Objectives

On completion of this program, participants should be able to:

- Describe the place of triple inhaled therapy versus dual bronchodilators in the management of COPD, and how treatable traits should drive the choice of treatment.
- Discuss the selection of inhaled drug therapy for COPD according to the patient.
- Describe the differences in ease of use and minimum peak inspiratory flow requirement for various COPD inhaler types.
- Discuss the safety profile of inhaled corticosteroids in triple combination regimens for COPD.
Pharmacist’s Role in COPD
Vignette 1

Disease Burden and Approach to Management
Burden of Symptoms

- Breathlessness
- Cough
- Sputum
- Wheeze
- chest tightness

Modified Medical Research Council (mMRC) questionnaire

<table>
<thead>
<tr>
<th>PLEASE TICK IN THE BOX THAT APPLIES TO YOU (ONE BOX ONLY) (Grades 0-4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>mMRC Grade 0. I only get breathless with strenuous exercise.</strong></td>
</tr>
<tr>
<td><strong>mMRC Grade 1. I get short of breath when hurrying on the level or walking up a slight hill.</strong></td>
</tr>
<tr>
<td><strong>mMRC Grade 2. I walk slower than people of the same age on the level because of breathlessness, or I have to stop for breath when walking on my own pace on the level.</strong></td>
</tr>
<tr>
<td><strong>mMRC Grade 3. I stop for breath after walking about 100 meters or after a few minutes on the level.</strong></td>
</tr>
<tr>
<td><strong>mMRC Grade 4. I am too breathless to leave the house or I am breathless when dressing or undressing.</strong></td>
</tr>
</tbody>
</table>

## Symptoms Impact on QoL

- Impairs day-to-day activities
- ↓ QoL

### COPD Assessment Test (CAT)

For each item below, place a mark (0) in the box that best describes you currently. Be sure to only select one response for each question.

<table>
<thead>
<tr>
<th>EXAMPLE: I am very happy</th>
<th>I am very sad</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I never cough</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I have no phlegm (mucus) in my chest at all</td>
<td></td>
<td></td>
</tr>
<tr>
<td>My chest does not feel tight at all</td>
<td></td>
<td></td>
</tr>
<tr>
<td>When I walk up a hill or one flight of stairs I am not breathless</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am not limited doing any activities at home</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I am confident leaving my home despite my lung condition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I sleep soundly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I have lots of energy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| My chest is completely full of phlegm (mucus) |       |
| My chest feels very tight |       |
| When I walk up a hill or one flight of stairs I am very breathless |       |
| I am very limited doing activities at home |       |
| I am not at all confident leaving my home because of my lung condition |       |
| I don’t sleep soundly because of my lung condition |       |
| I have no energy at all |       |

**TOTAL SCORE:**

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1. GOLD 2021 Report. 2. [https://www.catestonline.org/](https://www.catestonline.org/)
Exacerbation Frequency and Severity Increase Mortality Risk

A multivariate analysis in a prospective cohort of 304 men with COPD followed up for 5 years

Group A Patients with no acute exacerbations
Group B Patients with 1–2 acute exacerbations requiring hospital management
Group C Patients with > 3 acute exacerbations

Group 1 No acute exacerbations
Group 2 Acute exacerbations requiring emergency service visits without admission
Group 3 Patients with acute exacerbations requiring 1 hospital admission
Group 4 Patients with acute exacerbations requiring readmissions

COPD, chronic obstructive pulmonary disease; NS, not significant.
Pharmacotherapy

Treatable traits (symptoms, exacerbations) drive the choice of treatment

Eva, 72-Year Old Female with Moderate COPD

- Symptoms (cough, dyspnea) but no exacerbations with LAMA monotherapy
- Step up to LAMA/LABA → some relief, but symptoms not completely abated; interfering with day-to-day activities
- Inhaler technique is ok
- Non-pharmacologic management reviewed, reinforced
- Comorbidities controlled
- Blood eosinophil count 300 cells/μL
What would be the most appropriate next step if Eva’s COPD symptoms remain inadequately controlled?

A) Increase LAMA/LABA dosage
B) Switch to another LAMA/LABA combination
C) Step up to triple inhaled therapy (LAMA/LABA/ICS)
D) Add oral corticosteroid
Triple inhaled therapy (ICS/LAMA/LABA)

- Step-up option - can improve lung function, symptoms, and reduce exacerbations vs. LAMA or LAMA/LABA

- Recommended for:
  - Clinically significant symptoms despite dual therapy
  - Frequent/severe exacerbations (≥2 moderate exacerbations or ≥1 severe exacerbation requiring hospitalization in last year) despite LAMA/LABA
  - Step up from LAMA if severe exacerbation
  - Asthma-COPD Overlap Syndrome (ACOS)

- Single inhaler can simplify treatment

- Blood eosinophil count can help predict phenotype more likely to respond to ICS

Vignette 2

Triple Therapy for COPD: The Evidence
Triple therapy:
- ↓ moderate/severe exacerbations, better lung function and QoL vs. both dual therapies
- ↓ exacerbations regardless of eosinophil count, but greater reduction if ≥150 cells/µL
- ↓ hospitalizations vs. LAMA/LABA
- ↓ all-cause mortality vs. LAMA/LABA

↑ pneumonia in ICS groups than LAMA/LABA

**IMPACT**

- 52-week randomized, double-blind, parallel-group, multicentre trial
- Compared ICS/LAMA/LABA (fluticasone furoate/umeclidinium/vilanterol) with ICS/LABA (fluticasone furoate/vilanterol) or LAMA/LABA (umeclidinium/vilanterol), Ellipta inhaler for all
- n = 10,355

Blood Eosinophils Count (BEC) is associated with exacerbation frequency and ICS response

Prospective analysis of IMPACT confirms post hoc pooled RCT data (3 trials) with continuous modelling

In the non-FF–containing arm (UMEC/VI), the risk of exacerbations increases in proportion to BEC

Annual exacerbation rates (95% CI)

Blood Eosinophils Count (BEC) is associated with exacerbation frequency and ICS response
IMPACT: Mortality

Reduction in all-cause mortality

KRONOS

- 24-week double-blind, parallel-group, multicentre trial
- Compared ICS/LAMA/LABA (budesonide/glycopyrrolate/formoterol fumarate; MDI; not approved in Canada) with LAMA/LABA (glycopyrrolate/formoterol fumarate; MDI) and ICS/LABA (budesonide/formoterol fumarate, MDI; and budesonide/formoterol fumarate, DPI)
- n = 1902

- Triple therapy: ↑ FEV1
- Reduction in rate of moderate/severe exacerbations between triple therapy vs. LAMA/LABA, but not triple therapy vs. ICS/LABA
- Pneumonia (<2%) similar across treatments

Case Study: John

- 77-year old patient with moderate COPD, on LAMA/LABA
- Symptoms adequately controlled, but experienced 2 exacerbations this year; controlled with oral corticosteroid and antibiotic
- Comorbidities adequately controlled
- Blood eosinophil count 310 cells/µL
- Step-up to ICS/LAMA/LABA being considered
Case Study: John

Patients with which of the following would be appropriate for the addition of ICS to inhaled treatment for COPD?

A) Age >75 years
B) Comorbid diabetes and hypertension
C) Exacerbations despite dual inhaled therapy
D) Blood eosinophil count >300 cells/µL
Vignette 3

Selecting The Right Inhaler For The Patient
Common Myth and PIFR and COPD

PIFR* across various severities in COPD†

Figure 1. PIFR Distribution at Hospital Discharge

Distribution of PIFR (peak inspiratory flow rate) against simulated resistance of the DISKUS dry powder inhaler at hospital discharge

- 268 patients analyzed at multiple US sites
- PIFR < 60 L/minute in 31.7%
  - < 40 L/minute in 5.6%

*Measured through the Ellipta inhaler; †COPD patients were stratified by disease severity according to GOLD 2007: ‘mild’ (GOLD stage I), ‘moderate’ (GOLD stage II), ‘severe’ (GOLD stage III), or ‘very severe’ (GOLD stage IV).

Critical Errors With Inhalers

- Significantly reduce/completely inhibit drug delivery
  - Related to incorrect use of inhaler
  - Associated with poorer outcomes
  - Occur with all devices, hence need for patient education and training

Pharmacists play a key role in device education initially and providing ongoing support.

Pharmacists can identify:

- Patients with an increase in COPD symptoms
- Patients who are not reaching their COPD goals
- Nonadherence to pharmacotherapy
- Patients struggling with inhaler device

Regularly engaging with patients, identifying issues and collaborating with the prescriber is a key pharmacist role.
Vignette 4
ICS Risks and Benefits in COPD
Myth or Fact?
The risk of ICS outweigh the benefits of using triple therapy.
ICS in COPD: Benefits and Risks

**Benefits**

- ↓ bronchial mucosal eosinophilic inflammation
- → ↓ exacerbations
- ↓ mortality

**Risks**

- Altered microbiome, local immunosuppression
- → ↑ risk of adverse events including pneumonia (pneumonia incidence ~2%)

**Need to balance risks and benefits**

Impact: Pneumonia$^{1,2}$

There was a higher risk of pneumonia associated with FF/UMEC/VI (Trelegy®) versus UMEC/VI (Anoro®) (HR 1.53; 95% CI 1.22–1.92; $p < 0.001$)$^2$

Pneumonia events, taken into context with exacerbation events, support a positive benefit:risk profile with FF/UMEC/VI

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*The number of events in the UMEC/VI treatment group has been doubled to account for the 2:1 randomization scheme for FF/UMEC/VI/UMEC/VI.

AES, adverse event; CI, confidence interval; FF, fluticasone furoate; HR, hazard ratio; UMEC, umeclidinium; VI, vilanterol


These materials include scientiﬁc/medical content intended for non-prescribers, educational use only. Any opinions expressed are those of the authors and/or presenters.
So What Do We Conclude?


**EMA PRAC Review: Benefits Outweigh Risks**

**Benefits**
15-35% reduction in rate of moderate/severe exacerbations

**Risks**
~2% incidence of pneumonia (depends on patient population)
Myth or Fact?
Some ICS are associated with a lower risk of pneumonia than others.
No Difference in Pneumonia Risk for Different ICS

- FULFIL (fluticasone furoate vs. budesonide): Similar pneumonia risk ~2%
- Systematic review of studies with budesonide and fluticasone: No difference in serious pneumonia or risk of death

EMA’s PRAC Review: No differences in pneumonia risk between products

Appropriate Use of ICS in COPD

- Reserve ICS for use in triple therapy regimens
  - If despite dual LAMA/LABA:
    - Patient has symptoms, and/or
    - ≥2 moderate exacerbations, or ≥1 severe exacerbation requiring hospitalization or ED visit in the last year
  - Step up from LAMA if severe exacerbation
  - Patient has concomitant asthma
- ICS/LABA may be first choice if high risk for exacerbations and eosinophils ≥300 cells/µL
- ICS monotherapy not recommended

What you can do Tomorrow

- Engage patients with COPD
  - Ask about symptoms
  - Use mMRC or CAT
- Run reports for patients using different COPD inhalers with antibiotics or corticosteroid
- Ongoing device education
- Educate the patient on the importance of optimized control