

COPD

Is it All Smoke and Mirrors? Weighing the Evidence

Karen Dahri PharmD
Clinical Pharmacy Specialist, VGH
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Disclosure

I have no real or potential conflicts of interest to disclose.

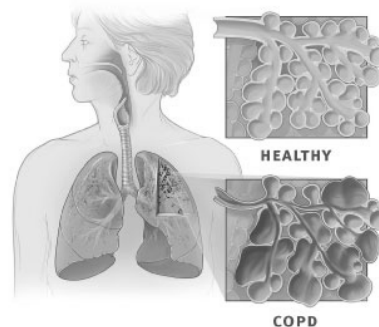
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Objectives

- Briefly review characteristics of COPD
- Review different COPD guidelines available and highlight areas where clinical questions exist
- Discuss the evidence for smoking cessation therapies in COPD
- Review the literature available comparing tiotropium to long-acting beta₂-agonists
- Highlight new areas of drug development in COPD

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COPD

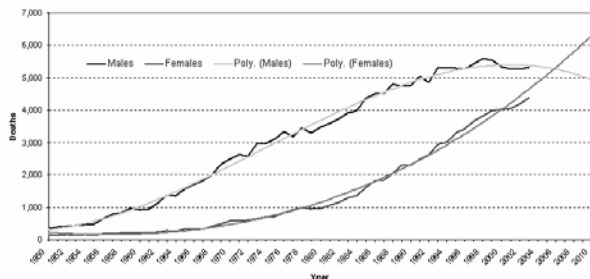


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Canadian Respiratory
Guidelines

COPD
Treatable Preventable

Number of Deaths for COPD by Sex in Canada, 1950-2003 (projections to 2010)



Sources: Centre for Chronic Disease Prevention, Public Health Agency of Canada; 2006 using Statistics Canada Data

CANADIAN THORACIC SOCIETY
SOCIÉTÉ CANADIENNE DE THORACOLOGIE

COPD – Classification

Classification by symptoms and disability

COPD stage	Symptoms
Mild	Shortness of breath from COPD [†] when hurrying on the level or walking up a slight hill (MRC 2)
Moderate	Shortness of breath from COPD [†] causing the patient to stop after walking approximately 100 m (or after a few minutes) on the level (MRC 3 to 4)
Severe	Shortness of breath from COPD [†] resulting in the patient being too breathless to leave the house, breathless when dressing or undressing (MRC 5), or the presence of chronic respiratory failure or clinical signs of right heart failure

Classification by impairment of lung function

COPD stage	Spirometry (postbronchodilator)
Mild	FEV ₁ ≥80% predicted, FEV ₁ /FVC <0.7
Moderate	50% ≤ FEV ₁ < 80% predicted, FEV ₁ /FVC <0.7
Severe	30% ≤ FEV ₁ < 50% predicted, FEV ₁ /FVC <0.7
Very severe	FEV ₁ <30% predicted, FEV ₁ /FVC <0.7

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COPD – Goals of Therapy

1. Prevent disease progression.
2. Reduce the frequency and severity of exacerbations.
3. Alleviate breathlessness and other respiratory symptoms.
4. Improve exercise tolerance and daily activity.
5. Treat exacerbations and complications of the disease.
6. Improve health status.
7. Reduce mortality.

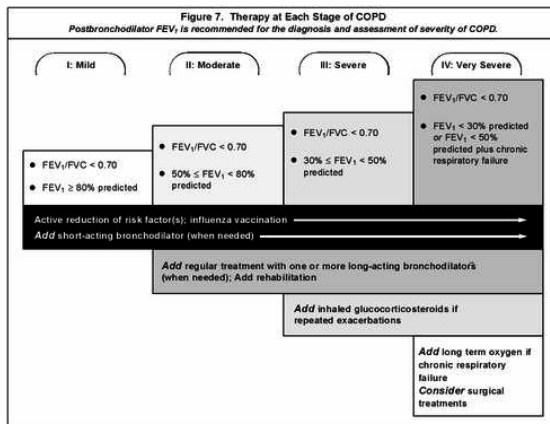
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COPD – Available Guidelines

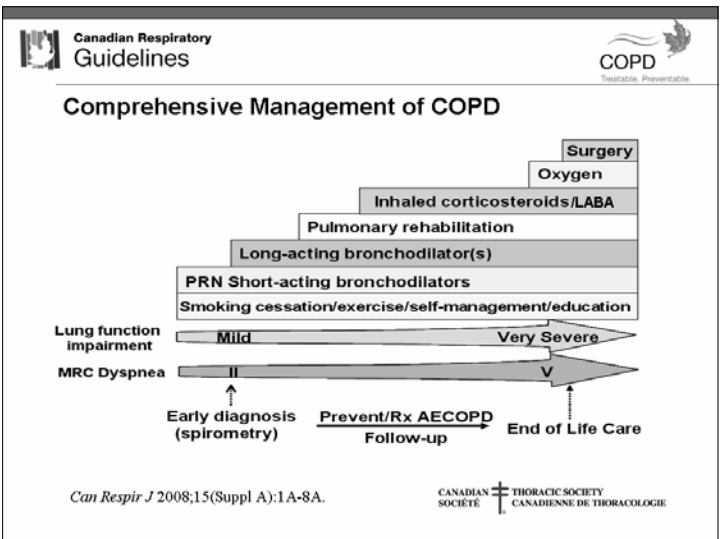
- Canadian Thoracic Society – 2007 (September)
- Global Initiative for Chronic Obstructive Lung Disease – 2008 (November)
- National Institute for Health and Clinical Excellence – 2004; update pending, projected release 2010
- American Thoracic Society – 2004

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GOLD Guidelines



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Clinical Scenario

You are counseling Mr. X on his inhalers for his COPD. You had noted in your work-up that he was a current smoker. Being the good pharmacist that you are you ask him if he is ready to quit smoking. He says yes....what do you do:

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Clinical Scenario

- A. Laugh and ask him if he is joking as in your many years as a pharmacist not one patient has actually expressed a desire to quit.
- B. Mumble something about a lot of different therapies being available and he should check with his community pharmacist after he is discharged about their options.
- C. Review the available therapies with him highlighting the ones that have been studied in COPD patients.

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Smoking Cessation and COPD



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Smoking cessation interventions in COPD: a network meta-analysis of randomised trials.

Eur Respir J 2009; 34: 1-7.

- To rank order the effectiveness of smoking cessation interventions for COPD patients.
- Patients
 - N = 7,477 patients (8 trials)
- Results
 - SCC w/ NRT had greatest effect on prolonged abstinence rates

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Clinical Scenario

You are rounding with the medical team reviewing a patient admitted with a COPD exacerbation. He was recently diagnosed in the community and was just using prn salbutamol prior to admission. The MSI has punched in the patient's spirometry into his Palm Pilot calculator and has determined that he is classified as having "moderate" COPD. As the guidelines recommend a long-acting bronchodilator to be added the team turns to you and ask you which one would you recommend – tiotropium or a LABA?

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LABA vs Tiotropium



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LABA vs Tiotropium

	LABA	Tiotropium
MOA	Relax airway smooth muscle by stimulation of β_2 -adrenergic receptors, which \uparrow cAMP and produce functional antagonism to bronchoconstriction.	Blockage of acetylcholine's effect on M3 and M1 receptors
Duration of Action	12hrs	24hrs
Dosing	Formoterol 12 μ g bid Salmeterol 25-50 μ g bid	18 μ g inhaled daily
Delivery Device	Formoterol – caps, turbuhaler Salmeterol – MDI, diskus	Caps
Adverse Effects	Tachycardia, palpitations, irritability, insomnia, muscle cramps, tremors	Dryness of the mouth More rare: prostatic symptoms, glaucoma (if local administration),
Cost	Formoterol - \$59 Salmeterol - \$69	Tiotropium - \$82

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LABA vs Tiotropium

	LABA	Tiotropium
prevent disease progression	X	?
\downarrow frequency & severity of exacerbations	\checkmark	\checkmark
\downarrow symptoms	\checkmark	\checkmark
\uparrow exercise tolerance/daily activities	?	\checkmark
\uparrow health status	\checkmark	\checkmark
\downarrow mortality	X	?

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LABA vs Tiotropium

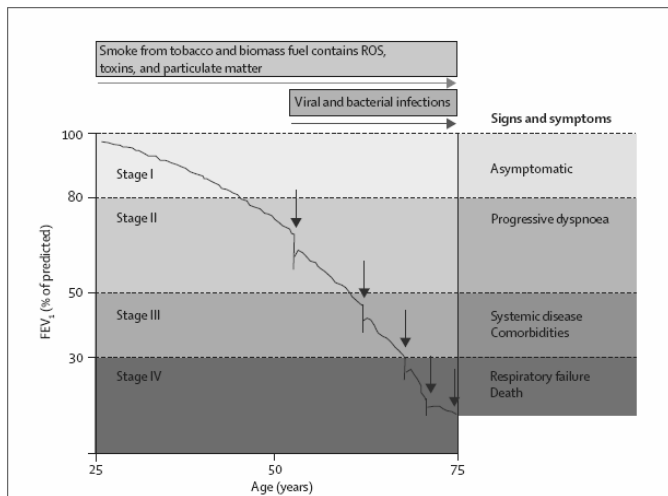
	Donohue 2002	Brusasco 2003	van Noord 2005	Briggs 2005
Design	R, PC, MC, DB	R, PC, MC, DB	R, DB, crossover	R, PC, MC, DB
Duration	6 months	6 months (x 2 studies)	3 x 6 weeks	12 weeks
Population	N=623 Mean Age = 65±8yrs; FEV1 40.2±12.1%	N=1207 Mean Age = 63.8-64.6 yrs FEV1 37.7-39.2%	N=71 Mean Age = 64.9±9.4 yrs FEV1 37.2±8.6%	N=653 Mean Age = 64yrs; FEV1 37.7%
Intervention	Tiotropium 18µg/d vs Salmeterol 50µg/d	Tiotropium 18µg/d vs Salmeterol 50µg/d	Tiotropium 18µg/d vs formoterol 12µg bid, Tiotropium 18µg + formoterol 12µg daily	Tiotropium 18µg/d vs Salmeterol 50µg/d
Results	Tiotropium > Salmeterol for FEV1, FVC, TDI score	Tiotropium > salmeterol for spirometry	Tiotropium > salmeterol for spirometry	Tiotropium > salmeterol for FEV1, FVC

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LABA vs Tiotropium

	LABA	Tiotropium
prevent disease progression	X	?
↓ frequency & severity of exacerbations	√	√
↓ symptoms	√	√
↑ exercise tolerance/daily activities	?	√
↑ health status	√	√
↓ mortality	X	?

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UPLIFT

N Engl J Med 2008; 359: 1543-54.

- To examine the long-term effects of tiotropium.
- R, DB, PC, MC
- Patients
 - N=5993, Mean Age=65±8yrs, FEV₁ = 39%
- Intervention
 - Tiotropium 18µg/d vs Placebo
- Results
 - No significant Δ in rate of decline in FEV₁

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Meta-analysis: Anticholinergics, but not β-agonists, reduce severe exacerbations & respiratory mortality in COPD

J Gen Intern Med 2006; 21: 1011-1019.

- To assess the safety & efficacy of anticholinergics & β₂-agonists in COPD.
- Patients
 - N=15,276 (22 trials)
- Results - β-agonists vs Anticholinergics
 - 7 trials, 2 w/ tiotropium
 - Rates of exacerbations requiring trial w/d
 - RR 2.02 (95% CI 1.39 to 2.93)
 - Severe exacerbations requiring hospitalization
 - RR 1.95 (95% CI 1.06 to 3.59)
 - Respiratory deaths
 - RR 6.91 (95% CI 0.85 to 55.97), p=0.07

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Pharmacological Treatments for COPD

Pharmacotherapy 2009; 29(8): 891-905.

- To assess the comparative efficacy of pharmacologic agents for the maintenance treatment of COPD.
- Patients
 - N=31,020 (43 trials)
- Results – Tiotropium vs LABA comparisons
 - Exacerbations
 - OR 0.82 (0.72-0.93)
 - Mortality
 - OR 0.78 (0.43-1.37)
 - Withdrawal
 - OR 0.81 (0.65-0.98)

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Safety



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Safety of Long-Acting β -Agonists in Stable COPD

Chest 2008; 133: 1079-1087.

- To assess the safety, as the primary outcome, & secondarily the efficacy of the use of LABAs in COPD pts compared w/ placebo & anticholinergics.
- Patients
 - N=20,527 (27 studies)
 - Mean age = 63.3 \pm 10.3 yrs, avg baseline FEV₁ 43% of predicted
- Results – LABA vs Tiotropium (3 studies)
 - Severe COPD Exacerbations
 - RR 0.52 (95% CI 0.31-0.86)
 - Change from baseline FEV₁
 - Δ mean FEV1 from baseline = 0.05 L (95% CI 0.02-0.07)

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Inhaled Anticholinergics & Risk of Major Adverse Cardiovascular Events in Patients with COPD

JAMA 2008; 300(12): 1439-1450.

- To ascertain the CV risks of inhaled anticholinergics (CV death, MI, stroke).
- Eligibility Criteria:
 - RCT for any inhaled anticholinergic w/ >30 days f/u
 - Diagnosis of COPD of any severity
 - Inhaled anticholinergic vs control (placebo or active control)
 - Trial had to report data on the incidence of serious CV adverse events
- Patients
 - N=14,783 (17 studies, 12 tiotropium)

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Inhaled Anticholinergics & Risk of Major Adverse Cardiovascular Events in Patients with COPD

JAMA 2008; 300(12): 1439-1450.

- Results
 - Composite = RR 1.58 (95% CI 1.21-2.06)
 - Individual Components = \uparrow CV death, \uparrow MI, no \uparrow stroke
 - No \uparrow in all-cause mortality
 - For tiotropium alone:
 - RR 2.12 (95% CI 1.22-3.67, p=0.008)

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LABA vs Tiotropium



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Clinical Scenario

Again you are on rounds and are reviewing a COPD patient. One of the residents mentions that he had read a recent study regarding PD4 inhibitors in COPD and he wanted to know if these were available in Canada yet....what is he talking about?

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Phosphodiesterase-4 Inhibition

- PDE4 is a cAMP-specific PDE
 - Inhibition raises intracellular levels of cAMP resulting in downregulation of signaling pathways in inflammatory cells
 - Major isoenzyme in inflammatory cells implicated in inflammatory airway disease
- Roflumilast
 - PDE4 inhibitor
 - Decreases airway inflammation in COPD

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Roflumilast

Dosing	500µg PO once daily
Pharmacokinetics	Oral bioavailability = 79% Peak plasma concentration in 1hr Mean half-life = 17hrs
Metabolism	Metabolized by cytochrome P450 3A4 and CYP 1A2 isozymes Active metabolite roflumilast N-oxide, accounts for 90% of pharmacologic effect
Adverse Effects	Diarrhea, nausea, headache

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Roflumilast—an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial

Klaus F Rabe, Eric D Bateman, Denis O'Donnell, Stephan Witz, Dirk Bredenkroeker, Thomas D Bethke

Effect of 1-Year Treatment with Roflumilast in Severe Chronic Obstructive Pulmonary Disease

Peter M. A. Calverley¹, Fernando Sanchez-Toril², Andrew McIvor³, Peter Teichmann⁴, Dirk Bredenkroeker⁵, and Leonardo M. Fabbri⁶

Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials

Leonardo M Fabbri¹, Peter MA Calverley², José Luis Izquierdo-Alonso, Daniela S Bundschuh, Manja Brose, Fernando J Martinez, Klaus F Rabe³, for the M2-127 and M2-128 study groups⁴

Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials

Peter MA Calverley¹, Klaus F Rabe², Udo Michael Goehring, Soren Kristiansen, Leonardo M Fabbri³, Fernando J Martinez⁴, for the M2-124 and M2-125 study groups⁵

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	Rabe 2005	Calverley 2007	Fabbri 2009*	Calverley 2009*
Design	Phase III, R, PC, DB, MC	R, PC, DB	R, PC, DB, MC	R, PC, DB, MC
Duration	24 wks	1 year	24 wks	52 wks
Population	N=1157; Median age = 63-65yrs FEV1=54-55%	N=1,513; FEV1 =41%	Tiotropium N=743; 64±9yrs, FEV1~53, 63-65% moderate COPD Salmeterol N=933; 65±9yrs, FEV1~52, 65-69% moderate COPD	N=3091 Age = 64±9yrs FEV1 ~ 33 61-64% Severe COPD
Intervention	Roflumilast 250µg vs 500µg vs placebo	Roflumilast 500µg daily vs placebo	Tiotropium or salmeterol vs roflumilast 500µg or placebo	Roflumilast 500µg daily vs placebo
Results	↑FEV1 No significant change in SGRQ vs placebo	↑FEV1	↑FEV1	↑FEV1 ↓ mod or severe exacerbations by 17% (95% CI 8-25)

*reported results of two studies combined

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Questions



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