COPD

An Evidence Update

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

TABLE OF CONTENTS

TABLES, FIGURE, AND APPENDICES

Tables

Figures

Appendices

ABBREVIATIONS

AE	Adverse effects
AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
ARD	Absolute risk difference
CAT	COPD Assessment Test
COPD	Chronic obstructive pulmonary disease
CTS	Canadian Thoracic Society
ED	Emergency Department
FEV_1	Forced expiratory volume in one second.
FEV_1/FVC ratio	Forced expiratory volume in one second/forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICS	Inhaled corticosteroid
LABA	Long-acting beta agonist
LABA-ICS	Long-acting beta agonist + inhaled corticosteroid
LAMA	Long-acting muscarinic antagonist
LAMA-LABA	Long-acting muscarinic antagonist + long-acting beta agonist
LAMA-LABA-ICS	Long-acting muscarinic antagonist + long-acting beta agonist + inhaled corticosteroid
L	Liters
MA	Meta-analysis
MCID	Minimum clinically important difference
MD	Mean difference
mL	Milliliters
mMRC	Modified Medical Research Council
NMA	Network meta-analysis
NNH	Number needed to harm
NNT	Number needed to treat
OR	Odds ratio
PRN	As needed
RCT	Randomized controlled trial
RR	Relative risk
RSV	Respiratory syncytial virus
SABA	Short-acting beta agonist
SABD	Short-acting bronchodilator
SGRQ	St. George's Respiratory Questionnaire
TDI	Transitional Dyspnea Index
Tdap	Tetanus, diphtheria, pertussis vaccine
U	Units
QoL	Quality of life

INTRODUCTION

- The purpose of this academic detailing document is to provide an updated evidence review of long-acting inhaler medications for the treatment of stable chronic obstructive pulmonary disease (COPD). This review also provides information on the characteristics of different inhaler devices.
  - This review does not address the management of acute exacerbations of COPD (AECOPD).
  - Non-pharmacologic measures for the management of COPD such as smoking cessation and vaccinations are also not a focus of this review. The Drug Evaluation Unit has developed a Smoking Cessation Toolkit available at Home - Drug Evaluation Unit (DEU) - LibGuides at Nova Scotia Health
- COPD is a heterogenous lung condition characterized by chronic respiratory symptoms, fixed airway obstruction, and persistent inflammation that leads to progressive airflow limitation.[1] COPD often goes undiagnosed.[2]
- Patients with COPD can have exacerbations, which are an acute worsening of symptoms (over hours or days), usually triggered by infection or environmental changes.[1]
- As the severity of COPD increases, exacerbations become more frequent and severe.[2] Increasing frequency and severity of exacerbations contributes to permanent decreases in patients' quality of life and wellbeing, accelerated decline in lung function and an increased risk of hospitalization, re-hospitalization, and death.[2]
- Long-acting inhalers are used as maintenance therapy in stable COPD with the goals of:[1,2]
  - Improving lung function.
  - Reducing dyspnea and other symptoms.
  - Enhancing health status.
  - Reducing acute exacerbations.

Sources of evidence and assumptions

- This review is an update from the "COPD: What to Do with All These New Inhalers?" 2017 Academic Detailing topic.[3]
  - Most evidence reported in this document comes from meta-analyses (MAs) of RCTs published since 2017.
  - Network meta-analysis (NMAs) and relevant RCTs are also included if they study unique comparisons or outcomes and add to the body of evidence.
  - The included MAs review long-acting inhalers as a drug class including long-acting beta agonists (LABAs), long-acting muscarinic antagonists (LAMAs), and inhaled corticosteroids (ICSs). This review considers that long-acting inhalers exert a class effect.
  - Numbers needed to treat (NNT) or to harm (NNH) are included if they were reported in the original MAs publications.
- The Canadian Thoracic Society (CTS) 2023 and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2026 guidelines, along with Choosing Wisely Canada statements and review articles are also included in this review.

Classes and Devices

- While this review considers that long-acting inhalers exert a class effect, there are differences in inhaler devices, dosing characteristics, cost, patient preferences, and environmental impacts which may make one inhaler device more suitable for a patient than another.

KEY MESSAGES

- Ensure a proper diagnosis of COPD and assess severity of airflow obstruction.

- Treatment should be individualized according to:
  1. Severity of airflow obstruction
  2. Burden of symptoms and health status
  3. Risk of future exacerbations.

- 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.
  - Monotherapy with an ICS is not recommended in the treatment of COPD.

- Dual long-acting bronchodilator therapy with a LAMA-LABA may be considered:
  - In patients with persistent symptoms despite treatment with one long-acting bronchodilator.
    OR
  - In individuals with moderate to severe disease, with persistent moderate to severe symptoms, who are at a low risk for experiencing a future moderate to severe exacerbation.

- Combination therapy with a LABA-ICS is not recommended for the maintenance treatment of COPD due to higher rates of pneumonia.
  - A LABA-ICS should only be considered in COPD patients who also have a diagnosis of asthma.
  - Review patients with COPD who are using LABA-ICS to optimize treatment.

- Triple therapy with a LAMA-LABA-ICS may be considered:
  - In patients with persistent symptoms despite treatment with a combination of two long-acting bronchodilators.
    OR
  - In individuals with moderate to severe disease, with persistent moderate to severe symptoms, who are at a high risk of experiencing a future moderate to severe exacerbation.

- There are differences in inhaler devices, dosing characteristics, cost, and environmental impacts which may make one more suitable than another for a specific patient. The choice of inhaler device should be individualized and depends on both the patient's ability and preference.

- Follow-up assessment for pharmacological treatment involves evaluating the individuals continued symptom burden and health status impairment, along with their future exacerbation risk.

- If the response to treatment is not appropriate, inhaler technique and adherence to therapy should be assessed first before concluding that current therapy requires modification.

- A short-acting inhaled bronchodilator should also be used as needed to provide short-term relief for acute breathlessness.

DIAGNOSIS AND ASSESSMENT

Who should be assessed for COPD?

- Individuals presenting with airway symptoms who have risk factors should be assessed for COPD.
  - Respiratory symptoms or functional limitations include the following:[1]
    - Dyspnea (shortness of breath)
    - Chronic cough and/or sputum production
    - Frequent respiratory tract infections[1]
  - Risk factors include a history of exposure to:[1]
    - Cigarette smoke
    - Occupational or household air pollution (e.g., burning of wood/other biomass fuels)
    - Occupational organic and inorganic dusts, chemical agents, and fumes
    - Family history of COPD (e.g. alpha-1-antitrypsin deficiency)[1]

How is COPD diagnosed?

- A diagnosis of COPD relies on a combination of clinical assessment (patient history and physical exam), along with a confirmation of the presence of airflow obstruction.[1,2]

- Postbronchodilator spirometry is essential to confirm the presence of airflow obstruction. A FEV_1/FVC ratio <0.70 (or 70%) is diagnostic for COPD.[1,2]
  - The fixed FEV_1/FVC ratio may underestimate airflow obstruction in younger individuals (<50 years of age); however, this is generally noted and accounted for in spirometry reports.[1,2]

DEFINITIONS:

FEV_1/FVC Ratio
A measure of airflow limitation expressed as a percentage; a value less than 0.7 or 70% adjusted for age, sex, height, ethnicity indicates the possibility of airflow obstruction.

Forced expiratory volume in one second (FEV_1)
The volume of air exhaled in the first second of forced expiration after a maximal inspiration. The normal value is approximately 80% or higher than the predicted value (based on age, sex, height, ethnicity).

Forced vital capacity (FVC)
The maximal volume of air that can be forcibly exhaled in one breath. The normal value is approximately 80% or higher than the predicted value (based on age, sex, height, ethnicity).

- In settings where COPD is suspected but spirometry access is limited or wait times are long, Choosing Wisely Canada suggests initiating therapy while simultaneously requesting spirometry.[4]
  - Long-term maintenance therapy in stable patients with suspected COPD without post-bronchodilator spirometry is not recommended.[4] This is based on the following:
    - Observational trials have found that more than a third of diagnoses for COPD on clinical grounds alone are incorrect.[5]

- A diagnosis of COPD without objective testing can lead to unnecessary medications or missed diagnosis of other conditions (e.g. heart failure, arrhythmia, infections, other respiratory conditions, anemia).[5]
- Individuals diagnosed with COPD on clinical grounds alone are often undertreated and at increased risk of experiencing an AECOPD.[5]

➢ Individuals with a negative spirometry assessment for COPD should be re-evaluated if symptoms recur.[4]

Local Clinical Expert - Spirometry for COPD Diagnosis

➢ If a patient is suspected of having COPD:
1. Order spirometry.
   - Spirometry takes approximately 15 minutes and is the only component of the pulmonary function test that is required for a diagnosis.
2. Start bronchodilation.
   - Established therapy with bronchodilators are considered when interpreting and reporting spirometry.
3. Counsel on smoking cessation (including stopping vaping/e-cigarettes)
4. Review vaccination status:
   - Yearly influenza vaccine and COVID booster
   - Pneumococcal vaccine
   - RSV vaccine if 60 or older
   - Tdap once every 10 years
5. Review comorbidities that will need to be addressed to ensure stability (e.g. obstructive sleep apnea, gastroesophageal reflux disease).

➢ For hospital admitted patients with a diagnosis of COPD but no previous spirometry:
   - Arrange spirometry while in hospital; however, the results of spirometry can be impacted by an AECOPD.

➢ Repeating spirometry is rarely necessary once a COPD diagnosis is established.
   - It may be repeated in individuals close to having evidence of airflow obstruction but do not quite meet diagnostic criteria.

What should be assessed before determining appropriate management in stable COPD?

➢ Determining COPD management requires confirming a diagnosis of COPD along with assessing symptom burden, health status impairment, and the risk of future exacerbations.[1,2]

➢ Individuals with stable COPD can be categorized according to:[1,2]
1. Severity of airflow obstruction
2. Burden of symptoms and health status impairment
3. Risk of future exacerbations

1. Classification of Airflow Obstruction

- While the diagnosis of COPD is confirmed by a reduced post-bronchodilator FEV_1/FVC ratio <0.7, the severity of airflow obstruction in COPD is evaluated by the magnitude of reduction in the post-bronchodilator FEV_1.[1]

- Specific FEV_1 cutoffs are used to assess the severity of airflow obstruction.[1]

Table 1: Classification of Severity based on post-bronchodilator FEV_1[1]

In individuals with a FEV_1/FVC <0.7:

GOLD COPD Stage	Severity Classification	FEV_1 % Predicted
1	Mild	$FEV_1 \geq 80\%$ predicted
2	Moderate	FEV_1 <80% to ≥ 50% predicted
3	Severe	FEV_1 <50% to ≥ 30% predicted
4	Very severe	FEV_1 <30% predicted

2. Assessing Symptom and Health Status Burden

- There is a weak correlation between the severity of airflow obstruction in COPD and the symptoms experienced by the patient or the impairment of their health status.[1]

- Therefore, patients' symptoms and health status should be evaluated using validated instruments that are suitable for clinic/office use. Two examples include the modified Medical Research Council Dyspnea Scale and the COPD Assessment Test.

- The modified Medical Research Council (mMRC) Dyspnea Scale is a validated self-rating tool for categorizing disability related to dyspnea and COPD disease severity that ranges from grade 0 to 4.[6]

Table 2: Modified Medical Research Council (mMRC) Dyspnea Scale
Adapted from Mahler DA, Chest 1998; 9: 580-586

mMRC* Grades	Description of Dyspnea
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill.
2	I walk slower than people of the same age on level ground because of breathlessness, or I must stop for breath when walking at my own pace on level ground.
3	I stop for breath after walking about 100 yards (91 meters), or after walking for a few minutes on level ground.
4	I am too breathless to leave the house, or I am breathless when dressing or undressing.

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

- The COPD Assessment Test (CAT) is an 8-item unidimensional tool for measuring health status impairment.[7]
  - The score ranges from 0 to 40[7] and a CAT score ≥ 10 corresponds to moderate to severe symptom burden.[1]

Figure 1: COPD Assessment Test
Adapted from Jones PW et al. ERJ 2009; 34: 648-654

How is your COPD? For each item below, place a mark in the box that best describes your experience								
	0	1	2	3	4	5		Score
I never cough	☐	☐	☐	☐	☐	☐	I cough all the time	
I have no phlegm (mucus) in my chest at all	☐	☐	☐	☐	☐	☐	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	☐	☐	☐	☐	☐	☐	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	☐	☐	☐	☐	☐	☐	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	☐	☐	☐	☐	☐	☐	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	☐	☐	☐	☐	☐	☐	I am not confident leaving my home because of my lung condition	
I sleep soundly	☐	☐	☐	☐	☐	☐	I don't sleep soundly because of my lung condition	
I have lots of energy	☐	☐	☐	☐	☐	☐	I have no energy at all	
							Total Score	

3. Assessing Exacerbation Risk

- An AECOPD is associated with worsening symptoms over a few hours or days, including increased dyspnea along with cough and/or increased sputum.[1,2]

- Often, an AECOPD is associated with increased local and systemic inflammation caused by infection, pollution, or another insult to the airways.[1]

- A moderate exacerbation is generally defined as an acute worsening of respiratory symptoms that require treatment with antibiotics and/or systemic corticosteroids.[1,2]

- A severe exacerbation is generally defined as an acute worsening of respiratory symptoms that result in a hospital admission [or emergency department (ED) visit].[1,2]

- A patient's future exacerbation risk is based on their exacerbation history.[8]
  - Patients have a low future risk of exacerbations, if they've experienced:
    - ≤1 moderate exacerbation, but no severe exacerbation(s) in the past year.
  - Patients have a high future risk of exacerbations, if they've experienced:
    - ≥ 2 moderate exacerbations, or ≥1 severe exacerbation(s) in the past year.

THERAPY TIPS:

- Ensure a proper diagnosis of COPD and assess severity of airflow obstruction.
  - A clinical diagnosis is confirmed with postbronchodilator spirometry and a FEV_1/FVC ratio <0.70 is diagnostic for COPD.
  - Specific FEV_1 cutoffs are used to assess the severity of airflow obstruction.

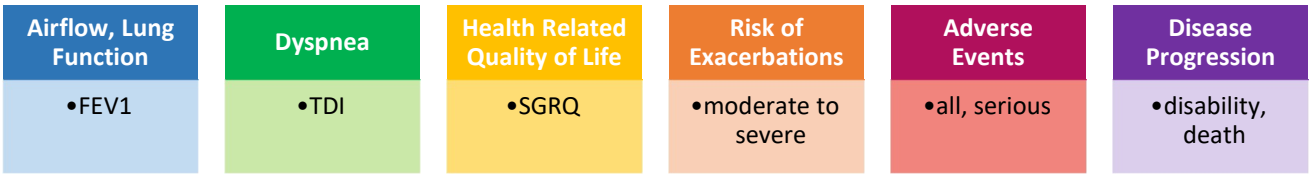
- Assess the burden of symptoms/health status impairment using validated tools that are suitable for clinic/office use. For example:
  - Modified Medical Research Council (mMRC) Dyspnea Scale
  - COPD Assessment Test (CAT)

- Assess future exacerbation risk based on the patient's history of exacerbations in the previous year.
  - *Low future risk:*
    - ≤1 moderate exacerbation (requiring antibiotics and/or systemic corticosteroids)
    - No severe exacerbation(s) (requiring hospitalization or an ED visit).
  - *High future risk*:
    - ≥ 2 moderate exacerbations, or
    - ≥1 severe exacerbation(s).

- Treatment should be individualized according to symptom severity and future exacerbation risk.

EVIDENCE REVIEW: LONG-ACTING INHALERS

Figure 2: Outcomes in MAs of Long-Acting Inhalers in COPD



- Trial outcomes reported to be most important to prescribers are changes in dyspnea and health status; along with reducing exacerbations and mortality.[2]

- Trial outcomes that are reported to be most important to patients are reducing or preventing exacerbations (including hospitalization due to an exacerbation); followed by adverse effects and symptom relief.[9]

Table 3: Outcome Measurements and Minimum Clinically Important Differences in COPD MAs of Long-acting Inhalers

Lung function (airflow obstruction)	Trough (pre-dose) FEV_1	The volume of air exhaled in the first second of forced expiration after a maximal inspiration. The normal value is approximately 80% or higher than the predicted value. Measured pre-dose (trough). Generally reported as mean differences (MDs) or the proportion of individuals who achieve the minimum clinically important difference (MCID): MCID = 100 mL (or 0.10 L) There is a weak correlation between FEV_1 and symptoms or quality of life (QoL)[1]
Dyspnea (breathlessness)	Transition Dyspnea Index (TDI)	An interview-based measurement of breathlessness related to activities of daily living. +9 = major improvement; -9 = major deterioration Generally reported as MDs or proportion of individuals who achieve the MCID. MCID = increase of 1 unit on 18-unit scale
Health Related Quality of Life	St George's Respiratory Questionnaire (SGRQ)	Scores the following on scale of 0-100. • Symptoms (frequency, severity) • Activity (activities that cause or are limited by dyspnea) • Impacts (psychosocial function) 0 = perfect health; 100 = most severe health status Generally reported as MDs or proportion of individuals who achieve the MCID. MCID = reduction of 4 or more units on 100-unit scale
Exacerbations	moderate: antibiotics +/or corticosteroids severe: hospitalization +/- ED visit	Event-based and symptom-based definition. Reported as relative risk, odds ratio, or rate ratio in MAs. No MCID

Who has been included in studies for long-acting inhalers?

- Studies evaluating the effects of long-acting inhalers have generally included patients based on lung function assessments. Using the FEV_1 as a measure of disease severity, studies have included individuals with moderate and/or severe disease (the range is most commonly 30% to <80%).

- Trials do not include people who are classed as having mild disease, are newly diagnosed, or are treatment naïve.

How long are COPD trials for long – acting inhalers?

- Studies generally range from 12 weeks to 52 weeks in duration.

What long-acting inhalers have been evaluated?

- The long-acting inhalers for COPD that are included in MAs and available in Canada are reported in Table 4.

Table 4: COPD medications available as long-acting inhalers.

Drug Name	Trade Name	Device Name	Device Class
LAMA = long-acting muscarinic antagonist			
Tiotropium	*Spiriva* *Spiriva, generics*	Respimat Handihaler	SMI DPI (capsules)
Umeclidinium	*Incruse*	Ellipta	DPI (pre-loaded)
Aclidinium	*Tudorza*	Ganuair	DPI (pre-loaded)
Glycopyrronium	*Seebri*	Breezhaler	DPI (capsules)
LABA = long-acting beta agonist			
Salmeterol	*Serevent*	Diskus	DPI (pre-loaded)
LAMA-LABA = long-acting muscarinic antagonist + long-acting beta agonist			
Aclidinium + formoterol	*Duaklir*	Genuair	DPI (pre-loaded)
Glycopyrronium + indacaterol	*Ultibro*	Breezhaler	DPI (capsules)
Tiotropium + olodaterol	*Inspiolto*	Respimat	SMI
Umeclidinium + vilanterol	*Anoro*	Ellipta	DPI (pre-loaded)
LABA-ICS = long-acting beta agonist + inhaled corticosteroid			
Formoterol + budesonide	*Symbicort*	Turbuhaler	DPI (pre-loaded)
Formoterol + fluticasone	*Advair* *Advair, generics*	HFA Diskus/Inhub	MDI DPI (pre-loaded)
Vilanterol + fluticasone	*Breo*	Ellipta	DPI (pre-loaded)
LAMA-LABA-ICS = long-acting muscarinic antagonist + long-acting beta agonist + inhaled corticosteroid			
Glycopyrronium + formoterol + budesonide	*Breztri*	Aerosphere	MDI
Umeclidinium + vilanterol + fluticasone	*Trelegy*	Ellipta	DPI (pre-loaded)

SMI = smooth mist inhaler, DPI = dry powder inhaler, MDI = metered dose inhaler

MONOTHERAPY (LAMA OR LABA)

- The study populations in MAs of LAMAs or LABAs have included predominantly symptomatic individuals with moderate to severe COPD, as defined by FEV_1.

- The exacerbation history was generally not considered a specific inclusion criterion in clinical trials, and the baseline exacerbation risk of study participants was generally not reported. However, a few trials specifically included a population with high exacerbation rates at baseline.

LAMA or LABA

- Trials comparing either a LAMA or a LABA with placebo have utilized SABAs for rescue therapy; therefore, as needed SABA therapy is considered the treatment comparator. Many trials also allowed co-therapy with ICS and other agents.

- Results tables of MAs for monotherapy are available on pages 30 - 31.

- MAs of RCTs comparing a LAMA vs. placebo have found:
  - A significant improvement in lung function. [10,11]
    - The MDs for changes in FEV_1 met the MCID. [10,11]
      - e.g. 100 mL to 125 mL.[10,11]
  - A significant improvement in dyspnea.[10,11]
    - The MDs for change in the TDI scale did not always achieve the MCID of ≥ 1 unit change.[10]
      - e.g. weighted MD 0.75 units, 95% CI 0.56 to 0.94[10]
    - However, more study participants achieved the MCID for changes in the TDI with a LAMA vs. placebo.[10]
  - A significant improvement in health related QoL.[10]
    - The MDs for change in the SGRQ did not always achieve the MCID of a reduction of 4 or more units.[10]
      - e.g. weighted MD – 2.50 units, 95% CI -3.32 to -1.69.[10]
    - However, more study participants achieved the MCID for improvements in health-related QoL with a LAMA vs. placebo.[10]
  - A significant reduction in the incidence or odds of experiencing exacerbations [10,11], including moderate to severe exacerbations with a LAMA vs. placebo[10] (moderate to severe: Rate Ratio 0.85, 95% CI 0.79 to 0.91)[10] .
  - No significant differences in the risk of experiencing an AE.[10] Withdrawals due to an AE were significantly lower with a LAMA than with placebo (7.3% LAMA vs. 8.93% placebo, P<0.00001).[11]

- MAs of RCTs comparing a LABA vs. placebo have found:
  - A significant improvement in lung function (GRADE low).[12]
    - The MDs did not achieve the MCID
      - MD 73 mL, 95% CI 48 to 98.[12]
  - Dyspnea was not reported.[12]
  - A significant improvement in health-related QoL.[12]
    - The MDs for change in SGRQ did not achieve the MCID of a reduction of 4 or more units.
      - MD – 2.32 units, 95 % CI -3.09 to -1.54; p=0.007.[12]

        - However, the odds of achieving the MCID for change in the SGRQ was higher if treated with a LABA vs. placebo (ARD 6%; OR 1.58, 95% 1.32 to 1.90)(GRADE moderate).[12]
    - A significant reduction in moderate or severe exacerbations favoring a LABA (GRADE moderate)
        - 52 fewer/1000 (95% CI 24 to 78).[12]
    - No significant differences in the odds of experiencing a serious AE.[12]

- When LAMAs and LABAs have been compared with each other, MAs have found:
    - No significant differences in lung function (GRADE low-moderate).[13,14]
    - No significant differences in dyspnea (GRADE low).[13-15]
    - No significant differences in health-related QoL (GRADE low-moderate).[13-15]
    - A significantly lower odds or risk of experiencing moderate to severe exacerbations but not severe exacerbations with a LAMA compared with a LABA[13-15] (GRADE moderate)[14].
        - Moderate to severe exacerbations: 31 fewer/1000 treated (95% CI 51 to 7 fewer/1000).[14]
    - A small significant difference favoring LAMAs over LABAs for any AEs, but not serious AEs.[13,15] One MA reported a small difference favoring LAMAs for both any AEs and serious AEs; however, there was a possibility of no difference for both outcomes (GRADE moderate).[14]
        - Any AE: 15 fewer/1000 people treated (95% CI 29 to 0 fewer)[14]
        - Serious AE: 6 fewer/1000 people treated (95% CI 13 to 0 fewer)[14]

- NMAs comparing LAMAs and LABAs through indirect comparisons have found no significant differences for changes in:
    - Health status[16]
    - Lung function[16]
    - Dyspnea[16]
    - Serious AE[16,17]

  The odds of experiencing moderate to severe exacerbations were higher with a LABA vs. a LAMA[16,17] (e.g. OR 1.17, 95% CI 1.05 to 1.29, 67 studies, N=116,131)[17].

THERAPY TIPS:

- A long-acting bronchodilator (i.e., LAMA or LABA) can be considered in patients with persistent symptoms.

- When used for symptoms only, there is no evidence to support one class of long-acting bronchodilator over another.
    - The choice of agent should depend on the patient's perception of symptom relief.[1]

COMBINATION THERAPIES (LAMA-LABA OR LABA-ICS)

- The study populations in MAs of LAMA-LABAs or LABA-ICSs have included predominantly symptomatic individuals with moderate to severe COPD, as defined by FEV_1.

- The exacerbation history was generally not considered a specific inclusion criterion in clinical trials, and the baseline exacerbation risk of study participants was generally not reported. However, a few trials specifically included a population with high exacerbation rates at baseline.

LAMA-LABA vs. Monotherapy (LAMA or LABA)

- LAMA-LABA trials have administered the medication either as a single combined device or via two separate devices; however, most trials have evaluated fixed dose combination inhaler therapies. Trials often allowed co-interventions, provided they were not part of the randomly assigned treatment.
  - For example, ICSs were used by 35% to 55% of the study populations.

- Results tables of MAs are available on pages 32 – 33.

- MAs of RCTs comparing a LAMA-LABA to a LAMA have found:
  - A significant improvement in FEV_1.
    - The MDs did not achieve the MCID of ≥ 100 mL[14,18] (GRADE moderate)[14].
    - Significantly more participants achieved the MCID for change in FEV_1.[18]
      - NNT 8, 95% CI 6 to 9.[18]
  - A significant improvement in the TDI.
    - The MDs did not achieve the MCID of ≥ 1 unit change (GRADE moderate).[14,18]
    - Significantly more participants achieved the MCID for change in the TDI.[18]
      - NNT 19, 95% CI 12 to 36[18]
  - A significant change in the SGRQ.
    - The MDs did not achieve the MCID of a reduction of at least 4 units (GRADE moderate-high).[14 18]
    - Significantly more participants achieved the MCID for change in the SGRQ.[18]
      - NNT 16, 95% CI 12 to 22[18]
  - No significant difference in the risk of any type of exacerbation (GRADE moderate).[14,44]
  - No significant differences in any AE, serious AE, or rates of pneumonia (GRADE moderate).[14]

- MAs of RCTs comparing a LAMA-LABA to a LABA have found:
  - Significant improvements in lung function (trough FEV_1).[14]
    - The MDs did not achieve the MCID.[14]
      - e.g. 0.08 L, 95% CI 0.06 to 0.09; p<0.00001 (GRADE moderate).[14]
  - No significant difference in the mean change in dyspnea.[14]
    - However, more participants achieved the MCID of ≥ 1 unit change on the TDI (GRADE moderate).[14]
      - 90 more/1000 treated (95% CI 41 to 147 more/1000)[14]
  - Significant improvements in health status, as measured using the SGRQ.[14]
    - The MDs did not achieve the MCID.[14]
    - More participants achieved the MCID of a reduction of at least 4 units on the SGRQ (GRADE moderate).[14]

- 65 more/1000 treated (95% CI 31 to 109 more/1000).[14]

- A significant reduction in the risk of moderate to severe exacerbations (GRADE moderate), but not severe exacerbations (GRADE low).[14]
  - Moderate to severe: 83 fewer/1000 treated (95% CI 104 to 61 fewer/1000)[14]
- No significant differences in AE (GRADE low).[14]

LABA-ICS vs. Monotherapy (LAMA or LABA)

- Trials often allowed co-interventions when they were not part of the randomly assigned treatment. Most trials evaluated fixed dose combination inhaler therapies.

- Results tables of MAs are available on page 34.

- MAs of RCTs comparing a LABA-ICS to a LABA have found:
  - Significant improvements in lung function (trough FEV_1).[14]
    - The MDs did not achieve the MCID (GRADE moderate).
      - MD 0.05 L, 95% CI 0.04 L to 0.05; p<0.000001[14]
  - No significant differences in dyspnea scores (GRADE low).[14]
  - No significant difference in the improvement in health-related QoL (GRADE high), including the proportion of responders who achieved the MCID (GRADE very low).[14]
  - Treatment with a LABA-ICS significantly reduced the risk of moderate to severe exacerbation rates compared with a LABA, but not severe exacerbations (GRADE moderate - high).[14]
    - Moderate to severe: 28 fewer/1000 treated (95% CI 40 to 14 fewer/1000)[14]
  - No significant differences in serious AE; however, the risk of pneumonia was higher with LABA-ICS vs. LABA (GRADE moderate - high).[14]
    - 14 more/1000 treated (95% CI 7 to 21 more/1000)[14]

- MAs of RCTs comparing a LABA-ICS to a LAMA have found:
  - No significant differences in lung function (GRADE low - moderate).[14,19]
  - No significant differences in dyspnea (GRADE low - moderate).[14,19]
  - No significant differences in health-related QoL (GRADE low – moderate).[14,19]
  - No significant differences in exacerbations risk (GRADE low).[14,19]
  - The risk of serious AEs and the risk of pneumonia were both significantly higher with LABA-ICS compared with LAMA.[14]
    - Serious AE: 28 more/1000 treated (95% CI 2 to 61 more/1000)[14]
    - Pneumonia: 16 more/1000 treated (95% CI 2 to 37 more/1000)[14]

LAMA-LABA vs. LABA-ICS

- Results tables of MAs are available on page 35.

- MAs of RCTs comparing a LAMA -LABA to a LABA-ICS have found:
  - Significant improvements in lung function (GRADE low - moderate).[14,20]
    - The MDs did not always achieve the MCID.[20]
      - e.g. MD 0.70 L, 95% CI 0.50 to 0.08; 0<0.000001.[20]
    - Significantly more participants treated with a LAMA-LABA vs. LABA-ICS achieved the MCID for improvement in lung function.[18]

- NNT = 6, 95% CI 5 to 7[18]

- No significant differences in improvement in dyspnea [14, 18] (GRADE very low)[14].
- No significant differences in improvement in health-related QoL (GRADE low - moderate).[14,20]
- No significant differences in exacerbation risk.[14,18,20] (GRADE moderate) [14,20].
- No significant differences in serious AE (GRADE moderate-high); however, the rates of pneumonia were significantly lower in individuals treated with a LAMA-LABA (GRADE high).[14,20]
  - e.g. 17 fewer/1000 treated (95% CI 21 to 12 fewer/1000)[14]

THERAPY TIPS:

- Dual therapy with a LAMA-LABA may be considered in individuals with
  - Persistent symptoms, despite treatment with one long-acting bronchodilator.
    OR
  - Moderate to severe disease (based on FEV_1), with persistent moderate to severe symptom burden, who have a low future risk of moderate to severe exacerbations.

- Combination therapy with a LABA-ICS is not recommended for the maintenance treatment of COPD due to higher rates of pneumonia.
  - LABA-ICS should only be considered in COPD patients who also have a diagnosis of asthma.
  - Review patients with COPD who are using LABA-ICS to optimize treatment.

TRIPLE THERAPY (LAMA-LABA-ICS)

- The study populations in MAs included individuals with moderate to very severe disease (based on FEV_1 cutoffs) who were symptomatic as baseline (CAT > 10 or mMRC ≥2), despite treatment for COPD
  - Most study participants had moderate to severe COPD.

- For inclusion, most trials comparing a LAMA-LABA-ICS with a LAMA-LABA have required a history of ≥ 2 moderate exacerbations or ≥ 1 severe exacerbation in the previous 12 months.
  - When trials were pooled in MAs, over 80% of participants had a history of moderate to severe exacerbations in the previous year.

- Trials comparing a LAMA-LABA-ICS with a LABA-ICS were more variable for requiring a history of exacerbations in the previous year. Nevertheless, when trials were pooled in MAs, over 80% of participants had a history of exacerbations in the previous 12 months.

- Some trials did not specifically exclude other respiratory conditions for study eligibility, including asthma. Overall, the baseline data of other respiratory health conditions was poorly reported.

- Patients were on a variety of treatments at baseline.
  - When reported, approximately 70% of patients were receiving ICS before study entry, with approximately 30% receiving ICS as part of triple therapy.
  - Individuals receiving an ICS at baseline had the ICS removed at study entry if they were randomized to a LAMA-LABA treatment arm.

- **Note:** Few trials have included symptomatic patients with moderate to severe disease (as established by FEV_1), without a history of moderate to severe exacerbations in the previous year. Treatment naive COPD patients, regardless of their exacerbation risk, have not been included in trials.

Triple therapy vs. LAMA-LABA

- Results tables of MAs are available on page 36.

- MAs of RCTs comparing a LAMA -LABA-ICS to a LAMA-LABA have found:
  - A significant improvement in lung function.
    - The MDs did not achieve the MCID (GRADE low - moderate).[14,21-23,25,26,36]
      - e.g. MD 0.04 L, 95 % CI 0.03 to 0.05, p<0.00001[14]
  - A significant improvement in TDI.
    - The MDs did not achieve the MCID (GRADE moderate).[14,22,27]
    - Significantly more participants achieved the MCID of ≥ 1 unit change on the TDI scale (GRADE moderate) [14,21]
      - 62 more/1000 treated (95% CI 24 to 104 more/1000)[14]
      - 63 more/1000 treated (95% CI 23 to 102 more/1000)[21]
  - A significant improvement in SGRQ.
    - The mean MDs did not achieve the MCID (GRADE moderate).[14,21-23,25,26,36]
    - Significantly more patients achieved the MCID of a reduction of 4 or more units on the SGRQ (GRADE moderate).[14,21,25]
      - 74 more/1000 treated (95% CI 56 to 96 more/1000)[14]

- 71 more/1000 treated (95% CI 54 to 89 more/1000)[21]

- Significant improvements in outcomes related to moderate-to-severe exacerbations.[14,21,23,25,26,36] and severe exacerbations[14,21,36].
  - The mean rate of moderate to severe exacerbations ranged from 0.59 -1.42/per year with a LAMA-LABA and 0.46-1.08/year with a LAMA-LABA-ICS (GRADE low).[21]
  - The risk of moderate to severe exacerbations was 3.1% with LAMA-LABA-ICS therapy vs. 6.4% with LAMA-LABA therapy (GRADE moderate).[14]
    - 13 fewer/1000 (95% CI 22 to 4 fewer/1000)[14]
- No significant differences in AE including serious AE[14,21-23,25,26,36] or cardiovascular AE (GRADE low)[14]. The risk of pneumonia was higher with LAMA-LABA-ICS vs. LAMA-LABA (GRADE moderate).[14,21-23,25,26,36]
  - Pneumonia: 17 more/1000 (95% CI 9 to 26 more/1000)[14]
  - Pneumonia: 13 more/1000 (95% CI 7 to 21 more/1000)[21]
- A significantly reduced risk of all-cause mortality with an ARD of approximately 0.6% (GRADE low - moderate).[14,21-24]
  - 6 fewer/1000 (95% CI 9 to 2 fewer/1000)[14,21]

Triple therapy vs. LABA-ICS

- Results tables of MAs are available on page 37.

- MAs of RCTs comparing a LAMA-LABA-ICS to a LABA-ICS have found:
  - Significantly improved lung function.
    - MDs achieved the MCID of ≥ 100 mL (GRADE moderate - high).[14,23,26,28,36]
  - A significant improvement in TDI.
    - The MDs did not achieve the MCID (GRADE moderate).[14,28]
    - Significantly more participants achieved the MCID of ≥ 1 unit change on the TDI (GRADE moderate).[14]
      - 67 more/1000 treated (95% CI 35 to 100 more/1000).[14]
  - A significant improvement in SGRQ.
    - The MDs did not achieve the MCID (GRADE high).[14,23,25,26,28,36]
    - Significantly more patients achieved the MCID of a reduction of 4 or more units on the SGRQ (GRADE moderate).[14,36]
      - 57 more/1000 (95% 29 to 89 more/1000).[14]
  - A significantly reduced risk of moderate to severe exacerbations but not severe exacerbations (GRADE moderate – high).[14,23,25,26,28,36]
    - Moderate to severe exacerbations
      - NNT 23; 95% CI 14 to 94[28]
      - 14 fewer/1000 treated (95% CI 21 to 6 fewer).[14]
  - No significant differences in the risk of adverse AE [14,22,23,25-27,36], serious AE[14,23,25,26,36], cardiovascular AE[14,23,25,26,34,36], or pneumonia[14,23,25,26,34,36](GRADE moderate). One MA evaluated the impact of triple therapy compared to LABA-ICS on MACE and reported that triple therapy was associated with a small significantly greater risk of MACE compared to therapy with LABA-ICS.[37]
  - No significant difference in the risk of all-cause mortality between LAMA-LABA-ICS and LABA-ICS[14,23,26,36] (GRADE moderate)[14] .

THERAPY TIPS:

- Triple therapy with LAMA-LABA-ICS may be considered in individuals with:
  - Persistent symptoms despite treatment with dual therapy with a LAMA-LABA.
    OR
  - Moderate to severe disease (based on FEV_1), with persistent moderate to severe symptoms, who are at a high future risk of experiencing a moderate to severe exacerbation.

ADDITIONAL EVIDENCE CONSIDERATIONS

Are there differences in efficacy and safety between long-acting inhalers in the same class?

- There are limited direct comparison trials of long-acting inhalers from the same class.

- Several NMAs have indirectly compared long-acting inhalers from the same class.[29-36]
  - Several NMAs report no significant differences.[29,30,31,34]
  - A few NMAs report small differences for some outcomes, but not all. Where differences have been found, they generally do not meet clinically important differences.[28,33,35]

- Bottom line: There is insufficient evidence to suggest any differences in the efficacy or safety of long-acting inhalers within the same class.

Does RCT evidence support the use of eosinophils when choosing therapy?

- Several guidelines report that blood eosinophil levels may be used to predict a response to therapy containing ICS.[1,2]

- Randomized controlled trial evidence evaluating the impact of blood eosinophil levels and the future exacerbation risk or response to long-acting inhaled therapy is limited to subgroup analyses.

- A 2023 Cochrane undertook a subgroup analysis of 4 RCTs that stratified study populations by blood eosinophil levels (n=15,397).[21]
  - The rate of reduction in moderate to severe exacerbations was greater when triple therapy was compared to dual LAMA-LABA in individuals with higher blood eosinophils (RR 0.67, 95% CI 0.60 to 0.75) versus comparisons with those with lower eosinophils (RR 0.87, 95% CI 0.81 to 0.93) (test for subgroup analysis $P<0.01$; I^2 80%- 94%).[21]
    - High blood eosinophil cut-offs were established as ≥ 150 cells/µL in three studies and ≥200 cells/µL in one study.[21]
  - It is important to note that these subgroup analyses are considered observational and should be interpreted with caution.

- Bottom line: Further study is required to define if blood eosinophil levels are a useful biomarker for predicting response to therapy with ICS.

RECENT COPD GUIDELINES

- The Canadian Thoracic Society (CTS) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines both provide recommendations for the use of long-acting inhalers in the treatment of stable COPD. Guideline recommendations for initial treatment and follow-up are outlined below.

Guideline Recommendations for Initial Treatment in Stable COPD

- The choice of initial pharmacotherapy is based on an appropriate diagnosis for COPD, the individual's symptom burden and health status impairment, along with their risk of experiencing a future AECOPD.

Table 5: CTS 2023 Recommendations for Initial Treatment of Stable COPD[2]

Patient Presentation	Assessment	Initial Treatment	Strength of Recommendation
Low risk of AECOPD **Low** symptom burden/health status impairment	FEV_1 ≥ 80% CAT < 10, mMRC 1 0 to 1 moderate exacerbation* in previous year	LAMA or LABA (+ SABD PRN)	Strong Moderate - high certainty evidence
Low risk of AECOPD **Moderate to severe** symptom burden/health status impairment	FEV_1 < 80% CAT ≥10, mMRC ≥2 0 to 1 moderate exacerbation* in previous year	LAMA – LABA (+ SABD PRN) ‡A LAMA-LABA is preferred over LABA-ICS except if concomitant asthma	Strong Moderate - high certainty evidence
High risk of AECOPD **Moderate to severe** symptom burden/health status impairment	FEV_1 < 80% CAT≥10, mMRC ≥2 ≥ 2 moderate exacerbations* or ≥ 1 severe exacerbation leading to hospitalization in previous year	LAMA-LABA-ICS (+ SABD PRN)	Strong Low – moderate certainty evidence

* Moderate exacerbation = event with prescribed antibiotics ± oral corticosteroid; AECOPD = acute exacerbation of COPD; FEV_1 = forced expiratory volume in 1 minute; CAT = COPD Assessment Test; mMRC = modified Medical Research Council Dyspnea Scale; LAMA = long-acting muscarinic antagonist; LABA=long-acting beta agonist; ICS = inhaled corticosteroids; SABD = short-acting bronchodilator; PRN = as needed

Table 6: GOLD 2026 Recommendations for Initial Treatment of COPD[1]

Patient Presentation	Assessment	Initial Treatment	Level of Evidence‡
Low risk of AECOPD **Low** symptom burden/health status impairment	FEV_1/FVC <0.7, FEV_1 GOLD grade 1-4¥ CAT < 10, mMRC 1 0 to 1 moderate exacerbation* in previous year	LAMA or LABA (+ SABD PRN)	A
Low risk of AECOPD **Moderate to severe** symptom burden/health status impairment	FEV_1/FVC <0.7, FEV_1 GOLD grade 1-4¥ CAT≥10, mMRC ≥ 2 0 to 1 moderate exacerbation* in previous year	LAMA – LABA (+ SABD PRN)	A
Risk of AECOPD¶ **Moderate to severe** symptom burden/health status impairment	FEV_1/FVC <0.7, FEV_1 GOLD grade 1-4¥ CAT ≥ 10, mMRC ≥ 2 ≥ 1 moderate to severe exacerbation leading to hospitalization in previous year¶	LAMA – LABA (+ SABD PRN) Consider LAMA-LABA-ICS if eosinophils ≥ 300 cells/µL or history of concomitant asthma	A B A

¥ = GOLD grade 1 FEV_1 ≥ 80%, GOLD grade 2 FEV_1 50-79%, GOLD grade 3 FEV_1 30-49%, GOLD grade 4 FEV_1<30%; ‡Level of evidence A = high quality evidence without any significant limitation or bias, ‡Level of evidence B = RCTs with important limitations; ¶ Risk of AECOPD = one or more moderate or severe exacerbation in the previous year; AECOPD = acute exacerbation of COPD; FEV_1 = forced expiratory volume in 1 minute; moderate exacerbation = event with prescribed antibiotics ± oral corticosteroids; severe exacerbation = requiring hospitalization or ED visit; CAT = COPD Assessment Test; mMRC = modified Medical Research Council Dyspnea Scale; LAMA = long-acting muscarinic antagonist; LABA = long-acting beta agonist; ICS = Inhaled corticosteroids; SABD = short-acting bronchodilator; PRN = as needed

Guideline Recommendations for Follow-up in Stable COPD

- **Canadian Thoracic Society:**[2]
  - The CTS recommend step-up to a LAMA-LABA-ICS from a dual LAMA-LABA in patients with moderate to severe COPD (based on FEV_1) who are at low risk for future exacerbations, but continue to have moderate to high symptom burden/health status impairment (Strong recommendation; Moderate certainty evidence).
  - CTS do not recommend stepping down from triple therapy to a dual LAMA-LABA in individuals with stable COPD at low risk of future exacerbations, who have a moderate to high symptom burden and/or health status impairment (Weak recommendation; Low certainty evidence).[2] Further information is available in Appendix II.

- **Global Initiative for Chronic Obstructive Lung Disease:**[1]
  - Before concluding that current therapy requires modification, GOLD specifically recommends assessing inhaler technique AND adherence to therapy.
  - In treated patients if there is persistent dyspnea or ≥ 1 moderate or severe exacerbations:
    - Step-up to LAMA-LABA therapy is recommended in patients treated with either a LAMA or a LABA.
    - Step up to a LAMA-LABA-ICS is recommended in patients treated with a LAMA-LABA (provided eosinophils levels are ≥ 100 cells/microliter).
  - GOLD does not support LABA-ICS use in COPD; therefore, they recommend assessing prior exacerbation history for patients on a LABA-ICS and note if there has been a response to the ICS treatment. If there is no relevant exacerbation history, consider changing to a LAMA-LABA.[1] Further information is available in Appendix II.

- **Note**: These guidelines do not provide directions on when patients should be reassessed**.**

Local Clinical Expert – Reasons to Consider Referral to a Respirologist

- Rapid worsening of symptoms in a short time (COPD is a slow worsening over years, punctuated by worsening of symptoms if patient suffers an exacerbation).
- Frequent and/or severe exacerbations.
- Consideration of pulmonary rehabilitation (access may differ across the province).
- Consideration of an alternative diagnosis.

- **GOLD Recommendation – Advanced Care Planning in COPD:**[1]
  - Advance care planning and palliative care are both important components of care of patients with advanced COPD. Advance care planning can reduce anxiety for patients and their families and ensure that care is consistent with their wishes. Early discussion is important along with a phased introduction of supportive care.[1]

CONSIDERATIONS WHEN CHOOSING AN INHALER DEVICE

- The selection of an inhaler device should be a shared provider-patient decision informed by: [39]
  - Patient inhaler technique
  - Patient preference
  - Cost/coverage
  - Clinical course of the disease, and
  - Environmental impact of otherwise equivalent inhaler options.[39]

- There is growing acknowledgment that inhaler devices have a notable impact on the carbon emissions generated by the health care sector.[39]
  - Pressurized metered dose-inhalers (MDIs) use hydrofluorocarbon (HFC) propellants to deliver medication, and HFCs act as potent greenhouse gases.[4,39-41]
    - It is estimated that 100 puffs of an average MDI can have the same carbon footprint as driving up to 170 km in a gas car.[41]
  - Breath-actuated inhalers such as dry-powder inhalers (DPIs) and soft mist inhalers (SMIs) do not use HFCs.
    - The carbon footprint of DPIs is approximately 10 times less than MDIs, based on both the use of the device and its disposal.[41]
  - Choosing Wisely Canada recommends the use of a DPI or a SMI rather than an MDI if the desired medication is available in this inhaler format.[4]
  - It is important to note; however, patient preference and adequate inhaler technique always need to be considered before choosing any inhaler device.[4]

- Primary care providers can help reduce greenhouse gas emissions associated with inhalers by: [40]
  - Limiting unnecessary prescribing.
  - Ensuring appropriate disease management.
  - Considering if a sustainable inhaler is appropriate.
  - Optimizing dosing technique to reduce emissions and waste.
  - Disposing of inhalers appropriately.[40]

- Working with patients to ensure they are using the right inhaler medication in the correct way should produce both better health outcomes and environmental benefits.[40]

Does my patient have good disease control?

- A diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough, and/or sputum production, with an appropriate history of exposure to harmful lung irritants.[1,2] However, not all patients with these symptoms have COPD and spirometry is required to make a definitive diagnosis.[4]

- An absence of confirmation of a diagnosis of COPD can result in unnecessary treatment, potentially exposing patients to side-effects, increased cost of medications, and delays in establishing an appropriate diagnosis.[4]

- Optimizing controller inhaler therapy should reduce the use of SABD reliever inhalers which are a common form of MDI use. [39,40]

- Optimizing patient compliance can help to ensure good disease control. Patient compliance can be improved when the same type of inhaler device is used, and when fixed dose combinations in one inhaler are used rather than non-fixed dose inhaler combinations.[1,39,43]

Local Clinical Expert Suggestion:

Using a long-acting inhaler medication with less frequent dosing will likely improve adherence (e.g. once daily vs. twice daily administration).

How should I assess my patients' ability to use an inhaler?

- Several patient-related factors determine the choice of inhaler including disease severity, comorbidities, level of coordination, manual dexterity, and cognitive function.[42]
  - MDIs require sufficient hand strength to actuate the inhaler.[1]
  - Breath-actuated inhalers (e.g. DPI or SMI) require a degree of strength and dexterity that can vary between products.[1]

- **Questions to consider when assessing the delivery mechanism:**[42]

1. *Is my patient able to take a deep, quick voluntary inhalation?*
   - If a patient is unable to perform this action, a DPI is not considered suitable.[42]
2. *Can my patient obtain sufficient inspiratory flow?*
   - All devices require a minimal inhalation flow to deliver the drug successfully. For MDIs this is > 10 L/min and for DPIs the optimal flow varies between devices, ranging from 20–60 L/min.[42]
   - Currently, there is no standardized way to measure the inspiratory flow in clinical practice but rather requires a clinical assessment by the health care provider.[42]
   - A DPI can be considered when the inspiratory flow is sufficient. If not sufficient, an MDI or SMI should be considered.[42]
   - If an MDI is required, using a spacer device can improve drug delivery and potentially reduce the amount of drug needed.[41]
3. *Does my patient have sufficient hand lung co-ordination?*
   - Hand – lung coordination is assessed by the judgement of the health care provider.[42]
   - If the patient does not have the ability to activate the device while slowly inhaling over 3–5 seconds, combine the MDI with a spacer.[42]
   - Gripping tools are also available to assist individuals with weaker hands to press the cannister in the MDI.[42]

Can I help optimize inhaler technique?

- Approximately 2/3 of patients using inhalers make at least one error in using their device.[1]
  - Errors often relate to problems with the inspiratory flow, the length of the inhalation, co-ordination of the device, preparing the dose, and breath holding following dose inhalation.[1]

- Poor inhaler technique and errors using devices are more common with advancing age, mainly due to confounders such cognitive impairment or reduced manual dexterity.[1]

- Physical training by either pharmacists, physicians, or nurses, as well as the use of video or web-based education have all been shown to be effective for inhaler training in the short term.[1] Device packaging is insufficient to provide proper education of patients regarding inhaler use.[1]
    - Inhaler instruction videos:
        - How to use your inhaler | Canadian Lung Association
        - Inhaler Resources | Lung Saskatchewan

- Patient education appears to wane over time, so it is important to check regularly (ideally, at each visit) to verify that patients continue to use their device correctly.[1]
    - Using a teach back approach works well to ensure the patient understands their inhaler technique (i.e. patients being asked to show how the device is used).
    - The use of placebo devices or encouraging the patient to bring their own device to clinic are both useful when assessing inhaler technique.[1]

Should I consider changing inhaler devices?

- Many patients prefer to use less carbon-intensive treatment options if available and appropriate.[39,41]

- Shared decision-making on switching an inhaler device can lead to improved medication adherence and health outcomes for many patients.[41]
    - For patients who wish to switch inhaler devices, it is important that patients get training on the new device, ensuring that they know how to use it properly.[1]

- It is important to note, some patients prefer MDIs, and device changes without patient agreement can reduce confidence in medications.[39,41] Additionally, multiple changes to drug therapy is a strong predictor of non-adherence which can lead to a loss of disease control.[39]

What can I recommend for inhaler disposal?

- Many community pharmacies accept inhaler returns to facilitate either recycling and/or incineration, both of which result in lower global warming potential byproducts.[39,41]

- Patients should be educated to return their inhalers to community pharmacies for proper disposal.[39,41]

Table 7: Considerations when choosing an inhaler device[39-43]

Device	How it works….	Good if patient….	Things to think about….
Dry Powder Inhaler (DPI)	Breathe in quick and deep through the mouthpiece; the medicine is in dry powder form.	Can breathe in quickly and strongly.	✓ • No propellant • No need to press and breathe at the same time • Small and easy to carry ⚠ • Needs a strong, quick breath • Some types may be difficult to load with weak or stiff hands
Metered Dose Inhaler (MDI)	Press the top of the cannister and breathe in slow and steady, the spray is made by a gas propellant.	Can time their slow steady breath in at the same time as pressing the cannister on the device.	✓ • Works best with a spacer • Good for people with low inspiration flow ⚠ • Harder with weak or stiff hands • Needs good timing to work unless used with a spacer • Contains propellant
Soft Mist Inhaler (SMI)	Press and breathe in slow and steady, it makes a soft cloud using a spring, not a gas.	Can't take a fast and deep breath.	✓ • Fine mist is gentle and easy to breathe in • Less effort needed, good for people with low inspiration flow • No propellant ⚠ • Can be harder to set up or load with weak or stiff hands
Spacer (with MDI)	A chamber that attaches to the MDI making it easier to breathe and spray in.	Has trouble taking in one slow breath or co-ordinating the breath with pressing the cannister.	✓ • Makes MDI easier to use • More medicine gets to lungs, less stuck in mouth ⚠ • Some spacers can be bulky to carry • Needs regular cleaning
Inhaler Gripping Aid (with MDI)	A tool to squeeze the MDI if the patients' hands can't press the cannister.	Has weaker hands.	✓ • Makes pressing the MDI easier • Helpful for weak hands ⚠ • Need to time breath with spray, unless used with a spacer.

- Further information on inhaled medicated devices is available as handouts on the Dalhousie University Academic Detailing webpage [Academic Detailing Service Resources - Continuing Professional Development and Medical Education - Dalhousie University](#).

RESOURCES/TOOLS

Guidelines
Canadian and international guidelines for COPD

- Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease: 2026 GOLD Report and Pocket Guide - Global Initiative for Chronic Obstructive Lung Disease - GOLD.
- Canadian Thoracic Society COPD Guidelines: 2023-CTS-COPD-Pharmacotherapy-Guideline-1.pdf

Inhaler Device Training
Video instructions

- Canadian Lung Association (several devices): How to use your inhaler | Canadian Lung Association
- Lung Sask (inhaler resources): https://www.lungsask.ca/education/programs-support/inhaler-resources

Smoking Cessation
Smoking cessation supports

- Smoking Cessation Toolkit: Home - Drug Evaluation Unit (DEU) - LibGuides at Nova Scotia Health
- Tobacco Free Nova Scotia: Home - Tobacco Free NS
- NSH Stopping Tobacco Use: Stopping Tobacco Use - HealthyNS - LibGuides at Nova Scotia Health

COPD Action Plans
Written plans can contain guidance for the early recognition of exacerbation symptoms and when to seek care or initiate medications.

- Canadian Thoracic Society: 5491_THOR_COPDActionPlanUpdate_2019_Editable_Eng_v2.pdf

Advance Care Planning and Palliative Care
Advance care planning and palliative care can reduce anxiety for patients and their families and are important components for the care of patients with advanced COPD.

- Advance Care Planning: Making Your Personal and Medical Wishes Known | Nova Scotia Health
- Nova Scotia Hospice Palliative Care Association
- Canadian Virtual Hospice
- Advance Care Planning Canada: A CHPCA Initiative

The INSPIRED COPD Outreach Program
Outreach program offers support to people in the later stages of COPD

- COPD - The INSPIRED COPD Outreach Program and COPD Care and Education Nova Scotia | Nova Scotia Health

Pulmonary Rehabilitation
Pulmonary rehabilitation includes exercise training and disease specific education. Pulmonary rehabilitation should be encouraged for patients with high symptom burden and risk of exacerbation.

- Halifax Pulmonary Rehabilitation Program - Referral Form | Nova Scotia Health

Nova Scotia Provincial Pharmacare Programs
Request Form for coverage of COPD

- COPD-Therapy-Form.pdf

Patient Information
COPD Canada Patient Education- Living with COPD

- Patient Education

Living Well With COPD

- Living well with a Chronic Obstructive Pulmonary Disease - COPD

RESULTS TABLES OF META-ANALYSES

MONOTHERAPY (LAMA OR LABA)

Table 8: LAMA vs. placebo (prn SABA)		
Lung function (Trough FEV_1) **MCID = increase ≥ 100 mL**	**Improved trough FEV_1:**	
	MDs between 100 mL and 125 mL.[10,11]	
Dyspnea (TDI) **MCID = increase ≥ 1 unit**	**Change from baseline in TDI score:**	
	WMD 0.75 U (95% CI 0.56 to 0.94)	9 trials, I^2=0%[10]
	MD 1.00 U (95% CI 0.83 to 1.17), p<0.00001	9 trials, N=5,059, I^2=0%[11]
	Proportion achieve the MCID for change in TDI:	
	Higher proportion reported in MA RR 1.29; 95% CI 1.23 to 1.35	13 trials, I^2=0%[10]
Health related quality of life (SGRQ) **MCID = reduction ≥ 4 units**	**Quality of life on SGRQ (MD):**	
	WMD – 2.50 U (95% CI -3.32 to -1.69)	9 trials, I^2=39%[10]
	MD -3.61 U (95% CI -4.27 to -2.95), P<0.0001	11 trials, N=5756, I^2=0%[11]
	Proportion achieve the MCID for change in SGRQ:	
	Higher proportion reported in MA RR 1.23 (95% CI 1.19 to 1.27)	11 trials, N=5756, I^2=0%[10]
Exacerbations	**Patients with one or more moderate to severe exacerbations:**	
	Rate Ratio: 0.85 (95% CI 0.79 to 0.91)	19 trials, I^2=69.9%[10]
	All exacerbations:	
	42% LAMA vs. 47.3% placebo OR 0.75 (95% CI 0.66 to 0.85)	19 trials, I^2=69.9% 16 RCTs, N=15,825, I^2=54%[11]
Adverse effects	**All adverse effects**	
	RR 1.01 (95% CI 1.00 to 1.02);	32 trials, I^2=15.2%[10]
	Withdrawal due to AE:	
	7.3% LAMA vs. 8.93% placebo RD -0.02 (95% CI -0.03 to -0.01), p=0.002	29 trials, N=20,929, I^2=66%[11]

SABA = short-acting beta agonist; mL = milliliter; MD = mean difference; WMD = weighted mean difference; L = liter; U = units; RR = relative risk; LAMA = long-acting muscarinic antagonist; OR = odds ratio; SGRQ = St. Georges Respiratory Questionnaire; TDI = transitional Dyspnea Index; RCT = randomized controlled trial; MCID = minimum clinically important difference; FEV_1 = forced expiratory volume in 1 second; RD = risk difference

Table 9: LABA vs. placebo (prn SABA)		
Lung function (Trough FEV_1) **MCID = increase ≥ 100 mL**	**Improved trough FEV_1:**	
	MD 73 mL (95% CI 48 to 98)	13 RCTs, N=6,125, I^2=71%, GRADE low[12]
Dyspnea (TDI) **MCID = increase ≥ 1 unit**	**Change from baseline in TDI score:**	
	Not reported	
Health related quality of life (SGRQ) **MCID = reduction ≥ 4 units**	**Change from baseline SGRQ:**	
	MD -2.32 U (95% CI -3.09 to -1.54) P= 0.007	17 RCTs, N=11,397, I^2=50%, GRADE moderate[12]
	Proportion achieve MCID for change in SGRQ:	
	39% vs. 33% OR 1.58 (95% 1.32 to 1.90)	17 RCTs, N=11,397, I^2=50%, GRADE moderate[12]
Exacerbations	**Moderate exacerbations:**	
	OR 0.73 (95% CI 0.61 to 0.87) 52 fewer/1000 (95% CI 24 to 78 fewer/1000)	7 RCTs, N=2,859, I^2=8%, GRADE moderate[12]
	Severe exacerbations:	
	OR 0.73 (95% CI 0.56 to 0.95) 18 fewer/1000 (95% CI 3 to 31 fewer/1000)	7 RCTs, N=2,859, I^2=20%, GRADE moderate[12]
Adverse effects	**Serious adverse event:**	
	OR 0.97 (95% CI 0.83 to 1.14)	20 RCTs, N=12,446, I^2=13%[12]

SABA = short-acting beta agonist; mL = milliliter; U = units; MD = mean difference; moderate exacerbations = requiring additional medications such as oral steroids or antibiotics; severe exacerbations = requiring hospitalization or ED visit; serious adverse event = one or more non-fatal serious adverse events; OR = odds ratio; LABA = long-acting beta agonist; SGRQ = St. Georges Respiratory Questionnaire; TDI = transitional Dyspnea Index; MCID = minimum clinically important difference; FEV_1=forced expiratory volume in 1 second

Table 10: LAMA vs. LABA		
Lung function (Trough FEV_1) **MCID = increase ≥ 100 mL**	**Improved trough FEV_1:**	
	No differences (GRADE low-moderate)[13,14]	
Dyspnea (TDI) **MCID = increase ≥ 1 unit**	**Change from baseline in TDI score:**	
	No differences (GRADE low)[13-15]	
Health related quality of life (SGRQ) **MCID = reduction ≥ 4 units**	**Change from baseline on SGRQ:**	
	No differences (GRADE low-moderate)[13-15]	
Exacerbations	**Patients with one or more exacerbation:**	
	29% LAMA vs. 33% LABA OR: 0.84 (95% CI 0.74 to 0.90) p = 0.004	14 trials, N= 21,962, I^2=61%[13]
	32% LAMA vs. 36% LABA OR 0.85 (95% CI 0.74 to 0.98)	12 RCTs, N= 19,821, I^2=71%[15]
	Risk of experiencing an exacerbation:	
	30.2% LAMA vs. 33.9% LABA RR 0.91 (95% CI 0.85 to 0.91) 31 fewer/1000 (95% CI 51 to 7 fewer/1000)	15 RCTs, N=13,124, I^2 >50%, GRADE moderate[14]
	Risk of Severe exacerbation:	
	6.2% LAMA vs. 8.9% LABA RR 0.81 (95% CI 0.62–1.01)	6 RCTs, N=11,943, I^2=51%, GRADE low[14]
Adverse effects	**Any adverse effect:**	
	OR 0.92 (95% CI 0.86–0.98), p = 0.007	15 RCTs, N= 22,212, I^2 =3%[13]
	OR 0.92 (95% CI 0.86 to 0.98), p = 0.02	15 RCTs, N=24,600, I^2 = 26%[15]
	48.9% LAMA vs. 49.1% LABA RR 0.97 (95% CI 0.94 to 1.00) 15 fewer/1000 (95% CI 29 fewer to 0/1000)	18 trials, N= 26,821, I^2=26%, GRADE moderate[14]
	Serious adverse effect:	
	OR 0.98 (95% CI 0.84 to 1.14)	14 trials, N= 19,235, I^2=26%[13]
	OR 0.93 (0.86 to 1.01), p = 0.08	17 trials, N=12,388, I^2 = 0%[15]
	10.5% LAMA vs. 10.8% LABA RR 0.94 (95% CI 0.88 to 1.00) 6 fewer/1000 (95% CI 13 fewer to 0/1000)	18 trials, N= 27,442, I^2=0%, GRADE moderate[14]

LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonist; FEV_1 = forced expiratory volume in 1 minute; MCID = minimal clinically important difference; mL = milliliter; TDI = Transitional Dyspnea Index; SGRQ = St. Georges Respiratory Questionnaire; moderate exacerbations = requiring additional medications such as oral steroids or antibiotics; Severe exacerbation = requiring hospitalization or ED visit; serious adverse event = one or more non-fatal serious adverse events; OR = odds ratio

COMBINATION THERAPIES (LAMA-LABA or LABA-ICS)

Table 11: LAMA-LABA vs. LAMA		
Lung function (Trough FEV_1) MCID = increase ≥ 100 mL (or 0.10 L)	**Change in FEV_1 (6 months):**	
	MD 0.07 L (95% CI 0.05 to 0.09), p<0.0001	12 RCTs, N=10,136, I^2=91%[18]
	MD 0.06 L (95% CI 0.04 to 0.07), p=0.0003	15 RCTs, N=13,690, I^2=81%, GRADE moderate[14]
	Change in FEV_1 (12 months):	
	MD 0.07 L (95% CI 0.05 to 0.10), p<0.0001	4 RCTs, N= 4,503, I^2=63%[18]
	MD 0.06 L (95% CI 0.04 to 0.08), 0=0.002	6 RCTs, N= 8,072, I^2=73%, GRADE moderate [14]
	Proportion achieve the MCID for change in FEV_1:	
	58% vs. 44% RR 1.33 (95% CI 1.20 to 1.46) NNT 8 (95% CI 6 to 9)	4 RCTs, N=4,005, I^2=55%[18]
Dyspnea (TDI) MCID = increase ≥ 1 unit	**Change in TDI (6 months):**	
	MD 0.29 U (95% CI 0.12 to 0.56), p<0.0006	5 RCTs, N=5,717, I^2=0%[18]
	MD 0.35 U (95% CI 0.23 to 0.48), p<0.00001	9 RCTs, N=8,320, I^2=0%, GRADE moderate [14]
	Change in TDI (12 months):	
	MD 0.26 U (95% CI 0.13 to 0.40), 0=0.0001	5 RCTs, N= 13,137, I^2=14%, GRADE moderate[14]
	Proportion achieve the MCID for change in TDI:	
	61% vs. 56% RR 1.12 (95% CI 1.06 to 1.18) NNT 19 (95% CI 12 to 36)	4 RCTs, N=4,005, I^2=55%[18]
	50.7% vs. 41.8% RR 1.21 (95% CI 1.10 to 1.34) 88 more/1000 (95% CI 42 to 142 more/1000)	2 RCTs, N=1757m I^2=0%, GRADE moderate [14]
Health related quality of life (SGRQ) MCID = reduction ≥ 4 units	**Change in SGRQ (6 months):**	
	MD -1.34 U (95% CI -1.94 to -0.75), p<0.001	6 RCTs, N=8,429, I^2=0%[18]
	MD -1.25 U (95% CI -1.93 to -0.57), p=0.0003	13 RCTs, N=11,441, I^2=34%, GRADE high [14]
	Change in SGRQ (12 months):	
	MD -1.21 U (95% CI -2.64 to 0.21), p=0.09	2 RCTs, N= 4,526, I^2=58%[18]
	MD -1.01 U (95% CI -1.65 to -0.57), 0=0.002	7 RCTs, N= 8,364, I^2=11%, GRADE moderate [14]
	Proportion achieve the MCID for change in SGRQ (6 months):	
	56% vs. 50% RR 1.14 (95% CI 1.09 to 1.20) NNT 16 (95% CI 12 to 22)	9 RCTs, n=9,835, I^2=39%[18]
	53% vs. 48.2% RR 1.11 (95% CI 1.07 to 1.15) 53 more/1000 (95% CI 34 to 72 more/1000)	11 RCTs, n=11,868, I^2=11%, GRADE moderate[14]
	Proportion achieve the MCID for change in SGRQ (12 months):	
	47.1% vs. 44.3% RR 1.10 (95% CI 1.03 to 1.18) 44 more/1000 (95% CI 13 to 80 more/1000)	2 RCTs, n=4,015, I^2=0%, GRADE moderate [14]
Exacerbations	No significant differences in reducing the risk of exacerbations (GRADE moderate).[14,44]	
Adverse effects	No differences in any adverse events, serious adverse events, or rates of pneumonia (GRADE moderate)[14]	

LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonist; FEV_1 = forced expiratory volume in 1 minute; mL = milliliter; L = liter; MCID = minimal clinically important difference; TDI = Transitional Dyspnea Index; U = unit; SGRQ = St. Georges Respiratory Questionnaire; moderate exacerbations = requiring additional medications such as oral steroids or antibiotics; severe exacerbation = requiring hospitalization or ED visit; serious adverse event = one or more non-fatal serious adverse events; MD = mean difference; RR = relative risk; OR =odds ratio

Table 12: LAMA-LABA vs. LABA		
Lung function (Trough FEV_1) MCID = increase ≥ 100 mL (or 0.10 L)	**Change from baseline 6 months:**	
	MD 0.08 L (95% CI 0.05 to 0.1), p<0.00001	8 RCTs, N=7,765, I^2=81%, GRADE moderate[14]
	Change from baseline 12 months: [14]	
	MD 0.08 L (95% CI 0.06 to 0.09), p<0.00001	5 RCTs, N=5,063, I^2=29%, GRADE moderate[14]
Dyspnea (TDI) MCID = increase ≥ 1 unit	**Change from baseline 6 months:**	
	MD 0.39 U (95% CI 0.24 to 0.54), p<0.00001	5 RCTs, N=5,747, I^2=0%, GRADE moderate[14]
	Change from baseline 12 months:	
	MD 0.08 U (95% CI 0.06 to 0.09), p<0.00001	3 RCTs, N=4,516, I^2=80%, GRADE moderate[14]
	Proportion achieve the MCID for change in TDI:	
	50% vs. 40.9% RR 1.22 (95% CI 1.10 to 1.36) 90 more/1000 (95% CI 41 to 147 more)	1 RCT, N=1,613, GRADE moderate[14]
Health related quality of life (SGRQ) MCID = reduction ≥ 4 units	**Overall Change from baseline:**	
	MD -1.06 U (95% CI -1.63 to -0.49), p=0.0003	8 RCTs, N=7,777, I^2=0%, GRADE moderate[14]
	Proportion achieve the MCID for change in SGRQ at 6 months:	
	51.3% vs. 43.7% RR 1.15 (95% CI 1.07 to 1.25) 65 more/1000 (95% CI 31 to 109 more)	7 RCTs, N=7,310, I^2=61%, GRADE moderate[14]
Exacerbations	**Moderate to severe:**	
	26.8% LABA-LAMA vs. 35.9% LABA RR 0.77 (95% CI 0.71 to 0.83) 83 fewer/1000 (95% CI 104 to 61 fewer)	8 RCTs, N=5,457, I^2=2%, GRADE moderate[14]
	Severe:	
	4.7% LABA-LAMA vs. 5.9% LABA RR 0.83 (95% CI 0.62 to 1.10)	6 RCTs, N=2,898, I^2=0%, GRADE low[14]
Adverse effects	**All AE:**	
	9.0% LABA-LAMA vs. 7.8% LABA RR 1.04 (95% CI 0.93 to 1.16)	16 RCTs, N=13,876, I^2=60%, GRADE moderate[14]
	Pneumonia:	
	1.8% LABA-LAMA vs. 1.2% LABA RR 1.15 (95% CI 0.79 to 1.67)	9 RCTs, N=9,200, I^2= 2%, GRADE low[14]
	Serious AE:	
	1.8% LABA-LAMA vs. 1.2% LABA RR 1.15 (95% CI 0.79 to 1.67)	8 RCTs, N=9,220, I^2=0%, GRADE low[14]

LABA = long-acting beta-agonis; LAMA = long-acting muscarinic antagonist; FEV_1 = forced expiratory volume in 1 minute; MCID = minimal clinically important difference; mL = milliliter; L = liter; TDI = Transitional Dyspnea Index; U = unit; SGRQ = St. Georges Respiratory Questionnaire; moderate exacerbations = requiring additional medications such as oral steroids or antibiotics; severe exacerbation = requiring hospitalization or ED visit; serious adverse event = one or more non-fatal serious adverse events; MD = mean difference; RR = relative risk

Table 13: LABA-ICS vs. LABA		
Lung function (Trough FEV_1) **MCID = increase ≥ 100 mL (or 0.10 L)**	**Overall change in FEV_1 (3-36 months):**	
	MD 0.05 L (95% CI 0.04 to 0.05), p<0.00001	21 RCTs, N=16,193, I^2=53%, GRADE moderate[14]
Dyspnea (TDI) **MCID = increase ≥ 1 unit**	**Change in TDI:**	
	No difference (GRADE low) [14]	
Health related quality of life (SGRQ) **MCID = reduction ≥ 4 units**	**Overall Change in SGRQ:**	
	MD -1.69 U (95% CI -2.19 to -1.19), p<0.00001	15 RCTs, N=13,560, I^2=10%, GRADE high[14]
	Proportion achieve the MCID for change in SGRQ:	
	42.1% vs. 39.2% RR 1.06 (95% CI 0.96 to 1.17)	7 RCTs, N=6,841, I^2=64%, GRADE very low[14]
Exacerbations	**Moderate to severe exacerbations:**	
	26% LABA-ICS vs. 28.5% LABA RR 0.90 (95% CI 0.86 to 0.95), 28 fewer/1000 (95% CI 40 to 14 fewer/1000)	17 RCTs, N=23,969, I^2=35%, GRADE high[14]
	Severe exacerbations:	
	6.2% LABA-ICS vs. 6.4% LABA RR 1.01 (95% CI 0.91 to 1.12)	12 RCTs, N=18,937, I^2=0%, GRADE moderate[14]
Adverse effects	**Serious AE:**	
	No significant differences in serious AE (GRADE moderate) [14]	
	Pneumonia:	
	4% LABA-ICS vs. 2.6% LABA RR 1.52 (95% CI 1.27 to 1.81) 14 more/1000 (95% CI 7 to 21 more/1000)	22 RCTs, N=30,748, I^2=16%, GRADE high[14]

LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroid; FEV_1 = forced expiratory volume in 1 minute; MCID = minimal clinically important difference; mL = milliliter; L = liter; TDI = Transitional Dyspnea Index; U = unit; SGRQ =St. Georges Respiratory Questionnaire; moderate exacerbations = requiring additional medications such as oral steroids or antibiotics; severe exacerbation = requiring hospitalization or ED visit; serious adverse event = one or more non-fatal serious adverse events; MD = mean difference; RR = relative risk

Table 14: LABA-ICS vs. LAMA		
Lung function (Trough FEV_1) **MCID = increase ≥ 100 mL**	**Change in FEV_1:**	
	No differences (GRADE low-moderate)[14,19]	
Dyspnea (TDI) **MCID = increase ≥ 1 unit**	**Change in TDI:**	
	No differences (GRADE low-moderate)[14,19]	
Health related quality of life (SGRQ) **MCID = reduction ≥ 4 units**	**Change in SGRQ:**	
	No differences (GRADE low-moderate)[14,19]	
Exacerbations	**Moderate to severe exacerbations:**	
	No differences (GRADE low)[14,19]	
Adverse effects	**Serious Adverse Effects:**	
	18.1% LABA-ICS vs. 15.5% LAMA RR 1.19 (95% CI 1.01 to 1.39), 28 more/1000 (95% CI 2 to 61 more/1000)	6 RCTs, N=2,664, I^2=0%, GRADE moderate[14,19]
	Pneumonia:	
	3.6% LABA-ICS vs. 1.8% LAMA RR 1.87 (95% CI 1.14 to 3.07), 16 more/1000 (95% CI 2 to 37 more/1000)	4 RCTs, N=2,465, I^2=0%, GRADE moderate[14,19]

LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonist; FEV_1 = forced expiratory volume in 1 minute; mL = milliliter; MCID = minimal clinically important difference; TDI = Transitional Dyspnea Index; SGRQ = St. Georges Respiratory Questionnaire; serious adverse event = one or more non-fatal serious adverse events; RR = relative risk

Table 15: LAMA-LABA vs. LABA-ICS		
Lung function (Trough FEV_1) **MCID = increase ≥ 100 mL (or 0.10 L)**	**Change in FEV_1 (from baseline to study end):**	
	MD 0.07 L (95% CI 0.50 to 0.08), p<0.000001	12 RCTs, N=14,681, I^2=73%, GRADE moderate[20]
	MD 0.07 L (95% CI 0.03 to 0.10), p=0.0001	11 RCTS, N=10,461, I^2= 98%, GRADE low[14]
	Proportion achieve the MCID for change in FEV_1:	
	59% vs. 41% RR 1.44 (95% CI 1.33 to 1.56), NNT 6 (95% CI 5 to 7) at 12 weeks	3 RCTs, N=3,920, I^2=0%[18]
Dyspnea (TDI) **MCID = increase ≥ 1 unit** **Health related quality**	**Change in TDI (12 weeks):**	
	MD 0.20 U (95% CI -0.30 to 0.42), p=0.09	4 RCTs, N=3,148, I^2=3%[18]
	Change in TDI (25 weeks):	
	MD 0.33 U (95% CI -0.28 to 0.95), p=0.20	2 RCTs, N=2,142, I^2=0%[18]
	Change in TDI (3-12 months):	
	MD 0.21 U (95 CI 0.03 to 0.46), p=0.09	9 RCTs, N-9,822, I^2=69%, GRADE very low[14]
Health related quality of life (SGRQ) **MCID = reduction ≥ 4 units**	**Change in SGRQ**	
	MD -0.26 U (95% CI -0.97 to 0.45), p=0.47	7 RCTs, N=9,471, I^2=18%, GRADE low[14]
	MD -0.57 U (95% CI -1.36 to 0.21), p=0.15	9 RCTs, N=14,437, I^2 = 78%; GRADE moderate[20]
	Proportion achieve the MCID for change in SGRQ:	
	44.7% vs. 43.3% RR 1.05 (95% CI 0.96 to 1.14)	6 RCTs, N=9,769, I^2=66%,GRADE very low[14]
	37.3% vs. 38.7% OR 1.06 (95% CI, 0.90 to 1.25)	4 RCTs, N=13,614, I^2 = 77%; GRADE moderate[20]
Exacerbations	**Participants with one or more exacerbations:**	
	OR 0.91 (95% CI 0.78 to 1.06)	13 RCTs, N=20,960, I^2=56%, 6 to 52 weeks, GRADE moderate[20]
	Moderate to severe exacerbations:	
	RR 0.96 (95% CI 0.86 to 1.08)	11 RCTs, N=19,669, I^2=19%,GRADE moderate[14]
	Severe:	
	RR 0.59 (95% CI 0.22 to 1.59)	2 RCTs, N=4,048, I^2=74%[18]
	RR 0.93 (95% CI 0.56 to 1.54)	6 RCTs, N=7,151, I^2=48%, GRADE low[14]
Adverse effects	**Pneumonia:**	
	RR 0.63 (95% CI 0.54 to 0.73), 17 fewer/1000 (95% CI 21 to 12 fewer/1000)	13 RCTs, N=21,522, I^2=0%, GRADE high[14]
	2.8% (95% CI 24 to 33) vs. 4.5% (12 to 52 weeks) OR 0.61 (95% CI 0.52 to 0.72)	14 RCTs, N=21,829, I^2=0% GRADE high [20]
	Serious AE:	
	RR 1.01 (95% CI 0.91 to 1.12)	14 RCTs, N=21,565, I^2=30%, GRADE moderate[14]
	1.5% (95% CI 1.35 to 1.66) vs. 1.48% OR 1.02 (95% CI 0.91 to 1.15) (6 to 52 weeks)	18 RCTs, N=23,158, I^2= 20%, GRADE high[20]

LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonist; FEV_1 = forced expiratory volume in 1 minute; MCID = minimal clinically important difference; mL = milliliter; L = liter; TDI = Transitional Dyspnea Index; U = unit; SGRQ = St. Georges Respiratory Questionnaire; moderate exacerbations = requiring additional medications such as oral steroids or antibiotics; severe exacerbation = requiring hospitalization or ED visit; serious adverse event = one or more non-fatal serious adverse events; MD = mean difference; RR = relative risk; OR = odds ratio

TRIPLE THERAPY (LAMA-LABA-ICS)

Table 16: LAMA-LABA-ICS vs. LAMA-LABA		
Lung function (Trough FEV_1) MCID = increase ≥ 100 (or 0.10 L)	**Change in FEV_1 (from baseline to study end):**	
	MD 0.04 L (95% CI 0.02 to 0.07), p=0	3 RCTs, N=4,275, I^2=27%; GRADE high[10]
	MD 0.09 L (95% CI 0.07 to 0.12), p<0.001	3 RCTs, I^2=79%[22]
	MD 0.03 L (95% CI 0.01 to 0.06), p=0.03	3 RCTs, N=3,622, I^2=72%[25]
	MD 38.40 mL (95% CI 7.05 to 69.75), p=0.02	2 RCTs, I^2= 86%[26]
	MD 0.04 L (95% CI 0.01 to 0.07) p<0.00001	2 RCTs, N=5,521, I^2=86%[23]
	MD 0.04 L (95% CI 0.03 to 0.05), p <0.00001	5 RCTs, N=9,527, I^2=50%, GRADE moderate[14]
	MD 38.68 mL (95% CI 22.58 to 54.77), p<0.00001	4 RCTs, N=11,352, I^2=62%, GRADE low[21]
Dyspnea (TDI) MCID = increase ≥ 1 unit	**Change in TDI (from baseline to study end):**	
	SMD 0.09 U (95% CI -0.01 to 0.19), p=0.42	3 RCTs, N=1,465, I^2=0%[27]
	MD 0.33 U (95% CI 0.18 to 0.48), p<0.00001	3 RCTs, N=5,521, I^2=6%[23]
	MD 0.36 U (95% CI 0.26 to 0.47), p<0.00001	3 RCTs, N=7,544, I^2=0%, GRADE moderate[14]
	Proportion Achieve the MCID for change in TDI:	
	36% vs. 29.5%; RR 1.21; 95% CI 1.08 to 1.35, p=0.0008 62 more/1000 (95% CI 24 to 104 more/1000)	1 RCT, N=3,044, GRADE moderate[14]
	36.3% vs. 30%; OR 1.33; 95% CI 1.13 to 1.57 63 more/1000 (95% CI 26 to 102 more/1000)	1 RCT, GRADE moderate [21]
Health related quality of life (SGRQ) MCID = reduction ≥ 4 units	**Change in SGRQ (from baseline to study end)**	
	MD -1.81 U (95% CI -2.57 to -1.04), p=0	3 RCTs, N=4,227, I^2=0%, GRADE high[36]
	MD -1.59 U (95% CI -2.24 to -0.95), p<0.00001	2 RCTs, I^2=0%[25]
	MD -1.59 U (95% CI -2.22 to -0.96), p<0.00001	3 RCTs, N=7,356, I^2=0%[26]
	MD -1.59 U (95% CI -2.05 to -1.14), p<0.01	4 RCTs, I^2=0%[22]
	MD -1.71 U (95% CI 0.64 to 0.83),p<0.00001	4 RCTs, N=13,267, I^2=78%[23]
	MD -1.68 U (95% CI -2.08 to -1.29), p<0.00001	5 RCTs, N=12,750, I^2= 0%, GRADE moderate[14]
	MD -1.65 U (95% CI -2.15 to – 1.15), p<0.00001	5 RCTs, N=13,879, I^2=0%[21]
	Proportion achieve the MCID for change in SGRQ:	
	OR 1.20 (95% CI 1.08 to 1.34), p=0.0006	2 RCTs, I^2=0%[25]
	42.8% vs. 35.3%; RR 1.21 (95% CI 1.16 to 1.27), p<0.00001 74 more/1000 (95% CI 56 to 96 more/1000)	3 RCTs, N=5,028, I^2=0%, GRADE moderate[14]
	42.4% vs. 35.3%; OR 1.35 (95% CI 1.26 to 1.45) 71 more/1000 (95% CI 54 to 89 more/1000)	4 RCTs, N=15,412, I^2=0%, GRADE moderate[21]
Exacerbations	**Moderate to severe exacerbations:**	
	RR 0.78 (95% CI 0.70 to 0.88), p=0	2 RCTs, N=4,915, I^2=46%, GRADE moderate[36]
	RR 0.75 (95% CI 0.69 to 0.83), p<0.01	4 RCTs, I^2=68%[25]
	RR 0.69 (95% CI 0.55 to 0.87)	3 RCTs, I^2=85%[26]
	RR 0.74 (95% CI 0.67 to 0.81) p<0.01	4 RCTs, I^2=71%[22]
	Rate Ratio 0.71 (95% CI 0.66 to 0.94) p<0.0003	4 RCTs, N=8,046, I^2=78%: GRADE moderate[14]
	Rate Ratio 0.74 (95% CI 0.67 to 0.81) P<0.00001	4 RCTs, N=15,397, I^2=68%; GRADE low [21]
	Severe:	
	RR 0.68 (95% CI 0.59 to 0.78), p=0	3 RCTs, N=5,153, I^2=0%, GRADE high[36]
	RR 0.75 (95% CI 0.67 to 0.84), p<0.00001	3 RCTs, N=14,131, I^2=57%: GRADE low[21]
	RR 0.68 (95% CI 0.59 to 0.78), p<0.00001	3 RCTs, N= 8,054, I^2=0%: GRADE moderate[14]
Adverse effects	**Pneumonia:**	
	RR 1.53 (95% CI 1.25 to 1.87), p=0	3 RCTs, N=5,060, I^2=20%, GRADE moderate[36]
	OR 1.25 (95% CI 1.03 to 1.97), p=0.03	3 RCTs, N=9,310, I^2=33%[25]
	RR 1.38 (95% CI 1.14 to 1.67), p=0.009	3 RCTs, N=9,017, I^2=48%[26]
	RR 1.55 (95% CI 2.35 to 1.80), p<0.0001	5 RCTs, N=17,535, I^2=0%[22]
	OR 1.52 (95% CI 1.15 to 2.00), p=0.003	5 RCTs, N=15,703, I^2=0%, GRADE moderate[23]
	5.4% vs. 3.4%; RR 1.49 (95% CI 1.27 to 1.76), p<0.00001 17 more/1000 (95% CI 9 to 26 more/1000)	5 RCTs, N=15,703, I^2=0%, GRADE moderate[14]
	3.3% vs. 1.9%; OR 1.74 (95% CI 1.39 to 2.18) p<0.00001 13 more/1000 (95% CI 7 to 21 more/1000)	4 RCTs, N=15,412, I^2=0%, GRADE moderate[21]
	Serious AE:	
	No significant differences.[14, 21, 22, 25, 26, 36]	

LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonist; FEV_1 = forced expiratory volume in 1 minute; MCID = minimal clinically important difference; mL = milliliter; L = liter; TDI = Transitional Dyspnea Index; U = unit; SGRQ = St. Georges Respiratory Questionnaire; moderate exacerbations = requiring additional medications such as oral steroids or antibiotics; severe exacerbations = requiring hospitalization or ED visit; serious AE = one or more non-fatal serious adverse events; MD = mean difference; RR = relative risk; OR = odds ratio

Table 17: LAMA-LABA-ICS vs. LABA-ICS		
Lung function (Trough FEV_1) MCID = increase ≥ 100 (or 0.10 L)	**Change in FEV_1 (from baseline to study end):**	
	MD: 0.11 L (95% CI 0.10 to 0.13)	12 RCTs, N=6,453, I^2=65%; GRADE moderate[36]
	MD: 104.86 mL (95% CI 86.74 to 122.99) NNT = 3.38 95% CI 2.84 to 4.24 increase in trough FEV_1 ≥ 100 mL	11 RCTs, I^2=84%; GRADE high[28]
	MD 0.10 L (95% CI 0.06 to 0.14), p<0.00001	4 RCTs, N=5,497, I^2=94%[26]
	MD 103.4 mL (95% CI 64.65 to 142.15), p<0.00001	4 RCTs, I^2= 94%[23]
	MD 0.10 L (95% CI 0.08 to 0.12), p <0.00001	15 RCTs, N=14,437, I^2=80%, GRADE moderate[14]
Dyspnea (TDI) MCID = increase ≥ 1 unit	**Change in TDI (from baseline to study end):**	
	MD: 0.29 U (95% CI 0.15 to 0.44)	4 RCTs, I^2=0%[28]
	MD: 0.29 U (95% CI 0.18 to 0.40), p<0.00001	3 RCTs, N=7,057, I^2=0%, GRADE moderate[14]
	Proportion achieve the MCID for change in TDI:	
	36% LAMA-LABA-ICS vs. 29.3% LABA-ICS RR: 1.23; 95% CI 1.12 to 1.34, p<0.00001 67 more/1000 (95% CI 35 to 100 more/1000)	1 RCT, N=3,044, GRADE moderate[14]
Health related quality of life (SGRQ) MCID = reduction ≥ 4 units	**Change in SGRQ (from baseline to study end)**	
	MD: -1.81 U (95% CI -2.28 to -1.35), p=0	11 RCTs, N=6,383, I^2=0%, GRADE high[36]
	MD: -1.70 U (95% CI -2.12 to -1.27), p>0.00001	7 RCTs, I^2=0%[25]
	MD: -1.73 U (95% CI -2.12 to -1.34)	7 RCTs, I^2=0%[28]
	MD: -1.53 U (95% CI -2.23 to -0.84), p<0.0001	4 RCTs, N=8,986, I^2=21%[26]
	MD: -1.42 U (95% CI -1.82 to -1.03), p<0.01	5 RCTs, I^2=23%[22]
	MD: -1.55 U (95% CI -1.94 to -1.17), p<0.00001	9 RCTs, N=17,587, I^2= 6%, GRADE high[14]
	Proportion achieve the MCID for change in SGRQ:	
	At endpoint: OR: 1.31 (95% CI 1.21 to 1.42) p<0.00001	6 RCTs, N=4,706; I^2=0%[25]
	12 months: 42.8% vs. 35.8% RR: 1.16, 95% CI 1.08 to 1.25; p<0.00001 57 more/1000 (95% CI 29 to 89 more/1000)	3 RCTs, N=14,543, I^2=66%, GRADE moderate[14]
Exacerbations	**Time to first exacerbation:**	
	HR: 0.84 (95% CI 0.79 to 0.90), p<0.01	2 RCTs, N=4,838, I^2=0%, GRADE high[36]
	HR: 0.86 (95% CI 0.80 to 0.90), p<0.01	3 RCTs, I^2=0%[22]
	Moderate to severe exacerbations:	
	RR: 0.77 (95% CI 0.66 to 0.91), p=0.03	3 RCTs, N=5749, I^2=64%, GRADE moderate[36]
	RR: 0.82 (95% CI 0.77 to 0.88), p<0.00001	5 RCTs, I^2=7%[25]
	RR: 0.81 (95% CI 0.73 to 0.89), p=0.002	4 RCTs, I^2=37%[26]
	Relative Risk: 0.78; 95% CI 0.71 to 0.85, NNT 23 (95% CI 14 to 94)	11 RCTs, I^2=44%; GRADE high[28]
	RR: 0.85 (95% CI 0.81 to 0.88), p<0.01	5 RCTs, I^2=1%[22]
	4.9% vs. 6.6%; Risk Ratio 0.79 (95% CI 0.69 to 0.91), 14 fewer/1000 (95% CI 21 to 6 fewer/1000)	12 RCTs, N=22,526, I^2=28%, GRADE high[14]
	Severe:	
	RR: 0.87 (95% CI 0.75 to 1.00), p=0.05	1 RCT, N=4,134, GRADE moderate[36]
	2.7% vs. 2.9% ; Risk Ratio 0.93; 95% CI 0.42 to 2.06, 2 fewer/1000 (95% CI 17 fewer to 30 more/1000)	1 RCT, GRADE moderate[14]
Adverse effects	**Pneumonia:**	
	No significant differences.[14, 22, 25, 26, 36]	
	Serious AE:	
	No significant differences.[14, 22, 25, 26, 36]	

LABA = long-acting beta-agonist; LAMA = long-acting muscarinic antagonist; FEV_1 = forced expiratory volume in 1 minute; MCID = minimal clinically important difference; mL = milliliter; L = liter; TDI =Transitional Dyspnea Index; U = unit; SGRQ = St. Georges Respiratory Questionnaire; moderate exacerbations = requiring additional medications such as oral steroids or antibiotics; severe exacerbation = requiring hospitalization or ED visit; serious adverse event = one or more non-fatal serious adverse events; MD = mean difference; RR = relative risk; OR = odds ratio

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APPENDIX I
EVIDENCE STATEMENT:
Roflumilast, Macrolides, N-acetylcysteine, and Oral Glucocorticoids

- There are several medications that are considered add-on therapies to inhalers in specific patient populations, some of which are described in guidelines (e.g. roflumilast or azithromycin). With the exception of roflumilast, these medications/classes do not have a Health Canada indication specific for the treatment of COPD.
- The table below provides an evidence statement from recent MAs for these drugs or drug classes. Information in the table provides a description of the types of patients included in trials along with study results. This is not a comprehensive evidence review and should not be interpreted as such.
- It is important to note that there are limitations in the available evidence for these therapies; therefore, it is difficult to define the potential place in therapy for the maintenance therapy of COPD.
- Other factors need to be considered before using these medications, including safety and tolerability.

Table 1: Evidence Statement: Roflumilast, Macrolides, N-acetylcysteine, and Oral Glucocorticoids

DRUG CLASS/DRUG	EVIDENCE STATEMENT
Oral Glucocorticoid [1]	• There is NO evidence of benefit with *long term use* of oral steroids in the management of COPD. • However, there is evidence that associates long term use with numerous systemic adverse events (AEs).
PDE-4 Inhibitor Roflumilast [2]	• In individuals with moderate to severe COPD as defined by FEV_1 (predominantly severe), receiving baseline treatment for COPD (generally with a LAMA, or LABA, or LABA-ICS), treated with roflumilast for 12-52 weeks. • Roflumilast vs. placebo ▪ Changes in lung function, symptoms, or QoL did not achieve the MCID. ▪ A small reduction in the percentage of participants with ≥ 1 exacerbation(s): estimated 4.5% reduction with roflumilast: RR 0.79, 95% CI 0.73 to 0.81, (16 RCTs, N=14,778, I^2=0%) as well as the rate of exacerbation 12%, RR 0.87 (95% CI 0.82 to 0.92) (8 RCTs, I^2=0%) ▪ Uncertain if the risk of moderate to severe exacerbations is reduced. ▪ High rates of AEs, including GI-related (diarrhea, nausea, vomiting, dyspepsia, weight loss), withdrawals due to AE, headache, and psychiatric AE. ▪ Does not reduce the risk of all-cause mortality compared with placebo.
Mucolytics N-acetylcysteine (NAC) [3]	• In individuals classified as mild to severe COPD (defined by FEV_1), most patients were defined as having chronic bronchitis. Baseline therapy for COPD is highly variable ranging from none, SABD, long-acting inhaled monotherapy or LABA-ICS, treated with NAC for one year or less; baseline exacerbation risk was not defined. • N-acetylcysteine (NAC) vs. placebo (9 RCTs, N=2137) ▪ NAC does not reduce the risk of moderate exacerbations or decline in lung function. ▪ There are no significant differences in reported AE. • Due to heterogeneity, treatment dose, duration of therapy, and concomitant COPD treatments, the efficacy of regular NAC therapy in COPD patients is uncertain.
Macrolides Azithromycin [4]	• In patients with moderate to severe COPD, treatment 3-12 months, predominantly azithromycin, receiving baseline treatment for COPD (generally LAMA or LABA or LABA-ICS). • Macrolide vs. placebo ▪ SGRQ: No significant difference (3 RCTs, N=1,007, I^2=94%, moderate certainty evidence). ▪ AE leading to discontinuation greater with macrolide: OR 1.29, 95% CI 1.0 to 1.66 (3 RCTs, I^2=0%) ▪ Odds of experiencing an exacerbation are lower with macrolide: OR 0.34 (95% CI: 0.19, 0.59, p < 0.001, I^2 = 72%) (8 RCTs, N=1,914). ▪ Odds of experiencing a severe exacerbation requiring hospitalization is lower with macrolide vs. placebo: OR 0.60; 95% CI: 0.37 – 0.97; p=0.004, I^2=42% (4 RCTs, N=1,636). • Antimicrobial resistance was not formally considered in the MA. However, trials have found stable COPD treated long term with a macrolide can result in significantly high rates of bacterial resistance.

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APPENDIX II
CONSIDERATIONS FOR INHALED CORTICOSTEROIDS IN COPD

- There is evidence to suggest that ICS increase oropharyngeal adverse effects, systemic effects of skin bruising, and pneumonia. Observational evidence also suggests associations with other respiratory infections, diabetes, bone effects/ fractures, and cataracts.[1,2]

- The benefit versus the risk for ICS therapy should be assessed in individuals with COPD.
  - Guidelines recommend treatment with an ICS:[3,4]
    - In individuals with COPD who also have a diagnosis of asthma, or
    - As part of triple therapy in specific patients (described in the main review section of this document).

- Guidelines outline clinical scenarios where removing an ICS may be considered, noting that the evaluation should always be individualized.[3,4]

I. CTS 2023 statements – Stepping down from triple therapy.[3]

- In individuals with moderate to high health status impairment (CAT ≥ 10) and or FEV 1 <80% predicted, there is a weak recommendation to continue triple therapy rather than stepping down to LAMA-LABA dual therapy. Withdrawing the ICS may result in worsening lung function and health status.[3]
  - Stepping down may be considered in patients when there are concerns that stepping up was not justified in the first place, or because of AE.[3]

- Step down from triple therapy to dual therapy is not suggested for individuals at high risk of exacerbations.[3]

II. GOLD 2026 statements – Management of patients currently on LABA-ICS.[4]

- For patients currently on LABA-ICS, it is important to review whether there is a relevant prior exacerbation history and whether there is a previous positive response to ICS treatment. Using this information, the following should be considered:[4]
  - If there is no relevant exacerbation history; consider changing to a LAMA-LABA.[4]
  - If there is a previous exacerbation history but currently there are no exacerbations; suggests a positive response to treatment.[4]
  - If the patient is currently suffering with exacerbations, then blood eosinophil counts can be used to guide treatment; if < 100 cells/µL consider changing to a LAMA-LABA, if ≥ 100 cells/µL consider triple therapy.[4]
  - The benefits and risks of ICS withdrawal should be carefully considered, with a blood eosinophil count ≥ 300 cells/µL being an indicator of increased risk of exacerbations with ICS withdrawal.[4]

Is there evidence for ICS withdrawal from triple therapy?

No trials have been specifically designed to assess both initiating ICS as part of triple therapy along with the impact of removing the ICS during the course of the trial. The best available evidence comes from two double blind RCTs that have compared the efficacy and safety of step down from triple therapy to dual LAMA- LABA therapy, removing the ICS (WISDOM and SUNSET). A limitation of both trials is that a majority of patients were already receiving ICS at study entry and the reasons for that treatment were not clearly defined. Both trials were non-inferiority RCTs.

WISDOM[5]

- A 12-month non-inferiority trial (N=2,488) in people with severe to very severe COPD with at least one exacerbation in the previous year (the severity of previous exacerbations was not reported).[5]
  - The trial compared triple therapy with tiotropium 18 mcg/d + salmeterol 50 mcg twice/d + fluticasone 500 mcg twice/d for up to 1 year vs. dual therapy with a LAMA-LABA.[5]
  - All patients started triple therapy for 6 weeks, after which fluticasone was reduced every 6 weeks until it was stopped in the LAMA-LABA treatment arm.[5]
  - The non-inferiority criterion was met for the primary outcome; no increase in moderate-severe exacerbations following ICS withdrawal (RR=1.06, 95% CI 0.94-1.19).[5]

SUNSET [6]

- A 26-week non-inferiority trial (N=1,053) in individuals with moderate to severe COPD and a history of no more than one moderate to severe exacerbation in the previous year.[6]
  - The trial compared triple therapy (tiotropium 18 mcg/d + salmeterol 50 mcg / fluticasone 500 mcg twice/d) vs. step down to once daily LAMA-LABA (glycopyrronium 50 mcg/indacaterol 110 mcg) following ICS discontinuation (without tapering).[6]
  - The primary outcome found that dual therapy did not meet the inferiority margin of -50 mL when compared to triple therapy for change in FEV_1 (MD -26 ml (95% confidence interval, -53 to 1 ml). However, the absolute difference was small and did not meet the minimum clinically important difference.[6]

Local Clinical Expert

- There are no trials designed specifically to determine who may be most likely to benefit from ICS withdrawal.
- Each patient must be carefully assessed to determine the best treatment regimen.
  - Consider stepping down in few patients.
- The risk of pneumonia must be weighed against the severity of COPD.
  - If a patient has quit smoking and is on a stable COPD trajectory, then the risk of pneumonia is a higher mortality risk (especially if they are elderly and frail).

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APPENDIX III
DRUG CLASS TABLES: LONG-ACTING INHALERS FOR COPD

Table 2:

Long-acting muscarinic antagonists (LAMA)[1-3]	
Mechanism of Action	Reduce cholinergic tone, promote bronchodilation, and improve airflow.
Reported Adverse Effects	Dry mouth (rinse and spit following inhalation) (12% to 16%) Constipation Aggravation of narrow angle glaucoma (especially with direct contact) Urinary retention (0.73%) CV adverse effects
Drug Interactions (not an exhaustive list)	Additive anticholinergic effects with other anticholinergics → avoid combining.
Contraindications	Hypersensitivity to drug/formulation components. Severe milk protein allergy (for lactose-containing DPIs). Not for acute bronchospasm treatment. Avoid concurrent LAMA therapy (duplicate therapy).
Precautions (not an exhaustive list)	Maintenance therapy only; SABA required for acute relief. Do not initiate in acutely deteriorating COPD; reassess if control worsens. Paradoxical bronchospasm risk → stop if occurs. Anticholinergic caution: narrow-angle glaucoma (avoid eyes), urinary retention/BPH/bladder outlet obstruction. Cardiovascular caution (risk of arrhythmia). Renal impairment: caution especially with tiotropium. Hepatic impairment: limited data; use caution. Hypersensitivity reactions possible (anaphylaxis, angioedema). May impair ability to drive/operate machinery if dizziness/blurred vision.

Table 3:

Long-acting beta agonists (LABA)[1-4]	
Mechanism of Action	Stimulating beta$_2$-adrenergic receptors in bronchial smooth muscle cause relaxation of smooth muscle fibers to produce bronchodilation and improve airflow.
Common 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 analyzed the safety of LABAs in COPD and found: Decramer et al. 2013. ○ 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
Drug Interactions (not an exhaustive list)	Use cautiously with drugs causing hypokalemia/QTc prolongation (diuretics, high-dose steroids, antiarrhythmics) Avoid regular combined use with other sympathomimetics MAOIs/TCAs: may potentiate CV effects; avoid within 14 days CYP3A4 inhibitors (ketoconazole, ritonavir, clarithromycin): increase serum concentration → QTc risk Beta-blockers: avoid non-selective; cardio-selective with caution Methylxanthines: interaction not fully evaluated
Contraindications	Cardiac tachyarrhythmias Hypersensitivity to salmeterol, lactose, milk proteins, or components causing anaphylaxis/angioedema
Precautions (not an exhaustive list)	Do not use for acute/deteriorating COPD Cardiovascular caution: palpitations, QTc prolongation, ↑ HR/BP, Arrhythmias Caution in seizure disorders, thyrotoxicosis Rare laryngeal spasm/irritation (stridor, choking) possible Metabolic: hyperglycemia, hypokalemia; caution in diabetes or low K^+ risk Hypersensitivity reactions (urticaria, angioedema, anaphylaxis) possible Paradoxical bronchospasm - discontinue immediately if occurs

Table 4:

Inhaled corticosteroids (ICS)[1-3,5]	
Mechanism of Action	Through suppression of airway inflammation, ICS reduce airway hyperresponsiveness and improve airflow.
Reported Adverse Effects	Sore mouth Sore throat Dysphonia Oral thrush (can be reduced by rinsing mouth or using a spacer) Skin bruising May decrease bone mineral density and increase fracture risk. Bone densitometry is suggested in patients who require high doses or have risk factors for osteoporosis. Cataracts Possible worsening of glaucoma - patients with personal or family history of glaucoma should have intraocular pressure checked soon after starting therapy and periodically thereafter.
Drug Interactions (not an exhaustive list)	Strong CYP3A4 inhibitors (ketoconazole, itraconazole, voriconazole, ritonavir, clarithromycin, cobicistat) ↑ systemic steroid exposure → adrenal suppression/Cushing's risk.
Contraindications	Hypersensitivity to ICS components. Not for acute bronchospasm/status asthmaticus. Active systemic infections (fungal, bacterial, viral, parasitic, TB). Severe milk protein allergy for lactose-DPI products.
Precautions (not an exhaustive list)	Maintenance only, not for acute relief. **Systemic steroid risks (dose-related):** adrenal suppression (HPA axis), reduced bone density, ocular effects (cataracts/glaucoma), hyperglycemia. ↑ Pneumonia risk in COPD patients. ↑ infection risk; caution in patients with active/quiescent TB/herpes simplex. Rare reports of systemic eosinophilic conditions (**eosinophilic granulomatosis with polyangiitis/Churg-Strauss syndrome**) during steroid withdrawal Rinse mouth after use to reduce oropharyngeal candidiasis risk. May slow pediatric growth, monitor height. Hepatic impairment may ↑ exposure (especially fluticasone furoate).

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APPENDIX IV
GLOSSARY OF EVIDENCE BASED MEDICINE TERMS

Number Needed to Treat (NNT) [1]
The number of subjects who need to be treated for one subject to have a favorable outcome. **Note:** It is the inverse of absolute risk reduction (1 ÷ absolute risk reduction). Thus, if the results of a study indicate that the probability of death in a control group is 25% and the probability of death in a treatment group is 10% the number needed to treat would be 1.0 ÷ (0.25 - 0.10) = 6.7, therefore 7 subjects.

Risk Difference (RD) (synonym: Absolute Risk Reduction, Absolute Difference) [1]
The value of the difference between the probability that an event will occur in the group exposed to a given factor and the probability that this event will occur in the group not exposed to this factor.
Note: For example, if the results of a trial were that the probability of death was 25% in the control group and 10% in the experimental group, the absolute risk reduction would be 0.25 – 0.10 = 0.15.

Relative Risk (RR) (synonym Risk Ratio) [1]
The ratio (quotient) of the risk that an event will occur among the subjects exposed to a given factor and the risk that this event will occur among the subjects not exposed to this factor. **Note:** A relative risk (RR) of 1 indicates that the risk is equal in the groups compared, and RR > 1 indicates that the factor increases the risk, and an RR < 1 indicates that the factor decreases the risk.

Odds Ratio (OR) [1]
The odds ratio is a measure of the effect of treatment that compares the probability of suffering an event in the treatment group with the probability of suffering it in the control group. For example, if the results of a trial indicate that the probability of death in the control group is 25% and the probability of death in the treatment group is 10%, the odds ratio would be 0.10 ÷ (1.0 – 0.10) ÷ (0.25 ÷ (1.0 – 0.25) = 0.33.

95% Confidence Interval (95% CI)[1]
A 95% confidence interval indicates that there is a 95% probability that the confidence interval calculated from a particular study includes the true value of the parameter. If the interval includes a null value (a difference in means of 0, and odds ratio or a relative risk of 1, or a correlation coefficient of 0, for example), the null hypotheses cannot be rejected. A narrow confidence interval around a point estimate indicates a more precise estimate than a wide confidence interval.

P-Value[2]
The P-value is used in hypothesis testing. The P value is the probability of obtaining the observed effect (or larger) under a null hypothesis, which is an assumption of no effect of the intervention. A P value that is very small indicates that the observed effect is unlikely to have arisen purely by chance and therefore provides evidence against the null hypothesis. It is common practice to interpret a P value by examining whether it is smaller than a particular threshold value. P values less than 0.05 are often reported as statistically significant and interpreted as being small enough to justify rejection of the null hypothesis.

I^2 [2]
A statistic for quantifying inconsistency (heterogeneity) in a meta-analysis. A rough guide to interpretation is as follows:

- 0% to 40%: might not be important.
- 30% to 60%: may represent moderate heterogeneity*.
- 50% to 90%: may represent substantial heterogeneity*.
- 75% to 100%: considerable heterogeneity*.

*The importance of the observed value of I2 depends on the magnitude and direction of effects, and the strength of evidence for heterogeneity (e.g., P value from the chi-squared test, or a confidence interval for I2).

Heterogeneity[2]
Studies brought together in a systematic review will differ. Any kind of variability among studies in a systematic review may be termed heterogeneity. The presence of heterogeneity affects the extent to which generalizable conclusions can be formed. It is important to identify heterogeneity in case there is sufficient information to explain it. Note: A distinction is sometimes made between "statistical heterogeneity" (differences in the reported effects), "methodological heterogeneity" (differences in study design) and "clinical heterogeneity" (differences between studies in key characteristics of the participants, interventions, or outcome measures). Statistical tests of heterogeneity are used to assess whether the observed variability in study results (effect sizes) is greater than that expected to occur by chance. However, these tests have low statistical power.

Hazard Ratio (HR)[3]
A hazard describes how many times more or less likely a participant is to suffer the event at a particular point in time if they receive the treatment rather than the comparator intervention. The intervention effect is expressed as a hazard ratio.

Mean Difference (MD)[3]
The mean difference measures the absolute difference between the mean value in two groups of a randomized trial. It estimates the amount by which the experimental intervention changes the outcome on average compared with the comparator intervention.

Rate ratio[3]
The ratio of the rate in the experimental intervention group to the rate in the comparator group. Analyses of rare events often focus on rates. Rates relate the counts to the amount of time during which they could have happened. For example, the result of one arm of a clinical trial could be that 18 myocardial infarctions (MIs) were experienced, across all participants in that arm, during a period of 314 person-years of follow-up (that is, the total number of years for which all the participants were collectively followed).

Meta-analysis[4]
Meta-analysis is the statistical combination of results from two or more separate studies. Potential advantages of meta-analyses include an improvement in precision, the ability to answer questions not posed by individual studies, and the opportunity to settle controversies arising from conflicting claims. However, they also have the potential to mislead, particularly if specific study designs, within-study biases, variation across studies, and reporting biases are not carefully considered.

Network Meta-analysis[5]
A network meta-analysis is a technique for comparing three or more interventions simultaneously in a single analysis by combining both direct and indirect evidence across a network of studies. A network meta-analysis produces estimates of the relative effects between any pair of interventions in the network and usually yields more precise estimates than a single direct or indirect estimate. It also allows estimation of the ranking and hierarchy of interventions. However, they also have the potential to mislead, particularly if specific study designs, within-study biases, variation across studies, and reporting biases are not carefully considered.

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