In patients with stable chronic obstructive pulmonary disease (COPD), is tiotropium more effective than placebo or other bronchodilators for reducing the risk of clinical end points?

**METHODS**

**Data sources:** Cochrane Airways Review Group specialised register, the Cochrane Central Register of Controlled Trials, Medline, EMBASE/Excerpta Medica, CINAHL, LILACS (to October 2004), hand searching 20 respiratory journals, conference abstracts, and bibliographies of relevant studies, and contacting authors.

**Study selection and assessment:** randomised controlled trials (RCTs) in any language that included patients >35 years of age with known stable COPD without evidence of an exacerbation for 1 month before study entry, and compared tiotropium with placebo, ipratropium bromide, or long acting β2 agonists (salbutamol or formoterol) for >1 month. Studies of patients with diseases other than COPD, previous asthma, cystic fibrosis, bronchiectasis, or other lung diseases were excluded. Study quality was assessed using Cochrane criteria for allocation concealment and the 5 point Jadad scale.

**Outcomes:** exacerbations (respiratory symptoms lasting >3 d), hospital admissions for exacerbations, and all cause mortality. Secondary outcomes included health related quality of life (HRQOL) assessed using the St George’s Respiratory Questionnaire (SGRQ) and the Transitional Dyspnea Index (TDI), change in FEV1, change in FVC, and adverse events.

**MAIN RESULTS**

9 RCTs (n = 6584) met the selection criteria. Permitted cotherapies were β2 agonists and inhaled corticosteroids. Allocation concealment was uncertain in 7 RCTs and adequate in 2 RCTs. 7 RCTs had a Jadad score of 4 out of 5 (range 3–5). Meta-analysis of 8 RCTs showed that tiotropium reduced exacerbations more than placebo (table). Tiotropium was more effective than ipratropium in 1 RCT (relative risk [RR] 0.77, 95% CI 0.62 to 0.95). 3 pooled RCTs showed that tiotropium reduced hospital admissions more than placebo (table). All cause mortality did not differ between tiotropium and placebo (table), ipratropium (1 RCT, RR 1.51, CI 0.41 to 5.50), or salmeterol (1 RCT, RR 0.17, CI 0.2 to 1.39). Tiotropium improved mean scores on the SGRQ (weighted mean difference [WMD] −3.27, CI −4.50 to −1.99) and the TDI (RR 1.53, CI 1.33 to 1.77); and increased FEV1 (WMD 204 ml, CI 185 to 223) and FVC (WMD 387 ml, CI 343 to 431) more than placebo. Dry mouth was a frequent adverse effect in the tiotropium group (table).

**CONCLUSION**

In patients with stable chronic obstructive pulmonary disease, tiotropium reduces exacerbations and hospital admissions, and improves health related quality of life. Abstract and commentary also appear in ACP Journal Club.

*Abbreviations defined in glossary; weighted event rates, RRR, RRI, NNT, NNH, and CI calculated from data in article using a fixed effects model.*

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**Table: Tiotropium vs placebo for chronic obstructive pulmonary disease at mean 6.3 months**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Number of trials (n)</th>
<th>Weighted event rates</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Tiotropium</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Exacerbations</td>
<td>8 (5644)</td>
<td>26%</td>
<td>31%</td>
<td>18% [10 to 25]</td>
</tr>
<tr>
<td>Hospital admissions</td>
<td>3 (3552)</td>
<td>5.4%</td>
<td>8.4%</td>
<td>33% [14 to 47]</td>
</tr>
<tr>
<td>All cause mortality</td>
<td>2 (1723)</td>
<td>0.6%</td>
<td>1.6%</td>
<td>50% [24 to 80]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3 (1791)</td>
<td>11%</td>
<td>2%</td>
<td>381% [109 to 672]</td>
</tr>
</tbody>
</table>

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**Commentary**

The well executed meta-analysis by Barr et al documents compelling evidence for the efficacy of tiotropium in COPD. Tiotropium has shown beneficial effects for most outcomes that clinicians and patients with COPD consider important. Notable exceptions include mortality and decline in lung function over time. However, no other medications have yet been proven to alter these outcomes either.

Evidence exists to support a preference for tiotropium over ipratropium, an older, short acting inhaled anticholinergic that has been the mainstay of COPD therapy for years. Barr et al identified 1 long term RCT comparing the 2 drugs. This study had the highest methodological validity of any tiotropium study, and showed benefits over ipratropium that were both clinically and statistically significant. The greater efficacy of tiotropium is biologically plausible because it has been shown to be more potent, selective, and longer lasting than ipratropium. Furthermore, because ipratropium must be given 4 times/day, compliance with once daily tiotropium is easier for patients. Finally, unlike tiotropium, no ipratropium studies have documented benefits for clinical outcomes, including exacerbations.

The major disadvantage of tiotropium is cost (up to 7 times more expensive than ipratropium). However, tiotropium is cost effective in moderate to severe COPD. This would support the use of tiotropium over ipratropium in such patients.

Whether further benefits can be achieved with tiotropium in combination with long acting β2 agonists and inhaled corticosteroids is the subject of a current, ongoing RCT. Other unanswered questions include whether a role exists for tiotropium in milder COPD and its role in inpatient management of COPD exacerbations.

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