Cost-Effectiveness of Therapy with Combinations of Long-Acting Bronchodilators and Inhaled Steroids for Treatment of COPD

An Economic Evaluation of the OPTIMAL Study

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Background

- **Chronic Obstructive Pulmonary Disease (COPD)** has a high burden to society*:
  - >800,000 are diagnosed with COPD
  - $3,196 CAD$ (2003) total annual costs/patient
  - 4th and 6th leading cause of death in men and women, respectively

- Several classes of medications for COPD *(short and long-acting anticholinergics, short- and long-acting beta-agonists, oral or inhaled corticosteroids, theophylline)*

- Little is known about combination therapy.  
  **GOLD recommendations**: Consider adding a second bronchodilator treatment rather than prescribing high dose bronchodilator mono-therapy to mitigate adverse effects #

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# Global Strategy for the Diagnosis, Management and Prevention of COPD. 2006, Global initiative for Chronic Obstructive Lung Disease (GOLD)
Optimal Clinical Trial*

- Multi-center, randomized, double-blind, controlled clinical trial
  - >=1 exacerbation of COPD requiring treatment with steroids/antibiotics in the past year.
  - Age > 35 years;
  - >=10 pack-years of cigarette smoking
  - documented FEV1/FVC<0.70 + postbronchodilator FEV1<65% of the predicted value

- One-year treatment of COPD with three treatment regimens
  1. TP: tiotropium 18 µg once daily + placebo twice daily
  2. TS: tiotropium 18 µg once daily + salmeterol 25 µg/puff, 2 puffs twice daily
  3. TFS: tiotropium 18 µg once daily + fluticasone/salmeterol 250/25 µg/puff, 2 puffs twice daily

Opimal RCT  cont.

- # of patients: $TP=156$, $TS=148$, $TFS=145$

- Primary outcome: Proportion of exacerbation-free patients at the end of one-year follow-up:
  
  $$TP:62.8\%, \ TS:64.8\%, \ TFS:60.0\% \ (P=NS)$$

  - Secondary outcomes:
    
    # of exacerbations: $TP=222$, $TS=226$, $TFS=188 \ (P=NS)$
    
    # of hospitalizations due to exacerbations: $TP=49$, $TS=38 \ (P=0.04)$, $TFS=26 \ (P=0.01)$
    
    Change in SGRQ scores: $TP=-4.5 \ (P=NS)$, $TS=-6.3 \ (P=0.02)$, $TFS=-8.6 \ (P=0.01)$

  - Discontinuation of study drugs:
    
    $TP=47\%$, $TS=43\%$, $TFS=26\% \ (P=0.001)$

Methods

• Prospective economic analysis:
  – Both resource use and effectiveness outcomes were collected during the trial
• Outcomes:
  – Incremental cost per exacerbation avoided,
  – Incremental cost per quality-adjusted life year (QALY) gained
• Unit costs for each item of resource utilization
• SGRQ scores converted to EQ5D scores (Meguro 2006), QALYs adjusted for difference in baseline utilities
• Only COPD-related hospitalization included

Methods cont.

- Rigorous sensitivity analysis: nested imputation and bootstrap
- Two sources of uncertainty: incomplete follow-up and finite sample size of the study
  - Incomplete follow-up - imputation
  - Finite sample size - bootstrapping
- Follow-up period divided into 13 periods (period length=28 days)
14 died during the trial
TP=3, TS=6, TSF=5

By definition, all costs and utilities after death were set to zero.

For the exacerbation outcome-
- Setting zero effectiveness after death is problematic as the treatment arm had excess mortality.

For exacerbations, death was treated as attrition (forced dropout)

Sensitivity analysis
- 0 exacerbation for each period after death, and 1 exacerbation for each period after death
## Unit costs (2006 CAN$)

<table>
<thead>
<tr>
<th>Item</th>
<th>Value* (2006 CAN$)</th>
<th>Unit</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Telephone to MD/healthcare professional</td>
<td>14.6</td>
<td>Per call</td>
<td>Medical Services Plan (MSP) Payment Schedule 2007</td>
</tr>
<tr>
<td>Urgent respiratory care visit in home</td>
<td>67.4</td>
<td>Per visit</td>
<td>MSP Payment Schedule 2007</td>
</tr>
<tr>
<td>Urgent MD visit</td>
<td>85.1</td>
<td>Per visit</td>
<td>MSP Payment Schedule 2007</td>
</tr>
<tr>
<td>Urgent ED visit</td>
<td>255.8</td>
<td>Per visit</td>
<td>Chapman, 2003</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>593.2</td>
<td>Per day</td>
<td>Vancouver General Hospital (VGH) fully allocated cost model</td>
</tr>
<tr>
<td>ICU admission</td>
<td>2337.5</td>
<td>Per day</td>
<td>VGH fully allocated cost model</td>
</tr>
<tr>
<td>Tiotropium 18 mcg</td>
<td>2.25</td>
<td>Per capsule</td>
<td>Pharmanet Drug Master List, 2008</td>
</tr>
<tr>
<td>Salmeterol 25 mcg</td>
<td>0.44</td>
<td>Per puff</td>
<td>Pharmanet Drug Master List, 2008</td>
</tr>
<tr>
<td>Fluticasone/Salmeterol 250/25 mcg</td>
<td>1.16</td>
<td>Per puff</td>
<td>Pharmanet Drug Master List, 2008</td>
</tr>
</tbody>
</table>
## Results *(outcomes)*

<table>
<thead>
<tr>
<th></th>
<th>TP</th>
<th>TS</th>
<th>TFS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost (2006 CAN$)</strong></td>
<td>2678 (1950 - 3536)</td>
<td>2801 (2306 – 3362)</td>
<td>4042 (3228 - 4994)</td>
</tr>
<tr>
<td><strong>Exacerbations per year</strong></td>
<td>1.56 (1.34 - 1.81)</td>
<td>1.69 (1.47 - 1.94)</td>
<td>1.35 (1.16 - 1.55)</td>
</tr>
<tr>
<td><strong>QALY</strong></td>
<td>0.7092 (0.6953-0.7228)</td>
<td>0.7124 (0.6931-0.7310)</td>
<td>0.7217 (0.7034-0.7389)</td>
</tr>
<tr>
<td><strong>Adjusted Incremental QALY †</strong></td>
<td>0 (reference)</td>
<td>-0.0052 (-0.0088 - 0.0032)</td>
<td>0.0056 (-0.0142 - 0.0251)</td>
</tr>
<tr>
<td><strong>ICER (exacerbation avoided)</strong></td>
<td>reference</td>
<td>dominated</td>
<td>$6,510</td>
</tr>
<tr>
<td><strong>ICER QALY</strong></td>
<td>reference</td>
<td>dominated</td>
<td>$243,180</td>
</tr>
</tbody>
</table>
Sensitivity Analysis

Cost-effectiveness plane
Sensitivity Analysis

Cost per exacerbation avoided

Cost per QALY gained

Cost-effectiveness acceptability curve
One-way sensitivity analysis

<table>
<thead>
<tr>
<th>Scenario †</th>
<th>Outcomes</th>
<th>TS vs. TP</th>
<th>TFS vs. TP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-COPD related Hospitalizations included</td>
<td>Cost/Exacerbation avoided Cost/QALY</td>
<td>2,958 342,484</td>
<td>5,463 96,271</td>
</tr>
<tr>
<td>Zero exacerbations after death</td>
<td>Cost/Exacerbation avoided</td>
<td>dominated</td>
<td>4,123</td>
</tr>
<tr>
<td>One exacerbation for each period after death ‡</td>
<td>Cost/Exacerbation avoided</td>
<td>dominated</td>
<td>47,768</td>
</tr>
<tr>
<td>Severe COPD (FEV1 &lt; 50% predicted)</td>
<td>Cost/Exacerbation avoided Cost/QALY</td>
<td>19,750 128,709</td>
<td>7,812 252,291</td>
</tr>
<tr>
<td>Moderate COPD (50% &lt; FEV1 &lt; 65% predicted)</td>
<td>Cost/Exacerbation avoided Cost/QALY</td>
<td>dominated 289,509</td>
<td>18,591 139,218</td>
</tr>
<tr>
<td>Disutility during exacerbation</td>
<td>Cost/QALY</td>
<td>dominated</td>
<td>139,459</td>
</tr>
</tbody>
</table>
Shortcomings

• Algorithm for converting SGRQ to utility is not externally validated

• Indirect costs not included
  *(though productivity loss are minimal in >65 y/o)*

• Determining a hospitalization as COPD-related is subjective

• The *clean* setting of an RCT vs. the *chaotic* reality
  *example: patients waiting for scheduled visit refrain from an unscheduled one*

• Time horizon of one year
  *extrapolation of results unlikely to change conclusions*

• Drug dispensing costs not included
Conclusions

- TFS had significantly better quality of life + fewer hospitalizations
- However, these improvements in health outcomes were associated with increased costs.
- Neither TFS nor TS are cost-effective alternatives for monotherapy with T
- Uncertainty in findings
  At WTP of 50,000$/QALY, the probability that T is the most cost-effective choice is 80%
- TS is cost effective in severe COPD