NEW EVIDENCE IN .....

Chronic Obstructive Pulmonary Disease

Academic Detailing Service

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Disclosure statements

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

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Tables and Figures

DEFINITIONS

Chronic obstructive pulmonary disease (COPD)

- A respiratory disorder largely caused by smoking, which is characterized by progressive, partially reversible airway obstruction, and lung hyperinflation, systemic manifestations, and increasing frequency and severity of exacerbations.[2]

Exacerbation

- A sustained worsening of dyspnea, cough, or sputum production leading to an increase in the use of maintenance medications and/or supplementation with additional medications **(level of evidence: 3)**.[2]
  - The term 'sustained' implies a change from baseline lasting 48 h or more.
  - In addition, exacerbations should be defined as either purulent or non-purulent because this is helpful in predicting the need for antibiotic therapy **(level of evidence: 2A)**.

Self-management plan

- A written plan produced for the purpose of patient self-management of COPD exacerbations. It informs patients about when and how to adjust and/or start medication in case of an exacerbation.[3]

Spirometry

- A method of assessing lung function by measuring the volume (ml or L) of air that a patient can forcibly expel from the lungs after a maximal inspiration.
- It is used to:
  - Differentiate between obstructive airways disorders (e.g. COPD) and restrictive diseases (e.g. fibrotic lung disease).
  - Determine the severity of airflow obstruction in COPD.
- Full pulmonary function tests are more comprehensive than spirometry but are **not required** to make the diagnosis of COPD.

Forced expiratory volume in one second (FEV_1)

- The volume of air exhaled in the first second of forced expiration after a maximal inspiration.
- Normal value is approximately 80% or higher than the predicted value for a person of the same race, sex, age, and height.[4]

Forced vital capacity (FVC)

- The maximal volume of air (in litres) that can be forcibly exhaled in one breath.
- Normal value is approximately 80% or higher than the predicted value for a person of the same race, sex, age and height.[4]

FEV_1 /FVC

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

Bronchodilator reversibility test

- Assessment by spirometry of the pulmonary response to inhalation of bronchodilators such as short-acting beta$_2$-agonists.
- An increase in post-bronchodilator FEV_1 of at least 12% and 200 ml above baseline indicates significant reversibility.[5]
- This test should be requested when ordering spirometry.

Pack years

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

Blinded adjudication

- Adjudication is the process by which researchers decide if an event fulfills the prespecified criteria for an outcome. For example, in this document each study prespecifies the definition of an exacerbation such as requiring "a sustained worsening of the patient's respiratory condition, from the stable state and beyond normal day-to-day variations, necessitating a change in regular medication. An acute change in regular COPD medications was defined as physician-directed, short-term use of oral or intravenous steroids, oral or intravenous antibiotics, or both therapies."[6]
  - In adjudication, the researchers review each reported exacerbation and decide if it meets these criteria.
  - In blinded adjudication, the researchers do not know to which study group the patient experiencing the reported exacerbation belonged.

DRUG CLASS AND NAME GUIDE

Anticholinergic, short-acting	
Ipratropium bromide	Atrovent®
Anticholinergic, long-acting	
Tiotropium bromide	Spiriva®
Beta$_2$-agonist, short-acting (SABA)	
Salbutamol sulfate	Ventolin® Airomir® (HFA) Generics
Terbutaline sulfate	Bricanyl®
Anticholinergic and beta$_2$-agonist combination, short-acting	
Ipratropium/fenoterol	Duovent® Nebules
Beta$_2$-agonist, long-acting (LABA)	
Formoterol fumarate	Foradil® Oxeze®
Salmeterol	Serevent®
Inhaled corticosteroids (ICS)	
Beclomethasone dipropionate	QVAR® Generics
Budesonide	Pulmicort®
Fluticasone propionate	Flovent®
Ciclesonide	Alvesco®
ICS/long-acting beta$_2$-agonist combination	
Fluticasone/salmeterol	Advair® Has official indication for COPD.
Budesonide/formoterol	Symbicort® Does not have official indication for COPD.

Legend: HFA=Hydrofluoroalkane (i.e. cfc-free)

ABBREVIATIONS

- AECOPD Acute exacerbation of COPD
- COPD Chronic obstructive pulmonary disease
- CRDQ Chronic Respiratory Disease Questionnaire (see Page 21) for description
- CTS Canadian Thoracic Society
- FEV_1 Forced expiratory volume in one second
- FVC Forced vital capacity
- GOLD Global Initiative for Chronic Obstructive Lung Disease
- ICS Inhaled corticosteroids
- LABA Long-acting $beta_2$-agonist
- MCID Minimum clinically important difference
- MRC Medical Research Council
- NNH Number need to harm
- NNT Number needed to treat
- OR Odds ratio
- QoL Quality of life
- RR Relative risk
- SABA Short-acting $beta_2$-agonist
- SGRQ St. George's Respiratory Questionnaire (see Page 21 for description)
- TDI Transition Dyspnea Index (see Page 21 for description)

CANADIAN THORACIC SOCIETY LEVELS OF EVIDENCE

Level
1. Evidence from one or more randomized trials
2. Evidence from one or more well-designed cohort or case-control study
3. Consensus from expert groups based on clinical experience

Evidence was further subdivided into a number of categories
A. Good evidence to support a recommendation for use
B. Moderate evidence to support a recommendation for use
C. Poor evidence to support a recommendation for or against use
D. Moderate evidence to support a recommendation against use
E. Good evidence to support a recommendation against use

SUMMARY STATEMENTS

DIAGNOSIS (PAGE 15)

- Objective demonstration of air flow obstruction by spirometry is essential for the diagnosis of COPD. Full pulmonary function tests are generally **not** required.
- Diagnosis requires a postbronchodilator FEV_1/FVC ratio of <70%.
- The diagnosis may be suspected in patients with a significant smoking **history** who present with
  - Progressive exertional dyspnea
  - Cough and/or sputum production
  - Frequent respiratory infections.
- Our content expert stresses the importance of early diagnosis of COPD.
- Early diagnosis is important because
  - Smoking cessation will slow the decline in lung function and alter the natural history of the disease.
  - All patients should be encouraged to maintain an active lifestyle and be cautioned about the negative consequences of prolonged inactivity.

CLASSIFICATION OF DISEASE SEVERITY (PAGE 16)

- Disease severity can be classified according to symptoms and/or lung function (FEV_1 and FEV_1/FVC). However, FEV_1 correlates poorly with:
  - Symptom severity,
  - Exercise capacity, and
  - Quality of life.
- The Canadian Thoracic Society (CTS) encourages classification of COPD based on the Medical Research Council (MRC) scale for dyspnea and disability assessment.

EVALUATING EFFECTIVENESS OF THERAPIES (PAGE 20)

- For evaluating the effectiveness of therapies, we are considering the following outcomes.
  - Mortality, hospitalizations, exacerbations
  - Quality of life, dyspnea symptoms, exercise capacity
  - Decline of lung function measured by FEV_1.
- It is also important to consider the **minimum change** in the outcome that is **clinically significant** (i.e. that is perceived by the average patient as beneficial). The effect on outcomes may be **statistically** significant, but not **clinically** significant.
- Minimum clinically significant differences using the validated scales described in

- Table 6, page 21 have been defined for measurements of **dyspnea, exercise capacity**, and **quality of life**. Not all studies use these scales, making interpretation difficult.

WHAT OUTCOMES WILL BENEFIT FROM THERAPY? (Page 22)

Mortality (Page 24)

- Few trials have studied mortality as a **primary** outcome. An exception is the TORCH trial.
- The Wilt meta-analysis states good evidence supports that monotherapies do not reduce mortality.
- SALM + FL has shown a **possible** reduction in mortality vs **placebo**, TIO, or FL.
  - NNT vs placebo = 36 (95% CI: 21 to 258) for 3 years (TORCH/Nannini)
  - NNT vs TIO=40 (95% CI: 21 to 327) for 2 years (INSPIRE)
- There is no evidence that SALM + FL provides additional benefit vs SALM alone.
- There is uncertainty as to whether TIO offers benefit vs placebo but there is evidence that TIO is **not associated** with **increased** mortality.
- Available evidence does not allow conclusions on differences in mortality rates between TIO, TIO+SALM, or TIO+SALM+FL.
- Long-term continuous oxygen therapy (≥ 15 hours per day or more to achieve an oxygen saturation of ≥ 90%) decreases mortality.

Hospitalizations for COPD exacerbations (Page 26)

- We found no trials in which hospitalization was studied as the sole primary outcome.
- TIO, SALM, and SALM + FL have been found to lead to fewer hospitalizations than **placebo**.
- TIO + SALM + FL led to fewer hospitalizations than TIO alone, NNT 7 (95% CI: 4 to 26) for 1 year.
- Other studies have found **no statistically significant difference** in the following comparisons:
  - TIO vs TIO + SALM
  - TIO vs SALM
  - TIO vs SALM+FL
  - TIO vs IPRA
  - ICS vs placebo
  - ICS vs ICS + LABA
  - LABA vs ICS + LABA
- The Wilt meta-analysis concluded that reductions in hospitalizations were not consistently observed and do not permit definitive conclusions on the relative effectiveness of inhaled therapies.

- Pulmonary rehabilitation and education/self-management plans have also been associated with fewer hospitalizations than usual care (NNT for 1 year= 5 for pulmonary rehabilitation).

Exacerbations (Page 27)

- Exacerbations are now one of the most frequently reported outcomes in COPD studies of long-acting agents and combination therapies; many studies show benefits from these therapies. However, data reporting and analysis create uncertainty about results.
- Acute exacerbations are the most frequent cause of medical visits, hospital admissions, and death among patients with COPD. In addition, frequent exacerbations are an important determinant of quality of life and contribute to accelerated rates of decline in lung function.
- Our meta-analysis of 1-year studies indicates that approximately 42% of patients in the placebo group had an exacerbation.
- For <u>monotherapies</u>
  - TIO, LABA, and ICS have all shown benefit vs placebo (NNT 15 to 18)
  - TIO but **not** LABA has shown benefit vs IPRA
  - TIO has **not** shown benefit over LABA
  - LABA has **not** shown benefit over ICS
- For <u>combination therapies</u>
  - SALM + FL has shown benefit vs placebo, SALM, and FL
  - TIO has **not** shown benefit versus
    - TIO + SALM
    - SALM + FL
    - TIO + SALM + FL.

Quality of life measured by SGRQ or CRDQ (Page 30)

- The Wilt meta-analysis states "Evidence indicates that **average** improvement in respiratory health status [from inhalation therapies] is **clinically insignificant**, but **some** individuals achieve a noticeable **improvement**."
- Our meta-analysis indicates that approximately 35% of study subjects achieve a clinically significant improvement in quality of life from **placebo**.
- Our calculations suggest that approximately **1 patient out of 7 to 14** will notice a benefit when switched from short-acting bronchodilators to long-acting agents.
- Because of the limited number of studies that were suitable for analysis, and other methodological issues related to the data **it is not possible to definitively recommend one therapy over another**.

Symptoms of dyspnea measured by TDI (Page 33)

- SABAs, TIO, and LABA + ICS have all been found to provide clinically significant benefit vs **placebo**.
- TIO led to a clinically significant benefit vs IPRA but no other head-to-head comparisons showed any clinically significant difference.

Exercise capacity (Page 34)

- Recent studies use constant work rate cycle exercise to measure exercise capacity. However, the minimum clinically significant difference for this measure has not been defined so we have reported results of 6-minute walk tests.
- Cochrane reviews report that SABAs, LABAs, and LABA + ICS provide **no clinically significant benefit** in exercise capacity (measured by the six-minute walk test) compared to **placebo**.
- TIO showed **no** clinically significant benefit over **placebo**.
- No head-to-head comparisons showed any clinically significant difference.
- A study on TIO and pulmonary rehabilitation found that patients taking TIO were able to exercise approximately 6 minutes longer than those on placebo immediately after and 12 weeks after an 8-week pulmonary rehabilitation program (TIO 22.4 mins vs placebo 15.8 mins, p=0.018).
    - Our content expert recommends that patients on bronchodilators be encouraged to increase their physical activity as much as possible to maximize benefit.

Decline in lung function (Page 35)

- Smoking cessation is the **only** intervention that has been definitively shown to slow the progression of COPD.
- Until recently, there has been evidence that pharmacological management of COPD (IPRA, TIO, ICS) does **not** reverse, slow, or prevent the progressive decline in lung function.
- However, a **post-hoc** analysis of TORCH suggests that there **may** be a beneficial effect from SALM and FL alone and in combination.
    - SALM and FL alone and in combination led to a lower yearly decline in FEV_1 by 13 to 16 ml compared to placebo.
    - This was a **post-hoc** analysis and measurement of FEV_1 was a secondary outcome. Therefore, these findings should be **viewed with caution** and confirmed by an appropriately designed study.

NON-INHALATION THERAPIES (PAGE 36)

- A disease-specific **self-management** plan including education, home exercise, and an action plan for acute exacerbation can lead to decreased hospitalizations for exacerbations. Such plans have not been shown conclusively to decrease exacerbations or improve quality of life compared to usual care.

- **Pulmonary rehabilitation** programs have statistically and clinically significant effects on hospitalizations and quality of life. Improvements in exercise capacity were statistically significant, but the clinical significance is questionable.
  - All patients should be encouraged to maintain an active lifestyle and be cautioned about the negative consequences of prolonged inactivity.
- Self-management plans and pulmonary rehabilitation are recommended by the CTS, but availability in Nova Scotia is limited.
  - Pulmonary rehabilitation services are available in Nova Scotia in the metro area at the Queen Elizabeth II Health Sciences Center and Cobequid Community Health Centre, Truro, and at the Cape Breton Regional Hospital. A program is planned for the Annapolis Valley.
- A Cochrane review concluded that, from the limited number of studies performed, inactivated **influenza vaccine** reduces exacerbations in COPD patients.
- A Cochrane review concluded that there is **no evidence** from RCTs that injectable **pneumococcal vaccination** in persons with COPD has a significant impact on morbidity or mortality.

Which patients will benefit from therapy? How do you evaluate the effect of therapy? (Page 39)

- The benefits of COPD therapies in patients in the **mild to moderate** airflow obstruction categories are **uncertain** and most evidence is limited to patients in the **moderate to severe** airflow obstruction category (**FEV_1 less than 60%** predicted).
- The 2003 CTS Recommendations suggest that several simple questions can help clinicians evaluate the effect of therapy:
  - "Did the new treatment help your breathing?"
  - If the answer is yes then ask "In what way has it helped you?"
  - A response indicating that the patient can perform tasks with less breathlessness or for longer periods of time indicates benefit.
  - If there is no subjective benefit then options include
    - Assess compliance (including inhaler technique),
    - Alter the dose (if appropriate),
    - Discontinue the drug and monitor for symptomatic deterioration. Recommence the drug if deterioration occurs.
- Our content expert suggests keeping a patient on therapy even if they have no symptomatic improvement if **preventing recurring exacerbations** is a consideration.
- The CTS 2007 Guidelines suggest that patients with moderate-to-severe COPD and **≥ 1 exacerbation per year**, on average for 2 consecutive years, be treated with TIO plus a LABA + ICS.

- Our content expert suggests that the threshold of 1 exacerbation per year is based on consensus. Exacerbations should be severe enough to require antibiotics, oral corticosteroids or an emergency room visit.

- The UK Guidelines suggest in moderate to severe COPD unresponsive to short-acting agents, a LABA+ICS can be tried but discontinue after 4 weeks if there is no benefit and the patient is not experiencing frequent exacerbations (**≥ 2 exacerbations** in a 12-month period.)
- When evaluating therapy, it is important to consider adverse events.

What are the adverse effects of therapy in COPD? (Page 41)

- **Mortality**
  - There is **inconsistent** evidence that IPRA is associated with increased mortality.
  - TIO, LABAs, and ICS do not appear to be associated with increased mortality.
- **Cardiovascular events**
  - There is **inconsistent** evidence that anticholinergics are associated with increased cardiovascular events.
  - A recent 4-year RCT found **no increased risk** in cardiac events, including stroke, for TIO versus placebo.
- **Pneumonia**
  - ICS alone or in combination with LABA is associated with an **increased** risk of pneumonia.
- **Fractures and cataracts**
  - Recent meta-analyses have reported that ICS alone or in combination with LABA does **not** appear to have any effect on fractures or cataracts in COPD. However, the longest duration of therapy was **3 years** and not all studies were designed to measure these outcomes.
  - The CTS suggests that ICS may be associated with decreased bone mineral density, posterior subcapsular cataracts, and glaucoma.
- **Oropharyngeal candidiasis, dysphonia, and skin bruising**
  - ICS alone or in combination with LABA is associated with an **increased** risk of oropharyngeal candidiasis, dysphonia, and skin bruising.

Table 1 2007 CTS recommendations and comments from Dalhousie Academic Detailing Service

Recommendations from CTS 2007 Update[1]		Level of evidence assigned by CTS Statements from CTS COPD Recommendations – 2007 Update Expert opinion and comments from Academic Detailing Service (ADS)
Patient description	**Recommended drugs**	
Symptoms only noticeable with exertion and having **minimal** disability – initial treatment	- Short-acting bronchodilator prn **or** - Regular SABA or ipratropium[2] **or** - Combination SABA + IPRA - Choice of initial therapy is based on clinical response and tolerance of adverse effects	CTS: Little information exists in patients with milder COPD (FEV_1 > 65% predicted) making evidence-based guidelines impossible for these patients. Short-acting agents show benefit in moderate to severe COPD. SABA + ipratropium produces superior **bronchodilation** in patients with moderate to severe disease. ADS: The 2007 update removed the comment (in the 2003 guideline) that SABA + ipratropium has **not** been shown superior to either agent alone in terms of dyspnea alleviation, exercise performance, or quality of life.
	- TIO **or** LABA + SABA prn if symptoms persist	**Level of evidence 3B** ADS: We suggest level of evidence **3C** since we found no studies for these drugs in **mild** COPD. Expert opinion: Bronchodilators should not be prescribed without inhaled corticosteroids if there is a possibility that the patient has asthma. (**Five to 10%** of COPD patients may have asthma. This is the same as the percentage in the general population.) Spirometry report of reversibility or asthmatic component **alone** does not confirm the diagnosis of asthma.
More persistent symptoms and **moderate to severe** airflow obstruction	- Long acting bronchodilator such as TIO[3] **or** - LABA (formoterol, salmeterol) - Continue SABA prn for immediate symptom relief	**Level of evidence 1A** ADS: 1A evidence is **questionable for LABAs** since they have been shown to provide clinically significant benefit over **placebo** but **not** ipratropium. 1A evidence **supports TIO** which has shown statistically significant **benefit** compared to **ipratropium** in exacerbations, and clinically significant benefits in quality of life (NNT 7) and dyspnea symptoms. CTS: TIO is an acceptable 1st choice long-acting bronchodilator in this group given its proven clinical efficacy, convenient once-daily dosing regimen, and safety profile. **Level of evidence 3B** ADS: We agree with 3B evidence. In head-to-head trials, TIO has **not** led to statistically significant benefits vs **LABA** in mortality, hospitalizations, or exacerbations or to clinically significant benefits in quality of life, dyspnea symptoms, or walking distance.
Moderate to severe COPD with persistent symptoms but **infrequent** exacerbations (<1 per yr on average for 2 consecutive yrs)	- Combination of TIO **and** a LABA - Continue SABA prn for immediate symptom relief	**Level of evidence 3B** CTS: The addition of SALM to TIO in patients with more advanced COPD was associated with consistent improvement in health status but not with significant improvement in spirometry or reduction in the frequency and severity of exacerbations compared with TIO alone. TIO plus LABA is recommended to maximize bronchodilation and lung deflation. ADS: We suggest level of evidence **3C** since no study has shown clinically significant benefits in health status with TIO + LABA vs TIO alone.[6,7] We and our content expert question this recommendation.

Recommendations from CTS 2007 Update[1]		Level of evidence assigned by CTS Statements from CTS COPD Recommendations – 2007 Update Expert opinion and comments from Academic Detailing Service (ADS)
Patient description	**Recommended drugs**	
Same as above but with persistent **dyspnea** despite use of both a TIO and a LABA	- TIO plus **lower dose** SALM/FL (50/250 BID) could be substituted for SALM (i.e. LABA) - Continue SABA prn for immediate symptom relief	**Level of evidence 3B** ADS: We suggest level of evidence **3C** since we found no studies in which **low** dose ICS was added to TIO + SALM.
Moderate to severe COPD with persistent symptoms and a history of **exacerbation** (≥ 1 per year, on average, for 2 consecutive years)	- Triple therapy with TIO+LABA+ICS - Continue SABA prn for immediate symptom relief	**Level of evidence 1A** ADS: We suggest level of evidence **1B** since triple therapy vs TIO did **not** show benefit in the **primary** outcome of reducing exacerbations. There was benefit in the **secondary** outcomes of hospitalizations and quality of life.[6] CTS: Consider LABA + ICS for patients with an FEV_1 <60% predicted and who experience ≥ 1 exacerbations per year. **Level of evidence 1A** ADS: This suggestion does **not** appear in the algorithm. We agree with this suggestion before trying triple therapy because there is level 1A evidence that LABA + ICS leads to fewer exacerbations than LABA or ICS alone.[8] Expert opinion: The number of exacerbations (≥ 1 per yr, on average, for 2 consecutive yrs) is based on consensus. Also, exacerbations should be severe enough to require treatment with antibiotics, oral steroids or an emergency room visit.
Severe symptoms despite use of both TIO + LABA/ICS	- Long-acting preparation of oral theophylline may be added to triple therapy	**Level of evidence 3B** CTS: Monitoring of blood levels, side effects, and potential drug interactions is necessary.

1 Can Respir J 2007;14(Suppl B):5B-32B.

2 CTS guidelines suggest short-acting anticholinergic. We have changed this to ipratropium since this is the only agent in this class.

3 CTS guidelines suggest long-acting anticholinergic. We have changed this to TIO since this is the only agent in this class.

ICS inhaled corticosteroid LABA long-acting $beta_2$agonist SABA short-acting $beta_2$-agonist SALM salmeterol TIO tiotropium

In Canada, salmeterol alone, formoterol alone, and salmeterol + fluticasone in combination have official indications for COPD. Inhaled corticosteroids alone do not have official indications for COPD.

INTRODUCTION

- This is an update to our 2004 academic detailing session which reviewed the Canadian Thoracic Society (CTS) 2003 Guidelines. It is based on
  - Recent primary publications
  - CTS 2007 Guidelines
  - Guidelines from Australia, United Kingdom, and the United States
  - Recent meta-analyses
    - A meta-analysis done for the Agency for Health Quality Research that was used to inform the 2007 American College of Physicians Clinical Practice Guidelines. We refer to this as the **Wilt meta-analysis** in recognition of the primary author.[1]
    - Several Cochrane reviews that have addressed pharmacological and non-pharmacological interventions.

For ease of reading we use abbreviations to refer to inhalation therapies

- IPRA ipratropium Atrovent
- TIO tiotropium Spiriva
- SALM salmeterol Serevent
- FL fluticasone Flovent

} Combination = Advair

- FORM formoterol Oxeze, Foradil
- BUD budesonide Pulmicort

} Combination = Symbicort

- For primary publications we will refer to drug names e.g., SALM, FL, FORM or BUD.
- For systematic reviews we will refer to drug classes e.g., LABA, ICS.
- There are more studies of SALM and FL than FORM and BUD.

- For **non-inhalation** interventions, we will report mostly systematic reviews and guideline statements/recommendations.
- For **inhalation** interventions, we will also report results of individual studies, including recent RCTs evaluating important outcomes. In the studies in Table 2 the primary outcome was **not statistically significant**.

Table 2 Features of recent important COPD studies

Name of study	Comparators	Approx N per group	Duration	Primary outcome
UPLIFT[9]	TIO vs placebo	3000	4 yrs	FEV_1 decline
INSPIRE[10]	TIO vs SALM+FL	660	2 yrs	Exacerbations
OPTIMAL[6]	TIO vs TIO+SALM vs TIO+SALM+FL[1]	150	1 yr	Exacerbations
TORCH[8]	Placebo vs SALM vs FL vs SALM+FL[1]	1525	3 yrs	Mortality

1 Dose of fluticasone is 500 ug twice daily.

- For outcomes of **hospitalizations** and **exacerbations**, we have conducted our own meta-analyses using a program called Comprehensive Meta-analysis. We included only studies that were **1 year** in duration because
  - This is a reasonable length of time to evaluate these outcomes.
  - It provides an intuitive period of time on which to base the number needed to treat.

This update will address 3 questions:

1. What outcomes will benefit from therapy?
   - What additional benefit is achieved with multiple therapies?
2. Which patients will benefit from therapy? How do you evaluate the effect of therapy?
3. What are possible adverse effects of therapies?

- We will also briefly review epidemiology, pathophysiology, diagnosis, and classification of COPD, and outcomes commonly measured.

Epidemiology

- Chronic obstructive pulmonary disease (COPD) is a major cause of disability and death, and affects about 4.4% (> 700,000) of Canadian adults age 35 and over.[2]
- More women than men are affected (4.8% vs 3.9%).
- In 2004, COPD was the fourth leading cause of death in both men and women in Canada.
- Cigarette smoke is the main inflammatory trigger in COPD but other environmental triggers such as occupational exposure and air pollution have also been implicated.[2]

Pathophysiology[2]

- Persistent inflammation of the small and large airways, as well as the lung parenchyma and its vasculature, occurs in a highly variable combination that differs from patient to patient.
- Evidence of airway inflammation is present even in early disease when spirometric abnormalities are minor.
- The inflammatory process persists long after the inciting stimulus (e.g., cigarette smoke) is withdrawn.
- The inflammatory process in COPD is different from that in asthma.
- Expiratory flow limitation is the pathophysiological hallmark of COPD and decreases the ability of patients to expel air during forced and quiet expiration. This leads to air trapping and lung overinflation.
- When the breathing rate acutely increases (and expiratory time diminishes) as, for example, during exercise , there is further lung overinflation as a result of air trapping, which contributes to dyspnea.
- Acute-on-chronic hyperinflation has been shown to be an important determinant of shortness of breath during exercise and with exacerbations.

DIAGNOSIS

- Diagnosis is often delayed until extensive lung damage has occurred because of large reserves in lung function and the slowly progressive nature of COPD.[2]
  - Our content expert suggests that many patients are not diagnosed with COPD until their FEV_1 is approximately 50% of predicted, which is considered severe COPD.
- Early diagnosis is important because
  - Smoking cessation will slow the decline in lung function and alter the natural history of the disease.
  - All patients should be encouraged to maintain an active lifestyle and be cautioned about the negative consequences of prolonged inactivity.[2]
- **Mass screening** of asymptomatic individuals for COPD is **not recommended**. However, **targeted** spirometry to detect early COPD in individuals at risk is recommended.
- There are no clinical, evidence-based criteria to select individuals who are at risk for COPD for diagnostic spirometry.[2]
- The diagnosis may be suspected in patients with a significant **smoking history** who present with
  - Progressive exertional dyspnea
  - Cough and/or sputum production
  - Frequent respiratory infections.[2]
- The Canadian Lung Association suggests that patients who are older than 40 years of age and who are current or ex-smokers should have spirometry if they answer yes to any **one** of the following questions:[2]
  - Do you cough regularly?
  - Do you cough up phlegm regularly?
  - Do even simple chores make you short of breath?
  - Do you wheeze when you exert yourself, or at night?
  - Do you get frequent colds that persist longer than those of other people you know?
- Acute exacerbation is a common initial clinical presentation of COPD.
- Therefore, it is recommended that long-term smokers (current or past) who seek medical attention for treatment of respiratory tract infection should be offered diagnostic spirometry **when acute symptoms subside** and their condition has stabilized.
- **Spirometry** is the most useful method of confirming a diagnosis of COPD and should be conducted when the patient's condition is stable.[4]
  - It provides three important values:
    - Forced expiratory volume in one second (FEV_1)
    - Forced vital capacity (FVC)
    - FEV_1/FVC ratio

(Spirometry values are expressed in millilitres or litres and/or as a percentage of the predicted normal for a person of the same race, sex, age, and height.) Examples of normal values from different age groups are in Table 3.[4]

Table 3. Examples of normal values for FEV_1 and FVC

Age	Male[1]		Female[2]	
	FEV_1(L)	**FVC(L)**	**FEV_1(L)**	**FVC(L)**
50-53	3.50	4.36	2.59	3.04
66-69	3.03	3.95	2.19	2.63

1 – height = 69", 175 cm 2 – height = 65", 165 cm

- Full pulmonary function tests are generally **not required** for diagnosis.

- **CTS Recommendations for diagnosis of COPD state:**
  - Objective demonstration of air flow obstruction by spirometry is essential for the diagnosis of COPD.
  - Diagnosis of COPD requires postbronchodilator FEV_1/FVC ratio **less than 70%.**[2]

CLASSIFICATION OF DISEASE SEVERITY

- Disease severity can be classified according to symptoms and/or lung function (FEV_1 and FEV_1/FVC). However, FEV_1 correlates poorly with:
  - Symptom severity,
  - Exercise capacity, and
  - Quality of life.[4]
- The CTS[2] encourages classification of COPD based on the Medical Research Council (MRC) scale for dyspnea and disability assessment.
- Table 4 shows the CTS and MRC classifications with the **approximate** relations to lung function. Our content expert considers that symptoms are a better predictor of disease severity than lung function.

Table 4. Classification of severity of COPD

CTS Stage	MRC Grades[1]	Symptoms	FEV_1[2] % predicted	FEV_1/FVC
Mild	2	SOB from COPD[3] hurrying on the level or walking up slight hill	≥ 80%	< 0.7
Moderate	3-4	Walks slower than people of same age on the level because of SOB from COPD[3] or has to stop for breath when walking at own pace on the level. SOB making patient stop after walking 100m or after a few minutes on the level	50-79%	< 0.7
Severe	5	SOB from COPD[3] making patient unable to leave the house **or** breathlessness when dressing or undressing **or** chronic respiratory failure **or** right heart failure	30-49%	< 0.7
Very Severe			< 30%	< 0.7

1 MRC grade 1 = breathless with strenuous exercise

2 Post-bronchodilator values

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

- Patients with an MRC grade of 3 to 5 are disabled and require intensive comprehensive management including inhalation and non-inhalation interventions from the outset.

- **Differentiating COPD from asthma**

  - Table 5 summarizes features of asthma and COPD. Our content expert suggests that 5% to 10% of COPD patients may also have asthma. This is the same percentage of patients with asthma in the general population.
  - **Spirometry** may help differentiate the 2 conditions by detecting improvements in FEV_1 in response to short-acting bronchodilators.
    - If the post-bronchodilator FEV_1 remains **subnormal**, the diagnosis may be either non-responsive asthma or COPD. However, if post-bronchodilator FEV_1 and the FEV_1/FVC **return to normal**, clinically significant COPD is **not present**.[11]
    - An increase in post-bronchodilator FEV_1 of at least 12% and 200 ml above baseline indicates significant reversibility.[5]
    - Asthma is more likely if the post-bronchodilator improvement in FEV_1 is > 400 ml or if day-to-day peak flow measurements vary by more than 20%.[11]
    - Our content expert suggests that a spirometry report of "reversibility" or "asthmatic component" **alone** does not confirm the diagnosis of asthma.

- Patients with combined asthma and COPD may benefit from combination therapy with both beta$_2$-agonist and anticholinergic bronchodilators, and if the asthma component is prominent, earlier introduction of ICS may be justified.[2]

Table 5. Clinical differences between asthma and COPD[2]

	Asthma	COPD
Age of onset	Usually < 40 years	Usually > 40 years
Smoking history	Not causal	Usually > 10 pack-years*
Sputum production	Infrequent	Often
Allergies	Often	Infrequent
Disease course	Stable (with exacerbations)	Progressive worsening (with exacerbations)
Spirometry	Often normalizes	May improve but never normalizes
Clinical symptoms	Intermittent and variable	Persistent

* pack-year = packs smoked per day X number of years smoked (see page 2)

- When a definite diagnosis cannot be made with spirometry and/or clinical findings, referral to a specialist is recommended.

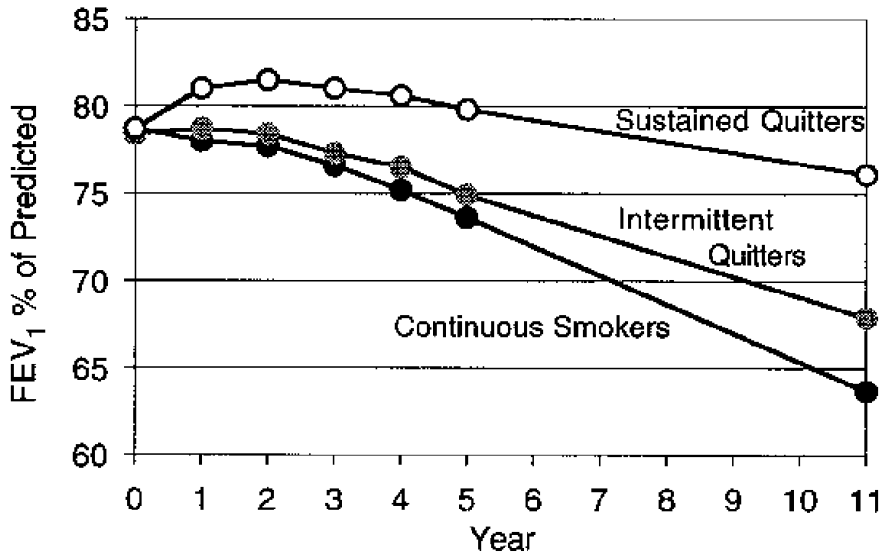
WHEN TO REFER TO A RESPIROLOGIST

- The CTS has suggested that primary care physicians consider referral to a specialist under the following circumstances:
  - Uncertainty over the diagnosis,
  - Symptoms are severe or disproportionate to the level of obstruction,
  - There is a decline of FEV_1 of 80 ml or more per year over a 2-year period,
  - Onset of symptoms occurs at a young age.
  - Specialists can also assist in patients who:
    - Fail to respond to bronchodilator therapy,
    - Require pulmonary rehabilitation,
    - Need assessment for oxygen therapy,
    - Have severe or recurrent exacerbations,
    - Have complex comorbidities or
    - Require assessment for surgery (bullectomy, lung volume reduction, lung transplantation.)[2]

CAUSE AND PREVENTION

- COPD is largely caused by smoking. **Smoking cessation** is the single most effective intervention to reduce the risk of developing COPD and the only intervention that has been **definitively** shown to slow the rate of lung function decline.[12]
  - However, a **post-hoc** analysis of TORCH **suggests** that SALM and/or FL **may** also slow the decline in lung function. See page 35 for discussion of this analysis.
- The normal age-related decline in FEV_1 is about **30 ml per year** in adults. Smokers in whom COPD is developing have decreases of **60-120 ml per year**.[4]
- Figure 1 indicates that the **rate** of age-related decline in lung function will return to normal if the patient stops smoking.[13]
- Approximately 25% of smokers older than 45 years have COPD.[2]

Figure 1. Effects of smoking cessation on lung function



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MANAGEMENT OF COPD

Goals of COPD Management

- The CTS has outlined the goals for COPD management as follows:[2]
  - Prevent disease progression (smoking cessation);
  - Reduce the frequency and severity of exacerbations;
  - Alleviate breathlessness and other respiratory symptoms;
  - Improve exercise tolerance and daily activity;
  - Treat exacerbations and complications of COPD;
  - Improve health status; and
  - Reduce mortality.

Evaluating effectiveness of therapies

- Two factors should be considered in assessing the relevance of various RCTs evaluating COPD therapies:
  1. **Identifying** clinically important outcomes
     - RCTs are designed to detect changes in the **primary outcome** of the trial. **Secondary outcomes**, although pre-specified in the trial design, are important but generally the trial is not specifically designed to detect changes in these outcomes.
     - Early RCTs for COPD therapies usually measured change in **lung function** (FEV_1) as the primary outcome. However, FEV_1 correlates poorly with symptom severity, exercise capacity, and quality of life.[4] RCTs now measure more meaningful outcomes such as mortality, hospitalizations, exacerbations, and quality of life.
  2. The **minimum change** in the outcome that is **clinically significant** (i.e. that is perceived by the average patient as beneficial). Minimum clinically important differences have been defined for
     - Dyspnea (BDI, TDI)
     - Quality of life (SGRQ, CRDQ)
     - 6-minute walk test
- Table 6 summarizes commonly reported outcomes and the minimum clinically important differences.

Table 6. Commonly reported outcomes in COPD trials

Outcome	Definition/Comment	Minimum clinically important difference
Exacerbations	• Definition varies between trials i.e., symptom based vs event based. • CTS definition is sustained worsening of dyspnea, cough, or sputum production leading to increase in use of maintenance medications and/or additional medications. • There are uncertainties concerning the reporting and analysis of exacerbations. (See page 27).	• Has not been defined
Hospitalizations due to COPD exacerbations	• Duration and frequency of hospitalization • No standard criteria are applied in clinical practice or research studies	• Has not been defined
Baseline dyspnea index (BDI) Transition dyspnea index (TDI)	• Scores each of following on scale of –3 to +3 - functional impairment - magnitude of task - magnitude of the effort • Measures change in dyspnea from baseline as measured by BDI	• Total change of at least 1 unit
Use of rescue medications	• Use of bronchodilators to relieve symptoms	• Has not been defined
6-minute walk test	• Measures exercise capacity • Distance patient can walk in 6 minutes under standard conditions	• 50-54 meters[14]
Quality of life		
St George's Respiratory Questionnaire (SGRQ)	• Scores each of the following on scale of 0-100 - symptoms (frequency, severity) - activity (activities that cause or are limited by dyspnea) - impacts (psychosocial function)	• 4 units
Chronic Respiratory Disease Questionnaire (CRDQ)	• 20 items measuring - dyspnea - fatigue - emotional function - mastery of disease	• 0.5 units for each domain[15]
Lung function		
FEV_1	• Used to assess lung function and reversibility to bronchodilators (measured as pre-dose (trough) or post-dose	• Expert opinion considers this is not defined

- **Other issues** in trials that complicate their interpretation and relevance include:
  - Use of other outcome measures and scales not listed in Table 6.
  - Inconsistent definition and analysis of exacerbations. (See page 27 for details.)
  - Inclusion of patients with a high degree of reversibility, reflecting a diagnosis of asthma rather than COPD.
  - Use of concomitant medications. For example, in one study of TIO, 80% of patients were also taking ICS.[16] It is not unusual for 50-80% of the study population to be on inhaled steroids.
  - Use of questionable appropriate comparator doses of proven therapy. For example, most studies comparing new therapies to IPRA use the dose of 40 mcg (2 puffs) qid, which is not the maximal dose.
  - High rates of dropouts (up to 50%[6,8,17]) and crossover to active therapies.[6]
  - In placebo-controlled trials, the true comparison is study drug plus SABA vs SABA because both groups were allowed to take SABAs as rescue therapy.
  - Studies of ICS in COPD generally use high doses; whether lower doses would provide similar efficacy or fewer side effects is not known.

- Where possible, we have extracted **percentages** of people that experienced a benefit. This allows calculation of numbers needed to treat.
  - In cases where it is not possible to report NNTs, we will report results based on mean differences between therapies.
  - For hospitalizations and exacerbations, we will concentrate on 1-year trials since this is a reasonable length of time to evaluate these outcomes and it provides an intuitive period of time on which to base the number needed to treat.
- For **lung function**, we will report effects on lung function **decline** rather than response to bronchodilators.

What outcomes will benefit from therapy?

- This section will review the evidence for efficacy of inhalation therapies and non-inhalation therapies on various COPD outcomes.

Inhalation Therapies

- We will present evidence about inhalation therapies
  - Compared to **placebo**. (Remember that in placebo-controlled studies the true comparison is study drug plus short-acting beta$_2$-agonist (SABA) vs SABA because both groups were allowed to take SABAs as rescue therapy. Trials do not always report the amount of SABA used as rescue.)
  - Compared to **other inhalation therapies** alone and in combination.
- The following page summarizes outcomes that do and do not benefit from therapeutic options that may be encountered in a step-wise approach to management of COPD.

Summary Response: what outcomes will benefit from inhalation therapy?

Most evidence is in moderate to severe COPD (FEV_1 < 65% predicted)

What is the benefit of long-acting bronchodilators over short-acting?	***LABA***		
	Benefit vs placebo (SABA)	*Hospitalizations, exacerbations* *Possibly quality of life*	*NNT 18 (13 to 34) for 1 year* *NNT 14 (8 to 43)*
	Equal to placebo	Mortality, dyspnea	
	Equal to IPRA	Exacerbations, quality of life, dyspnea, exercise	
	TIO		
	Benefit vs placebo (SABA)	*Dyspnea, exacerbations* *Hospitalizations* *Possibly quality of life*	*NNT 15 (11 to 24) for 1 year* *NNT 42 (20 to 500) for 1 year* *NNT 8 (5 to 16)*
	Benefit vs IPRA	*Exacerbations, dyspnea* *Possibly quality of life*	*NNT 7 (4 to 12)*
	Equal to placebo	Mortality, exercise	
	Equal to IPRA	Hospitalizations	
Is there any benefit for TIO vs LABA?	**TIO vs LABA**	Equal for mortality, hospitalizations, exacerbations, quality of life, dyspnea, exercise	
Is there benefit to using both TIO and LABA?	**TIO + LABA**		
	Equal to TIO	Hospitalizations, exacerbations, quality of life, dyspnea, exercise	
	Equal to LABA	Quality of life	
	Equal to TIO+LABA+ICS	Hospitalizations, exacerbations, quality of life, dyspnea	
Is there benefit to adding ICS to LABA?	**LABA+ICS**		
	Benefit vs LABA	*Exacerbations* *Possibly quality of life*	*NNT 9 (6 to 17)*
	Equal to LABA	Mortality, hospitalizations, dyspnea	
How does LABA+ICS compare with TIO?	**LABA+ICS**		
	Benefit vs TIO	*Possibly mortality* *Possibly quality of life*	*NNT 40 (21 to 327) for 2 years* *NNT 22*
	Equal to TIO	Hospitalizations, exacerbations	
How does TIO+LABA+ICS compare to TIO?	**TIO+LABA+ICS**		
	Benefit vs TIO	*Quality of life, hospitalizations*	*NNT 7 (4 to 26) for 1 year*
	Equal to TIO	Exacerbations, dyspnea	
How do long-acting agents compare to regularly administered SABAs?		No published evidence	
How does TIO+LABA+ICS compare to LABA?		No published evidence	
Is there benefit to adding ICS to TIO?		No published evidence	

Text in italics indicates drugs and outcomes that have shown benefit.

Outcomes based on **statistically** significant differences are: mortality, COPD hospitalizations, and exacerbations

Outcomes based on **clinically** significant differences are: quality of life, dyspnea, and exercise

Possible benefits indicate inconsistency in results arising from different analyses of data and should be interpreted cautiously.

IPRA = ipratropium SABA = short-acting $beta_2$ agonist LABA = long-acting $beta_2$ agonist ICS= inhaled corticosteroid TIO = tiotropium

NNT = number needed to treat. Calculations are based on a limited number of studies and are meant to provide an **approximate** estimate. Where two outcomes appear before an NNT, the NNT refers to the second listed outcome. Parentheses indicate 95% confidence intervals. No time frame given for quality of life estimates because studies of different duration (3 months to 4 years) were used in calculations.

Mortality

- Few trials have studied mortality as a primary outcome. An exception is the TORCH trial which is summarized below.

Comparisons to placebo

Salmeterol plus fluticasone

- TORCH, a large 3-year trial compared the effects of **SALM and FL** alone and in combination to placebo.[8]
  - The decrease in mortality from the combination approached but **did not achieve** statistical significance.
  - Mortality rates were:

		P-value vs placebo
Placebo	15.2%	
SALM	13.5%	0.18
FL	16%	0.53
SALM + FL	12.6%	0.052

  - A limitation of this study is that ~40% of patients withdrew. Most patients withdrew in the placebo group (44%) and fewest withdrew in the combination therapy group (34%). This may affect the outcomes analysis of the study.
- The Wilt meta-analysis which included TORCH found conflicting results when data comparing LABA+ICS to placebo were presented in relative vs absolute terms:
  - Relative risk ~ 0.82 (95% CI: 0.69 to 0.98).[1] **statistically significant**
  - Absolute risk reduction -1% (95% CI: -3% to 1%)[1] **not statistically significant**
- A Cochrane review states there is an overall reduction in mortality with LABA+ICS vs placebo, but this outcome is dominated by the results of TORCH.
  - Further studies on BUD+FORM are required because most studies involved SALM + FL.[18]
  - The review reported an NNT of 36 (95% CI: 21 to 258), assuming a placebo mortality rate of 15.2% over 3 years.[18]

Tiotropium

- UPLIFT compared TIO vs placebo and found different results depending on the analysis. Patients were allowed to take all respiratory medications except other inhaled anticholinergics. Of interest, **no increased** mortality with TIO was shown.
  - **Non-significant** difference using intention-to-treat analysis at 1470 days:
    - 14.9% vs 16.5%; hazard ratio 0.89 (95% CI: 0.79 to 1.02).
  - **Significant** decrease in mortality with TIO using protocol-defined study-period at 1440 days:
    - 14.4% vs 16.3%; hazard ratio 0.87 (95% CI: 0.76 to 0.99).

Oxygen

- Long-term continuous oxygen therapy (≥ 15 hours per day or more to achieve an oxygen saturation of ≥ 90%) decreases mortality
  - In patients with stable COPD and severe hypoxemia (partial pressure of arterial oxygen ≤ 55 mm Hg **or**
  - When the partial pressure of arterial oxygen is < 60 mm Hg in the presence of bilateral ankle edema, cor pulmonale, or hematocrit >56%.[12]

Comparisons between therapies

Salmeterol plus fluticasone vs salmeterol, fluticasone, or tiotropium

- TORCH found that **SALM + FL** led to
  - No statistically significant benefit over SALM alone.
  - Statistically significantly lower mortality than FL alone.
    - Hazard ratio 0.77 (95% CI: 0.64 to 0.90) P=0.007.
- The Wilt meta-analysis found
  - No difference in mortality between LABA + ICS and LABA.
  - No difference in mortality between LABA + ICS and ICS in absolute risk reduction but benefit in relative risk reduction.
- INSPIRE found that SALM + FL led to lower mortality over 2 years compared to TIO
  - 3% vs 6%; NNT 40 (95% CI: 21 to 327) P=0.032.[10]
  - The clinical significance of this result is uncertain since the study was not designed to test for differences in mortality. Also, there was no placebo group so it is unclear if the result was due to benefit from SALM+FL or harm from TIO.[10]

Tiotropium vs tiotropium + salmeterol, or tiotropium + salmeterol + fluticasone

- OPTIMAL reported incidence of all-cause mortality, but no statistical analyses of the data were presented.
  - TIO 2.6% (4 deaths)
  - TIO+SALM 4.1% (6 deaths)
  - TIO+SALM+FL 4.1% (6 deaths)

Tiotropium vs LABA

- A Cochrane review[19] reported no statistically significant difference in mortality for the comparison of LABA vs TIO.

- **Academic Detailing Service comments on mortality**
  - The Wilt meta-analysis states good evidence supports that monotherapies do not reduce mortality.
  - SALM + FL has shown a **possible** reduction in mortality vs placebo, TIO, or FL.
  - There is no evidence that SALM + FL provides additional benefit vs SALM alone.
  - Available evidence does not allow conclusions on differences in mortality rates between TIO, TIO+SALM, or TIO+SALM+FL.

Hospitalizations for COPD Exacerbations

- We found no trials in which hospitalization was studied as the sole primary outcome.
- Exacerbations severe enough to cause hospitalization are serious events with substantial morbidity and mortality. Short-term mortality in patients with mild to moderate COPD who are admitted to hospital is 4% and can rise to 24% if they are admitted to an intensive care unit with respiratory failure.[2]
- Our content expert estimates in-hospital mortality is approximately 10% and 2-year mortality following a hospitalization for a COPD exacerbation is approximately 50%, twice that of a myocardial infarction.
- We found two 1-year studies that provided data on percentages of patients in the **placebo** group who were hospitalized for exacerbations.[20,21]
  - Both compared placebo to **TIO**.
  - We performed a meta-analysis of these studies; results are in Table 7.

Tiotropium vs other therapies

- One-year comparisons of TIO vs other drugs are also summarized in Table 7.

Table 7 Efficacy of tiotropium on hospitalizations for COPD exacerbations

Comparator	Event Rate		ARR	RRR	NNT for 1 year	
	Comparator	TIO			NNT	95% CIs
Placebo[20,21]	7.8%	5.3%	2%	33%	42	20 to 500
IPRA[16]	11.7%	7.3%	4%	38%	NS	
TIO+ SALM[6]	26%	31%	6%	18%	NS	
TIO+SALM+FL[6]	18%	31%	14%[1]	43%[1]	7	4 to 26
SALM+FL [10]	16%	13%	3%	19%	NS	

1 Comparator superior to TIO so risk reductions and NNT refer to benefit from comparator. E.g., TIO+SALM+FL is superior to TIO alone.

- OPTIMAL (1-year study)[6] found
  - The combination of **TIO + SALM + FL** led to **fewer** hospitalizations for COPD exacerbations than TIO alone (NNT 7 [95% CI: 4 to 26]).
  - There was **no** statistically significant **difference** between **TIO plus SALM** vs **TIO alone** (Table 7).
- UPLIFT found **no** statistically significant **differences** in mean number of hospitalizations for exacerbations between **TIO** and **placebo** but there was a significant delay in time to first hospitalization.[9]
- INSPIRE found **no** statistically significant **differences** in hospitalizations between **TIO** and **SALM + FL.**[10]

Salmeterol + fluticasone vs salmeterol, fluticasone or placebo

- TORCH (3-year study) showed **benefit** from **SALM** and **SALM + FL** vs **placebo**. The annual rates of hospitalization for severe exacerbation were:

		P-value vs placebo
• Placebo	0.19	
• SALM	0.16	0.02
• FL	0.17	0.10 (not statistically significant)
• SALM+FL	0.16	0.03

  - The authors state that both SALM and SALM+FL reduced hospitalization rates by 17% compared to placebo yielding a 1-year NNT of 32.
  - However, this estimate is based on hospitalizations per person per year and does not consider the effect of some patients having more than 1 hospitalization. The real NNT may be higher (see Appendix A).[22]

Other comparisons

- Other studies have found **no statistically significant difference** in the following comparisons for hospitalizations:
  - TIO vs TIO + SALM[6]
  - TIO vs SALM[19]
  - TIO vs IPRA[19]
  - ICS vs placebo[8]
  - ICS vs ICS + LABA[8]
  - LABA vs ICS + LABA[8]
- The Wilt meta-analysis concluded that reductions in hospitalizations were not consistently observed and do not permit definitive conclusions on the relative effectiveness of inhaled therapies.[1]
- **Academic Detailing Service comments on hospitalizations**
  - TIO has not shown benefit over IPRA.
  - TIO, SALM, and SALM + FL have shown benefit over **placebo** in decreasing hospitalizations.
  - TIO + SALM + FL showed benefit over TIO alone but this was a **secondary** outcome.
  - TIO and LABA+ICS have similar benefit.
  - The addition of ICS to LABA did **not** provide benefit over LABA or ICS alone.

Exacerbations

- A COPD exacerbation is defined as a sustained worsening of dyspnea, cough, or sputum production leading to an increase in the use of maintenance medications and/or supplementation with additional medications **(level of evidence: 3)**.[2]
  - The term 'sustained' implies a change from baseline lasting 48 hours or more.

- In addition, exacerbations should be defined as either purulent or nonpurulent because this is helpful in predicting the need for antibiotic therapy **(level of evidence: 2A)**.

- Acute exacerbations are the most frequent cause of medical visits, hospital admissions, and death among patients with COPD. In addition, frequent exacerbations are an important determinant of quality of life and contribute to accelerated rates of decline in lung function.[2]
- Exacerbations are one of the most frequently reported outcomes in COPD studies of long-acting agents and combination therapies; many studies show benefits from these therapies. However, several issues have been raised about the reporting and analysis of exacerbations in these studies.[22-24]
  - Not all trials used an intention-to-treat analysis in which patients who prematurely stopped study medications were retained in the trial to see if they subsequently had exacerbations.[23] This may lead to over or underestimation of treatment effect.
  - Few trials had blinded adjudication of the occurrence of exacerbations to see if they were consistent with pre-specified definitions.[23]
  - Few trials had a system to define whether an exacerbation was new, a slow-to-resolve exacerbation, or a relapse.
    - For instance, a patient may present with symptoms of cough, dyspnea, and sputum on day 1 and receive an antibiotic, then present again on day 7 for identical symptoms and receive a second antibiotic, then present again on day 14 with the same symptoms and receive oral steroids.
    - The question is: are these truly separate events or are these latter two events simply relapses or continuations of the original exacerbation?[23]
  - The result is that there is some **uncertainty** about the results presented showing effects of therapies on exacerbations.

Comparisons vs placebo

- The Wilt meta-analysis showed that, compared to **placebo**
  - IPRA showed no statistically significant benefit.
  - LABAs, TIO, and ICS all showed a similar benefit with a statistically significant **relative** risk reduction of approximately **15%**.
  - Combined LABAs and ICS showed a **relative** risk reduction of **23%** which was not statistically significant.
- To get an idea of the percentage of patients who have an exacerbation per year and respond to the various agents we did a meta-analysis of all the 1-year trials and found the event rate in the **placebo group** to be **42%**.
- From the relative risks calculated in the Wilt meta-analysis and assuming that 42% of patients in the placebo group will have an exacerbation, we calculated the numbers needed to treat for each drug (Table 8).
  - This provides a **rough estimate** for a **NNT of 15 to 18** to prevent 1 person per year from having an exacerbation compared to **placebo.**

Table 8 Efficacy of inhaled agents vs placebo on exacerbations in one-year studies

Comparator vs Placebo	Event Rate		ARR[1]	RRR[2]	NNT[3] for 1 year	
	Placebo	Comparator			NNT	95% CIs
TIO	42%	35%	6.7%	16%	15	11 to 24
LABA	42%	37%	5.5%	13%	18	13 to 34
ICS	42%	36%	6.3%	15%	16	10 to 60
LABA + ICS	42%	32%	9.7%	23%	NS[4]	

1. ARR = absolute risk reduction
2. RRR = relative risk reduction
3. NNT = number needed to treat
4. NS = not significant. TORCH showed statistically significant benefit of LABA+ICS vs placebo over 3 years.[8] Data from TORCH could not be included in Wilt meta-analysis but were reported separately (see below).

Other comparisons

- The Wilt meta-analysis also compared various drugs and combinations.[1]
  - TIO was **superior** to IPRA (relative risk 0.77, 95% CI: 0.62 to 0.95).
  - There was **no statistically significant difference** in the following comparisons:
    - TIO vs LABA
    - TIO vs TIO + LABA
    - TIO vs TIO + LABA + ICS
    - LABA vs IPRA
    - LABA vs ICS
    - LABA vs LABA + ICS

Salmeterol plus fluticasone

- Data from TORCH could not be included in the Wilt meta-analysis but was discussed in the text of the publication.
- TORCH found that the combination of SALM + FL provided statistically significant benefit in the number of exacerbations per patient per year compared to placebo or either agent alone. SALM and FL also statistically significantly reduced exacerbations compared with placebo.

Treatment	Exacerbations per patient per year	P-value vs placebo
Placebo	1.13	
SALM	0.97	<0.001
FL	0.93	<0.001
SALM + FL	0.85	<0.001

- Exacerbations were a **secondary outcome** and the primary outcome of mortality was **not** statistically significant.
- We could not estimate a 1-year NNT for these comparisons.

- The TORCH publication states that the NNT to prevent one exacerbation per year for SALM plus FL vs placebo is 4 but an article by Aaron states this is incorrect because some patients may have had more than one exacerbation.[22] (See appendix A for details of calculations.)
- A recent RCT[25]which reported moderate to severe exacerbations as the primary outcome found a statistically significant **benefit** with SALM+FL compared to SALM.

Tiotropium

- Two other studies which had exacerbations as their **primary** outcomes found **no** statistically significant **difference** in exacerbations for the following comparisons:
  - TIO vs TIO + SALM or vs TIO + SALM + FL (OPTIMAL)[6]
  - TIO vs SALM + FL (INSPIRE)[10]
- **Academic Detailing Service comments on exacerbations**
  - For monotherapies
    - TIO, LABA, and ICS have all shown benefit vs placebo (NNT 15 to 18).
    - TIO but not LABA has shown benefit vs IPRA.
  - For combination therapies
    - SALM + FL has shown benefit vs placebo, SALM, and FL.
    - The following combinations have **not** shown benefit vs TIO
      - TIO + SALM
      - SALM + FL
      - TIO + SALM + FL

Quality of life

- The main scales used to measure quality of life are the St George's Respiratory Questionnaire (SGRQ) and the Chronic Respiratory Disease Questionnaire (CRDQ) (Table 6)
  - The minimum clinically significant difference for the SGRQ is 4 points.
  - The minimum clinically significant difference for the CRDQ is 0.5 points per item.
- Studies often report the **mean differences** in scale scores between different treatments. Meta-analyses and large primary studies based on **mean** differences report the following comparisons **do** and **do not** result in **clinically** significant differences.

	Based on MEAN differences the following comparisons	
	DO NOT show clinically significant differences in quality of life	**DO** show clinically significant differences in quality of life
Comparisons vs **placebo**	IPRA[26,27] TIO[1,7,19] LABA[7,8,28] FL[8] TIO + LABA[7]	
Comparisons vs **other agents**	TIO vs IPRA[16] LABA vs IPRA[29] SALM + FL vs SALM[8,25] SALM + FL vs FL[8] TIO vs LABA[1,19] TIO vs TIO + LABA[6,7] TIO vs SALM + FL[10]	TIO + SALM + FL vs TIO[6]

- There is some **uncertainty** about the comparison between **LABA+ICS and placebo**.
  - A Cochrane meta-analysis indicates there was a clinically significant difference between FORM+BUD and placebo but **not** between SALM + FL and placebo.[18]
  - TORCH showed there was **no clinically significant** benefit for SALM + FL vs placebo in SGRQ scores.[8]
- The Wilt meta-analysis states "Evidence indicates that **average** improvement in respiratory health status [from inhalation therapies] is **clinically insignificant**, but **some** individuals achieve a noticeable **improvement**."[1]
- To give an idea of the **percentage** of patients who might benefit we have analyzed results from studies that reported the percentages of patients who achieved a clinically significant difference in quality of life, the same approach we used for hospitalizations and exacerbations. These 10 studies represent approximately 25% of commonly reported COPD trials involving these therapies.
- The **percentages** of patients reporting a clinically significant difference are in Table 9.

Table 9 Percentage of study subjects reporting a clinically significant difference in SGRQ or CRDQ

Comparator	Percentage	95% CI	Studies
Placebo	34%	30% to 38%	9, 20, 26, 27, 30, 31
IPRA	38%	34% to 43%	16, 26, 27
TIO	44%	36% to 52%	9, 10, 16, 20, 30
SALM	38%	30% to 47%	25-27, 30, 31
SALM+FL	37%	28% to 47%	10, 25

- We then carried out a meta-analysis of the comparisons in the various studies to estimate the numbers needed to treat (Table 10).
  - In some cases, there may be no clinically significant benefits based on **mean** differences, but the percentage of patients showing a clinically significant benefit will be statistically significant. For example, consider **TIO vs IPRA**.
    - Based on **mean** difference, there is no clinically significant difference (Page 31).
    - Based on percent achieving statistically significant difference, TIO shows benefit over IPRA, 52% vs 35%, NNT 7 (95% CI: 4 to 12) (Table 10).

Table 10 Clinically significant benefits in SGRQ or CRDQ based on percentage of patients responding

Comparators	Event Rate		Absolute benefit	Relative benefit	NNT	
	Comp 1[1]	Comp 2[2]			NNT[3]	95% CIs P-value
IPRA vs placebo[26,27]	40%	32%	8.0%	25%	NS[4]	P=0.054
TIO vs placebo[9,20,30]	49%	35%	12%	35%	8	5 to 16 P<0.001
SALM 50 ug vs placebo[26,27,30,31]	42%	33%	7.3%	27%	14	8 to 43 P=0.004
TIO vs IPRA[16]	52%	35%	17.0%	49%	7	4 to 12 P=0.001
TIO vs SALM[30]	49%	43%	5.7%	88%	NS[4]	
SALM 50 ug vs IPRA[26,27]	46%	40%	5.9%	23%	NS[4]	
SALM+FL vs SALM[25]	30%	42%	12%	28%	9	6 to 17 P=0.002
SALM+FL vs TIO[10]	32%	27%	4.6%	15%	22	CIs not calculated[5] P=0.021

1. Comparator 1, for example in row 1, Comp 1 = IPRA
2. Comparator 2, for example in row 1, Comp 2 = placebo
3. NNT = number needed to treat. No time frame given because studies of different duration were used in calculations (3 months to 4 years).
4. Number needed to treat not calculated if result is not statistically significant
5. Confidence intervals not calculated because results based on **unadjusted** data in paper and supplied by author were not statistically significant. **Adjusted** data were statistically significant but did not allow us to calculate confidence intervals. P value of 0.021 was provided in paper from adjusted analysis.

- **Academic Detailing Service comments on quality of life**
- Approximately 35% of patients respond to **placebo** therapy.
  - The placebo groups were allowed to take short-acting bronchodilators as required and response rates probably reflect their benefit. Of note, patients taking the study drugs were also allowed to take short-acting bronchodilators.
  - Our content expert suggests that patients taking part in COPD studies may improve just from being in a study.

- Because of the limited number of studies that were suitable for analysis, and other methodological issues related to the data **it is not possible to definitively recommend one therapy over another**.
  - However, our calculations suggest that approximately **1 patient out of 7 to 14** will notice a benefit when switched from short-acting bronchodilators to long-acting agents.
  - From the data presented above, it is apparent that up to 50% of patients will notice an improved quality of life no matter which inhalation treatment(s) they use, including placebo which is equivalent to prn use of SABA.

Symptoms of dyspnea

- The Transitional Dyspea Index (TDI) is the validated scale most frequently used to measure symptoms of dyspnea.
  - The minimum clinically significant difference is 1.0 unit.
- We did not find enough studies that reported percentages achieving a minimum clinically significant difference in the TDI to be able to report NNTs as we did for quality of life.
- However, from Cochrane reviews and other meta-analyses we found the following comparisons **do** and **do not** show clinically significant differences based on **means.**

	Based on <u>MEAN</u> differences the following comparisons	
	DO NOT show clinically significant differences in dyspnea	**DO** show clinically significant differences in dyspnea
Comparisons vs **placebo**	SALM[28]	SABA[32] TIO[19] LABA+ICS[18]
Comparisons vs **other agents**	SABA vs IPRA[29] SALM vs TIO[1] LABA vs LABA + IPRA[33] LABA vs LABA + ICS[34] ICS vs LABA + ICS[35] TIO vs TIO + SALM[6] TIO + SALM vs TIO + SALM + ICS[6] TIO vs TIO + SALM + ICS[6]	TIO vs IPRA[19]

- **Academic Detailing Service comments for dyspnea**
  - SABAs, TIO, and LABA + ICS have all been found to provide **clinically significant** benefit vs **placebo**.
  - TIO led to a **clinically significant** benefit vs IPRA but no other head-to-head comparisons showed any clinically significant difference.

Exercise capacity

- There are many measures of exercise capacity. Recent studies use constant work rate cycle exercise to measure exercise capacity. However, the minimum clinically significant difference for this measure has not been defined so we have reported results of 6-minute walk tests to measure exercise capacity. We also limited our reporting primarily to Cochrane reviews.
- The following studies reported **no clinically significant benefit** from the following drugs compared to **placebo**:
    - SABA[32]
    - TIO[7]
    - LABA[28]
    - TIO + FM[7]
    - LABA + ICS[18]
- The following studies showed **no clinically significant benefit** from the following **drug comparisons**:
    - SABA vs IPRA[29]
    - TIO vs TIO + FM[7]
    - TIO + FM vs FM[7]
    - LABA vs IPRA[33]
    - LABA+ICS vs LABA[34]
    - LABA+ICS vs ICS[35]
- One study cited by the Cochrane review[36] gave the percentage of patients who experienced a clinically significant improvement in a shuttle walk test
    - FOR 41%
    - IPRA 38%
    - Placebo 30%
        - Note the similarity of results between formoterol and IPRA. A Cochrane review also concluded that there is **little difference** between LABAs and IPRA in improving exercise tolerance.[33]
- A study on TIO and pulmonary rehabilitation found that patients taking TIO were able to exercise approximately 6 minutes longer than those on placebo immediately after and 12 weeks after an 8-week pulmonary rehabilitation program (TIO 22.4 mins vs placebo 15.8 mins, p=0.018).[37]

Academic Detailing Comment on exercise

- Our content expert recommends that patients on bronchodilators be encouraged to increase their physical activity as much as possible to maximize benefit.

Decline in lung function

- **Smoking cessation** is the only intervention that has been definitively shown to slow the rate of lung function decline.[12]
- Until recently there has been evidence that pharmacological management of COPD (IPRA,[38] TIO,[9] ICS[17,39-41]) does **not** reverse, slow, or prevent the progressive decline in lung function.[4]
- However, a post-hoc analysis of TORCH suggests that there **may** be a beneficial effect from SALM and FL alone and in combination.[42]
- Over the 3 years of the study the decline in FEV_1 in the study groups was

		P-value vs placebo
• Placebo	55 ml/yr	
• SALM	42 ml/yr	0.003
• FL	42 ml/yr	0.003
• SALM + FL	39 ml/yr	<0.001

- All 3 treatments were statistically significant vs placebo.
- Of note, the decline in former smokers in the study was **36.6 ml per year,** an indication of the importance of smoking cessation.
- A commentary has raised the point that the analysis was not done on a true intent-to-treat basis.[43]
    - The 26,000 measurements of FEV_1 were collected only until the patients discontinued treatment, so that around 10,000 measurements were missing from the proper intent-to-treat analysis.
    - The data are not randomly missing. Nearly 18% of patients allocated to placebo did not contribute a single FEV_1 value, compared with 9% for combination therapy, and there are more missing FEV_1 values in the latter part of the follow-up period than earlier on.
    - Despite this limitation, the analysis concludes there is **possible** evidence that medication can modify the decline in lung function associated with COPD and states that SALM is the desired drug since there are concerns of adverse effects of ICS. (See page 44.)
- Another commentary points out that measurement of FEV_1 while patients have study drugs in their systems (as was the case in TORCH) is the same as measuring FEV_1 before and after 2 puffs of SABA and concluding the drug has changed the disease. The acid test for determining change in the course of the disease is measurement **after** the study drug has been **washed out**.[44]
- **Comments from Academic Detailing Service.**
    - Most evidence indicates that pharmacological management of COPD does **not** reverse, slow, or prevent the progressive decline in lung function.[4]
    - However, the findings of the **post-hoc** analysis of TORCH suggest there **may** be a beneficial effect from SALM and FL alone and in combination.[42] These findings were from a **secondary** outcome. They should be **viewed with caution** and confirmed by an appropriately designed study.

Oxygen Therapy

- The Wilt meta-analysis states ambulatory oxygen does not improve respiratory health status measures, exercise capacity, or hospitalizations over the short term.[1]
- The CTS Guidelines state current evidence does not justify the widespread provision of **ambulatory** oxygen to patients with COPD **(level of evidence: 1C)**.[2]

Non-inhalation therapies

Education and self-management plans

- A 2007 Cochrane review[3] defined education as
  - A formal program which transfers information about COPD and treatment of COPD from a health care provider to a patient where the primary goal was to improve the knowledge and understanding of COPD. The educational program might be directed towards smoking cessation, improving exercise, nutrition, self-treatment of exacerbations, inhalation technique or coping with activities of daily living, or a combination of these.
- The definition of a self-management plan is a written plan produced for the purpose of patient self-management of COPD exacerbations. It informs patients about when and how to adjust and/or start medication in case of an exacerbation.
- The Cochrane review reported a clinically and statistically significant reduction of the probability of at least one **hospital admission** among patients receiving self-management education compared to those receiving regular care (OR 0.64; [95% CI 0.47 to 0.89]).
  - NNT for individual studies varied between 10 and 30, depending on risk of hospitalization of patients in the placebo group.
- For **exacerbations**, the Cochrane review showed **inconclusive** results with 1 study showing fewer and 1 showing more exacerbations. There tended to be increased use of oral corticosteroids and antibiotics in the self-management groups but this was not a consistent finding. It may be that people in the self-management groups started taking these medications earlier because they recognized the onset of an exacerbation sooner.[3]
- The Cochrane review reported[3]
  - **No clinically** significant benefit in the SGRQ or other **quality of life** scales. They did report "small but significant" benefit in dyspnea.
  - **No statistically** significant benefit in **exercise capacity** or **change in lung function**.
- It concluded that the benefit in hospitalizations was reason enough to recommend self-management education. It also noted that it was not possible to recommend a particular form or content of self-management program because studies varied in their interventions, study populations, follow-up time, and outcome measures.

CTS Recommendation

Educational intervention for the patient and family with supervision and support based on disease-specific self-management principles is valuable, and should be part of the continuum of optimal COPD management in Canada. **Level of evidence 1A**

- Information about education and self-management plans is available through the Lung Association of Nova Scotia at 443-8141, their web site at www.lung.ca or www.lung.ca/breathworks.

Pulmonary rehabilitation

- A 2006 Cochrane review defines pulmonary rehabilitation as a "multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy." Programs usually consist of education, exercise, smoking cessation, and nutritional counselling.
- The Cochrane review on pulmonary rehabilitation did not report on **mortality** or **hospitalizations**.
  - The Canadian guidelines report that trials have not been designed to study the effects of rehabilitation on mortality but there is a trend toward reduced mortality.[2]
  - A Canadian study reported pulmonary rehabilitation led to **fewer** patients requiring at least 1 hospitalization over 1 year (51% vs 31%, NNT 5 [95% CI: 3 to 22]).[45]
- **For quality of life**, The Cochrane review reported that pulmonary rehabilitation led to clinically significant **benefits** in the mean scores for all domains of the SGRQ.[14]
- From a meta-analysis of 16 studies, the Cochrane review found the overall mean benefit on the **6-minute walk test** from pulmonary rehabilitation was 48 metres (95% CI: 32 to 65) and stated the clinical significance of this benefit "**remains uncertain.**"[14]
- The Cochrane review concluded that pulmonary rehabilitation relieves dyspnea and fatigue, improves emotional function, and enhances patients' sense of control over their condition. These improvements are moderately large and clinically significant. Rehabilitation forms an important component of the management of COPD.
- Pulmonary rehabilitation services are available in Nova Scotia in the metro area at the Queen Elizabeth II Health Sciences Center, Cobequid Community Health Centre, Truro, and the Cape Breton Regional Hospital. A program is planned for the Annapolis Valley.

CTS recommendations

- All patients should be encouraged to maintain an active lifestyle and be cautioned about the negative consequences of prolonged inactivity in this disease **(level of evidence: 3A)**.
- Clinically stable patients who remain dyspneic and limited in their exercise capacity despite optimal pharmacotherapy should be referred for supervised pulmonary rehabilitation **(level of evidence: 1A)**.

Influenza vaccination

- The effectiveness of influenza immunization will depend on how much influenza-related respiratory infections are present and how well the vaccines are matched to the virus.[46]
- A 2007 Cochrane review[46] reported there is **limited evidence** from RCTs on the efficacy of influenza vaccination in COPD. The review reported **no effect** of influenza vaccination on:
  - Mortality: 2 RCTs
  - Hospitalizations: 2 RCTs
  - Exercise capacity: 1 RCT
  - Lung function: 2 RCTs
- For **exacerbations,** it is important to distinguish exacerbations that occur in the "early" period after immunization (3 to 4 weeks) from those that occur "late" after which immunity has had time to develop. Theoretically, exacerbations occurring early could be attributed to the vaccine itself.[46]
  - The Cochrane review reports results of 2 small RCTs on exacerbations. Both found a decrease in "late" exacerbations (mean difference in number of exacerbations -0.39, [95% CI -0.61 to -0.18], P = 0.0004) with no increase in "early" exacerbations.
  - These findings are consistent with those from observational studies.[46]
- The Cochrane review concluded that, from the limited number of studies performed, inactivated vaccine reduces exacerbations in COPD patients.

CTS Recommendations

Annual influenza vaccination is recommended for all COPD patients who do not have a contraindication **(level of evidence: 2A)**.

Pneumococcal vaccination

- A 2006 Cochrane review[47] reported 4 RCTS that showed **no benefit** from pneumococcal vaccination on:
  - Mortality: 3 RCTs
  - Hospitalizations: 2 RCTs
  - Exacerbations: 1 RCT
- Changes in exercise capacity and lung function were not reported.
- The Cochrane review concluded that there is no evidence from RCTs that injectable pneumococcal vaccination in persons with COPD has a significant impact on morbidity or mortality. Further large randomised controlled trials are needed to ascertain if the small benefits suggested by individual studies are real.

CTS Recommendations

Pneumococcal vaccination should be given to all COPD patients at least once in their lives; in high-risk patients, consideration should be given to repeating the vaccine in five to 10 years **(level of evidence: 3C)**.

Which patients will benefit from therapy? How do you evaluate the effect of therapy?

Summary Response

- The benefits of COPD therapies in patients in the **mild to moderate** airflow obstruction categories are **uncertain** and most evidence is limited to patients in the **moderate to severe** airflow obstruction category (**FEV_1 less than 60%** predicted).
- The 2003 CTS Recommendations suggest asking several simple questions to evaluate the effect of therapy. If there is no subjective benefit
  - Assess compliance including inhaler technique, or alter the dose if appropriate.
  - Discontinue the drug and monitor for symptomatic deterioration. Recommence the drug if deterioration occurs.
- Our content expert suggests keeping a patient on therapy even if they have no symptomatic improvement if **preventing recurring exacerbations** is a consideration.

- Inclusion criteria in most COPD studies was an FEV_1 of **<65%** predicted. Generally, the **mean** FEV_1 was **<50%** predicted, the severe category.
- The Wilt meta-analysis states that current evidence suggests that COPD treatment benefits are primarily related to reduced exacerbations among exacerbation-prone adults with activity-limiting dyspnea and **FEV_1 less than 60%** predicted.[1]

- The US family physician guidelines make a strong recommendation that treatment for stable COPD should be reserved for patients who have respiratory symptoms and FEV_1 less than 60% predicted, as documented by spirometry.[48]
- The CTS guidelines state that little information exists concerning the efficacy of pharmacotherapy in patients with milder COPD (i.e., FEV_1 > 65% predicted), making evidence-based guidelines for this subpopulation impossible.
- Therefore, the benefits of COPD therapies in patients in the mild to moderate categories are **uncertain** and most evidence is limited to patients in the moderate to severe category.
- The 2003 CTS Recommendations[49] suggest that several simple questions can help clinicians evaluate the effect of therapy:
  - "Did the new treatment help your breathing?"
  - If the answer is yes then ask "In what way has it helped you?"
  - A response indicating that the patient can perform tasks with less breathlessness or for longer periods of time indicates benefit.
  - If there is no subjective benefit then options include
    - Assess compliance (including inhaler technique)
    - Alter the dose (if appropriate)
    - Discontinue the drug and monitor for symptomatic deterioration. Recommence the drug if deterioration occurs.
- Our content expert suggests keeping a patient on therapy even if they have no symptomatic improvement if **preventing recurring exacerbations** is a consideration.
- The CTS 2007 Guidelines suggest that patients with moderate-to-severe COPD and **≥ 1 exacerbation per year** on average, for 2 consecutive years be treated with TIO + LABA + ICS. In the 2003 guidelines, the threshold was ≥ 3 exacerbations for prescribing inhaled corticosteroid.
  - Our content expert suggests
    - The threshold of 1 exacerbation per year is based on consensus. Exacerbations should be severe enough to require antibiotics, oral corticosteroids or an emergency room visit.
- The UK Guidelines suggest in moderate to severe COPD unresponsive to short-acting agents, a LABA+ICS can be tried but discontinue after 4 weeks if there is no benefit and the patient is not experiencing frequent exacerbations (≥ 2 exacerbations in a 12-month period.)

What are possible adverse effects of therapies in COPD?

Summary response

- **Mortality**
  - There is **inconsistent** evidence that IPRA is associated with increased mortality.
  - TIO, LABAs, and ICS do not appear to be associated with increased mortality.
- **Cardiovascular events**
  - There is **inconsistent** evidence that anticholinergics are associated with increased cardiovascular events.
- **Pneumonia**
  - ICS alone or in combination with LABA is associated with an **increased** risk of pneumonia.
- **Fractures and cataracts**
  - ICS alone or in combination with LABA does **not** appear to have any effect on fractures or cataracts in COPD. However, the longest duration of therapy was **3 years** and not all studies were designed to measure these outcomes.
- **Oropharyngeal candidiasis, dysphonia, and skin bruising**
  - ICS alone or in combination with LABA is associated with an **increased** risk of oropharyngeal candidiasis, dysphonia, and skin bruising.

- Adverse events reported in product monographs are listed below.[50] Please check individual product monographs for more complete lists of adverse events.

Anticholinergics	$Beta_2$ Agonists	Inhaled corticosteroids
Dry mouth	Tremor	Candidiasis (mouth & throat)
Constipation	Headache	Hoarseness, dysphonia
Increased heart rate	Sinus tachycardia	Adrenal suppression
Supraventricular tachycardia	Muscle spasms	↓ bone mineral density
Atrial fibrillation	Hypokalemia (rare)	Glaucoma, cataracts
Blurred vision		
Acute glaucoma		
Urinary difficulty		

- Publications have raised concern for **increased**
  - Stroke and other cardiovascular events with anticholinergic agents
  - Respiratory deaths with LABAs, and
  - Pneumonia, osteoporosis, and cataracts with ICS.
- Some recent publications (meta analyses, case-control, and randomized controlled trials) addressing adverse events of inhaled medications are summarized below.

Adverse effects of anticholinergics

- A meta-analysis[51] of 17 studies including 14,783 patients reported that anticholinergics (TIO, IPRA) increased the risk of the **primary composite outcome of CV death, MI, or stroke:**
  - Anticholinergics 1.8% vs 1.2% control, RR 1.58 (95% CI: 1.21- 2.06) P <0.001
  - The increased risk was statistically significant with IPRA alone but **not** TIO alone.
    - Anticholinergics **increased** rates of
      - **MI** 1.2% vs 0.8%, RR 1.53 (95% CI: 1.05 to 2.23) P=0.03
        - Estimated **NNH 174** (95% CI, 75 to 1835 for 1 year).
      - **CV death** 0.9% vs 0.5% RR 1.80 (95% CI: 1.17-2.77) P = 0.008
        - Estimated **NNH 40** (95% CI: 18 to 185 for 1 year)

        (NNHs were calculated by authors from baseline risks in separate studies.)
    - Anticholinergics **did not increase** the risk of
      - **Stroke** or **all cause mortality**

- Analysis of studies **over 6 months** (N=7267) resulted in a statistically significant **increased risk of CV death, MI and stroke** when IPRA and TIO were analyzed together or separately.
  - Anticholinergics 2.9% vs 1.8% for control, RR 1.73 (95% CI: 1.27 to 2.36) P<0.001
  - TIO RR 2.12 (95% CI: 1.22 to 3.67) P=0.008
  - IPRA RR 1.57 (95% CI: 1.08 to 2.28) P=0.02
  - Increased risk for these outcomes was not statistically significant in **short-term** studies.
  - Limitations of the study include:
    - Studies were not designed to specifically monitor cardiovascular outcomes.
    - CV outcomes were not adjudicated.
    - There was no stratification analysis based on confounding factors: e.g., FEV_1, existing coronary artery disease, use of cardioprotective agents etc.
  - The authors concluded that adequately powered prospective studies are required to determine whether anticholinergics affect cardiovascular risk and whether any increase in risk is an acceptable trade-off for the symptomatic benefit.
- Another recent **meta-analysis**[1] included 9 trials and found **no significant difference in mortality rates** between either IPRA or TIO vs. placebo.
  - IPRA vs placebo RR 1.20 (95% CI: 0.81 to 1.78) (4 trials)
  - TIO vs placebo RR 0.94 (95% CI: 0.60 to 1.47) (5 trials)
  - Causes of death were not provided.
- A **case-control study** (32,130 cases and 320,501 controls) using the US Veterans Affairs database found that
  - **IPRA increased** the risk of [52]
    - All-cause mortality, odds ratio 1.11 (95% CI: 1.08 to 1.15) and
    - CV death, odds ratio 1.34 (95% CI: 1.22 to 1.47)

- IPRA **did not** statistically increase
  - Respiratory deaths: odds ratio 1.06 (95% CI:0.93–1.22)
- TIO was not included in this analysis.
- The authors conclude that IPRA has a **possible** association with increased risk of these adverse events but causation has not been proven, therefore more studies are needed.
- The increased risks are considered to represent a weak association, as an odds ratio of > 2 is required in studies of harm.[53]

- UPLIFT (4 years, RCT, N=5993[9]*)* comparing **TIO with placebo** found different results for all cause mortality depending on the analysis. There was **no statistically significant increase** in cardiovascular events with TIO and no effect on risk of stroke.
  - Mortality:
    - Non-significant difference with intention to treat analysis at 1470 days:
      - 14.9% vs 16.5%: hazard ratio 0.89 (95% CI: 0.79 to 1.02)
    - Significant difference with protocol defined analysis at 1440 days:
      - 14.4% vs 16.3%: hazard ratio 0.87 (95% CI: 0.76 to 0.99)
  - Cardiac events: Relative risk 0.84 (95% CI 0.73 to 0.98) p<0.05
    - MI: TIO 67 patients, placebo 85 patients
      - Relative risk 0.73 (95% CI: 0.53 to 1.00)
    - Stroke: TIO 82 patients, placebo 80 patients
      - Relative risk 0.95 (95% CI: 0.70 to 1.29).
- INSPIRE (2 years, RCT, N=1323)[10] comparing the combination of SALM + FL to TIO found an increase in the secondary outcome of **all-cause mortality** for TIO (3% vs 6% p = 0.032).
  - The authors comment that this study was not powered to detect mortality and more study is needed to quantify risks.
  - There was no placebo group so it is unclear if the result was a result of benefit from SALM+FL or harm from TIO. However, other studies have not demonstrated an increased risk with TIO vs. placebo.
- The use of both IPRA and TIO is **not** recommended due to increased potential for adverse events with **no** added benefit.[50]

Academic Detailing Service comments on adverse effects of anticholinergics

- There is **inconsistent** evidence that IPRA is associated with increased **mortality**.
- There is evidence that TIO is **not** associated with increased **mortality or stroke** compared to placebo. It may be associated with decreased mortality.
- There is **inconsistent** evidence that anticholinergics are associated with increased **cardiovascular events**.

Adverse effects LABA and/or LABA +ICS in COPD

- Results of a meta-analysis[54] raised concern that beta$_2$-agonist use, (12 of the 13 studies included were for LABA) could lead to an increased risk for respiratory deaths in patients with COPD. However, the number of deaths the analysis was based on was small and this and other methodological limitations make results inconclusive. Increased rates of **asthma**-related deaths in the SALM arm of a large RCT[55] resulted in warnings being issued for LABAs by Health Canada and the FDA.

- Rodrigo et al, 2008 performed a **meta-analysis** which restricted the analysis to LABAs in studies 3 months to 3 years duration and reported the following results.[56]
  - **All-cause mortality** (N= 8400, 13 studies)
    - **No** statistically significant **difference** between LABA and placebo
      - RR 0.90 (95% CI: 0.76 to 1.06) p = 0.20.
      - There were no significant differences between SALM and FORM subgroups and patients taking or not taking ICS.
  - **Respiratory death** (N=8049, 12 studies)
    - **No** statistically significant **difference** between LABA vs placebo
      - RR 1.09 (95% CI: 0.45 to 2.64) (5 studies)
    - Statistically significant **reduction** for LABA + ICS vs LABA
      - RR 0.35 (95% CI: 0.14 to 0.93) p= 0.03 (2 studies)
- The Wilt meta-analysis of 14 RCTS[1] also reported
  - **No** significant **increase** in all cause **mortality** for LABA or LABA + ICS vs placebo.
- TORCH (3 years, RCT, N=6112) studied **mortality** as a **primary** outcome.
  - Results were consistent with the meta analyses above. There were **no** statistically significant **differences** in all cause mortality or COPD–related deaths with SALM or SALM+ FL vs placebo.

Academic Detailing Service comments on adverse effects of LABA and/or LABA+ICS

- There is evidence that LABAs alone or in combination with ICS do **not** increase all cause or respiratory **deaths** compare to placebo.

Adverse effects of ICS in COPD

- Three recent meta-analyses,[1,57,58] one of which was a Cochrane review,[57] reported on rates of adverse reactions to ICS. Each meta-analysis included slightly different combinations of trials although many were common to each analysis.

Mortality

- Drummond et al[58] reported **no** statistically significant **difference** in **all cause mortality** at 1 year (n= 9233, 5 studies lasting at least 6 months)
  - ICS 2.76% vs 3.22% control (active or placebo)
    - Relative risk 0.86 (95% CI: 0.68 to 1.09) p=0.20
  - Similar results were found for 2 and 3-year studies.
- The Cochrane meta-analysis[57] reported **no** significant **difference in mortality** compared to **placebo** (n=8390, 9 RCTs > 6 months)
  - Odds ratio 0.98 (95% CI: 0.83 to 1.16)
- The Wilt meta-analysis[1] included studies of at least 3 months (N=8369, 10 studies) duration and found **no** significant **difference in mortality** between ICS and **placebo**.
  - Relative risk 1.0 (95% CI: 0.86-1.16)

Pneumonia

- The meta-analysis[58] which included pneumonia as an outcome reported **statistically significant increases** with ICS. (7 RCTs n=10,776)
  - ICS 14.4%, control 10.4%, RR 1.34 (95% CI: 1.03-1.75) p=0.03
  - Higher risk was found in the following subgroups
    - Highest ICS dose
    - Shorter (<2 years) duration of ICS use
    - Higher baseline COPD severity (i.e., mean FEV_1<40% predicted)
    - Combination therapy
- Three RCTs contributed the most weight to the Drummond meta-analysis.[8,10,25] The rates reported in individual trials varied considerably, which may be a reflection of the lack of common definition used for pneumonia. Of note, confirmation of the diagnosis of pneumonia was not required in any of the 3 studies.
  - **TORCH, 3 years**, was the only trial that provided statistics on comparisons:[8]
    - There was a statistically significant **increase** in pneumonia in groups receiving ICS compared to **placebo**.
      - Placebo 12.3%
      - SALM 13.3%
      - FL 18.3% p<0.001 vs placebo, NNH 17 (95% CI: 12 to 29)
      - SALM+FL 19.6% p<0.001 vs placebo, NNH 14 (95% CI: 10 to 21)
  - **Kardos 2007, 44 weeks**[25]
    - SALM + FL N=23 (4.5%) vs SALM N=7 (1.4%)
      - NNH 32 (95% CI: 10 to 100)
  - **INSPIRE 2008, 2 years**[10]
    - SALM + FL N= 50 (8%) vs TIO N= 24 (4%)
      - NNH 25 (95% CI: 15 to 66)

Fractures

- Drummond et al[58] reported **no statistically significant** difference in the risk for fractures with ICS. (n=8131, 3 RCTs)
  - ICS 4.8% Control 4.4%
  - RR 1.09; 95% CI, 0.89-1.33; *P*=0.40
- The Yang meta-analysis[57] concluded that of the few long term studies measuring the effects of ICS on bone, no major differences in fractures or bone mineral density were shown over 3 years.
- The CTS recommendations state that ICS in doses greater than 1.5 mg/day of beclomethasone equivalent may be associated with decreased bone mineral density.[2]

Other adverse effects of ICS

- Yang[57] reported the following **statistically significant** increases vs. placebo
  - Oropharyngeal candidiasis odds ratio 2.49 (95% CI 1.78 to 3.49)
  - Hoarseness or dysphonia odds ratio 1.95 (95% CI 1.41 to 2.70)
  - Skin bruising odds ratio 1.86 (95% CI 1.39 to 2.48)
  - There was **no** significant **increase** in cataracts OR 1.06 (95% CI 0.80, 1.39)
- The CTS recommendations state that long-term high dose ICS is associated with posterior subcapsular cataracts and rarely ocular hypertension and glaucoma.[2]

Academic Detailing Service comments on adverse effects of ICS

- Use of ICS in COPD
  - Does **not appear** to have any effect on all cause **mortality, fractures, or cataracts.** However, the longest duration of therapy was **3 years** and not all studies were designed to measure these outcomes.
  - **Is** associated with an **increased** risk of **pneumonia, oropharyngeal candidiasis, dysphonia, and skin bruising**.

Appendix A Calculating NNT for exacerbations

- In the example in the table, 10 patients receive placebo for 1 year and 10 patients receive treatment for 1 year. The treatment is designed to prevent COPD exacerbations.[22]
- In the **placebo** group
  - 7 patients have no exacerbations
  - 1 patient has 1 exacerbation
  - 2 patients have 6 exacerbations each (total of 12 exacerbations)
  - There are 13 exacerbations per 10 patient-years = 1.3 per patient per year
  - 30% of patients have at least 1 exacerbation
- In the **treatment** group
  - 8 patients have no exacerbations
  - 1 patient has 3 exacerbations
  - 1 patient has 5 exacerbations
  - There are 8 exacerbations per 10 patient-years = 0.8 per patient per year
  - 20% of patients have at least 1 exacerbation
- NNT based on **exacerbations per patient-year**
  - 1÷ (1.3 - 0.8) = 2
- NNT based on **percent** of patients having at least one exacerbation
  - 1÷ (0.3 – 0.2) = 10 (This is the **correct** calculation.)

	Number of exacerbations in 1 year	
Patient number	**Placebo**	**Treatment**
1	0	0
2	0	0
3	0	0
4	0	0
5	0	0
6	0	0
7	0	0
8	1	0
9	6	3
10	6	5
Total	**13**	**8**
Annual rate of exacerbations per patient-year	1.3 (13 exacerbations per 10 patient-years)	0.8 (8 exacerbations per 10 patient-years)
Percent of patients having an exacerbation	30%	20%
Event-based NNT	1÷ (1.3 – 0.8) = 2	
Traditional NNT	1÷ (0.3 – 0.2) = 10	(The correct calculation)

APPENDIX B: INHALER COST COMPARISON CHART

Trade name, device Chemical name	Strength	Doses/ inhaler[1]	Wholesale cost per inhaler[2] ($)	Benefit status Full benefit (FB) Exception (E)
Anticholinergic, short-acting				
Atrovent® MDI Ipratropium bromide	20 mcg	200	20	FB
Anticholinergic, long-acting				
Spiriva Handihaler® TIO bromide	18 mcg	30	68	E
Beta$_2$-agonist, short-acting				
Ventolin®, Airomir (HFA), generic MDI Salbutamol sulfate	100 mcg	200	7.74[3]	FB
Bricanyl Turbuhaler Terbutaline sulfate	500 mcg	200	16	FB
Beta$_2$-agonist, long-acting				
Foradil Aerolizer® Formoterol fumarate	12 mcg	60	51	E
Oxeze Turbuhaler® Formoterol fumarate	6 mcg 12	60 60	35 47	E
Serevent® SALM xinafoate **Diskus**	50	60	59	E
ICS				
QVAR® HFA MDI Beclomethasone dipropionate	50 mcg 100	200 200	31 64	FB
Pulmicort® Turbuhaler Budesonide	100mcg 200 400	200 200 200	33 66 119	FB
Alvesco® Ciclesonide	100 mcg 200	120 120	45 74	FB
Flovent® Diskus FL propionate	50 mcg 100 250 500	60 60 60 60	16 26 44 88	FB
Flovent HFA MDI FL propionate	50 mcg 125 250	120 120 120	26 44 88	FB
Long-acting beta$_2$ agonist + ICS combinations				
Advair Diskus® SALM 50 mcg + FL 100, 250 or 500 mcg	100mcg 250 500	60 60 60	85 102 144	E
Advair® HFA MDI SALM 50 mcg + FL 125, 250 mcg	125mcg 250	120 120	102 144	E
Symbicort Turbuhaler® Formoterol 12 mcg + budesonide 100 or 200 mcg	100 mcg 200	120 120	65 85	E

1 Several inhalers contain 200 puffs and, based on dose, may last up to 3 months.

2 McKesson Canada; Dispensing fees not included; Prices rounded to nearest dollar, January 2009.

3 Maximum Allowable Cost (MAC) – Nova Scotia Pharmacare Program

Legend: MDI = Metered Dose Inhaler, HFA = Hydrofluoroalkane (i.e., cfc-free)

APPENDIX C: Demonstrating inhaler techniques

MDI alone

1. Remove cap*	Verbal _	Demonstrated _
2. Shake inhaler*	Verbal _	Demonstrated _
3. Exhale gently*	Verbal _	Demonstrated _
4. Open mouth wide*	Verbal _	Demonstrated _
5. Chin level or tilted up*	Verbal _	Demonstrated _
6. Hold inhaler upright, 2 finger widths outside of mouth	Verbal _	Demonstrated _
7. Activate inhaler just after beginning to breathe in	Verbal _	Demonstrated _
8. Continue to breathe in slowly and deeply	Verbal _	Demonstrated _
9. Hold breath for 6-10 seconds	Verbal _	Demonstrated _
10. Exhale easily	Verbal _	Demonstrated _
11. Wait at least 30 seconds between puffs	Verbal _	
12. Repeat steps 2. to 10. correctly	Verbal _	
13. Rinse mouth after using ICS	Verbal _	
14. Knows how to tell if inhaler is empty	Verbal _	Demonstrated _

*Order of these steps does not matter

MDI with spacer device

1. Remove caps from inhaler & spacer (optional)	Verbal _ Demonstrated _
2. Shake inhaler *	Verbal _ Demonstrated _
3. Place inhaler in correct end of spacer *	Verbal _ Demonstrated _
4. Activate upright inhaler into spacer once *	Verbal _ Demonstrated _
5. Exhale gently *	Verbal _ Demonstrated _
6. Place spacer in mouth, close lips, chin level or tilted up*	Verbal _ Demonstrated _
7. Inhale medication out of spacer (slowly and deeply)	Verbal _ Demonstrated _
8. Do not activate whistle (if present in spacer device)	Verbal _ Demonstrated _
9. Hold breath for 6-10 seconds or as long as comfortable	Verbal _ Demonstrated _
10. Exhale easily	Verbal _ Demonstrated _
11. Wait at least 30 seconds between puffs	Verbal _ Demonstrated _
12. Repeat steps 2. to 10. correctly	Verbal _
13. Knows how to check for empty inhaler	Verbal _
14. Knows to rinse, gargle and expectorate after use of ICS	Verbal _

Note: * = Order does not matter

DPI (Diskus)

1. Open the cover	Verbal _ Demonstrated _
2. Slide the dose release lever.	Verbal _ Demonstrated _
3. Exhale gently.	Verbal _ Demonstrated _
4. Place mouthpiece between lips.	Verbal _ Demonstrated _
5. Inhale through mouthpiece.	Verbal _ Demonstrated _
6. Hold breath for 6-10 seconds or as long as comfortable.	Verbal _ Demonstrated _
7. Knows how to tell Diskus is empty (counter on side).	Verbal _ Demonstrated _
8. Knows to rinse, gargle and expectorate following use of ICS	Verbal _

DPI (Handihaler)

1. Open mouthpiece, dust cap by pressing green button.	Verbal _ Demonstrated _
2. Open blister pack, remove capsule, peel foil from capsule.	Verbal _ Demonstrated _
3. Place capsule in the chamber.	Verbal _ Demonstrated _
4. Close mouthpiece (hear a click).	Verbal _ Demonstrated _
5. Hold device upright. Press and release green button.	Verbal _ Demonstrated _
6. Breathe out completely.	Verbal _ Demonstrated _
7. Close lips around mouthpiece, breathe in slowly and deeply. (capsule will vibrate).	Verbal _ Demonstrated _
8. Hold breath for as long as comfortable.	Verbal _ Demonstrated _
9. Repeat steps 6,7, and 8.	Verbal _ Demonstrated _
10. Tip out capsule, dispose of the capsule without touching.	Verbal _ Demonstrated _
11. Close mouthpiece and dust cap.	Verbal _ Demonstrated _
12. Knows how to clean device.	Verbal _ Demonstrated _

DPI (Turbuhaler)

1. Unscrew and lift off cover. Verbal _ Demonstrated _
2. Hold inhaler upright, colored grip downwards. Verbal _ Demonstrated _
3. Turn colored grip as far as it will go in one direction, then turn back as far as it will go in other direction (hear a click). Verbal _ Demonstrated _
4. Breathe out completely. Verbal _ Demonstrated _
5. Place mouthpiece between teeth, close lips. Verbal _ Demonstrated _
6. Breathe in forcefully and deeply. Verbal _ Demonstrated _
7. Hold breath for as long as comfortable. Verbal _ Demonstrated _
8. Replace the cover. Verbal _ Demonstrated _
9. Knows to rinse, gargle and expectorate following use of ICS Verbal _

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