COPD 2016
What to do with all these New Inhalers?

Academic Detailing Service

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"Seek simplicity, and mistrust it."
Alfred North Whitehead

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Tables, Figures and Appendices

Abbreviations

CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CTS	Canadian Thoracic Society
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICS	Inhaled corticosteroid
LAAC	Long acting anticholinergic
LABA	Long acting $beta_2$ agonist
LAMA	Long acting muscarinic antagonist
MCID	Minimal clinically important difference
MD	Mean difference
MRC	Medical Research Council
NNT/NNH	Number needed to treat, number needed to harm
OR	Odds ratio
RCT	Randomized controlled trial
RR	Relative risk or rate ratio
SGRQ	St George's Respiratory Questionnaire
TDI	Transition dyspnea index

Summary

Purpose: The purpose of this academic detailing document is to update the evidence of efficacy and safety for COPD therapies and to provide information on the characteristics of new inhaler devices.

Question 1: Is spirometry necessary to diagnose COPD? Page 16

- International and Canadian guidelines state that post bronchodilator spirometry is required to make the diagnosis of COPD to confirm the presence of airflow limitation.

Question 2: Should a long acting muscarinic antagonist (LAMA) or long acting beta$_2$ agonist (LABA) be prescribed when short acting bronchodilators are not controlling symptoms? Page 18

- **LAMA vs placebo**
  - Benefits for LAMA in dyspnea, lung function, quality of life, patients experiencing ≥ 1 exacerbation and hospitalization for exacerbations.
- **LAMA vs SAMA (ipratropium)**
  - Benefits for LAMA in lung function, patients experiencing ≥ 1 exacerbation or hospitalizations for exacerbations, fewer patients with serious side effects and fewer withdrawals from clinical trials.
- **LABA vs placebo**
  - Benefits for LABA in fewer patients experiencing moderate or severe exacerbations, possibly improvement in quality of life and possibly improvements in dyspnea.
- Individual LAMAs have comparable efficacy and safety and choice should depend on physician and patient preference and inhaler device.
- Individual LABAs have comparable efficacy and safety and choice should depend on physician and patient preference and inhaler device.
- **LAMAs vs LABAs**
  - LAMAs have shown advantage over LABAs for the outcomes of patients experiencing one or more exacerbations for 1 year (NNT 29 [95% CI 19 to 59]) and exacerbations requiring hospitalization (ARR 2%).
  - LABAs and LAMAs similarly improve lung function, symptom control and quality of life.
  - LABAs and LAMAs have similar rates of adverse events and study withdrawals (both outcomes slightly lower with LAMAs).

Therapy Tips

- Short acting bronchodilators are recommended for patients with occasional symptoms.
- A single long acting bronchodilator (LAMA or LABA) is suggested for patients with persistent symptoms. When used for **symptoms only**, there is no evidence to support one class of bronchodilator over another and choice depends on the patient's perception of relief of symptoms.
- In patients experiencing **exacerbations,** a LAMA may be preferred over a LABA.
- Inhaler technique AND adherence to therapy should be assessed before concluding that current therapy requires modification.

Question 3. What is the evidence for benefit or harm for the combination of a LAMA plus LABA compared with either agent alone? Page 29

Based on a Cochrane Review

- **Tiotropium plus LABA vs tiotropium**
  - The tiotropium plus LABA group showed a statistically significant improvement in health related quality of life.
    - More patients in the combination group achieved a minimum clinically important 4 point difference (MCID) in the SGRQ quality of life scale. NNT 15 (95% CI 11 to 23) for 6 months.
  - All other reported outcomes showed either no clinical or statistical difference.
- **Tiotropium plus LABA vs LABA**
  - Benefits with tiotropium plus LABA in
    - Exacerbation rates
    - Potential benefit in lung function
    - Quality of life: NNT 9 (95% CI 7 to 15) for 6 months for proportion meeting MCID
  - All other reported outcomes showed either no clinical or statistical difference.

Trials of newer agents in combination versus the individual components do not appear to offer different results from the Cochrane Review.

Therapy Tips: Recommendations from GOLD 2017:

- Use dual bronchodilators in patients who have persistent dyspnea on one bronchodilator. (Evidence A)
- In a patient being treated for symptoms only, if the addition of the second bronchodilator does not improve symptoms, treatment should be stepped back down to a single bronchodilator.

Question 4: Who should have an inhaled corticosteroid (ICS) added to therapy?

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- **LABA/ICS vs placebo**
  - Benefits for LABA/ICS in
    - Exacerbation rates: based on an average of 1 to 2 exacerbations per year, LABA/ICS would lead to a reduction of one exacerbation every 2 to 4 years.
    - Mortality NNT 42 (95% CI 24 to 775) for 3 years
  - Results for LABA/ICS showed small benefits in effects on health related quality of life, symptoms, lung function, use of rescue medication and withdrawal rates. In some cases, the benefits reached accepted levels of clinical significance, but only just.
  - Increased risk of pneumonia: NNH =17 (95%CI 12 to 27) for 3 years based on the TORCH trial.

LABA/ICS vs LABA

  - Reduction in exacerbation rates corresponds to 1 exacerbation/pt/year in the LABA group vs 0.76 exacerbations/pt/year in the LABA/ICS group
  - Reduction in patients experiencing ≥ 1 exacerbation
    - NNT 22 (95% CI 13 to 85) for 1 year
  - Adverse events
    - Pneumonia: Increased rates with LABA/ICS vs LABA
      - ARI 1.3% : NNH 17 (95% CI 12 to 29) for 156 weeks
    - Candidiasis and upper respiratory infections were more frequent with LABA/ICS.

- **LABA/ICS vs Tiotropium**
  - There was no difference in the annual rate of moderate or severe exacerbations.
  - Reduction in all cause hospitalization with tiotropium vs LABA/ICS
  - Exacerbations requiring oral steroids were less frequent with LABA/ICS: those requiring antibiotics were more frequent with LABA/ICS vs tiotropium.
  - Pneumonia: increased rates with LABA/ICS ARI 4% NNH 25 (95% CI 16 to 64)
  - Mortality: possible increase risk with tiotropium; however, authors suggest caution in interpreting this data due to high withdrawal rates in the trial.

- **LAMA/LABA vs LABA/ICS**
  - LAMA/LABA reduced the annual rate and time to first moderate or severe exacerbation.
  - LAMA/LABA reduced the annual rate and time to first exacerbation of *any* severity.
  - LAMA/LABA decreased the number of patients experiencing ≥ 1 exacerbation, NNT 20 (95% CI 13 to 44) for 1 year.
  - LAMA/LABA increased the proportion of patients with a clinically relevant improvement in quality of life, NNT 18 (95% CI 11 to 47) for 1 year.

- There was no difference between treatments for rates of exacerbations leading to hospitalizations.
- Fewer cases of pneumonia, candidiasis and influenza with LAMA/LABA.

- **LABA/ICS/LAMA (triple therapy) vs. LAMA**
  - Triple therapy reduced all cause hospitalization NNT 20 (95%CI 11 to 124)
  - Triple therapy increased the proportion of patients with a clinically relevant improvement in quality of life (49.5% vs 40%)
  - Results for other outcomes were either not statistically significant or clinically relevant including exacerbation rates.

- **LABA/ICS/LAMA vs LAMA/LABA**
  - There is insufficient information to draw conclusions on whether the addition of ICS to patients taking LAMA/LABA offers clinically relevant benefits.

Therapy Tips

- In patients experiencing exacerbations, appropriate therapy may be LAMA, LAMA/LABA or LABA/ICS.
- In patients with a history and/or findings suggestive of both asthma and COPD, a LABA/ICS may be preferred.
- Escalation to triple therapy (LABA/ICS + LAMA) is dependent on persistent symptoms and further exacerbations, although evidence in this population is lacking.
- Evidence assessing the impact of withdrawal of an ICS on symptoms, lung function and exacerbations is equivocal.

Question 5: How to choose between the various new inhalers? Page 51

- Factors to consider when choosing an inhaler device include: ease of set-up, requirement for hand-breath coordination or breath activation, patient's dexterity, dose counter and indication that dose has been taken.
- Choice of inhaler device should be individualized and will depend on the patient's ability and preference.

Therapy Tip

- Inhaler technique and compliance with therapy should be assessed before concluding that the patient's current therapy is insufficient.

Question 6: What are the adverse effects of inhaled COPD medications?

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- The following adverse effects have been reported with muscarinic antagonists (i.e. anticholinergics): dry mouth, constipation, aggravation of narrow angle glaucoma, urinary retention and cardiovascular adverse effects.
- The following adverse effects have been reported with $beta_2$ agonists: headache, tremor, leg cramps, palpitations/arrhythmias, changes in blood glucose and serum potassium (rare) and paradoxical bronchospasm (very rare).
- The following adverse effects have been reported with inhaled corticosteroids: hoarse voice, oral candidiasis and increased risk of pneumonia. There are conflicting results for fracture risk.

COPD Tips for Therapy

Patient Description	Severity	Therapy (based on GOLD 2017)
THERAPY PRIMARILY BASED ON SYMPTOMS		
Symptoms • Breathless with strenuous exercise or when hurrying on the level or walking up a slight hill **Exacerbations** • 0 to 1/year (not leading to hospitalization)	mMRC 0 to 1 CAT < 10	Short acting bronchodilators • Salbutamol • Ipratropium • Combination of both
Symptoms • Breathlessness: **more** severe than SOB when hurrying on the level or walking up a slight hill **Exacerbations** • 0 to 1/year (not leading to hospitalization)	mMRC ≥ 2 CAT ≥ 10	LAMA **or** LABA + rescue inhaler • LAMAs and LABAs similarly improve lung function, symptom control and quality of life. • Choose either LAMA or LABA and if inadequate response, trial of the other. Use the 1 bronchodilator the patient prefers. ***If symptoms persist*** LAMA + LABA Farne Cochrane Review 2015 • Benefit vs LABA in quality of life: NNT 9 (7 to 15) for 6 months • Potential benefit in lung function vs. LABA Donohue 2013 • Benefit vs LAMA in quality of life: NNT 15 (11-23) for 6 months • Many outcomes show no benefit for combo vs individual agents If symptoms do not improve, consider going back to 1 agent
*THERAPY BASED ON **EXACERBATIONS** AND SYMPTOMS*		
Exacerbations • ≥ 2/year or ≥ 1 exacerbation requiring hospitalization/year **Symptoms** • Breathless with strenuous exercise or when hurrying on the level or walking up a slight hill	mMRC 0 to 1 CAT < 10	LAMA + rescue inhaler LAMA compared to LABA Chong Cochrane Review 2012 • Fewer patients experiencing ≥ 1exacerbations per year NNT 29 (19 to 59) for 1 year • Fewer severe exacerbations leading to hospitalization (ARR 2%) ***If further exacerbations*** LAMA/LABA **or** LABA/ICS - both combinations decrease exacerbation rates vs. LABA but not vs LAMA alone. Farne & Welsh Cochranes LAMA/LABA compared to LABA/ICS Wedzicha FLAME 2016 • LAMA/LABA benefit in exacerbations and time to 1st exacerbation (all exacerbations and moderate or severe) • Fewer patients experiencing ≥ 1 exacerbation/year NNT 20 (13 to 44) for 1 year • No difference in exacerbations leading to hospitalization • More patients had benefit in quality of life NNT 18 (11 to 47) 1yr • Fewer cases of pneumonia with LAMA/LABA ARR 1.6%

Exacerbations • ≥ 2/year or ≥ 1 exacerbation requiring hospitalization/year **Symptoms** • Breathlessness: **more** severe than SOB when hurrying on the level or walking up a slight hill	mMRC ≥ 2 CAT ≥ 10	LAMA **or** LAMA/LABA **or** LABA/ICS + rescue inhaler ***Persistent symptoms or further exacerbations*** LAMA+ LABA/ICS LAMA+LABA/ICS vs LAMA[Rojas-Reyes Cochrane Review 2016] • All cause hospitalization reduced NNT 20 (11 to 124) for 1 year • Potential improvement in quality of life LAMA+LABA/ICS vs LAMA/LABA • Insufficient evidence to make choice[Karner Cochrane Review 2011]

CAT= COPD Assessment Tool (CAT>10 threshold for considering regular treatment for symptoms); mMRC = modified Medical Research Council (See Table 1 page 17 for more details)

- The COPD Assessment Test (CAT)
  - An 8-item unidimensional tool for measuring health status impairment.
  - Score ranges from 0-40.
  - The cut-point for considering regular treatment for symptoms, including breathlessness is 10. According to GOLD 2017, this also corresponds to the severity of patients included in COPD trials that provide the evidence base for treatment recommendations.
  - Available at http://www.catestonline.org/images/pdfs/CATest.pdf

Introduction

Purpose: The purpose of this academic detailing document is to update the evidence of efficacy and safety for COPD therapies and to provide information on the characteristics of new inhaler devices to address the following clinical questions:

1. Is spirometry necessary to diagnose COPD?
2. Should a long acting muscarinic antagonist (LAMA) or long acting beta$_2$ agonist (LABA) be prescribed when short acting bronchodilators are not controlling symptoms?
    a. What is the evidence for benefit over short acting bronchodilators?
    b. What is the evidence for differences in benefit between LABA or LAMA?
3. What is the evidence for benefit or harm for the combination of a LAMA plus LABA compared with either agent alone?
4. Who should have an inhaled corticosteroid (ICS) added to therapy?
    a. Should an ICS ever be discontinued?
    b. Who should be prescribed triple therapy? (LABA +ICS +LAMA)
    c. What is the evidence for benefits or harms?
5. How to choose between the various new inhalers?
    a. Characteristics of inhaler devices, e.g., Respimat®, Breezhaler®, Ellipta®, Genuair®.
6. What are the adverse effects of inhaled COPD medications?

Sources of evidence and assumptions:

- The majority of evidence reported in this document is from recent Cochrane systematic reviews and meta-analyses.
- Network meta-analysis and relevant, new RCTs are included if they study unique comparisons or outcomes and add to the body of evidence. If meta-analytic data are available for different agents within a class, the evidence is presented for each agent. Numbers needed to treat or to harm have been calculated using the Dalhousie Clinical Significance Calculator, if not provided in a publication. https://www.dal.ca/faculty/healthprofessions/cpe/services/katie-program/tools.html
- We consider that long acting beta$_2$ agonists (LABAs), long acting muscarinic antagonists, (LAMAs, also referred to as long acting anticholinergics), alone or in combination or LABAs in combination with inhaled corticosteroids (ICS), as a general rule exert a class effect.

New agents and devices

- The number of new bronchodilators and devices recently introduced to the Canadian market have increased tremendously since the last Academic Detailing on COPD in 2009.

- While we consider them to exert a class effect, there are differences in inhaler devices, dosing characteristics (once vs twice a day dosing) and/or cost which may make one more suitable for a patient than another. We have provided you with tools to highlight these characteristics.

Useful links

Global Strategy for the Diagnosis, Management and Prevention of COPD (GOLD 2017)
http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/

COPD Assessment Test (CAT) http://www.catestonline.org/english/indexEN.htm

Canadian Thoracic Society COPD Guidelines:
http://www.respiratoryguidelines.ca/guideline/chronic-obstructive-pulmonary-disease

Inhaler Device Instructions

- Canadian Lung Association (several devices)
  http://www.lung.ca/lung-health/get-help/how-use-your-inhaler
- Turbuhaler
  - https://www.lung.ca/lung-health/get-help/how-use-your-inhaler/turbuhaler%C2%AE
- MDI
  - https://www.lung.ca/lung-health/get-help/how-use-your-inhaler/mdi-no-spacer
- Spacer
  - https://www.lung.ca/lung-health/get-help/how-use-your-inhaler/mdi-spacer-adult
- Diskus
  - https://www.lung.ca/lung-health/get-help/how-use-your-inhaler/diskus
- Ellipta
  - https://www.lung.ca/lung-health/get-help/how-use-your-inhaler/ellipta
- Genuair
  - https://www.youtube.com/watch?v=_jV0dSA3GwE
- Breezhaler:
  - https://www.youtube.com/watch?v=cUSCWhGkIcw
- *Handihaler*
  - https://www.youtube.com/watch?v=bXHHFmZ_DRI
- Respimat Inhaler
  - https://www.youtube.com/watch?v=NfI1ogOyWLE

Smoking Cessation

- **Canadian Lung Association:** https://www.lung.ca/lung-health/smoking-and-tobacco
- **NS Lung Association**: https://ns.lung.ca/our-programs/quit-cold-turkey-challenge
- **Tobacco Free Nova Scotia:** https://tobaccofree.novascotia.ca/

Dalhousie Clinical Significance Calculator

- https://www.dal.ca/faculty/healthprofessions/cpe/services/katie-program/tools.html

Criner GJ et al. Prevention of Acute Exacerbations of COPD American College of Chest Physicians and Canadian Thoracic Society Guideline CHEST 2015; 147 (4): 894- 942
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4388124/pdf/chest_147_4_894.pdf

Institute for Safe Medication Practices (ISMP): Correct use and safety considerations with inhalers

- https://www.ismp.org/newsletters/acutecare/showarticle.aspx?id=1143
- https://www.ismp-canada.org/download/safetyBulletins/2016/ISMPCSB2016-03_InhalationDevices.pdf

Outcomes in COPD Trials

- Please refer to Appendix 1 for definitions and interpretation of minimum clinically important differences (MCID) of outcomes used in COPD trials e.g. exacerbations, hospitalizations, dyspnea scores and quality of life.

Question 1: Is spirometry necessary to diagnose COPD?

Summary: International and Canadian guidelines state that post bronchodilator spirometry is required to make the diagnosis of COPD to confirm the presence of airflow limitation.[1–3)]

A clinical diagnosis of COPD should be considered in a patient with the following symptoms

- Dyspnea
- Chronic cough
- Sputum production or
- History of exposure to risk factors (e.g. smoking).

Spirometry is required to make the diagnosis of COPD in patients who have the above symptoms. Spirometry should be performed after the administration of an adequate dose of a short-acting inhaled bronchodilator in order to minimize variability.

- The forced expiratory volume in 1 second to forced vital capacity ratio (FEV_1/FVC) is the most important measurement for the identification of an obstructive impairment.[1]
- A post bronchodilator FEV_1/FVC ratio of less than 0.7 defines airflow obstruction that is not fully reversible, and is necessary to establish a diagnosis of COPD.
    - This fixed ratio criterion is simple and independent of reference values. However, its use to define airflow limitation may result in more frequent diagnosis of COPD in the elderly and less frequent diagnosis in adults < 45 years especially in mild disease, compared to using a cut-off based on the lower limit of normal values for FEV_1/FVC based on age, height, sex and race.[31]
    - Reversibility testing does not help with differential diagnosis or predict the response to bronchodilators or inhaled corticosteroids.
    - Screening spirometry does not direct management decisions or improve outcomes in patients identified before experiencing significant symptoms.
    - There is no single diagnostic test for COPD.
    - A diagnosis relies on clinical judgement based on a combination of
        - History
        - Physical examination
        - Confirmation of the presence of airflow obstruction using spirometry.

Cigarette smoking is identified as the most common risk factor for COPD and smoking cessation is an important step toward prevention and control of COPD. It is the only intervention that has been shown definitely to slow the progression of lung decline in COPD patients.

Other important risk factors for COPD include occupational dusts and chemicals, and indoor air pollution from biomass cooking and heating in poorly ventilated dwellings.[2]

Table 1: COPD Classification of Severity based on MRC and mMRC dyspnea Scale[1,2]

MRC Grades[a]	mMRC Grades[b]	Symptoms
1	0	Only get breathless with strenuous exercise
2	1	SOB from COPD[c] when hurrying on the level or walking up slight hill
3	2	Walks slower than people of same age on the level because of SOB from COPD[c] or has to stop for breath when walking at own pace on the level.
4	3	SOB from COPD[c] making patient stop for breath after walking about 100 meters or after a few minutes on the level
5	4	SOB from COPD[c] making patient unable to leave the house **or** breathlessness when dressing or undressing

a = Medical Research Council used by Canadian Thoracic Society

b = Modified Medical Research Council used by GOLD.

c = In the presence of non-COPD conditions that may cause shortness of breath (e.g., cardiac dysfunction, anemia, muscle weakness, metabolic disorders), symptoms may not appropriately reflect COPD disease severity. Classification of COPD severity should be undertaken with care in patients with comorbid diseases or other possible contributors to shortness of breath.

Table 2: Classification of Severity based on post-bronchodilator FEV_1[2]

GOLD Stage	Description	FEV_1/FVC	FEV_1 % predicted
1	Mild	< 0.70	≥ 80%
2	Moderate	< 0.70	50-79%
3	Severe	< 0.70	30-49%
4	Very Severe	< 0.70	< 30%

Goals of COPD Management

Table 3: The goals for treatment of stable COPD[2,3]

↓ SYMPTOMS
• Relieve symptoms
• Improve exercise tolerance
• Improve health status
↓ RISK
• Prevent disease progression (i.e., smoking cessation)
• Prevent and treat exacerbations
• Reduce mortality

Question 2: Should a long acting muscarinic antagonist (LAMA) or long acting beta$_2$ agonist (LABA) be prescribed when short acting bronchodilators are not controlling symptoms?

a. What are the expected benefits or harms shown in clinical trials for short acting bronchodilators?

b. What is the evidence for benefit of long acting vs. short acting bronchodilators?

c. What is the evidence for differences in benefits between LABA and LAMA?

Question 2a: Short acting bronchodilators

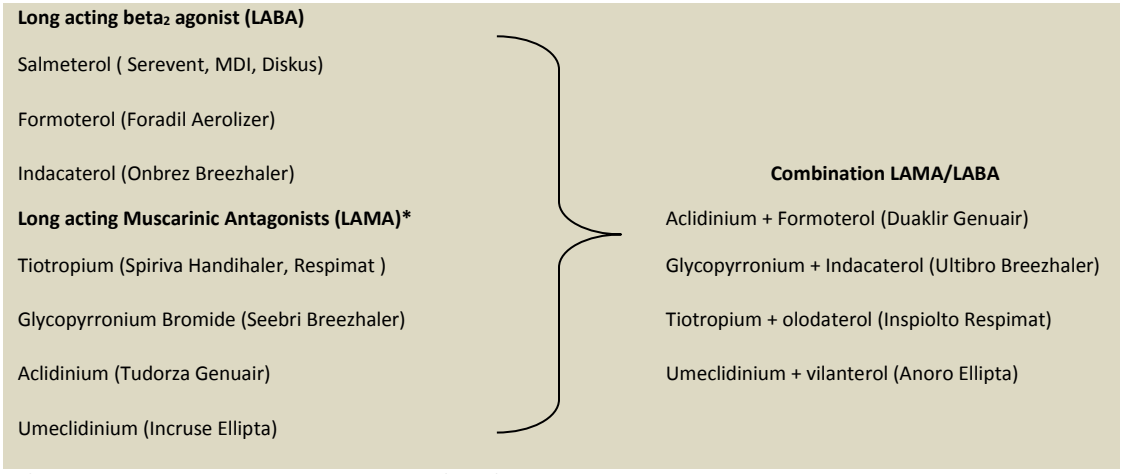
Short acting beta$_2$ agonist (salbutamol, terbutaline)
Short acting anticholinergic, also referred to as muscarinic antagonist (ipratropium)

- Treatment of mild COPD generally begins with short acting beta$_2$ agonists (SABA) such as salbutamol (Ventolin®) or short acting anticholinergics such as ipratropium (Atrovent®) or both agents in combination (Combivent Respimat®).
- Short acting bronchodilators given on a regular and as-needed basis:
  - Improve FEV$_1$ and symptoms. (Evidence level B)[2]
- High doses of short-acting beta$_2$-agonists on an as-needed basis in addition to long-acting bronchodilators are not supported by evidence and is not recommended.[3]
- Short acting anticholinergics (ipratropium) demonstrate small benefits over short-acting beta$_2$ agonists in lung function, quality of life and a reduction in oral steroids.[4]
- Combinations of short-acting beta$_2$-agonists and anticholinergics are superior compared to either medication alone in improving:[2]
  - FEV$_1$
  - Symptoms related to COPD
- Duration of action of the short acting anticholinergic (ipratropium) is longer than the short acting beta$_2$ agonists (up to 8 hours vs. 4-6 hours).[2]

Question 2b: What is the evidence for benefit of long acting vs. short acting bronchodilators?

Summary:

- **LAMA vs placebo**
  - Benefits for LAMA in dyspnea, lung function, quality of life, patients experiencing ≥ 1 exacerbation and hospitalization for exacerbations.
- **LAMA vs SAMA (ipratropium)**
  - Benefits for LAMA in lung function, patients experiencing ≥ 1 exacerbation or hospitalizations for exacerbations, fewer patients with serious side effects and fewer withdrawals from clinical trials.
- **LABA vs placebo**
  - Benefits for LABA in fewer patients experiencing moderate or severe exacerbations, possibly improvement in quality of life and possibly improvements in dyspnea.
- Individual LAMAs have comparable efficacy and safety and choice should depend on physician and patient preference and inhaler device.
- Individual LABAs have comparable efficacy and safety and choice should depend on physician and patient preference and inhaler device.



***Also referred to as long acting anticholinergic (LAAC)**

Long acting muscarinic antagonists (LAMAs) vs. placebo

- Trials comparing a LAMA such as tiotropium to placebo allow the use of short acting beta$_2$ agonist for rescue, so technically that is the comparator rather than placebo.

- The evidence for comparisons of long acting agents to placebo will be briefly summarized for completeness. However, since the step-wise approach generally includes ipratropium given on a regular basis prior to initiation of a long acting agent, it is likely the more relevant comparison.
- There are Cochrane systematic reviews published for the comparisons of tiotropium vs. placebo[5] and aclidinium vs. placebo[6]. There are Cochrane Reviews underway assessing glycopyrronium vs. placebo or tiotropium[7] and umeclidinium vs. placebo[8] which will provide more data to assess the relative benefits and harms of LAMAs.
- Studies range in duration from 12-52 weeks and generally enroll moderate to severe COPD patients with FEV_1 predicted of 60% or less.
- In general, **LAMAs** show benefit **compared with placebo** for the following outcomes: (note: not all studies report the same outcomes).[6,7]
    - **Quality of Life** (St. George's Respiratory Questionnaire): LAMAs increase the proportion of patients with a clinically significant improvement in quality of life (SGRQ ≥ 4); although the *mean differences* do not consistently achieve a 4 point difference.
        - Proportion with SGRQ ≥ 4:
            - Tiotropium 49% vs. 39%, NNT 10 (95% CI 8 to 12) for 3-48 months (the timeframe is based on length of trials in the meta-analysis)
                - OR 1.52 (95% CI 1.38 to 1.68)
                - Greater effect may be seen in patients with more severe COPD
            - Aclidinium 49.4% vs 39.6% NNT 10 (95% CI 8 to 15) for 12-52 weeks
                - OR 1.49 (95% CI 1.31 to 1.70)
    - **Exacerbations:**
        - Patients experiencing ≥ one exacerbation
            - Tiotropium (38% vs. 44%) NNT 16 (95% CI 10 to 36) for 1 year.
                - OR 0.78 (95% CI 0.70 to 0.87)
        - Patients experiencing ≥ one hospitalization for an exacerbation
            - Tiotropium 10.4% vs. 13.2% NNT 37 (95% CI 28 to 54) for 3-48 months
                - OR 0.85 (95% CI 0.72 to 1.00)
        - Hospitalizations for exacerbations (severe exacerbations)
            - Aclidinium 2.4% vs. 3.7% NNT 77 (95% CI 51 to 233) for 4-52 weeks
                - OR 0.64 (95% CI 0.46 to 0.88)
        - Moderate (requiring antibiotics and/or oral steroids) to severe exacerbations
            - Aclidinium did not significantly reduce:
                - OR 0.88 (95% CI 0.74 to 1.04)
    - **All cause hospitalizations**
        - Tiotropium did not reduce all-cause hospitalizations.[5]
    - **Lung function**: Trough FEV_1 (measured prior to dose). See **Appendix 1** for discussion of clinically meaningful differences.

- LAMAs show modest improvements in trough FEV_1 vs. placebo with mean differences ranging between 100 ml and 125 ml.

- **Dyspnea (Transitional Dyspnea Index {TDI})**
  - Proportion of patients with a clinically significant improvement of 1 point on the TDI shown for
    - Aclidinium OR 1.73 (95% CI 1.52 to 1.98)
    - Tiotropium OR 1.96 (95% CI 1.58 to 2.44)[5,9]
  - The mean difference in TDI was inconsistent for all the LAMAs, with some trials demonstrating a mean difference of 1 point while others did not. The 95% confidence intervals include a 1 point difference indicating that some but not all patients will experience improvement in breathlessness.[8,10,11]
- **Adverse events**
  - No difference in non-fatal, serious adverse events
    - One umeclidinium study (N=1536) reported that 6% of patients in the umeclidinium group compared with 3% in the placebo group experienced one or more serious adverse events. Withdrawals due to adverse events were also higher in this study (8% umeclidinium vs. 3% placebo).[11]
- **Mortality**
  - Tiotropium vs placebo: No difference in all-cause mortality
    - OR 0.98 (95% CI 0.86 to 1.11)
  - Subgroup analysis found a significant difference in mortality between tiotropium inhaler formats.
    - Handihaler OR 0.92 (95% CI 0.80 to 1.05) N= 16,787 (19 studies)
    - Respimat OR 1.47 (95% CI 1.04 to 2.08) P<0.01 N=6522 (3 studies).
    - The authors qualify this with the limitation that event numbers were low and may have been affected by withdrawal rates which were generally higher than the mortality rate.[5]
  - Aclidinium showed no difference in mortality vs. placebo.[7]

Long-acting muscarinic antagonists (LAMAs) vs. short acting muscarinic antagonist (ipratropium)

Tiotropium (Spiriva) vs. Ipratropium (Atrovent)

The majority of evidence for long vs. short acting bronchodilators is from comparisons of tiotropium and ipratropium.

Cochrane Review 2015[12]

- A 2015 Cochrane Review included two studies (N=1073) that compared tiotropium to ipratropium.
  - The duration of one study was 12 weeks and the other 1 year.

- Patients had a mean FEV_1 of 40% predicted indicating moderate to severe COPD.
- Evidence was rated moderate to high quality with moderate levels of heterogeneity.
- The results are shown in the table below.

Table 4: Cochrane Review: Tiotropium vs. Ipratropium[12]

	Event rates from meta-analysis		Result (95% Confidence Interval)	p-Value NNT
	Ipratropium	Tiotropium		
Patients experiencing ≥ 1 exacerbation	297 per 1000	231 per 1000 (95% CI 180 to 286)	OR 0.71 (95% CI 0.52 to 0.95)	<0.001 **NNT 16** (95% CI 8 to 178) for 12 weeks to 1 year
Mean # exacerbations/pt/yr	Not reported		MD -0.2395% CI (- 0.39 to -0.07)	P=0.006
≥ 1 Exacerbation leading to hospitalization	6.7%	3.9%	OR 0.56 (95% CI 0.31 to 0.99)	P=0.045 **NNT 36** (95% CI 17 to 674) for 12 weeks to 1 year
All cause hospitalization	84 per 1000	30 per 1000 (95% CI 14 to 65)	OR 0.34 (95% CI 0.15 to 0.76)	P=0.0087
Quality of Life SGRQ (MCID 4 points)	Not reported		MD -3.30 (95% CI -5.63 to -0.97)	Not provided
***Lung Function @3 months Trough FEV_1**	Decrease of 20-30 ml	Increase of 109 ml (95% CI 81 to137)	MD 109 (95% CI 80 to 137)	p<0.00001
Transition Dyspnea Index(TDI)	Not reported		MD 0.90 (95% CI 0.39 to 1.41)	Not provided

OR= odds ratio; MD=Mean difference; NNT=number needed to treat; MCID=minimal clinically important difference

* Researchers considered MCID for trough FEV_1= 150 ml; NNTs calculated from meta-analyses trials of 12 weeks to 1 year

- **Benefits:**
  - **Tiotropium** compared with **ipratropium** showed statistically significant benefit for
    - Patients experiencing at least one exacerbation
      - NNT 16 (95% CI 8 to 178) for 12 weeks to 1 year
    - Patients with ≥ 1 exacerbation leading to hospitalizations
      - NNT 36 (95% CI 17 to 674) for 12 weeks to 1 year
    - Fewer patients with at least one serious adverse event
      - OR 0.23 (95% CI 0.07 to 0.79)
    - Fewer patients withdrew from the tiotropium group
      - OR 0.58 (95% CI 0.4 to 0.83)
  - Several outcomes were statistically significantly improved with tiotropium; however, the clinical relevance is questionable since the mean difference did not achieve the minimal clinically important difference (MCID). Since the 95% confidence interval does include the MCID, some patients may perceive benefit.
    - Quality of Life
    - Lung Function (Trough FEV_1).
      - Of note researchers defined MCID as 150 ml
    - Symptoms of Dyspnea (TDI)

- **No statistically significant difference** was shown in all-cause mortality.
  - Ipratropium 1.1% vs. tiotropium 1.5%
    - OR 1.39 (95%CI 0.44 to 4.39)

Is there a difference between long acting muscarinic antagonists (LAMAs)?

Two recent network meta-analyses (NMA) assessed the relative efficacy of LAMAs. Until there are head to head trials comparing the new long acting muscarinic antagonists, indirect comparisons from a NMA can help to inform choice.

- One NMA compared the effects of the following agents for the outcomes of lung function, health status (SGRQ) and breathlessness (TDI): tiotropium 18 µg once daily compared with new agents aclidinium 400 µg twice daily, glycopyrronium 50 µg once daily, and umeclidinium 62.5 µg once daily.[13]
- The other NMA assessed the impact of LAMAs on moderate to severe and severe exacerbations and included umeclidinium, tiotropium and glycopyrronium.[14]

Results of Ismaila NMA[13]

- All LAMAs have comparable efficacy to tiotropium for outcomes studied and choice should depend on physician's and patient's preference.

Results of Oba NMA:[14]

- All LAMAs in this analysis reduced moderate-to-severe exacerbations compared with placebo with no statistically significant differences among LAMAs in preventing moderate-to-severe or severe exacerbations.

Cochrane Review aclidinium vs. tiotropium[6]

- The results of the two NMAs agree with a Cochrane Review that reported outcomes for the comparison between aclidinium vs. tiotropium.
  - Two studies enrolling a total of 729 participants contributed to the outcomes. Studies ranged from 4 to 52 weeks in duration.
  - The quality of the evidence from the two studies based on the GRADE criteria was considered **very low**.[6]
  - There was **no statistically significant difference** in the following outcomes between aclidinium and tiotropium:
    - Mortality (no deaths in either group)
    - Exacerbations requiring steroids, antibiotics or hospital admissions
    - Non-fatal serious events.
  - No studies measured quality of life or functional capacity.

Long-acting beta$_2$ Agonists (LABAs) vs. placebo[15,16]

There are currently three single agent long acting beta$_2$ agonists marketed in Canada. There are two Cochrane Reviews assessing their benefits and harms compared with placebo. The first by Kew et al included studies of salmeterol and formoterol and the second, by Geake et al., studied indacaterol compared with placebo.

In COPD trials, short acting beta$_2$ agonist use is allowed for relief of shortness of breath; therefore, clinical trials labeled LABA vs. placebo are really a comparison with as needed short acting beta$_2$ agonist.

A Cochrane Review and meta-analysis of 26 RCTs (N= 14,939) of moderate quality compared the LABAs **salmeterol 50 µg twice daily, formoterol 12 µg twice daily or formoterol 24 µg** twice daily with placebo.

- Patients were primarily male with moderate to severe COPD (FEV_1 33% to 55% predicted).
- The median duration of the studies was six months and the evidence was rated as having moderate quality.[15]

- **Results**
  - **Benefits LABAs vs placebo**
    - Modest benefits were demonstrated for reduction in **moderate and severe exacerbations leading to hospitalization.**
      - 52 (95% CI 24 to 78) fewer moderate exacerbations **per 1000** treated for 8 months
      - 18 (95% CI 3 to 31) fewer exacerbations leading to hospitalization **per 1000** treated for 7 months
    - An improved quality of life was achieved by some patients. The mean difference in SGRQ scores did not achieve the MCID of 4 points; however, more patients achieved the MCID with use of a LABA. OR 1.58 (95% CI 1.32 to 1.90)
    - Patients were less likely to withdraw from LABA group: OR 0.74 (95% CI 0.69 to 0.80)
    - No difference in adverse events
  - **No benefit or questionable clinical significance:**
    - No statistically significant benefit in mortality OR 0.90 (95% CI 0.75 to 1.08). (Mortality rates 3-4%)
    - The degree of lung function improvement did not achieve a clinically meaningful difference. Mean difference 73 ml (48-98 ml)
    - No significant difference in the combined outcome of moderate plus severe exacerbations.

- The following outcomes were not reported in this meta-analysis:
  - Patients experiencing ≥ 1 exacerbation
  - Mean number of exacerbations per year
  - Dyspnea (TDI) scores
  - Use of rescue bronchodilator

Table 5: Cochrane meta-analysis: LABA (salmeterol or formoterol) vs. placebo[15]

	Event rates from meta-analysis		Result (95% Confidence Interval)	p-Value or NNT
	PBO	LABA		
Moderate exacerbations (requiring additional medications such as oral steroids or antibiotics)	**238 per 1000**	**186 per 1000** (95% CI 160 to 214)	OR 0.73(95% CI 0.61 to 0.87)	52 (95% CI 24 to 78) fewer exacerbations per 1000 treated for 8 months
Severe exacerbation leading to hospitalization	**71 per 1000**	**53 per 1000** (95% CI 40 to 68)	OR 0.73 (95% CI 0.56 to 0.95)	18 (95% CI 3 to 31) fewer exacerbations leading to hospitalization per 1000 treated for 7 months
Health Status (SGRQ) **Proportion with MCID of 4 points**	- 39%	- 50%	SGRQ MD -2.32 (95% CI -3.09 to -1.54) Achieved MCID with LABA OR 1.58 (95% 1.32 to 1.90)	P= 0.007 but did not achieve MCID P= 0.0007
Lung function Trough FEV_1	-	-	MD 73 ml (95% CI 48-98 ml)	MD not clinically relevant

MD= Mean Difference between comparators; OR = Odds Ratio; MCID minimal clinically important difference

Indacaterol vs. Placebo[16]

Trials of indacaterol were included in a separate 2015 Cochrane Review and meta-analysis. It included 10 RCTs (N=8562) of high quality and low risk of bias comparing indacaterol with placebo.

- Trials were between 12 weeks and 52 weeks in duration.
- Included patients with stable COPD and a mean FEV_1 of approximately 50% predicted.[16]
- Concomitant inhaled corticosteroids were allowed in the studies.

- **Results:**
  - **Benefits:** Indacaterol vs. placebo resulted in
    - Fewer participants experiencing one or more exacerbations.
      - The definition of an exacerbation was not standardized across trials, and definitions of exacerbations were not universally reported. The severity of exacerbations was not reported in this Cochrane Review.

- An improvement in mean quality of life score (SGRQ) which was below the MCID of 4 points, although the 95% CI included a 4 point difference and a greater proportion of participants experienced clinically important improvements in SGRQ score.
  - 121 more participants (95% CI 94 to 151) for each **1000** treated for 12 to 52 weeks would see an improvement in quality of life
- An improvement in trough FEV_1 which is considered clinically meaningful.
- An improvement in mean TDI dyspnea score which is considered clinically important.
  - 166 more participants (95% CI 136 to 196) per 1000 treated for 12 to 52 weeks achieved clinically significant improvement in dyspnea
- No difference in serious adverse events.

- **No statistically significant benefit** in **mortality** OR 0.42 (95% CI 0.16 to 1.08) but there were very few deaths.
- Not reported in this meta-analysis
  - Moderate exacerbations (requiring additional medications such as oral steroids or antibiotics)
  - Mean # exacerbations/patient/year
  - Severe exacerbation leading to hospitalization
  - All cause hospitalization

Table 6: Cochrane meta-analysis indacaterol vs. placebo [16]

	Event rates from meta-analysis		Result (95% Confidence Interval)	p-Value or NNT
	Placebo	Indacaterol		
Patients experiencing ≥ 1 exacerbation	222 per 1000	188 per 1000 (95% CI 167 to 212)	OR 0.81 (95% CI 0.7 to 0.94)	P= 0.0057
Health Status (SGRQ) **Proportion with MCID 4 points**	**425 per 1000**	**546 per 1000** (95% CI 519 to 576)	MD -3.60 (95% CI -4.36 to -2.83) Achieved MCID: OR 1.63 (95% CI 1.46 to 1.84)	121 more participants (95% CI 94 to 151) for each 1000 treated for 12 to 52 weeks, would experience a clinically significant improvement in quality of life if treated with indacaterol
Lung Function (Trough FEV_1)	-	-	MD 149 ml (95% CI 137 to 161)	Clinically important
Transition Dyspnea Index(TDI) **Proportion with MCID of 1 point**	**440 per 1000**	**607 per 1000** (95% CI576 to 636)	MD 1.00 (95% CI 0.82 to 1.17) Achieved MCID: OR 1.96 (95% CI 1.73 to 2.22)	166 more participants (95% CI 136 to 196) per 1000 treated for 12 to 52 weeks achieve a clinically significant improvement in dyspnea with indacaterol

MD= Mean Difference between comparators; OR = Odds Ratio; MCID minimal clinically important difference

Question 2c: What is the evidence for differences in benefits between LABA and LAMA?

Summary:

- LAMAs have shown advantage over LABAs for the outcomes of patients experiencing one or more exacerbations (NNT 29 [95% CI 19 to 59]) for 1 year and exacerbations requiring hospitalization (ARR 2%).
- LABAs and LAMAs similarly improve lung function, symptom control and quality of life.
- LABAs and LAMAs have similar rates of adverse events and study withdrawals (both outcomes slightly lower with LAMAs).

Tiotropium vs. LABA[17]

The Chong Cochrane Review included 7 good quality RCTs enrolling 12,223 patients with moderate to severe COPD.

- Studies compared tiotropium (via HandiHaler) with salmeterol (four studies, 8936 participants), formoterol (one study, 431 participants) or indacaterol (two studies, 2856 participants).
- Participants could receive inhaled corticosteroids (ICS) at a stable dose. The duration of the studies ranged from 3-12 months.
- Results were rated very low to moderate quality evidence.

- **Results:**
  - **Benefits:** Tiotropium vs. LABA
    - Tiotropium reduced the number of patients experiencing one or more exacerbations.
      - NNT 29 (95% CI 19 to 59)
      - There was no difference between individual LABAs.
    - Tiotropium reduced the number of severe exacerbations requiring hospitalization
      - OR 0.87 (95% CI 0.77 to 0.99)
    - Slightly lower rate of non-fatal serious adverse events with tiotropium and fewer study withdrawals: 10.1% vs. 11.1% (OR 0.88 [95% CI 0.78 to 0.99]).
  - **No statistically significant difference** between tiotropium and LABAs for:
    - All cause hospitalizations OR 0.93 (95% CI 0.57 to 1.54)
    - Mortality 1.4% vs 1.1% OR 0.82 (95% CI 0.60 to 1.13)
    - Measures of lung function or dyspnea
    - Likely no clinically important differences in health related quality of life although outcomes were unable to be pooled because of a high level of heterogeneity amongst studies.

- The following outcomes were not reported in this meta-analysis
  - Number of moderate exacerbations requiring oral steroids and/or antibiotics
  - Mean number of exacerbations/patient/year.
- **Limitations**
  - Chong et al identified that for quality of life assessment, it is insufficient to look only at the average response, as this may disguise subgroups of responders. The proportion of participants who achieved a clinically important benefit (e.g. a decrease of ≥ 4 units in SGRQ score) should not be interpreted alone as an outcome unless the number who had a clinically important deterioration is also reported.

Table 7: Cochrane Review: tiotropium vs LABA 2012[17]

	Event rates from Meta-analysis		Result (95% Confidence Interval)	p-Value or NNT
	TIO	LABA		
Patients experiencing ≥ 1 exacerbation	26% (25-28%)	29%	**OR 0.86 (95% CI 0.79 to 0.93)**	NNT 29 (95% CI 19 to 59) for 1 year
Severe exacerbation leading to hospitalization	11%	13%	Tiotropium vs. LABA 0R 0.87 (95% CI 0.77 to 0.99)	P= 0.029
All cause hospitalization	4.3%	4.9%	OR 0.93 (95% CI 0.57 to 1.54)	Not statistically significant (p=0.79)
Lung Function (Trough FEV_1)	-	-	MD 11 ml (95% CI -11 to 32)	Not statistically significant (p=0.35)
Transition Dyspnea Index(TDI) MCID 1 point	-	-	MD -0.22 (95% CI -0.63 to 0.19)	Not statistically significant (p=0.29)

MD= Mean Difference between comparators; OR = Odds Ratio; MCID minimal clinically important difference; NNT=number needed to treat

How to choose between LABA or Tiotropium?

- The authors suggest that until further information is available, and given such small differences in effect between tiotropium and LABAs, plus the relatively large NNT for benefit on exacerbations, one approach may be to give a COPD patient a substantial trial of tiotropium, followed by a LABA (or vice versa), then to continue prescribing the long-acting bronchodilator that the patient prefers.

Therapy Tips

- Short acting bronchodilators are recommended for patients with occasional symptoms.
- A single long acting bronchodilator (LAMA or LABA) is suggested for patients with persistent symptoms. When used for **symptoms only**, there is no evidence to support one class of bronchodilator over another and choice depends on the patient's perception of relief of symptoms.
- In patients experiencing **exacerbations,** a LAMA may be preferred over a LABA.
- Inhaler technique AND adherence to therapy should be assessed before concluding that current therapy requires modification.

Question 3. What is the evidence for benefit or harm for the combination of a LAMA plus LABA compared with either agent alone?

Summary:

Based on a Cochrane Review

- **Tiotropium plus LABA vs tiotropium**
  - The tiotropium plus LABA group showed a statistically significant improvement in health related quality of life.
    - More patients in the combination group achieved a minimum clinically important 4 point difference (MCID) in the SGRQ quality of life scale. NNT 15 (95% CI 11 to 23) for 6 months
  - All other reported outcomes showed either no clinical or statistical difference.
- **Tiotropium plus LABA vs LABA**
  - Benefits for tiotropium plus LABA in
    - Exacerbation rates
    - Potential benefit in lung function
    - Quality of life: NNT 9 (95% CI 7 to 15) for 6 months for proportion meeting MCID
  - All other reported outcomes showed either no clinical or statistical difference.

Trials of newer agents in combination versus the individual components do not appear to offer different results from the Cochrane Review.

Cochrane Review[18]

- This systematic review and meta-analysis of 10 RCTs (N=10,894) included patients with moderate or severe COPD.
  - The studies compared tiotropium plus LABA to tiotropium alone, and four trials also compared LAMA plus LABA with LABA alone.
  - The duration of studies included in the review was 3-12 months.
  - The meta-analysis included four studies with olodaterol, three with indacaterol, two with formoterol, and one with salmeterol.
  - Outcomes studied: quality of life, exacerbations, symptoms, lung function and serious adverse events.

- **Results: Tiotropium plus LABA vs tiotropium**
  - **Benefits:** tiotropium plus LABA vs tiotropium showed statistically significant improvements in:
    - Health-related quality of life (SGRQ) MD -1.34, (95% CI -1.87 to -0.80) but the mean did not achieve the 4 point MCID. Most data were from the tiotropium plus olodaterol vs. tiotropium studies.
      - More patients (55% vs. 48%) achieved the SGRQ MCID of 4 points in the combination group.
        - OR 1.32 (95% CI 1.19 to 1.46) NNT 15 (95% CI 11 to 23) for 6 months
    - Trough FEV_1 Mean Difference 0.06L (95% CI 0.05 to 0.07). This difference is **not** clinically relevant.
  - **No statistically significant difference** between tiotropium plus LABA vs tiotropium in the following outcomes
    - All cause hospital admission OR 1.01 (95% CI 0.86 to 1.19)
    - Hospital admission for exacerbation OR 1.02 (95% CI 0.80 to 1.28)
    - Mortality OR 1.24 (95%CI 0.81 to 1.90)
    - Symptom scores
    - Serious adverse events or withdrawals
  - The following outcomes were **not reported** in this meta-analysis
    - Patients experiencing ≥ 1 exacerbation
    - Moderate exacerbations (requiring additional medications such as oral steroids or antibiotics)
    - Mean # exacerbations/patient/year
    - Dyspnea (TDI scores)

Table 8: Cochrane Review: tiotropium vs tiotropium + LABA[18]

	Event rates		Result (95% Confidence Interval)	p-Value or NNT
	TIO + LABA	Tio		
Severe exacerbation leading to hospitalization	6% (5-8%)	6%	OR 1.02 (95% CI 0.80 to 1.28)	Not statistically significant p=0.90
All cause hospitalization	14% (12-16%)	14%	OR 1.01 (95% CI 0.86 to 1.19)	Not statistically significant p= 0.86
Health Status (SGRQ) Proportion with MCID 4 points	55%	48%	OR 1.32 (95% CI 1.19 to 1.46)	ARR 7% NNT 15 (95% CI 11-23) for 6 months
Lung Function (Trough FEV_1)	0.120 L	0.06L	MD 0.06 L (95% CI 0.05 to 0.07)	Not a clinically significant difference but combination achieved MCID
Mortality	10%	8%	OR 1.24 (0.81 to 1.90)	Not statistically significant p= 0.31

MD= Mean Difference between comparators; OR = Odds Ratio; MCID minimal clinically important difference; NNTs from meta-analysis data

Tiotropium plus LABA vs. LABA[18]

- The analysis of tiotropium plus LABA vs LABA included data on four different LABAs:
  - Salmeterol and formoterol administered twice daily
  - Indacaterol and olodaterol administered once daily.
  - The results were largely from olodaterol studies and there was insufficient information to assess whether the other LABAs were equivalent to olodaterol or each other.
  - Duration of studies was 3-12 months.

- **Results:**
  - **Benefits:** Tiotropium plus LABA vs. LABA demonstrated statistically significant improvements in:
    - SGRQ (MD -1.25, 95% CI -2.14 to -0.37). The mean difference did not achieve the 4 point MCID.
      - Proportion reaching MCID 55.4% vs 44.8% NNT 9 (95% CI 7 to 15) for 6 months
    - FEV_1 (MD 0.07 L, 95% CI 0.06 to 0.09). The mean difference did not reach the MCID however, the combination achieved a potentially clinically important improvement compared with LABA alone.
    - Exacerbation rates (OR 0.80, 95% CI 0.69 to 0.93)
  - The following outcomes were **not reported**:
    - Patients experiencing ≥ 1 exacerbation
    - Moderate exacerbations (requiring additional medications such as oral steroids or antibiotics) or mean # exacerbations/patient/year
    - Dyspnea (TDI scores)

Table 9: Cochrane Review: Tiotropium plus LABA vs LABA[18]

	Event rates		Result (95% Confidence Interval)	p-Value or NNT
	TIO + LABA	**LABA**		
Severe exacerbation leading to hospitalization	**5%** (95% CI 4 to 7)	6%	OR 0.90 (0.66 to 1.22)	Not statistically significant p= 0.50
Exacerbations	**28.5%**	31%	OR 0.80 (95% CI 0.69 to 0.93)	P= 0.0045
All cause hospitalization	13% (95% CI 11-15)	14%	OR 0.93 (0.76 to 1.14)	Not statistically significant P=0.50
Health Status (SGRQ)	mean change -1.25 (95% CI -2.14 to - 0.37)	-5.7 points	MD -1.25, (-2.14 to -0.37)	
Proportion with MCID 4 points	55.4%	44.8%	OR 1.53 (95% CI 1.31 to 1.79)	ARR 10.6% (95% CI 6.7 to 14.4) NNT 9 (95% CI 7 to 15 for 6 months)
Lung Function (Trough FEV_1) Mean change from baseline	0.120 L (95% CI 0.11 to 0.14L)	0.05 L	MD 0.07 L (95% CI 0.06 to 0.09)	Not a clinically significant difference between comparisons. Combination achieved potential MCID
All cause mortality	1.3% (95% CI 0.7 to 2.4)	1.1%	OR 1.15 (0.62 to 2.13)	Not statistically significant p= 0.66

ARR=absolute risk reduction MD= Mean Difference; OR=Odds Ratio; MCID minimal clinically important difference; NNT from meta-analysis data

- **Limitations**
  - Outcomes may be limited by short studies, infrequent events and lack of power to detect a difference in these outcomes.
  - The authors conclude it is not clear how clinically important the small differences between treatments are and that additional long-term (12 months or longer) larger studies are needed to clarify the risks and benefits of tiotropium plus LABA treatment compared to either drug alone.
- **Additional studies of LAMA/LABA combinations**
  - Several newly marketed combinations of LAMA/LABAs were excluded from the Farne Cochrane Review[18] as it specifically looked at tiotropium comparisons. These include combinations of aclidinium plus formoterol, glycopyrronium plus indacaterol, and umeclidinium plus vilanterol.
  - The most relevant comparisons for the combinations are against one of the components or an alternative drug or combination within the same class.
  - The following information summarizes outcomes from clinical trials of these combinations:[19]

Table 10: Outcomes for aclidinium/formoterol vs aclidinium(LAMA) or formoterol (LABA)

	Aclidinium/formoterol (400/12mcg twice daily) Pooled analysis of ACLIFORM and AUGMENT studies[19] Outcomes for LAMA/LABA vs. LAMA or LABA at 24 weeks		
Patient Characteristics	**Patients mean age 64 years; diagnosis of stable moderate to severe COPD; smoking history of ≥ 10 pack years FEV_1 54% predicted; < 1 exacerbation in previous year; GOLD category B and D**		
	Aclidinium 400 mcg Formoterol 12 mcg N=720	**Aclidinium 400 mcg N=720**	**Formoterol 12 mcg N=715**
Any exacerbation Rate per pt / yr	0.36 NS vs. individual agents	0.41	0.45
Moderate to severe exacerbation Rate per pt / yr	0.29 NS vs. individual agents	0.35	0.36
Dyspnea Number achieving MCID of 1 point	62% NS vs. individual agents	56%	57%
Lung function* Trough FEV_1 (vs. placebo) Least square means	143 ml Statistically significant vs. formoterol	117ml	58 ml
Relief medication (Puffs per day)	-1.73 (95% CI -1.88 to -1.57) NS vs. individual agents	-1.37 (95%CI -1.52 to -1.21)	-1.52 (95%CI -1.68 to -1.37)

* Data from the ACLIFORM-COPD trial Singh 2014(20); NS = not statistically significant

Indacaterol/ glycopyrronium (Ultibro Breezhaler)

- The efficacy of this LAMA/LABA combination has been studied in a group of 11 randomized multicentre, international phase III trials collectively identified as IGNITE.[21]
  - Patient populations have included those at low risk of exacerbations (SHINE[22], ILLUMINATE[23]) as well as those with high risk of exacerbations (SPARK[24]).
  - Most of the completed trials have studied lung function parameters or adverse events as primary outcomes, while one (SPARK[24]) included assessment of exacerbation differences between the combination and LAMA monotherapy.
  - One of the trials in the IGNITE series is the FLAME trial which compared LABA/ICS to LAMA/LABA and is summarized on page 43.
- Characteristics of studies included in IGNITE trials
  - Trials enrolled patients with moderate to severe (FEV_1 predicted 50-60%) or severe to very severe (SPARK) (FEV_1 predicted < 50%) COPD.
  - Mean age between 62-69 years
  - Primarily male (at least 60% of patients in all studies)
  - Approximately 60% were former smokers and the remaining current smokers
- **Results**
  - **Mean trough FEV_1**
    - There are inconsistent results reported on whether the combination of indacaterol/ glycopyrronium offers benefit compared with the individual agents as monotherapy. The BEACON study[25] reported no statistically significant differences between these groups.
    - Other trials (SHINE, SPARK[22,24]) reported statistically significant increases with indacaterol/ glycopyrronium compared with either agent or tiotropium given as monotherapy in trials up to 64 weeks in duration.
      - The mean differences in FEV_1compared with indacaterol, glycopyrronium or tiotropium were all less than the 100 ml MCID (differences ranged between 60-90 ml).
      - A higher percentage of patients in the LAMA/LABA group experienced at least a 100 ml increase in trough FEV_1 (64%) compared with indacaterol 46% and glycopyrronium 43%.
  - **Dyspnea**
    - In general, indacaterol/ glycopyrronium did not improve breathlessness compared with either component given as monotherapy.
    - In one study (BLAZE[26]), indacaterol/ glycopyrronium achieved a significantly greater number of patients with a clinically important improvement of 1 point on the TDI (36%) than those in the tiotropium arm (24%), $p < 0.05$.

- **Quality of life (SGRQ)**
  - Indacaterol/glycopyrronium did not improve health status compared with indacaterol monotherapy.
  - Despite statistically significant difference, indacaterol/ glycopyrronium did not attain the MCID of 4 points compared with glycopyrronium or tiotropium.
- **Exacerbations (SPARK)**[26]
  - Annualized rate of **moderate or severe exacerbations:** indacaterol/ glycopyrronium vs. glycopyrronium: 0.84 vs. 0.95; RR 0.88 (95% CI 0.77 to 0.99) p= 0.038
    - Difference between indacaterol/ glycopyrronium vs. tiotropium was not statistically significant RR 0.90 (95% CI 0.79 to 1.02) p=0.09
  - Annualized rate of **mild exacerbations:** indacaterol/ glycopyrronium vs.
    - Glycopyrronium 2.51 vs 2.96; RR 0.85 (95% CI 0.75 to 0.96) p = 0.007
    - Tiotropium 2.51 vs. 2.98; RR 0.84 (95% CI 0.75 to 0.95) p = 0.005
  - Annualized rate of **all exacerbations:** indacaterol/ glycopyrronium vs.
    - Glycopyrronium 3.44 vs. 4.04; RR 0.85 (95% CI 0.77 to 0.94) p = 0.001
    - Tiotropium 3.44 vs. 4.02; RR 0.86 (95% CI 0.78 to 0.94) p = 0.002
  - There were no significant differences between indacaterol/ glycopyrronium compared with either the glycopyrronium or tiotropium in rates of **severe exacerbations.**
  - Data were not presented for the percentage of patients experiencing ≥ 1 exacerbation/year.

Umeclidinium/vilanterol (Anoro Ellipta) vs. LABA or LAMA

- The main trials assessing umeclidinium/vilanterol compared the combination to the individual components as monotherapy or tiotropium. The evidence summarized below is from four 24 week, randomized, double blind, double-dummy studies:
  - Decramer 2014[27] (2 studies included in one publication), N=1718
    - Study 1 included two strengths of umeclidinium/vilanterol (62.5/25mcg and 125/25mcg) vs. vilanterol 25mcg or tiotropium 18mcg
    - Study 2 included the two strengths of umeclidinium/vilanterol vs. umeclidinium 125 mcg or tiotropium 18 mcg
  - Maleki-Yazdi[28], 2014, N=905 umeclidinium/vilanterol vs tiotropium
  - Donohue, 2013[29] N=1532 umeclidinium/vilanterol vs umeclidinium or vilanterol
- Patient characteristics were similar in the studies: primarily male population, smokers or ex-smokers, mean age approximately 64, with moderate to severe COPD.
- The primary outcome in all studies was trough FEV_1. Dyspnea and health status were also assessed.
- Results are presented for only umeclidinium/vilanterol 62.5/25mcg as it is the only strength marketed in Canada.

- **Results**
  - **Trough FEV_1**
    - Decramer[27]
      - Umeclidinium/vilanterol (62.5/25mcg) significantly improved trough FEV_1 vs. tiotropium 18 mcg or vilanterol 25 mcg but not vs. umeclidinium. The mean differences are below 100 ml which is considered as the MCID.
        - Study 1 Difference between tiotropium or vilanterol of 0.090 L (95% CI 0.039 to 0.142L) p=0.0006
        - Study 2 Difference of 0.060 L (95% CI 0.010 to 0.109L); p=0.0182 vs tiotropium;
          - No statistically significant difference vs. umeclidinium 125 mcg
    - Maleki-Yazdi[28]
      - Umeclidinium/vilanterol (62.5/25mcg) significantly improved trough FEV_1 vs. tiotropium 18 mcg
      - 0.112 L (95% CI 0.081 to 0.144L) p<0.001
    - Donohue 2013[29]
      - Umeclidinium/ vilanterol (62.5/25 mcg) significantly improved trough FEV_1 vs. umeclidinium or vilanterol monotherapy.
        - vs umeclidinium 0.052 L (95% CI 0.017 to 0.087L) p=0.004
        - vs vilanterol 0.095 L (95% CI 0.060 to 0.130L) p<0.001
  - **Dyspnea (TDI)**
    - Decramer:[27] Study 1 or 2: All therapies improved by at least 1 point (MCID) with no differences between therapies.
    - Donohue 2013:[29] All therapies increased the TDI by the 1 point MCID with no differences between umeclidinium/vilanterol and umeclidinium or vilanterol monotherapy.
  - **Health Status (SGRQ)**
    - Decramer:[27] Study 1 or 2: All treatments achieved at least a 4 point difference in SGRQ (MCID) with no differences between therapies.
    - Maleki-Yazdi:[28] both therapies improved by at least 4 points (MCID). The umeclidinium/vilanterol 62.5/25mcg showed a statistically significant benefit vs. tiotropium; however, the difference did not achieve the 4 point MCID.
      - Umeclidinium/vilanterol vs. tiotropium: −2.10 (95% CI −3.61 to −0.59; p=0.006)
    - Donohue 2013:[29] umeclidinium/ vilanterol (62.5/25 mcg) and monotherapies improved SGRQ scores with no significant difference between therapies.
  - **Exacerbations**
    - Decramer:[27] Study 1 or 2: There were a small number of exacerbations with no difference between therapies and no difference in time to first exacerbation.

- Donohue 2013:[29] umeclidinium/ vilanterol (62.5/25 mcg) and umeclidinium statistically significantly lowered the risk for time to first COPD exacerbation compared with placebo although the study was not powered to assess exacerbations. No statistical analysis was presented for comparisons between treatments.

Therapy Tips: Recommendation from GOLD 2017:

- Use dual bronchodilators in patients who have persistent dyspnea on one bronchodilator. (Evidence A)
- In a patient being treated for symptoms only, if the addition of the second bronchodilator does not improve symptoms, treatment should be stepped back down to a single bronchodilator.

Question 4: Who should have an inhaled corticosteroid (ICS) added to therapy?

Summary:

- **LABA/ICS vs placebo**
  - Benefits for LABA/ICS in
    - Exacerbation rates: based on an average of 1 to 2 exacerbations per year, LABA/ICS would lead to a reduction of one exacerbation every 2 to 4 years.
    - Mortality NNT 42 (95% CI 24 to 775) for 3 years
  - Results for LABA/ICS showed small benefits in effects on health related quality of life, symptoms, lung function, use of rescue medication and withdrawal rates. In some cases, the benefits reached accepted levels of clinical significance, but only just.
  - Increased risk of pneumonia: NNH =17 (95%CI 12 to 27) for 3 years based on the TORCH trial.

LABA/ICS vs LABA

- Reduction in exacerbation rates corresponds to 1 exacerbation/pt/year in the LABA group vs 0.76 exacerbations/pt/year in the LABA/ICS group
- Reduction in patients experiencing ≥ 1 exacerbation
  - NNT 22 (95% CI 13 to 85) for 1 year
- Adverse events
  - Pneumonia: Increased rates with LABA/ICS vs LABA
    - ARI 1.3% : NNH 17 (95% CI 12-29) for 156 weeks
  - Candidiasis and upper respiratory infections were more frequent with LABA/ICS.

- **LABA/ICS vs Tiotropium**
  - There was no difference in the annual rate of moderate or severe exacerbations.
  - Reduction in all cause hospitalization with tiotropium vs LABA/ICS
  - Exacerbations requiring oral steroids were less frequent with LABA/ICS: those requiring antibiotics were more frequent with LABA/ICS vs tiotropium.
  - Pneumonia: increased rates with LABA/ICS ARI 4% NNH 25 (95% CI 16 to 64)
  - Mortality: possible increase risk with tiotropium; however, authors suggest caution in interpreting this data due to high withdrawal rates in the trial.
- **LAMA/LABA vs LABA/ICS**
  - LAMA/LABA reduced the annual rate and time to first moderate or severe exacerbation.
  - LAMA/LABA reduced the annual rate and time to first exacerbation of *any* severity.
  - LAMA/LABA decreased the number of patients experiencing ≥ 1 exacerbation, NNT 20 (95% CI 13 to 44) for 1 year.
  - LAMA/LABA increased the proportion of patients with a clinically relevant improvement in quality of life, NNT 18 (95% CI 11 to 47) for 1 year
  - There was no difference between treatments for rates of exacerbations leading to hospitalizations.
  - Fewer cases of pneumonia, candidiasis and influenza with LAMA/LABA
- **LABA/ICS/LAMA (triple therapy) vs. LAMA**
  - Triple therapy reduced all cause hospitalization NNT 20 (95%CI 11-124)
  - Triple therapy increased the proportion of patients with a clinically relevant improvement in quality of life (49.5% vs 40%)
  - Results for other outcomes were either not statistically significant or clinically relevant including exacerbation rates.
- **LABA/ICS/LAMA vs LAMA/LABA**
  - There is insufficient information to draw conclusions on whether the addition of ICS to patients taking LAMA/LABA offers clinically relevant benefits.

LABA/ICS vs. ICS

A Cochrane Review compared LABA/ICS vs. ICS.[30] The results of this Review will not be presented in detail.

- Mortality rates were statistically significantly **higher** in patients treated with ICS alone than LABA/ICS treated patients.
- Exacerbation rates were also lower for LABA/ICS vs. ICS alone.

- Therefore, unlike in asthma, ICS are not recommended to be used without a LABA in COPD.

LABA/ICS vs. placebo

A combination inhaler of LABA/ICS has been recommended in COPD guidelines as an option when patients are experiencing exacerbations.

- The 2017 GOLD[31] recommendations suggest patients with 2 exacerbations in one year or 1 exacerbation requiring hospitalization **despite appropriate therapy with long acting bronchodilators** can be considered for LABA/ICS therapy.
- The increased risk of pneumonia demonstrated in COPD trials requires an assessment of benefit to risk.
- Only moderate to high doses of ICS have been studied in long-term COPD clinical trials.

Comparison of LABA/ICS in one inhaler vs. placebo[30]

A Cochrane Review included 19 studies and 10,400 participants with comparisons of three combination inhalers, fluticasone/salmeterol, budesonide/formoterol or mometasone/formoterol vs. placebo.

- Trials lasted between 4 and 156 weeks, (mean 42 weeks).
- The quality of the evidence was primarily rated as moderate.
- Withdrawal rates were high in most of the studies creating uncertain degrees of bias, although the TORCH study followed the vital status of patients after withdrawal, reducing attrition bias.
- The TORCH study provided most of the weight for the outcomes.

➢ **Results:**

- **Benefits LABA/ICS vs. placebo**
  - Reduction in **exacerbation rates:**
    - Based on an average of one or two exacerbations per year, treatment with LABA/ICS would lead to a reduction of one exacerbation every two to four years.
  - An overall reduction in **mortality.**
    - Outcome is dominated by the results of one study (TORCH) which studied mortality as a primary outcome.
    - NNT 42 (95% CI 24 to 775) for three years (based on risk of death in the placebo group of 15.2% from TORCH study). The confidence intervals are wide and include an NNT up to 775 patients which decreases our confidence in the validity of this result.
  - **Health Status**: All active treatments led to statistically significant improvement in health status measurements although mean differences were generally below the 4 point MCID for all of the LABA/ICS combinations with the exception of budesonide/formoterol 320mg/9 mg.(Mean difference of -4.11 (-6.18 to -2.04).

        - The 95% confidence intervals of other comparisons include a 4 point difference indicating some but not all patients may have a noticeable improvement in health status. These results were not pooled in a meta-analysis.
    - **Symptoms and lung function** assessments are suggested to favour the combined treatments but these results were not pooled in a meta-analysis.
- The authors conclude that results for each combined inhaler showed small benefits over placebo in effects on health-related quality of life, symptoms, lung function, use of rescue medication and withdrawal rates. In some cases, the benefits reached accepted levels of clinical significance, but only just.
- **Adverse effects**
    - Increased risk of **pneumonia** with LABA/ICS vs. placebo treatment (moderate quality evidence) OR 1.62 (95% CI 1.36 to 1.94)
        - NNH = 17 (95% CI 12 to 27) for 3 years for one extra case of pneumonia. This is based on a 12.3% risk of pneumonia in the placebo arm of TORCH.[32]
- **No statistically significant benefit for:**
    - Exacerbations requiring hospitalization (i.e., severe COPD exacerbations)
    - Did not report all cause hospitalization
- The authors concluded that current evidence does not suggest any major differences between the various combination inhalers in terms of effects, nor is the evidence strong enough to demonstrate that all are equivalent. Head to head comparisons are needed.

Table 11: Cochrane Review LABA/ICS vs placebo [30]

	Event rates from meta-analysis		Result (95% Confidence Interval)	p-Value or NNT
	LABA/ICS	PBO		
Patients experiencing ≥ 1 exacerbation	25.1% (95% CI 22.1 to 28.6)	30.1%	OR 0.78 (95% CI 0.66 to 0.93)	Reduction of 1 exacerbation every 2-4 years
Exacerbations	0.99 (95% CI 0.93 to 1.05)	1.35	RR 0.73 (95% CI 0.69 to 0.78)	
Hospitalization for severe exacerbation	10.8%	11.5%	OR 0.93 (95% CI 0.81 to 1.06)	Not statistically significant
Pneumonia	8.5% (95% CI 7.3 to 10.1)	5.5%	OR 1.62 (95% CI 1.36 to 1.94)	NNH =17 (95%CI 12 to 27) for 3 years (Based on TORCH trial)
Mortality	5%	6%	OR 0.82 (95% CI 0.68 to 0.99)	NNT 42 (95% CI 24 to 775) for 3 years

RR= rate ratio; OR = odds ratio; NNT/NNH number needed to treat/harm

LABA/ ICS combined in one inhaler vs. LABA[33]

- This Cochrane review included 14 studies (N=11,794) in patients with severe COPD.
    - Ten studies assessed fluticasone plus salmeterol (FPS) and four studies assessed budesonide plus formoterol (BDF).
    - The studies were well-designed but had high withdrawal rates.
    - The quality of the evidence was rated very low to moderate.

- **Results:**
  - **Benefits:**
    - **Exacerbation rates** were lower with LABA/ICS vs. LABA alone, (low quality evidence and statistical heterogeneity, decreasing the confidence in the result).
      - The reduction corresponds to one exacerbation/patient/year on a LABA vs. 0.76 exacerbations/patient/year on LABA/ICS. (Rate Ratio 0.76; 95% CI 0.68 to 0.84).
      - The number of patients experiencing one or more exacerbations was lower in a study of the combination of fluticasone/salmeterol vs. salmeterol.
        - ARR 5% over 1 year OR 0.83 (95% CI 0.70 to 0.98)
  - **Questionable clinically relevant outcomes:**
    - LABA/ICS improved SGRQ but the difference was not 4 units vs. LABA and the 95% CI did not include the MCID.
    - There were small differences in dyspnea scores and FEV_1 which favored the combination therapy but the authors of the Cochrane Review say they are of unlikely clinical relevance.
  - **No statistically significant difference** between LABA/ICS and LABA for the following outcomes:
    - Hospitalizations
    - Mortality
  - **Adverse events**
    - **Pneumonia:** increased rates with LABA/ICS vs LABA.
      - Absolute risk increase (ARI) 1%
      - NNH 17 (95% CI 12 to 29) for 156 weeks using data from the TORCH trial where baseline rate was 13%
    - Candidiasis and upper respiratory infections were more frequent with LABA/ICS.
  - Nannini et al[33] comment that based on the data available, the superiority of LABA/ICS over LABA alone is questionable in preventing exacerbations.
    - In addition, the effects on hospitalizations were inconsistent and require additional study.
    - There was an increased risk of pneumonia with LABA/ICS but this did not result in differences in mortality.
    - The quality of life, symptoms score, rescue medication use and FEV_1 improved more on LABA/ICS than on LABA, but the average differences were probably not clinically significant for these outcomes. They conclude, “to an individual patient the increased risk of pneumonia needs to be balanced against the possible reduction in exacerbations.”

Table 12: Cochrane Review: LABA/ICS vs. LABA[33]

	Event rates from meta-analysis		Result (95% Confidence Interval)	p-Value or NNT
	LABA/ICS	LABA		
Patients experiencing ≥ 1 exacerbation **FPS vs S**	42%	47%	OR 0.83 (95% CI 0.70 to 0.98)	NNT 22 (95% CI 13 to 85) for 1 year
Annual exacerbations	0.76 (95% CI 0.68 to 0.84)	1	RR 0.76 (95% CI 0.68 to 0.84)	0.32 (95% CI 0 to 16) fewer exacerbations follow up 1 year
Annual hospitalization rate	0.15/pt/yr	0.16/pt/yr	RR 0.79 (95% CI 0.55 to 1.13)	Not statistically significant P=0.19
Health Status (SGRQ) Proportion with MCID 4 points			Mean difference:	
FPS vs S	-	-	-1.58 (95% CI -2.15 to -1.01)	Not clinically relevant
BDF vs F	-	-	-2.69 (95% CI -3.82 to -1.55)	
Lung Function (Trough FEV_1)			Mean difference:	
FPS vs S	-	-	0.07L (95% CI 0.05 to 0.10)	MD not clinically relevant
BDF vs F	-	-	0.05L (95% CI 0.00 to 0.09)	
Transition Dyspnea Index (TDI) MCID 1 point			Mean Difference	
FPS vs S	-	-	-0.09 (95% CI -0.13 to -0.05)	MD not clinically relevant
BDF vs F	-	-	-0.07 (95% CI -0.12 to -0.01) (breathlessness score)	
Mortality	0.7%	0.8%	OR 0.92 (95% CI 0.76 to 1.11)	Not statistically significant p=0.40
Pneumonia	4% (95% CI 3.2 to -5.4)	2.7%	OR 1.55 (95% CI 1.20 to 2.01)	NNH 17 (95% CI 12 to 29) From TORCH where baseline rate 13% 156 weeks

Fluticasone + salmeterol (FPS); budesonide + formoterol (BDF); MD = mean difference; RR =Rate ratio; NNT/NNH number needed to treat/harm

New LABA/ICS combination: Fluticasone furoate plus vilanterol (Breo Ellipta)

- Fluticasone furoate plus vilaterol is a relatively new LABA/ICS and the clinical studies have not been included in the above meta-analyses.
- Based on the Common Drug Review summaries of evidence and additional clinical trial evidence there appear to be similar results for outcomes measuring lung function, quality of life or exacerbation rates compared with other LABA/ICS agents.[34–36]
- Similar to other LABA/ICS agents, an increased risk of pneumonia is a potential adverse effect. (http://ca.gsk.com/media/1219797/breo-ellipta.pdf)

LABA/ICS vs. Tiotropium[37]

- A Cochrane Review included one large, two-year trial (INSPIRE) and two smaller, shorter trials (total n=1528). The results from these trials were not pooled.
  - The authors comment that the number of withdrawals from each arm of the INSPIRE trial was large and imbalanced and outcome data were not collected for patients who withdrew, raising concerns about the reliability of the results from this study.
  - Since there were no meta-analyses of the data to include all 3 trials, these results reflect those of the INSPIRE trial. INSPIRE was a 2-year trial enrolling 1323 patients with moderate to severe COPD.
- **Results:**
  - **Mortality:** more deaths in the tiotropium group vs. fluticasone/salmeterol
    - Odds ratio (OR) 0.55 95% CI 0.33 to 0.93
    - Caution advised in the interpretation of this outcome due to the large number of withdrawals from each of the groups which was 11 times greater than the observed number of deaths in the fluticasone/salmeterol group and seven times greater than in the tiotropium group.
  - **All cause hospitalization:** There were more all-cause hospital admissions in patients on fluticasone/salmeterol than those on tiotropium.
    - OR 1.32; (95% CI 1.04 to 1.67)
  - **Exacerbations leading to hospitalization**: No statistically significant difference in hospital admissions due to exacerbations (primary outcome INSPIRE).
    - OR 1.28 (95% CI 0.94 to 1.74)
  - Exacerbations requiring treatment with oral corticosteroids were less frequent with fluticasone/salmeterol.
  - Exacerbations requiring treatment with antibiotics were more frequent with fluticasone/salmeterol.
  - Patients with ≥ 1 exacerbation or exacerbations of any type: no difference between fluticasone/salmeterol and tiotropium
  - **Pneumonia: increased rates** with fluticasone/salmeterol vs tiotropium
    - OR 2.13 (95% CI 1.33 to 3.40) ARI 4% NNH 25 (95% CI 16 to 64)
    - There is uncertainty arising from unknown outcome data for patients who withdrew.

Table 13: Cochrane Review LABA/ICS vs TIO[37]

	Event rates from Meta-analysis		Result (95% Confidence Interval)	p-Value or NNT
	LABA/ICS	LAMA tiotropium		
Number of patients experiencing ≥ 1 exacerbation	62%	59%	1.13 (95% CI 0.91 to 1.41)	Not statistically significant p= 0.28
Mean # exacerbations/pt/yr	1.28	1.32	RR 0.97 (95% CI 0.84 to 1.12)	Not statistically significant
Moderate exacerbation Requiring oral steroids Requiring antibiotics	 - -	 - -	 Requiring corticosteroids RR 0.81 (95% CI 0.67 to 0.99) Requiring antibiotics RR 1.19 (95% CI 1.02 to 1.38)	
Severe exacerbation leading to hospitalization	105/658 (16%)	86/665 (13%)	OR 1.28 (95% CI 0.94 to 1.74)	Not statistically significant p= 0.118
All cause hospitalization	215/658 (33%)	179/665 (27%)	OR 1.32 (95% CI 1.04 to1.67)	
Health Status (SGRQ) Proportion with MCID 4 points	35%	27%	MD -2.07 (95% CI -4.02 to -0.12) OR 1.29 (95% CI 1.04 to 1.60)	
Lung Function (Trough FEV_1)			At 2 years: MD -0.02L (95% CI -0.05 to 0.01)	MD not clinically relevant
Mortality (all-cause)	21/658 (3%)	38/665 (6%)	OR 0.55 (95% CI 0.33 to 0.93)	
Pneumonia	50/658 (7.6%)	24/665 (3.6%)	OR 2.13 (95% CI 1.33 to 3.40)	NNH 25 (95% CI 16 to 64)

OR = odds ratio; MD = mean difference; RR= Rate ratio

LAMA/LABA vs. LABA/ICS

FLAME Study [38]

The FLAME study is one of the first RCTs to assess the impact on exacerbation rates of two long acting bronchodilators in one inhaler to the combination of LABA/ICS. There is interest to determine if combinations of long acting bronchodilators provide an alternative to LABA/ICS in preventing exacerbations and avoiding some of the adverse effects associated with ICS, in particular pneumonia. It is unfortunate that this study did not include an arm of LAMA alone.

- **FLAME** study characteristics:
  - FLAME was a well-designed, 52-week, randomized, double-blind, double-dummy, multicentre (43 countries) noninferiority/superiority trial. It was funded by Novartis, the manufacturer of Ultibro Breezhaler®.
  - There was a 4- week run-in where everyone received tiotropium during which 32% discontinued therapy.
  - Enrolled 3362 patients with moderate to severe COPD at high risk of exacerbation (i.e., had a history of at least one exacerbation during the previous year requiring systemic glucocorticoids and/or antibiotics).

- Inclusion criteria included patients who were ≥ 40 years old with a post-bronchodilator FEV_1 25-59% and FEV_1/FVC < 70%, and were current or ex-smokers with smoking history ≥ 10 pack-years.
- The combination of the LAMA glycopyrronium (50 µg) plus LABA indacaterol (110 µg) once daily (Ultibro Breezhaler®) was compared with the LABA salmeterol (50 µg) plus the ICS, fluticasone (500 µg) twice daily (Advair®) i.e., LAMA/LABA vs LABA/ICS.
- The primary outcome was the **annual rate of all COPD exacerbations**.
- Exacerbations classified by severity were a secondary outcome in addition to quality of life, lung function and adverse effects.
- Patients with risk of adverse events from anticholinergics (e.g. BPH, urinary retention) were excluded.

➢ **Patient Characteristics:**

- Primarily male (75%)
- 75% of patients were GOLD group D (high risk for exacerbations and high symptom burden) with an average duration of COPD of 7 years. Remaining patients (24.4%) were primarily GOLD group B (heavy symptom burden but low risk of exacerbations).
- Mean age 65 years
- Current smokers 40%
- 80.6% experienced one COPD exacerbation and 19.3% experienced ≥ 2 COPD exacerbations in the previous year.
- Post-bronchodilator FEV_1 44.1%, post-bronchodilator FEV_1/FVC 41.6%
- Previous medications: ICS 56.3%, LAMA 60.6%, LABA 67.1%
- Co morbidity: Hypertension 47.9%, hyperlipidemia 21.3%, Type 2 diabetes 12.3%

➢ **RESULTS**

- **Benefits:** The LAMA/LABA, glycopyrronium/indacaterol showed noninferiority and superiority to salmeterol/fluticasone in
  - COPD exacerbation reduction;
    - annual rate 3.59 vs. 4.03; rate ratio 0.89 (95% CI 0.83 to 0.96) P = 0.003
  - Longer time to the first exacerbation
    - 71 days (95% CI 60 to 82) vs. 51 days (95% CI 46 to 57)
      HR 0.84 (95% CI 0.78 to 0.91) P<0.001
  - Moderate or severe exacerbation
    - annual rate 0.98 vs. 1.19; rate ratio 0.83 (95% CI 0.75 to 0.91) P<0.001
  - Time to first moderate or severe exacerbation
    - HR 0.78 (95% CI 0.70 to 0.86) P<0.001

- Time to the first severe exacerbation
  - HR 0.81 (95% CI 0.66 to 1.00) P = 0.046
- The mean difference in quality of life scores did not achieve the 4 point MCID: -1.3 (95% CI -2.1 to -0.4).
  - The percentage of patients achieving the 4 point difference was higher in the LAMA/LABA group.
- The difference in lung function did not reach the MCID of at least 100 ml.
- The reduction in rescue medication use per day was approximately 1 puff in the LAMA/LABA group vs 0.76 puffs in the LABA/ICS group. During the one year trial, the LAMA/LABA group had 13% of days with no rescue compared with 8% in the LABA/ICS group.
- Pneumonia was increased in the LABA/ICS group vs LAMA/LABA: 4.8% vs. 3.2% (P = 0.02).
- Rates of influenza (3.3% vs. 2.1%) and oral candidiasis (4.2% vs. 1.2%) were higher in the LABA/ICS group.
- Similar rates of withdrawals and withdrawals for adverse events were seen in both groups
  - Withdrawals LABA/ LAMA 16.6%
    - 46% of withdrawals related to an adverse event
  - Withdrawals LABA/ICS 19%
    - 45% of withdrawals related to an adverse event

Table 14: FLAME RCT LABA/ICS vs LAMA/LABA[38]

	Event Rates		Result (95% Confidence Interval)	ARR/NNT/p value (LAMA/LABA VS LABA/ICS)
	LABA/ICS N=1682	LAMA/LABA N=1680		
Exacerbations (of any severity)	4.09%	3.59%	RR 0.88 (95% CI 0.82 to 0.94)	P<0.001
Patients experiencing ≥ 1 exacerbation	82%	77%		ARR 5% NNT 20 (95% CI 13 to 44) X 1yr
Mild exacerbations (rate/yr)	2.72%	2.46%	0.91 (95% CI 0.83 to 0.99)	ARR 0.26 P=0.03
Moderate exacerbations (rate/yr)	0.98	0.81	0.83 (95% CI 0.74 to 0.92)	ARR 0.17
Severe exacerbation leading to hospitalization	0.17	0.15	0.87 (95% CI 0.69 to 1.09)	Not significant P=0.231
Health Status (SGRQ) % with MCID	43.7%	49.2%	RR 1.30	NNT 18 (95% CI 11 to 47) P<0.001
Lung Function change from baseline (Trough FEV_1)	-0.048 L	0.015 L	Mean Difference 0.062 (95% CI 0.048 to 0.077)	Not clinically relevant
Pneumonia	4.8%	3.2%		ARR 1.6% P=0.02
Influenza	3.3%	2.1%		ARR 1.2% P=0.026
Candidiasis	4.2%	1.2%		ARR 3% P<0.001

ARR = absolute risk reduction; NNT= number needed to treat; MD = Mean Difference; RR= rate ratio

LAMA/LABA vs. LABA/ICS Summary

- Glycopyrronium/indacaterol reduced exacerbations of any severity compared with fluticasone/salmeterol; however the reduction is small and of questionable clinical relevance.
  - The majority of exacerbations were rated as mild.
  - Severe exacerbations leading to hospitalizations were not significantly reduced.
  - Adverse effects including pneumonia, influenza and oral candidiasis were significantly higher in the LABA/ICS group.
  - Mortality rates and serious adverse events were not different between groups.
- The FLAME trial did not include a group of patients receiving only the LAMA. This would have been of interest since previous trials comparing LAMA/LABA to LAMA have not found significant differences in exacerbation rates and other outcomes.

Does the FLAME trial change the role of LABA/ICS therapy in COPD?

- FLAME is a **single trial** showing that LAMA/LABAs have similar benefit to LABA/ICS in reducing primarily mild exacerbations.
- LABA/ICS have many trials which have demonstrated reduction in exacerbation rates.
- The FLAME results demonstrate that LAMA/LABA is an alternative therapy to LABA/ICS for patients experiencing exacerbations. This may be especially relevant in patients with a history or risk of pneumonia **or in those who may have been prescribed a LABA/ICS without a history of exacerbations.**
- Further study of the LAMA/LABA combination in comparison with triple therapy or monotherapy with LAMA will help to determine its place in therapy.

TRIPLE THERAPY (LABA+ICS+ LAMA)[39]

The 2016 update of this Cochrane Review included six studies (N=1902). Five of the six studies used the LABA/ICS, salmeterol/fluticasone and the other used formoterol/budesonide.

- The studies compared tiotropium in addition to inhaled corticosteroid and long-acting beta$_2$-agonist combination therapy versus tiotropium alone.
- The evidence was rated as moderate-quality.
- Four of the six studies enrolled patients considered eligible for triple therapy according to the current guidelines at the time of the Review.

LABA +ICS+LAMA vs. LAMA[39]

- **Results:**
  - **Benefits:**
    - All cause hospitalization was statistically significantly reduced. (NNT 20, 95% CI 11 to 124) for 1 year.

- The mean change in quality of life score was statistically significantly improved with potential clinically important differences. (low quality evidence).
  - Percentage of participants with **improvement** in SGRQ score greater than 4 units, was reported in **one** study.
    - Tiotropium + LABA/ICS 49.5% vs. tiotropium 40.0%. P = 0.016
  - Percentage of participants with **deterioration** in SGRQ score greater than 4 units
    - Tiotropium + LABA/ICS 27.6% vs. tiotropium 29.7%.

- There was **no statistically significant difference** in pooled data for the following outcomes for LABA/ICS + LAMA vs LAMA
  - Adverse events (OR 1.16, 95% CI 0.92 to 1.47)
  - Serious adverse events (OR 0.86, 95%CI 0.57 to 1.30)
  - Pneumonia (OR 1.62, 95% CI 0.54 to 4.82)
  - Mortality (OR 1.80, 95% CI 0.55 to 5.91). This result is based on 2 studies including patients that meet GOLD 2015 criteria for triple therapy.
  - Exacerbation data were heterogeneous and not combined in a meta-analysis.
    - Data from **one** study rated as low quality reported exacerbation rates at 12-months which were not statistically significant.
      - 62.8% vs. 60.1% (48.6 to 70.4); OR 0.89 (95% CI 0.56 to 1.41)
  - Lung function; no clinically relevant difference

Table 15: Cochrane Review LAMA/LABA + ICS vs LAMA[39]

	Event rates from meta-analysis		Result (95% CI)	p-Value or NNT (95% CI)
	LAMA/LABA + ICS	LAMA		
All cause hospitalization	10.5%	15.6%	OR 0.61 (95% CI 0.40 to 0.92)	NNT 20 (95% CI 11 to 124) for 1 year
Health Status (SGRQ)	-	-	(MD) -3.46 (95% CI -5.05 to -1.87) at 6 months	Potentially clinically relevant p < 0.0001
Lung Function (Trough FEV_1)	-	-	MD 0.06, (95% CI 0.04 to 0.08)	Not clinically relevant
Mortality	1.48%	0.82%	OR 1.80 (95% CI 0.55 to 5.91)	p = 0.33
Pneumonia	0.92%	0.56%	OR 1.62 (95% CI 0.54 to 4.82)	p = 0.39

MD = mean difference; OR = odds ratio; NNT = Number needed to treat; CI= Confidence interval

LABA+ICS+LAMA vs. LABA/ICS

One study comparing triple therapy to LABA/ICS included a small sample size (N=60) and lacked power to draw conclusions.

TRIPLE THERAPY: LABA+ICS+LAMA vs. LAMA/LABA

Karner 2011[40] studied the effect of adding inhaled corticosteroids to patients receiving tiotropium and long-acting beta$_2$-agonists. Their search identified only one trial, conducted in Canada in 293 patients (Aaron 2007[41]).

- Although the study was of good methodological quality, there were high and uneven withdrawal rates between the treatment arms. This limitation and lack of statistically significant differences in the majority of outcomes contributed to the conclusion that there is **insufficient evidence** to know how much difference the addition of inhaled corticosteroids makes to people who are taking tiotropium and a long-acting beta$_2$-agonist for COPD.

Can an inhaled corticosteroid (ICS) be safely discontinued in a patient with COPD?

The addition of an ICS to bronchodilator therapy has generally been reserved for patients with severe airflow limitation (FEV_1 < 50% predicted) and/or experiencing frequent exacerbations (>2 /year).

- However, many patients with moderate COPD and not experiencing frequent exacerbations are being treated with ICS in clinical practice.
- There is increasing concern regarding the clinical benefit and safety of long term ICS use in COPD.

Several studies have assessed the withdrawal of inhaled corticosteroids in patients with COPD.

- A systematic review identified the risk of an exacerbation was not statistically different between those who stopped or remained on ICS OR 1.11 (95% CI 0.84 to 1.46) and no evidence that withdrawal of ICS results in important deterioration in patient outcomes.
  - The authors emphasize limitations of their analysis due to differences in exacerbation definitions and reporting procedures, as well as, reporting of the use of other medications.[42]

The following two studies maintained patients on bronchodilation with either LABA, LAMA or a combination of both; however, the studies differ in the severity of COPD and the method of ICS withdrawal.

- The OPTIMO study was conducted in 914 patients receiving maintenance therapy with bronchodilators and an ICS with an FEV_1 > 50% predicted and < 2 exacerbations /year.[43]
  - Excluded patients included those with a history of asthma, or if they had an exacerbation or respiratory infection in the past month.
  - Following physician assessment, 41% had the ICS discontinued while 59% continued the ICS, and both groups were observed over a 6 month period.

- **Results:** There was no difference in the deterioration of lung function or exacerbation rates between the two groups.
  - 816 patient finished the study
  - Symptom scores and FEV_1 did not change in either group in the 6 month period.
  - Patients experiencing at least 1 exacerbation: ICS 29% ; no ICS 26%, p=0.321
  - LABA-ICS therapy was changed to tiotropium (27%), LABA (44%) or a combination of tiotropium plus LABA (20%). Statistical comparison was not performed to compare outcomes between these groups.
- Due to the real life nature of this study and the relatively short duration of follow-up, there are several limitations to this study; however, it offers preliminary evidence that it may be possible to withdraw ICS in patients **at low risk of exacerbation** who continue on maintenance treatment with long acting bronchodilators.

- The WISDOM study evaluated the stepwise withdrawal of ICS in 2485 COPD patients (GOLD 3-4, FEV_1< 50% predicted) with a history of at least one exacerbation in the year prior to screening and receiving dual bronchodilation.[44]
  - Subjects received triple therapy with LABA/ICS plus LAMA (tiotropium, salmeterol and fluticasone) during a 6-week run-in period.
  - Patients were randomized to stay on triple therapy or initiate step-wise withdrawal of the ICS.
    - The stepwise reduction in fluticasone at 6 weeks intervals went from a total daily dose of 1000 μg to 500 μg, 200 μg, then 0 μg. Withdrawal was complete at 18 weeks.
  - The primary end point was time to first moderate or severe exacerbation following randomized treatment over 52 weeks.
  - **Results** (N=2027 patients completed the study)
    - First moderate or severe COPD exacerbation HR 1.06 (95% CI 0.94 to 1.19) which indicated noninferiority was met.
    - Event rate for moderate or severe exacerbations (adjusted)
      - ICS withdrawal group 0.95 per patient-year (95% CI 0.87 to 1.04)
      - ICS continued group 0.91 per patient-year (95% CI 0.83 to 0.99)
      - There was a transient increase in the number of severe exacerbations after the complete withdrawal of ICS which was not statistically significant and was not maintained.
    - FEV_1
      - Mean reduction in trough FEV_1 at week 18 and 52 (adjusted) from baseline
        - 38 ml and 43 ml greater reduction in the ICS withdrawal group than the continuation group (P<0.001) respectively.

- SGRQ: There were no clinically relevant differences between groups in health status.
- Adverse event rates were similar between groups including the **rates of pneumonia (no ICS 5.5% vs. ICS 5.8%)**

- A population based cohort study from Quebec assessed the effect of ICS discontinuation on the incidence of serious pneumonia (required hospitalization).[45]
  - A cohort of 103,386 new users of ICS were identified and the analysis included a mean follow-up of 4.9 years.
  - 14,020 patients were hospitalized for pneumonia at least once or died from pneumonia outside of hospital.
  - Rate of serious pneumonia in a matched cohort of patients who discontinued ICS was decreased 37%. (RR 0.63 95% CI 0.60 to 0.66)
    - The risk of pneumonia was more pronounced with fluticasone and less so with budesonide
    - The increased risk of pneumonia remained for 4 months after ICS discontinuation
  - Limitations of this study include the observational nature and the lack of radiographic information for the diagnosis of pneumonia.
  - The authors conclude that, "limiting the use of ICSs to the patients with COPD who are likely to benefit, such as patients with an asthma component, and weaning the others off ICSs will result in a major reduction in the risk of serious pneumonia."

GOLD 2017[31]

- The withdrawal of ICS is addressed in the GOLD 2017 update. It describes the evidence on the withdrawal of ICS on symptoms, lung function and exacerbations as equivocal. Some studies have shown an increase in exacerbation rates while others have not. A modest reduction in FEV_1, as demonstrated in the WISDOM trial, has also been shown.
- If patients receiving triple therapy with LABA/ICS and LAMA continue experiencing exacerbations, the guidelines suggest stopping the ICS as an option based on the fact that the patient shows
  - Lack of efficacy in preventing exacerbations,
  - An increased risk of potential adverse events (pneumonia) and
  - Evidence showing no harms related to withdrawal.

Therapy Tips

- In patients experiencing exacerbations, appropriate therapy may be LAMA, LAMA/LABA or LABA/ICS.
- In patients with a history and/or findings suggestive of both asthma and COPD, a LABA/ICS may be preferred.
- Escalation to triple therapy (LABA/ICS + LAMA) is dependent on persistent symptoms and further exacerbations, although evidence in this population is lacking.
- Evidence assessing the impact of withdrawal of an ICS on symptoms, lung function and exacerbations is equivocal.

Question 5: How to choose between the various new inhalers?

- Several new inhaler devices have recently been marketed including Breezhaler®, Ellipta®, Genuair® and Respimat®.
  - Older inhaler devices still available include Metered Dose Inhalers, Turbuhalers, Diskus and Handihaler.
- Factors to consider when choosing an inhaler device include: ease of set-up, requirement for hand-breath coordination or breath activation, patients' dexterity, dose counter and indication that dose has been taken.
- Choice of inhaler device should be individualized and will depend on the patient's ability and preference.[31]
- Please note that the dose of vilanterol 25 mcg + fluticasone furoate 200 mcg (Breo®) is indicated in **asthma** but not COPD.
- Inhalers differ in the number of times a day they need to be taken which could affect adherence to therapy.
- The table below provides some information on the newer inhaler devices.

Therapy Tip: According to GOLD 2017, inhaler technique and compliance with therapy should be assessed before concluding that the patient's current therapy is insufficient.[31]

Table 16: New inhaler devices[46,47]

Device	Drug (s)	Trade Name®	Drug Class	Image of Device	Characteristics of Device
Breezhaler®	Indacaterol 75 mcg	Onbrez	LABA	 30 doses	• Low inspiratory effort needed • Rattling/whirring heard if contents inhaled correctly • Multi-step set-up: may be difficult for patients with poor manual dexterity or cognitive impairment • Capsules must be placed in correct compartment
	Glycopyrronium 50mcg	Seebri	LAMA		
	Glycopyrronium 50 mcg + Indacaterol 110 mcg	Ultibro	LAMA/LABA		
Ellipta®	Umeclidinium 62.5 mcg	Incruse	LAMA	 30 doses	• Simple to use: Slide open the mouthpiece cover until a click is heard to activate dose • Requires sharp forceful inhalation to get full dose • Dose counter with large print • No way to identify if proper inspiratory effort is being achieved • Hold horizontally to prevent loss of dose
	Vilanterol 25 mcg + Fluticasone furoate 100 mcg or (200 mcg only approved for asthma)	Breo	LABA/ICS		
	Umeclidinium 62.5 mcg+ Vilanterol 25 mcg	Anoro	LAMA/LABA		
Genuair®	Aclidinium 400 mcg	Tudorza	LAMA	 60 doses	• **Simple to use** • Press and release coloured button. Do not hold down button while inhaling • Provides visual (window changes green to red) & audible click feedback when dose taken correctly • hold horizontally to prevent loss of dose
	Aclidinium 400 mcg + Formoterol 12mcg	Duaklir	LAMA/LABA		

Device	Ingredient	Trade Name®	Drug Class	Image of Device	Characteristics
Respimat®	Tiotropium 2.5 mcg	Spiriva	LAMA	 60 puffs (30 doses)	- Uses a spring to deliver soft mist - Low inspiratory flow required - Requires priming as directed for each product - Requires reasonable strength to spring-load dose - Dose counter: loading base **locks** to signal empty - Requires slow, deep breath and holding of breath
Respimat®	Ipratropium 20 mcg + Salbutamol 100 mcg	Combivent	SABA/SAMA	 120 doses	
Respimat®	Tiotropium 2.5 mcg + Olodaterol 2.5 mcg	Inspiolto	LAMA/LABA	 60 puffs (30 doses)	

LAMA = long acting muscarinic antagonist; LABA= long acting beta$_2$ agonist; ICS = inhaled corticosteroid;
SAMA= short acting muscarinic antagonist; SABA= short acting beta$_2$ agonist

Question 6: What are the adverse effects of inhaled COPD medications?

- **Anticholinergic** reported adverse effects:
  - Dry mouth (Rinse and spit following inhalation) (12 to 16%)[1]
  - Constipation
  - Aggravation of narrow angle glaucoma (especially with direct contact)
  - Urinary retention (0.73%)[1]
  - CV adverse effects
    - GOLD 2017 reports that COPD patients receiving regular treatment with ipratropium have a small increase in cardiovascular events.
    - There were initial concerns with increased risk of cardiovascular events with the tiotropium Respimat inhaler format; however, subsequent large trials have not found an increase in mortality or exacerbation rates.[31]
- A pooled analysis of 28 tiotropium Handihaler and 7 Respimat studies found lower rates of serious adverse events (RR 0.94, 95% CI 0.89 to 0.99) and similar rates of fatal adverse events (0.90, 95%CI 0.79 to 1.01) for both devices compared with placebo.[48]

- **Beta$_2$ agonist** reported adverse effects:
  - Headache
  - Tremor, leg cramps
  - Palpitations, arrhythmias, asymptomatic ventricular tachycardia
  - Changes in blood glucose and serum potassium (rare)
  - Paradoxical bronchospasm (very rare)
  - A systematic review of 20 studies analyzing the safety of LABAs in **COPD** reported:[49]
    - No evidence for LABAs to increase exacerbations or other COPD-related adverse events.
    - No increase in mortality
    - Low rates of tremors or palpitations (< 1%)
    - No increased risk of cardiac arrhythmias. The authors caution that an increased risk of arrhythmia has been shown in observational studies.
  - A recent RCT studied the effect of LABA/ICS (vilanterol/fluticasone furoate) vs. vilanterol, fluticasone furoate or placebo on mortality in **patients with a history, or at increased risk of a cardiovascular event**.[35]
    - N=16, 590 from 43 countries were enrolled; median follow-up 1.8 years
    - There was no effect on mortality for any active drug or the combination vs. placebo.
    - There was no effect on the outcome of composite cardiovascular events (cardiovascular death, myocardial infarction, stroke, unstable angina, and transient ischemic attack) for any active drug or combination vs. placebo.
    - Adverse cardiac events occurred at similar rates in the four groups: Placebo 17%; combination LABA/ICS 18%; ICS 17% and LABA 17%.
  - It should be noted that there is evidence that LABA monotherapy (i.e., without ICSs) in **asthma** may increase the risk of life-threatening exacerbations and respiratory-related death and there are warnings that LABAs should be used only in combination with an ICS in asthma.

- **Inhaled Corticosteroid** reported adverse effects:

  There are possibilities for topical and systemic effects for inhaled corticosteroids. Systemic effects are primarily related to higher daily doses.
  - Hoarse voice and oral candidiasis
    - Can be diminished by a “rinse and spit” following administration.

- **Pneumonia**
  - RCTs have demonstrated that ICSs increase the risk of pneumonia.[31]
  - The increased risk of pneumonia is reported in most but not all RCTs. For example there was no increased risk between either the LABA/ICS, fluticasone furoate/vilanterol or the ICS alone compared with placebo in the SUMMIT trial.[35]
  - A Quebec database study by Suissa evaluated the effects of different ICS on incidence of serious pneumonia (fatal or requiring hospitalization).[50]
    - The cohort included 163, 514 patients with COPD
    - Use of ICS increased the risk of serious pneumonia Rate ratio 1.69 (95% CI 1.63 to 1.75)
      - High dose increased risk to a greater extent; RR 1.86 (95% CI 1.77 to 1.94)
      - Risk was particularly elevated with high dose fluticasone RR 2.22 (95% CI 2.10 to 2.34) but not with high dose budesonide RR 1.13 (95% CI 1.02 to 1.26)
    - The limitations of observational studies must be acknowledged.
  - A Cochrane review of 43 studies of budesonide (n= 17) and fluticasone (n=26), enrolling a total of 31,397 patients, reported an increased risk of **pneumonia requiring hospital admission** versus placebo, with no significant difference between the two ICS.[51]
    - **Fluticasone**: Odds ratio (OR) 1.78, 95% CI 1.50 to 2.12) corresponding to 18 more events per 1000 treated over 18 months (high quality evidence). The increase in risk was the same when the ICS was administered with a LABA, at different doses, trial durations or baseline COPD severity.
    - **Budesonide**: the increased risk was based on shorter trials and the confidence interval is wide indicating a lack of precision (OR 1.62, 95% CI 1.00 to 2.62). This corresponded to six more events per 1000 treated over nine months; (moderate quality evidence).
    - No increased risk of mortality was associated with the increased rates of pneumonia.
  - Despite inconsistencies between trials, the GOLD 2017 guidelines report Level A evidence that regular ICS treatment increases the risk of pneumonia especially in those with severe disease.[31]
- **Bone density and Fracture risk**
  - There is controversy on the effects of ICS on bone health and risk of fracture.
    - A subset of patients from the TORCH trial assessed the effects of salmeterol/fluticasone propionate 50/500mcg, fluticasone 500 mcg and salmeterol 50mcg, all given twice daily vs. placebo on bone mineral density (BMD) and fracture risk over a three year period. N=658

- No significant differences were observed between treatment arms in mean change in BMD (adjusted) at the hip or lumbar spine.
- Fracture rates were low and not significantly different between groups.

▪ In contrast, a systematic review of 16 RCTs and 7 observational studies of ICS (fluticasone propionate, N=14 RCTs and budesonide, N= 2 RCTs), found a modest increase risk of fractures, particularly with higher doses of ICS.[52]

- Risk of fracture with ICS exposure:
  - RCTs (N=17,513 patients) OR 1.27 (95% CI 1.01 to 1.58) p=0.04
    - NNH 83 (95% CI 38 to 2107) over 3 years
  - Observational studies OR 1.21 (95% CI 1.12 to 1.32) p<0.001

- Conflicting results for fracture risk with ICS may be due to study design, differences between individual ICS and doses used, and confounding comorbidities which affect the risk of osteoporosis and fractures.

o Additional adverse effects associated with ICS but with less evidence on which to draw conclusions include:[31]

- Increased risk or poor control of diabetes.
- Cataracts
- Tuberculosis

APPENDIX 1: Outcomes in Clinical Trials

Outcome	Definition/Comment	Minimum clinically important difference (MCID)
Exacerbation	• an event in the natural course of the disease characterized by a baseline change in the patient's dyspnea, cough, and/or sputum that is beyond the normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD . [2] • Categorized as o mild - clinical symptoms present but no change in treatment or outcome is recorded o Moderate - results in a change in medication (i.e., antibiotics and systemic corticosteroids) o Severe - event leads to a hospitalization	• Not defined Definition varies between trials i.e., symptom based vs. event based There are uncertainties concerning the reporting and analysis of exacerbations.
Hospitalizations due to COPD exacerbations	• Duration and frequency of hospitalization • No standard criteria are applied in clinical practice or research studies	• Not defined
Baseline dyspnea index (BDI)	• BDI scores each of following on scale of –3 to +3 - functional impairment - magnitude of task - magnitude of the effort	• Total change of at least 1 unit
Transition dyspnea index (TDI)	• TDI Measures change in dyspnea from baseline as measured by BDI	
Use of rescue medications	• Use of short acting bronchodilators to relieve symptoms	• Not defined
6-minute walk test	• Measures exercise capacity • Distance patient can walk in 6 minutes under standard conditions	• reduction in the 6MWD of 30 m or more is associated with increased risk of death but not hospitalization due to exacerbation in patients with COPD and represents a clinically significant minimally important difference **(30)**
Quality of life		
St George's Respiratory Questionnaire (SGRQ)	• Scores each of the following on scale of 0-100 - symptoms (frequency, severity) - activity (activities that cause or are limited by dyspnea) - impacts (psychosocial function)	• 4 units
Lung Function **FEV_1**	• Used to assess lung function and reversibility to bronchodilators (measured as pre-dose (trough) or post-dose	• Regulators MCID 5% to 10% difference in FEV_1 from baseline and < 3% as not clinically important. • ATS/ERS: change in FEV_1 should be ≥ 20% in short-term trials (of weeks of duration) and ≥ 15 % in long-term trials (≥1 yr) to be confident that a clinically meaningful change has occurred. • ATS/ERS 100 to 140 ml difference. • Minimal improvement in trough FEV_1 of 100 ml (Donahue 2005)

APPENDIX 2: Definitions

Chronic obstructive pulmonary disease (COPD)
CTS 2007 definition

The Canadian Thoracic Society (CTS) defines COPD as a respiratory disorder largely caused by smoking, which is characterized by progressive, partially reversible airway obstruction, and lung hyperinflation, systemic manifestations, and increasing frequency and severity of exacerbations.[1]

Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016[2]

Chronic obstructive pulmonary disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients**."**

GOLD is a project initiated by the National Heart, Lung, and Blood Institute (NHLBI) and the World Health Organization (WHO).

Emphysema and Chronic Bronchitis according to the GOLD guidelines[2]

Emphysema, (destruction of the gas-exchanging surfaces of the lung (alveoli), is a pathological term that is often (but incorrectly) used clinically and describes only one of several structural abnormalities present in patients with COPD.

Chronic bronchitis is "the presence of cough and sputum production for at least 3 months in each of two consecutive years". However, "chronic cough and sputum production (chronic bronchitis) is an independent disease entity that may precede or follow the development of airflow limitation and may be associated with development and/or acceleration of fixed airflow limitation. Chronic bronchitis also exists in patients with normal spirometry."

Education, action plans and Case Management
"There is no consensus on the definition of education, action plans, and case management in COPD care. ATS/ We defined education as formal delivery of information on topics related to COPD with the aim of improving the knowledge and understanding of COPD. Patient education was categorized as self-management education (e.g., education aiming at patient self-management)."[2]

Exacerbation
A sustained worsening of dyspnea, cough, or sputum production leading to an increase in the use of maintenance medications and/or supplementation with additional medications.[1]
The term 'sustained' implies a change from baseline lasting 48 h or more.
In addition, exacerbations should be defined as either purulent or non-purulent because this is helpful in predicting the need for antibiotic therapy.

2015 ACCP/CTS guidelines[53] on the prevention of COPD exacerbations define exacerbation as:

> An event in the natural course of the disease characterized by a baseline change in the patient's dyspnea, cough, and/or sputum that is beyond the normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.
> Exacerbation treatment in clinical trials usually is defined by the use of antibiotics, systemic corticosteroids, or both. The severity of the exacerbation is then ranked or stratified according to the outcome:
>
> - **mild,** when the clinical symptoms are present but no change in treatment or outcome is recorded;

- **moderate,** when the event results in a change in medication such as the use of antibiotics and systemic corticosteroids;
- **severe,** when the event leads to a hospitalization.[1]

Modified Medical Research Council Questionnaire
Questionnaire to assess the severity of symptoms related to COPD.

Spirometry
A method of assessing lung function by measuring the volume (ml or L) of air that a patient can forcibly expel from the lungs after a maximal inspiration.
It is used to:

- Differentiate between obstructive airways disorders (e.g. COPD) and restrictive diseases (e.g. fibrotic lung disease).
- Determine the severity of airflow obstruction in COPD.

Full pulmonary function tests are more comprehensive than spirometry but are not required to make the diagnosis of COPD.

Forced expiratory volume in one second (FEV1)
The volume of air exhaled in the first second of forced expiration after a maximal inspiration.
Normal value is approximately 80% or higher than the predicted value for a person of the same race, sex, age, and height.[3]

Forced vital capacity (FVC)
FVC is the maximal volume of air (in litres) that can be forcibly exhaled in one breath.
Normal value is approximately 80% or higher than the predicted value for a person of the same race, sex, age and height.

FEV1 /FVC
Measure of airflow limitation expressed as percentage; a value less than 70% (adjusted for age) indicates possibility of airflow obstruction.

Network meta-analysis
The classical meta-analysis compares two treatments while network meta-analysis (or multiple treatment meta-analysis) can provide estimates of treatment efficacy of multiple treatment regimens, even when direct comparisons are unavailable by indirect comparisons http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3049418/

Pack years
The packs of cigarettes smoked per day multiplied by the number of years smoked (e.g. 1½ packs/day x 10 years = 15 pack years).

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