COPD
Is it All Smoke and Mirrors?
Weighing the Evidence

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

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

Canadian Respiratory Guidelines

COPD – Number of Deaths in Canada, 1950-2003 (projections to 2010)

COPD – Classification

<table>
<thead>
<tr>
<th>Classification by symptoms and disability</th>
<th>COPD stage</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Shortness of breath from COPD when hurrying on the level or walking up a slight hill (MRC 2)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>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)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Classification by impairment of lung function</th>
<th>COPD stage</th>
<th>Spirometry (postbronchodilator)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>FEV1, &gt;80% predicted. FEV1/FVC &gt;0.7</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>50% ≤ FEV1, &lt; 80% predicted. FEV1/FVC &gt;0.7</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>30% ≤ FEV1, &lt; 50% predicted. FEV1/FVC &gt;0.7</td>
<td></td>
</tr>
<tr>
<td>Very severe</td>
<td>FEV1, &lt;30% predicted. FEV1/FVC &lt;0.7</td>
<td></td>
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</tbody>
</table>
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.

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

GOLD Guidelines

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:

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.
Smoking Cessation and COPD

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

• 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

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?

LABA vs Tiotropium

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<tr>
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<th>LABA</th>
<th>Tiotropium</th>
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<tr>
<td>MOA</td>
<td>Relax airway smooth muscle by stimulation of β2-adrenergic receptors, which cAMP and produce functional antagonism to bronchoconstriction.</td>
<td>Blockage of acetylcholine’s effect on M3 and M1 receptors</td>
</tr>
<tr>
<td>Duration of Action</td>
<td>12hrs</td>
<td>24hrs</td>
</tr>
<tr>
<td>Dosing</td>
<td>Formoterol 12 µg bid</td>
<td>Salmeterol 25-50 µg bid</td>
</tr>
<tr>
<td></td>
<td>Salmeterol</td>
<td>16 µg inhaled daily</td>
</tr>
<tr>
<td></td>
<td>– caps, turbuhaler</td>
<td>Salmeterol – MDI, diskus</td>
</tr>
<tr>
<td>Delivery Device</td>
<td>Formoterol – caps,</td>
<td>Caps</td>
</tr>
<tr>
<td></td>
<td>turbuhaler</td>
<td></td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Tachycardia, palpitations,</td>
<td>Dryness of the mouth More rare: prostatic symptoms, glaucoma (if local administration).</td>
</tr>
<tr>
<td></td>
<td>irritability, insomnia, muscle cramps, tremors</td>
<td></td>
</tr>
<tr>
<td>Cost</td>
<td>Formoterol - $59</td>
<td>Tiotropium - $82</td>
</tr>
<tr>
<td></td>
<td>Salmeterol - $69</td>
<td></td>
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LABA vs Tiotropium

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<tr>
<td>prevent disease progression</td>
<td>X</td>
<td>?</td>
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<tr>
<td>↓ frequency &amp; severity of exacerbations</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>↓ symptoms</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>↑ exercise tolerance/daily activities</td>
<td>?</td>
<td>√</td>
</tr>
<tr>
<td>↑ health status</td>
<td>√</td>
<td>√</td>
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<tr>
<td>↓ mortality</td>
<td>X</td>
<td>?</td>
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LABA vs Tiotropium

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<tr>
<th>Design</th>
<th>Duration</th>
<th>Population</th>
<th>Intervention</th>
<th>Results</th>
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<tr>
<td>Donohue 2002</td>
<td>6 months</td>
<td>N=623; Mean Age = 65±8 yrs, FEV1 = 40.2±12.1%</td>
<td>Tiotropium 18µg/d vs Salmeterol 50µg/d</td>
<td>Tiotropium &gt; Salmeterol for spirometry, TDI score</td>
</tr>
<tr>
<td>Brusasco 2003</td>
<td>6 months</td>
<td>N=1207; Mean Age = 63.8±6.6 yrs, FEV1 = 37.7-39.2%</td>
<td>Tiotropium 18µg/d vs formoterol 12µg bid, Tiotropium 18µg + formoterol 12µg daily</td>
<td>Tiotropium &gt; Salmeterol for spirometry, TDI score</td>
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<td>van Noord 2005</td>
<td>3 x 6 weeks</td>
<td>N=71; Mean Age = 64.9±9.4 yrs, FEV1 = 37.8±6%</td>
<td>Tiotropium 18µg/d vs Salmeterol 50µg/d</td>
<td>Tiotropium &gt; Salmeterol for spirometry, TDI score</td>
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<td>Briggs 2005</td>
<td>12 weeks</td>
<td>N=653; Mean Age = 64 yrs, FEV1 = 37.7%</td>
<td>Tiotropium 18µg/d vs Salmeterol 50µg/d</td>
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**Results**

- **Signs and symptoms**
  - Tiotropium > Salmeterol for spirometry, TDI score
  - Tiotropium > Salmeterol for FEV1, FVC

**Intervention**

- N=653; Mean Age = 64 yrs; FEV1 = 37.7%
- Mean Age = 64.9±9.4 yrs, FEV1 = 37.8±6%
- Mean Age = 63.8±6.6 yrs, FEV1 = 37.7-39.2%

**Population**

- N=623; Mean Age = 65±8 yrs, FEV1 = 40.2±12.1%
- N=1207; Mean Age = 63.8±6.6 yrs, FEV1 = 37.7-39.2%
- N=71; Mean Age = 64.9±9.4 yrs, FEV1 = 37.8±6%
- N=653; Mean Age = 64 yrs, FEV1 = 37.7%

**Design**

- R, PC, MC, DB
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- R, PC, MC, DB

**Duration**

- 6 months
- 6 months
- 3 x 6 weeks
- 12 weeks

**Population**

- N=623
- N=1207
- N=71
- N=653

**Intervention**

- 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 spirometry, TDI score
- Tiotropium > Salmeterol for FEV1, FVC

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

- 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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**UPLIFT**

- 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 ∆ in rate of decline in FEV1

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**Pharmacological Treatments for COPD**

- 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)
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±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
    - ∆ mean FEV1 from baseline = 0.05 L (95% CI 0.02-0.07)

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)

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

LABA vs Tiotropium

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?
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

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

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


Design
- Phase III, R, PC, DB, MC
- Phase II, R, PC, DB, MC
- R, PC, DB, MC
- R, PC, DB, MC

Duration
- 24 wks
- 1 year
- 24 wks
- 52 wks

Population
- N=1,157; Median age = 63-65yrs
- FEV1 = 54-55%
- N=1,513
- FEV1 = 54-55%
- N=3091
- Age = 64-65yrs
- Severe COPD

Intervention
- Roflumilast 250µg 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 vs placebo
- FEV1 vs placebo
- FEV1 vs placebo

*reported results of two studies combined

References

3. www.rxfiles.ca