TITLE: Long-acting Beta-agonists and Inhaled Corticosteroids for Treatment of Chronic Obstructive Pulmonary Disease: A Review of the Clinical Efficacy and Cost-effectiveness

DATE: 01 May 2013

CONTEXT AND POLICY ISSUES

Chronic obstructive pulmonary disease (COPD) is a major respiratory illness affecting over 700,000 Canadians and is preventable and treatable, but not curable. It is the fourth leading cause of death in Canada, with mortality rates increasing over the past fifteen years, especially in women. According to the Canadian Institute for Health Information, COPD accounts for the highest rate of hospital admission and readmission among major chronic diseases in Canada. Exacerbations are the principal cause of hospitalizations.

COPD is characterized by progressive airway obstruction, inflammation, limited expiratory flow with subsequent lung hyperinflation, and increasing frequency and severity of exacerbations. It can be classified by symptoms or by impairment of lung function tests, known as spirometry. The Canadian Thoracic Society defines moderate COPD as "shortness of breath from COPD causing the patient to stop after walking approximately 100m (or after a few minutes) on the level" and severe COPD as "shortness of breath from COPD resulting in the patient being too breathless to leave the house, breathless when dressing or undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure." Post-bronchodilator forced expiratory volume in one second (FEV₁) to forced vital capacity (FVC) ratio less than 0.7 is diagnostic of COPD. A lower FEV₁ indicates poorer lung function and limited expiratory flow. COPD classification based on spirometry post-bronchodilator is as follows: for moderate COPD 50% ≤ FEV₁ <80% predicted normal value, and for severe COPD 30% ≤ FEV₁ <50% predicted normal value.

Management of COPD consists of a combination of risk factor reduction, pharmacotherapy, education, pulmonary rehabilitation, and exercise programs. Pharmacotherapy is introduced in a step-wise approach. Bronchodilators are the cornerstone of COPD therapy and include inhaled short or long acting anticholinergics (SAAC or LAAC) and short or long acting β2 agonists (SABA or LABA). They act by decreasing airway smooth muscle tone, which increases expiratory flow rates and reduces hyperinflation with a subsequent reduction in dyspnea, improved exercise tolerance, and health status. Three anticholinergics available in Canada for COPD are ipratropium bromide (SAAC, nebuliser and metered dose inhaler), tiotropium bromide (LAAC, Handihaler), and glycopyrronium.
bromide (LAAC, breezhaler). The three commonly used LABA are formoterol (dry power capsule), salmeterol (Diskhaler), and indacaterol (Breezhaler). Among the LABAs formoterol and salmeterol can be used alone or in combination with inhaled corticosteroids (ICS), that are Symbicort (budesonide plus formoterol, 100µg/6µg or 200µg/6µg) and Advair (fluticasone plus salmeterol, 100µg/50µg, 250µg/50µg or 500µg/50µg).

The Canadian Thoracic Society guideline and Institute for Clinical Systems Improvement (ICSI) recommended that use of LAAC or LABA alone, or LAAC in combination with LABA, or LAAC in combination with LABA plus ICS for patients with moderate to severe COPD depending on the severity. In some jurisdictions, Salmeterol and Advair are listed for both asthma and COPD patients whereas formoterol and Symbicort are not listed for COPD patients. Salmeterol, Advair, formoterol and Symbicort all have the Health Canada indication for COPD. Hence, there is still continuing pressure for policy makers to provide salmeterol and Advair as a general benefit. A review of the literature for new evidence regarding the clinical effectiveness of formoterol (alone or in combination with budesonide) as an addition to standard anticholinergic treatment (ipratropium or tiotropium) compared with standard anticholinergic treatment alone or with salmeterol (alone or in combination with fluticasone) or indacaterol as an addition to standard anticholinergic treatment may help to clarify if a change in policy is warranted.

RESEARCH QUESTIONS

1. What is the comparative clinical efficacy of formoterol combined with standard anticholinergic treatment versus standard treatment alone for patients with chronic obstructive pulmonary disease?

2. What is the cost-effectiveness of formoterol combined with standard anticholinergic treatment versus standard treatment alone for patients with chronic obstructive pulmonary disease?

3. What is the comparative clinical efficacy of formoterol combined with standard anticholinergic treatment versus salmeterol or indacaterol plus standard treatment for patients with chronic obstructive pulmonary disease?

4. What is the cost-effectiveness of formoterol combined with standard anticholinergic treatment versus salmeterol or indacaterol plus standard treatment for patients with chronic obstructive pulmonary disease?

5. What is the comparative clinical efficacy of formoterol plus budesonide combined with standard anticholinergic treatment versus standard treatment alone for patients with chronic obstructive pulmonary disease?

6. What is the cost-effectiveness of formoterol plus budesonide combined with standard anticholinergic treatment versus standard treatment alone for patients with chronic obstructive pulmonary disease?

7. What is the comparative clinical efficacy of formoterol plus budesonide combined with standard anticholinergic treatment versus salmeterol plus fluticasone combined with standard treatment for patients with chronic obstructive pulmonary disease?
8. What is the cost-effectiveness of formoterol plus budesonide combined with standard anticholinergic treatment versus salmeterol plus fluticasone combined with standard treatment for patients with chronic obstructive pulmonary disease?

KEY FINDINGS

Compared with tiotropium monotherapy, adding formoterol to tiotropium statistically significantly improved the lung function (FEV1) in the treatment of patients with moderate to severe COPD; Adding budesonide/formoterol to tiotropium statistically significantly improved lung function (FEV1) and reduced the frequency of severe exacerbation, and appears cost effective compared with tiotropium monotherapy in the treatment of severe COPD. The long term comparative clinical effectiveness, harms and the cost effectiveness of these COPD treatment strategies remain to be established.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, Embase, The Cochrane Library (2013, Issue 2), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval to study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2003 and March 21, 2013.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients with chronic obstructive pulmonary disease (COPD)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any age</td>
</tr>
<tr>
<td></td>
<td>Any severity</td>
</tr>
<tr>
<td>Intervention</td>
<td>Formoterol alone or in combination with budesonide as an addition to standard anticholinergic treatment (ipratropium or tiotropium)</td>
</tr>
<tr>
<td>Comparator</td>
<td>Standard anticholinergic treatment alone (ipratropium or tiotropium)</td>
</tr>
<tr>
<td></td>
<td>Indacaterol</td>
</tr>
<tr>
<td></td>
<td>Salmeterol alone or in combination with fluticasone as an addition to standard anticholinergic treatment</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Clinical efficacy, adverse events, cost-effectiveness</td>
</tr>
<tr>
<td>Study Designs</td>
<td>HTA/ Systematic review/Meta-analysis</td>
</tr>
<tr>
<td></td>
<td>Randomized controlled trials</td>
</tr>
<tr>
<td></td>
<td>Economic evaluations</td>
</tr>
</tbody>
</table>
Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 1, duplicate publications of the same study, or the study included in a selected systematic review or meta-analysis.

Critical Appraisal of Individual Studies

The methodological quality of the included SR/MA were assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) tool. RCTs were assessed with Scottish Intercollegiate Guidelines Network, Methodology checklist 2 (SIGN 50 Check list 2). Economic evaluation was assessed using the 35-item Drummond’s checklist. A numeric score was not calculated for each study. Instead, the strengths and weakness of each study were summarized and described.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded 423 citations. Upon screening titles and abstracts, Forty five potentially relevant articles were retrieved for full-text review. Eight additional potential relevant reports were retrieved from other sources. Of the 53 potentially relevant articles, six reports were included in this review. There are one MA, two SRs, two RCTs and one cost-effectiveness evaluation report. Four studies evaluated the comparative clinical efficacy and harms of formoterol combined with tiotropium versus tiotropium alone for patients with moderate to severe COPD (for research question 1) and one RCT reported the comparative clinical efficacy and harms of budesonide/formoterol (BUD/FOR) combined with tiotropium versus tiotropium alone for patients with severe COPD (for research question 5). The sixth study examined cost-effectiveness of BUD/FOR combined with tiotropium versus tiotropium alone in the treatment of patients with severe COPD (for research question 6). No evidence was identified for research questions 2, 3, 4, 7 and 8. The study selection process is outlined in a PRISMA flowchart (Appendix 1).

Summary of Study Characteristics

What is the comparative clinical efficacy of formoterol combined with standard anticholinergic treatment versus standard treatment alone for patients with chronic obstructive pulmonary disease?

A summary of the study characteristics can be found in Appendix 2.

Meta-analysis and systematic reviews

The meta-analysis by Wang et al. was published in 2011. Eight RCTs, involving 1868 patients, compared formoterol combined with tiotropium versus tiotropium treatment were included in the meta-analysis. Duration of the included studies ranged from two weeks to six months. The majority (6 out of 8) of trials duration were less than 12 weeks (two were for two weeks, one for four week and three for six weeks). Formoterol dose ranged from 10 µg to 20 µg twice daily. Four of eight included studies in the MA used formoterol 12 µg twice daily, which is the dose approved by Health Canada. Tiotropium dose, 18 µg once daily, which is the Health Canada approved dose for COPD was used in all included studies. Patients were required to have a postbronchodilator FEV1 of ≤60-80% and ≥30% of the predicted normal value. In all included studies, patients were ≥40 years of age, and had a smoking history of ≥10-15 pack-years in all included studies, except two RCTs in which smoking history was not reported. Patients were excluded if they had a history of asthma or a significant
disease other than COPD. Main outcomes included FEV1, COPD exacerbations, hospitalizations, mortality and quality of life and dyspnea captured by Transitional Dyspnea Index (TDI).

Studies included in two other systematic reviews conducted by Karner et al.\textsuperscript{21} and Chen et al.\textsuperscript{20} were all included in the meta-analysis by Wang.\textsuperscript{19} However, the outcomes (hospitalization or rescue medication use) reported in these two SRs were not reported in the meta-analysis. Therefore, there will no double counting of the findings from the included studies in terms of the outcomes of interest.

**Randomized controlled trial**

In the randomized control trial by Di Marco,\textsuperscript{23} twenty-one patients with acute exacerbation (mild to moderate COPD) were randomized to receive formoterol plus tiotropium or placebo plus tiotropium. Ninety percent were male patients with a mean age (±SD) of 72 ± 8 years. It was a one day duration trial. The primary outcome was the post dose FEV1 after 24 hours.

**What is the comparative clinical efficacy of formoterol plus budesonide combined with standard anticholinergic treatment versus standard treatment alone for patients with chronic obstructive pulmonary disease?**

The study by Welte et al.\textsuperscript{22} was a multicenter and double-blind RCT (also known as CLIMB study). In this trial, the comparative effectiveness of BUD/FOR, (320µg/9 µg, twice daily) plus tiotropium (TIO, 18µg, daily) versus TIO alone (18µg, daily) was studied in patient with severe COPD (FEV1 < 50% predicted normal value). In total, 660 adult patients were randomized to BUD/FOR (twice daily) added to tiotropium (once daily) or tiotropium alone. Mean age was ≥40 years. The trial duration was 12 weeks. The primary outcome was pre-dose (or trough) FEV1. Other outcomes were the health status, morning symptoms and activities, and morning reliever use, severe exacerbations, and tolerability.

**What is the cost-effectiveness of formoterol plus budesonide combined with standard anticholinergic treatment versus standard treatment alone for patients with chronic obstructive pulmonary disease?**

Mittmann et al.\textsuperscript{24} retrospectively evaluated cost-effectiveness of BUD/FOR (Symbicort) added to tiotropium compared with tiotropium monotherapy in severe COPD patients over a 3-month period, based on the findings of the CLIMB study (Welte et al.\textsuperscript{22}). The effectiveness variable used for this analysis was the reduction of the number of severe exacerbations, which was defined as a requirement for systemic glucocorticosteroids and/or emergency department (ED) visits and/or hospitalization. Direct costs (medications, hospitalizations, ED and general practice [GP] visits) were calculated by applying year 2009 unit costs from Canada ($Can). One-way sensitivity analyses for mean incremental cost-effectiveness ratio and sensitivity to overall exacerbations were conducted. Bootstrapping was performed to estimate the variation around resource use, exacerbations and mean incremental cost-effectiveness ratio. (See Appendix 3)

**Summary of Critical Appraisal**

The strengths and limitations of included studies are summarized in Appendix 4 and Appendix 5. For research question one, the meta-analysis report by Wang\textsuperscript{19} met most AMSTAR criteria. It performed comprehensive literature searches and study selection and data extraction were performed by two independent reviewers. Unmet AMSTAR criteria included providing a list of excluded studies and appropriately considering the scientific quality of the included studies in formulating conclusions. The methodological quality of both included systematic reviews\textsuperscript{20,21} were considered poor per AMSTAR criteria because literature search was not comprehensive. In terms of
the reported outcomes of interest, only one study included in Karner et al.\textsuperscript{21} or Chen et al.\textsuperscript{20} compared formoterol added to tiotropium with tiotropium alone. The methodological quality of the RCT by Di Marco\textsuperscript{23} was poor because the randomization method and allocation concealment and baseline characteristics were not well described. The methodological quality of the RCT by Welte et al.\textsuperscript{23} was considered poor because of the allocation concealment and true ITT analysis were not reported. (See Appendix 4)

The economic evaluation report was considered to be good but have some methodological limitations because elements of the study design, such as the selection process of the clinical study used for the cost-effectiveness analysis was not reported. The analysis was based only on one RCT, which was not powered to show a difference in exacerbations or healthcare utilization. Pooling resource use and exacerbation data assumed that care in each country was a weighted mean over all countries. Assumptions were not clearly reported. A 12-week time horizon is relatively short. Results beyond 12 weeks must be extrapolated carefully. Indirect cost related to lost productivity of patients/caregivers was not included. (See Appendix 5)

**Summary of Findings**

**What is the comparative clinical efficacy of formoterol combined with standard anticholinergic treatment versus standard treatment alone for patients with chronic obstructive pulmonary disease?**

**Meta-analysis/systematic reviews**

Wang et al.\textsuperscript{19} found that treatment with tiotropium plus formoterol statistically, but not clinically significantly improved the trough FEV1 [Weighted mean difference (WMD): 53 mL, 95% confidence interval (CI): 30 to 76mL] compared with tiotropium alone (P<0.0001). A difference of 100mL to 140ml is usually considered the minimum clinically important difference of FEV1.\textsuperscript{25} The mean change in transitional dyspnoea index (TDI) was greater (but not clinically important) with tiotropium plus formoterol (WMD 1.50, 95% CI: 1.01 to 1.99) than with tiotropium alone (P<0.0001). The accepted minimum clinically important difference of TDI is 1.\textsuperscript{26} More than twice the number of patients in the tiotropium plus formoterol group achieved a clinically significant change in TDI compared with that in tiotropium alone group [Odds ratio (OR): 2.34, 95% CI: 1.58 to 3.46]. Fewer adverse events and COPD exacerbations with tiotropium plus formoterol were observed compared with tiotropium alone, but the differences were not statistically significant. The author concluded that adding formoterol to tiotropium significantly improved lung function and symptom scores compared with tiotropium alone. The difference was not statistically significant in terms of adverse events. The author also suggested that long-term trials are necessary to evaluate the effects of tiotropium plus formoterol and to clarify the role of combination therapy, compared with tiotropium alone.

Karner et al.\textsuperscript{21} reported that there was no statistically significant difference observed between tiotropium plus formoterol and tiotropium alone in terms of mean health-related quality of life (St George's Respiratory Questionnaire (SGRQ) [mean difference -1.61; 95% CI (-3.71 to 1.70)], hospitalizations for all cause [OR: 0.95, 95% CI 0.36 to 2.50]) or hospitalizations for COPD exacerbation [OR: 0.64 95% CI 0.15 to 2.69]

Chen et al.\textsuperscript{20} reported that compared with tiotropium alone, treatment with tiotropium plus formoterol significantly reduced the daytime rescue inhaler use [FOR+TIO: 1.81±0.13 vs. TIO: 2.41±0.14, P<0.0001], but not nighttime rescue inhaler use [FOR+TIO: 0.52±0.05 vs. TIO: 0.56±0.05, P>0.05]
Randomized controlled trial

In the RCT by Di Marco et al., it was reported that formoterol in combination with tiotropium showed a significantly faster onset, greater maximum bronchodilation effect than tiotropium alone in terms of FEV1. The results of this study have indicated that, although the time course of the effects of evaluated drugs differs significantly from that in stable COPD, with a shorter bronchodilation both for tiotropium and formoterol, these two long-acting bronchodilators appear to also be complementary in patients with mild to moderate acute exacerbation COPD. (See Appendix 6)

What is the comparative clinical efficacy of formoterol plus budesonide combined with standard anticholinergic treatment versus standard treatment alone for patients with chronic obstructive pulmonary disease?

Welte et al. reported that over 12 weeks, BUD/FOR plus tiotropium significantly increased pre-dose FEV1 by 6% (65 ml) and post-dose FEV1 by 11% (131 ml at 60 min post-dose) versus tiotropium alone (P < 0.001 for both pre and post-dose FEV1). Other outcomes all significantly improved with BUD/FOR plus tiotropium versus tiotropium alone. The number of severe exacerbations decreased by 62% (rate ratio, 0.38; 95% CI: 0.25-0.57; P < 0.001). Both treatments were well tolerated. The authors concluded that in patients with COPD, BUD/FOR added to tiotropium versus tiotropium alone provides rapid and sustained improvements in lung function, health status, morning symptoms and activities, and reduces severe exacerbations. The main study findings and authors’ conclusions from the RCT can be found in Appendix 6.

What is the cost-effectiveness of formoterol plus budesonide combined with standard anticholinergic treatment versus standard treatment alone for patients with chronic obstructive pulmonary disease?

The clinical effectiveness data reported in the CLIMB study (Welte et al.) was used for the cost-effective analysis (see Table 2). In the CLIMB study, a 62% reduction in the rate of severe exacerbations, statistically fewer GP visits were reported in the arm of BUD/FOR added to tiotropium than tiotropium alone, but no statistically significant difference was found in terms of hospitalization and ED visit (see Table 2). The unit cost of resource including health care visit and medication was based on the year of 2009 value in Canada (see Table 3). The analysis found that treatment with BUD/FOR added to tiotropium cost less in Canada ($Can4.51, see Table 4). That is, the savings associated with fewer exacerbations more than offset the additional BUD/FOR drug cost in Canada. The authors concluded that BUD/FOR added to tiotropium was the dominant strategy (achieving fewer exacerbations at a lower cost) compared with placebo added to tiotropium based on a 12-week study in COPD patients with severe COPD in Canada.

Table 2: Mean resource use and exacerbation per 3-month period

<table>
<thead>
<tr>
<th>Resource</th>
<th>BUD/FOR+TIO (n=329)</th>
<th>PBO+TIO (=330)</th>
<th>Mean difference (95%CI) (BUD/FOR+TIO vs. PBO+TIO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthcare visits/patients/3mos</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization (total day)</td>
<td>0.1(28)</td>
<td>0.31(88)*</td>
<td>-0.21(-0.48, 0.04)</td>
</tr>
<tr>
<td>ED visit (total visits)</td>
<td>0.01(3)</td>
<td>0.04(11)</td>
<td>-0.03(-0.05, 0.00)</td>
</tr>
<tr>
<td>GP visit (total visits)</td>
<td>0.07(20)</td>
<td>0.16(45)</td>
<td>-0.1(-0.15, -0.05)</td>
</tr>
<tr>
<td>Medication/patient/3mos</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUD/FOR (symbicort Turbuhaler 320/9µg) inhalations per day</td>
<td>182.63</td>
<td>0</td>
<td>182.63</td>
</tr>
<tr>
<td>Tiotropium (Spiriva handhaler 18 µg) inhalations per day</td>
<td>91.31(1)</td>
<td>91.31(1)</td>
<td>0</td>
</tr>
</tbody>
</table>
### Table 3: Unit cost for healthcare resources ($Can, year 2009 value)

<table>
<thead>
<tr>
<th>Resource</th>
<th>Direct unit cost ($Can)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthcare visits</td>
<td>1027</td>
</tr>
<tr>
<td>Hospitalization/day(^a)</td>
<td>132</td>
</tr>
<tr>
<td>ED visit</td>
<td>286</td>
</tr>
<tr>
<td>GP visit(^b)</td>
<td>2.6</td>
</tr>
<tr>
<td>Medication cost</td>
<td>2.1</td>
</tr>
<tr>
<td>Turbutalin inhaled (Bricanyl Turbuhaler 0.5mg) per day</td>
<td>0.07</td>
</tr>
<tr>
<td>Systematic GCS (Prednisolone) per day</td>
<td>0.88</td>
</tr>
</tbody>
</table>

\(^a\) Based on DRG cost code related to an international classification of disease (10th edition) code (J441) in Canada.

\(^b\) Patients who had their first systematic GCS prescription and did not go to the ED or hospital were cost as a GP visit and the cost of GCS by assumption; subsequently systemic GCS courses were cost as a represcription of a GCS course.

### Table 4: Mean direct costs and ICER per avoided severe exacerbation per patient over 3-month period (year 2009 value)

<table>
<thead>
<tr>
<th>Resource</th>
<th>Mean direct costs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BUD/FOR+TIO (n=329)</td>
</tr>
<tr>
<td>Healthcare visits</td>
<td>113.02</td>
</tr>
<tr>
<td>Medication cost</td>
<td>449.17</td>
</tr>
<tr>
<td>Total cost</td>
<td>562.19</td>
</tr>
<tr>
<td>Mean difference of cost (BUD/FOR+TIO vs. PBO+TIO)</td>
<td>-4.51</td>
</tr>
<tr>
<td>ICER</td>
<td>Dominant</td>
</tr>
</tbody>
</table>

BUD/FOR=budesonide/formoterol; ED=emergency department; GCS=glucocorticosteroids; GP=general practice; PBO=placebo; TIO=tiotropium; ICER=incremental cost-effectiveness ratio.

\(^a\) Based on DRG cost code related to an international classification of disease (10th edition) code (J441) in Canada.

\(^b\) Patients who had their first systematic GCS prescription and did not go to the ED or hospital were cost as a GP visit and the cost of GCS by assumption; subsequently systemic GCS courses were cost as a represcription of a GCS course.

### Limitations

Despite the methodological strength of these meta-analyses/systematic reviews that focused on a variety of patient-focused and clinically important outcomes, and use appropriate comparator dose of tiotropium (18µg once daily), there are multiple limitations that influence both internal and external validity. In Wang’s meta-analysis\(^{19}\), the doses of formoterol used in the included studies varied from 10µg to 20 µg twice daily, only four of the eight included studies used 12 µg twice daily, which is the Health Canada approved dose for COPD.\(^8\) The duration of the majority (6 out of 8) of trials was less than 12 weeks (two were for two weeks, one for four weeks and three for six weeks). The duration...
was not the optimal for determining the change of pulmonary function measurement (such as FEV1) and long term clinical outcomes. Furthermore, two of the studies used the nebulized formoterol (also known as arformoterol), which was not marketed in Canada. The two systematic reviews by Karner et al.\textsuperscript{21} and Chen et al.\textsuperscript{20} only included one study for the outcome of interest, which was not reported in Wang’s report. Those factors mentioned above limit interpretability and generalizability. The limitation of the RCT by Welte et al.\textsuperscript{22} was that the allocation concealment was not reported and the analysis was not a true intention to treat analysis, which could cause some potential bias, although the direction and magnitude of the potential bias, if any, is uncertain. Regarding the cost-effectiveness analysis report, the main limitation is the time horizon was too short (3 months); the results beyond 12 weeks must be extrapolated with caution.

**CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING**

Compared with tiotropium alone, formoterol plus tiotropium showed a statistically but not clinically significant improved lung function (FEV1) and symptoms (TDI) in the treatment of patients with moderate to severe COPD. There were numerically fewer adverse events in the formoterol plus tiotropium group, but the difference was not statistically significant. Similarly, adding BUD/FOR to tiotropium achieved statistically significant improvements in lung function and health status, as well as statistically significant reduction of severe exacerbations in patients with severe COPD compared with tiotropium alone. The limited evidence also showed that compared with the tiotropium alone, adding BUD/FOR to tiotropium was a cost-effective strategy (achieved less severe COPD exacerbations and saved CDN$4.51 per patient in a three month period). However, the above findings must be interpreted with caution due to the methodological limitations and clinical heterogeneities in the included studies. Well-designed, longer duration clinical trials are needed to fully evaluate the comparative clinical effectiveness, safety profile of the dual treatment of formoterol combined with tiotropium in patients with moderate to severe COPD or of the triple therapy of BUD/FOR plus tiotropium in patients with severe COPD compared with tiotropium monotherapy. No evidence was identified to assess the cost-effectiveness of formoterol plus tiotropium combination therapy with tiotropium monotherapy in the treatment of COPD. No evidence was found to assess the comparative effectiveness, safety profile, as well as the cost-effective analysis between formoterol plus tiotropium and salmeterol or indacaterol plus tiotropium (dual therapies) or between BUD/FOR plus tiotropium and fluticasone/salmeterol plus tiotropium (triple therapies) in the treatment of patient with COPD.
REFERENCES


APPENDIX 1: Selection of Included Studies

423 citations identified from electronic literature search and screened

378 citations excluded

45 potentially relevant articles retrieved for scrutiny (full text, if available)

8 potentially relevant reports retrieved from other sources (grey literature, hand search)

53 potentially relevant reports

47 reports excluded:
- irrelevant intervention (32)
- irrelevant comparator (5)
- irrelevant outcomes (1)
- already included in at least one of the selected systematic reviews or MA(7)
- other (review articles, editorials)(2)

6 reports included in review
## APPENDIX 2: Characteristics of Included Studies

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Study Design/ Length of Follow-up</th>
<th>Patient Characteristics, Sample Size (n)</th>
<th>Intervention</th>
<th>Comparator(s)</th>
<th>Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meta-analysis/systematic review</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Wang 19 2011, China</td>
<td>MA N=8 studies (1868 patients) included in the MA; 2 weeks to 24 weeks</td>
<td>Patients with moderate to severe COPD</td>
<td>FOR(10µg -20µg) bid* + TIO(18 µg. qd.)</td>
<td>TIO (18 µg qd)</td>
<td>tFEV1 TDI COPD exacerbation</td>
</tr>
<tr>
<td>Karner 21 2012, UK</td>
<td>SR N=1 study included in the subgroup of interest 24 weeks</td>
<td>Patients with moderate to severe COPD</td>
<td>FOR 10 µg bid. +TIO 18 µg qd</td>
<td>TIO 18 µg qd</td>
<td>FEV1 2 hours post dose after 24 weeks treatment, COPD exacerbation symptom scores, rescue medication use, QOL.</td>
</tr>
<tr>
<td>Chen 20 2008, China</td>
<td>SR N=1 study included in the SR for the outcome of interest; 6 weeks</td>
<td>Patients with moderate to severe COPD</td>
<td>FOR 12 µg bid +TIO 18 µg qd</td>
<td>TIO 18 µg qd</td>
<td>Average FEV1 (L, 0-24 hours) Mean(SE) Daytime rescue inhaler use</td>
</tr>
<tr>
<td><strong>RCT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Di Marco 23 2006 Italy</td>
<td>RCT 24 hours</td>
<td>Patients with acute exacerbation (mild to moderate) COPD N=21, male: 90%; Age: mean(SD): 72±8 years</td>
<td>FOR+TIO (12ug bid +18 ug qd)</td>
<td>TIO 18 ug</td>
<td>FEV1</td>
</tr>
<tr>
<td>Welte, 22 2009, Canada, and 8 European countries</td>
<td>RCT 12 weeks</td>
<td>Patient with severe COPD (FEV1 &lt; 50% predicted normal value) n=660 Male: 75% Duration: 3 months</td>
<td>FOR+BUD+TIO FOR+BUD (320/9µg) bid +TIO 18µg. qd.</td>
<td>PBO+TIO: PBO bid +TIO 18µg. qd.</td>
<td>FEV1 Reliever medication use; COPD exacerbation; Symptoms</td>
</tr>
</tbody>
</table>

*nebulized formoterol (aformoterol) was used in two studies

Bid=twice a day; BUD=budesonide; COPD= chronic obstructive pulmonary disease; FEV1= forced expiratory volume in 1 second; FOR=formoterol; HTA=health technology assessment; MA=meta-analyses; qd= once a day; PBO=placebo; RCTs=randomized control trials; SGRQ=St. George Respiratory Questionnaire; SR= systematic review; TDI= Transitional Dyspnea Index; tFEV1= trough (or pre-dose) FEV1; TIO=tiotropium
## APPENDIX 3: Characteristics of Included Economic Evaluations

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Study Design, Time horizon</th>
<th>Patient Characteristics</th>
<th>Intervention</th>
<th>Comparators</th>
<th>Assumptions</th>
</tr>
</thead>
</table>
| Mittmann 2011, Canada, Australia and Sweden | Cost effectiveness analysis Time horizon: 3 months | Patients with severe COPD | BUD/FOR+TIO [(BUD/FOR 320/9µg) bid +TIO 18µg. qd]. | PBO bid +TIO 18µg. qd. | • Cost effectiveness analysis: based on the CLIMB study.  
• Assumed that care in each country was a weighted mean over all countries.  
Other characteristics:  
• Canadian healthcare system/payer perspective was used.  
• A group mean approach was used to calculate average exacerbation frequencies and resource use.  
• Effectiveness variable: number of reduction of severe exacerbations.  
• Direct costs (medications, hospitalizations, ED and GP visits): calculated by applying year 2009 unit costs from Canada ($Can) to the study's pooled resource use.  
• QALY was not assessed  
• One-way sensitivity analyses for mean ICER and sensitivity to overall exacerbations were conducted.  
• Bootstrapping: performed to estimate the variation around resource use, exacerbations and ICER. (1000 bootstrapped datasets) |

Bid= twice daily; BUD=budesonide; FOR=formoterol; QALY= Quality-adjusted life year; ED=emergency department; GP=general practitioner; ICER=incremental cost-effectiveness ratio; PBO=placebo; qd.= once daily; TIO=tiotropim
## APPENDIX 4: Summary of Study Strengths and Limitations

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systematic Review and Meta-analysis assessed with AMSTAR</strong>^15^</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Wang 2011, China | • Research questions and selection criteria were defined and presented  
• Comprehensive literature search based on pre-defined criteria  
• 2 independent investigators performed study selection, and data extraction  
• List of included studies provided  
• Quality assessment of the included studies was described  
• Methods used to combine the findings was clearly reported  
• Publication bias was assessed  
• Conflict of interests declared | • List of excluded studies not provided  
• Whether the quality of included studies was considered in the analysis and conclusion was not clearly indicated |
| Karner 2012, UK | • Research questions and selection criteria were defined and presented  
• 2 independent investigators performed study selection, and data extraction  
• List of included and excluded studies provided  
• Quality assessment of the included studies was described  
• Conflict of interests was declared | • While literature search was comprehensive, only one study was included for the interested subgroup (FOR+TIO vs. TIO)  
• Publication bias was not assessed. |
| Chen 2008 | • Research questions and selection criteria were defined and presented  
• List of included studies provided  
• Conflict of interests declared | • Only one database was searched  
• Limited to English language publication  
• Grey literature was not searched  
• The selection and data extraction were not performed in a duplicate process  
• Characteristics of included studies was not reported  
• The list of excluded study was not presented  
• Quality assessment of the included studies was not described  
• Publication bias was not assessed |
| **RCT assessed with SIGN 50 Check list**^16^ | | |
| Di Marco 2006 | • Research question was clearly defined  
• Double blinding process was clearly described  
• Key patient characteristics at baseline are comparable in the treatment and control groups  
• Only difference between groups is treatment under investigation  
• Outcome was standard, valid and reliable  
• No drop-out | • Randomization method was not clearly described  
• Allocation concealment was not reported.  
• Baseline characteristics in the two arms were not well reported. |
| Welte, 2009, Canada, and 8 European | • Research question was clearly defined  
• Randomization method was not clearly described  
• Double blinding process was clearly | • Allocation concealment was not reported.  
• No ITT analysis was performed. |
<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>countries</td>
<td>described • Baseline characteristics in the two arms were well reported. • Only difference between groups is treatment under investigation • Outcome was standard, valid and reliable • Drop out are comparable in two groups (&lt;10% in each group)</td>
<td></td>
</tr>
</tbody>
</table>

RCT=randomized controlled trial; SR=systematic review; AMSTAR=A Measurement Tool to Assess the Methodological Quality of Systematic Reviews; COPD=chronic obstructive pulmonary disease; ITT=intention to treat.
APPENDIX 5: Critical Appraisal of Included Economic Evaluations with Drummond’s checklist

<table>
<thead>
<tr>
<th>First Author, Publication Year, Country</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Mittmann 2011, Australia, Canada, and Sweden | • The effectiveness data was based on a well conducted RCT and was justified.  
• The cost was based on the direct cost.  
• Research question was well defined.  
• The analysis method was clearly stated  
• The key parameters on which the analysis was based were justified.  
• The viewpoints in Canadian settings was stated and justified  
• Sample size and time horizon was clearly specified.  
• Conflict of interests was declared. | • The selection process of the clinical study used for the cost-effectiveness analysis was not reported.  
• The analysis was based only on one single RCT, which was not powered to show a difference in exacerbations or healthcare utilization.  
• Pooling resource use and exacerbation data assumes that care in each country was a weighted mean over all countries.  
• Assumptions were not clearly reported  
• 12 week time horizon is relatively short. Results beyond 12 weeks must be extrapolated carefully.  
• Indirect cost related to lost productivity of patients/caregivers was not included. |

RCT=randomized controlled trial.
## APPENDIX 6: Main Study Findings and Authors’ Conclusions

<table>
<thead>
<tr>
<th>First Author, Publication Year</th>
<th>Main Study Findings</th>
<th>Author’s Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Meta-analysis / systematic review</strong></td>
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<tr>
<td>Wang 2011, China</td>
<td>FOR+TIO vs. TIO: tFEV1(L): MD of change from baseline 0.05(0.03, 0.08) TDI: MD: 1.5 (1.01, 1.99) Clinical significant change in TDI (TDI &gt;1) OR (95%CI): 2.34(1.58, 3.46) COPD exacerbation: OR(95%CI): 0.93(0.45-1.93) Overall AE: OR (95%CI): 0.88(0.70-1.11)</td>
<td>Tiotropium plus formoterol significantly improved lung function and symptom scores compared with tiotropium alone. There was a trend towards a reduction in adverse events, although the difference was not statistically significant. Long-term trials are necessary to evaluate the effects of tiotropium plus formoterol and to clarify the role of combination therapy, compared with tiotropium alone. <em>(p350)</em></td>
</tr>
<tr>
<td>Karner 2012, UK</td>
<td>Data were extracted from the subgroup [(FOR+TIO) vs. TIO]: (only one RCT included) QOL (SGRQ): MD of change from baseline: -1 (-3.71, 1.70) Hospitalizations for all cause OR: 0.95(0.36, 2.50) Hospitalizations for COPD exacerbation: OR: 0.64(0.15, 2.69) Mortality for all cause: Not estimable</td>
<td>The results from this review indicate a small mean improvement in health-related quality of life for patients on a combination of tiotropium and long-acting beta2-agonist compared to tiotropium alone, but it is not clear how clinically important this mean difference may be. Hospital admission and mortality have not been shown to be altered by adding long-acting beta2-agonists to tiotropium. There were not enough data to determine the relative efficacy and safety of tiotropium plus long-acting beta2-agonist compared to long-acting beta2-agonist alone. There were insufficient data to make comparisons between the different long-acting beta2-agonists when used in addition to tiotropium. <em>(p2)</em></td>
</tr>
<tr>
<td>Chen 2008</td>
<td>FOR+TIO vs. TIO (data from one RCT) Daytime rescue inhaler use: FOR+TIO: 1.81±0.13 vs. TIO: 2.41±0.14 (P&lt;0.0001) Nighttime rescue inhaler use: FOR+TIO: 0.52±0.05 vs. TIO: 0.56±0.05 (NS, P&gt;0.05)</td>
<td>Tiotropium appears to be the best option as a first-line drug for patients with moderate-to-severe COPD because of its ability to sustain bronchodilator effect, improve quality of life, reduce COPD exacerbations, and reduce health resource usage. Patients who remain symptomatic may benefit from the addition of a long-acting beta (2)-agonist to tiotropium monotherapy. <em>(p1832)</em></td>
</tr>
<tr>
<td><strong>RCTs</strong></td>
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<tr>
<td>Di Marco 2006</td>
<td>FOR+TIO vs. TIO FEV1 AUROC (0-24 hours) FOR+TIO &gt; TIO; data not extractable (presented in figure) P &lt;0.01 in favor of FOR+TIO; FEV1 change from baseline at 24 hours after taking medication: FOR+TIO (L): 0.04(0.01-0.07) vs. TIO: 0</td>
<td><em>(The author indicated that)</em> Formoterol, either alone or in combination with tiotropium, elicited a significantly faster onset of action, and combination elicited a greater maximum bronchodilation than both single drugs in terms of FEV1 and FVC. After 24h the bronchodilating effect of the three treatments disappeared, with the exception of the combination on FEV1. The results of this study have documented that, although the time course of the effects of evaluated drugs differs significantly from that in stable COPD, with a shorter bronchodilation both for tiotropium and formoterol, these two long-acting bronchodilators appear to also be complementary in mild to moderate AECOPD. <em>(p1925-1926)</em></td>
</tr>
<tr>
<td>Welte, 2009, Canada, and 8 European countries</td>
<td>BUD/FOR+TIO vs. PBO+TIO: FEV1(L): pre-dose at 12 weeks MD: 0.065 FEV1(L) at 60 mini post-dose at 12 weeks: MD: 0.131 Reliever use, MD of number of inhalations(95%CI) Morning: -0.4(–0.564, –0.236) P&lt;0.001; Nighttime: -0.313(–0.456, –0.169) P&lt;0.01; Daytime (including morning): -0.508 (–0.772, –</td>
<td><em>(In patients with chronic obstructive pulmonary disease, budesonide/formoterol added to tiotropium versus tiotropium alone provides rapid and sustained improvements in lung function, health status, morning symptoms and activities, and reduces severe exacerbations.)</em> <em>(p741)</em></td>
</tr>
<tr>
<td>First Author, Publication Year</td>
<td>Main Study Findings</td>
<td>Author’s Conclusions</td>
</tr>
<tr>
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<td></td>
<td>0.244)</td>
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<tr>
<td></td>
<td>GCSQ (scale, 0–4) at pre-dose: MD: (95% CI) Breathlessness: -0.148 (–0.238, –0.058) P=0.001; Chest tightness: -0.090 (–0.181, 0.001); P=0.051 COPD Symptoms (scale 0-4): Breathlessness: -0.142 (–0.214, –0.069); P&lt;0.001; Nighttime awakenings: -0.157 (–0.222, –0.092); P&lt; 0.001; Chest tightness: -0.142 (–0.212, –0.072); P&lt;0.001; Cough: -0.161 (–0.238, –0.084); P&lt;0.001 Any AE: n (%) BUD/FOR+TIO: 82(25) PBO+TIO: 81(25) SAE: n (%) BUD/FOR+TIO: 24(7) PBO+TIO: 18(5) Death: BUD/FOR+TIO: 1 PBO+TIO: 0 COPD exacerbation event/patient/ 3 months: BUD/FOR+TIO vs. PBO+TIO Rate ratio (poisson regression): 0.38 (0.25, 0.57) P&lt;0.01 Hospitalizations/ER treatment events/patient/3mos: BUD/FOR+TIO vs. PBO+TIO Rate ratio (poisson regression): 0.35 (0.16, 0.78) P=0.011)</td>
<td>“Budesonide/formoterol added to tiotropium was the dominant strategy compared with placebo added to tiotropium based on a 12-week study in COPD patients eligible for ICS/LABA combination therapy in Australia and Canada, and appears to be a cost-effective strategy in Sweden.”(p404)</td>
</tr>
<tr>
<td>Mittmann 24</td>
<td>See table 1, 2, 3 in the main text</td>
<td></td>
</tr>
</tbody>
</table>

AECOPD= acute exacerbation chronic obstructive pulmonary disease; CI=confidence interval; COPD=chronic obstructive pulmonary disease; FEV1= forced expiratory volume in 1 second; BUD/FOR= budesonide/formoterol; GCSQ = Global Chest Symptoms Questionnaire; MD=mean difference; NNT=number needed to treat; OR=odds ratio PBO=placebo; QOL= quality of life; RR= relative risk; RCTs= randomized control trials; SAE: serious adverse events; SGRQ=St. George’s Respiratory Questionnaire; TDI=Transitional Dyspnea Index; TIO=tiotropium; WMD=weighted mean difference;