# Review: Long-acting $\beta_2$-adrenoceptor agonists are effective in poorly reversible chronic obstructive pulmonary disease

Appleton S, Poole P, Smith B, et al. **Long-acting beta2-agonists for poorly reversible chronic obstructive pulmonary disease.** Cochrane Database Syst Rev. 2006(3):CD001104.

**Clinical impact ratings:** GIM/FP/GP ★★★★★☆☆ Pulmonology ★★★★★★☆


## QUESTION

In patients with chronic obstructive pulmonary disease (COPD) and poor reversibility to short-acting bronchodilators, how effective are long-acting $\beta_2$-adrenoceptor agonists (LABAs)?

## METHODS

**Data sources:** MEDLINE, EMBASE/Excerpta Medica, **CINAHL,** Cochrane Central Register of Controlled Trials, Cochrane Airways Group Specialised Register (to July 2005), online registries of published and unpublished clinical trials, lists of conference abstracts, and bibliographies of relevant studies.

**Study selection and assessment:** Randomized controlled trials (RCTs) that compared inhaled LABAs (salmeterol or formoterol) given for ≥ 4 weeks with placebo in patients who had stable, moderately severe COPD without asthma; $FEV_1 \leq 75\%$ or $FEV_1/FVC \leq 70\%$ of predicted value; poor reversibility after short-dose short-acting $\beta_2$-agonist (≤ 15% reversibility of $FEV_1$ from baseline or as a percentage of predicted normal value); and no infections, exacerbations, or hospitalizations in the past month. Individual study quality was assessed using the 5-point Jadad scale. 23 RCTs ($n$ = 6061, mean age range 58 to 72 y) met the selection criteria and had Jadad scores between 3 and 5.

**Outcomes:** Lung function ($FEV_1$, FVC, and PEF), exercise tolerance, quality of life (St. George's Respiratory Questionnaire [SGRQ] or Chronic Respiratory Diseases Questionnaire [CRDQ]), dyspnea (transition dyspnea index [TDI]) and symptoms, exacerbations, use of rescue medication, and withdrawals.

## MAIN RESULTS

Meta-analyses showed that salmeterol was better than placebo for improving lung function ($FEV_1$), quality of life (SGRQ and CRDQ domains of fatigue and dyspnea), and shortness of breath, and reducing use of rescue medication, withdrawals, and exacerbations (Table); salmeterol and placebo did not differ for dyspnea (TDI) (Table). Single RCTs showed that formoterol was better than placebo for lung function ($FEV_1$ and FVC), symptoms, and exercise tolerance, but did not differ for quality of life (SGRQ) and exacerbations; salmeterol and placebo did not differ for exercise tolerance.

## CONCLUSION

In patients with chronic obstructive pulmonary disease and poor reversibility to short-acting bronchodilators, long-acting $\beta_2$-adrenoceptor agonists reduced exacerbations and improved lung function and quality of life.


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**Salmeterol vs placebo in chronic obstructive pulmonary disease at 4 to 54 weeks***

| Outcomes | Number of trials (*n*) | Weighted mean difference (95% CI) |
|---|---|---|
| Change in $FEV_1$ (mL) | 8 (2026) | 51 (32 to 70) |
| Quality of life (SGRQ)† | 4 (1248) | –2.2 (–3.7 to –0.7) |
| Quality of life (CRDQ-fatigue) | 2 (208) | 1.9 (0.4 to 3.4) |
| Quality of life (CRDQ-dyspnea) | 2 (208) | 2.2 (0.5 to 4.0) |
| Dyspnea (TDI) | 3 (372) | 0.2 (–0.4 to 0.7)‡ |
| Symptom scores (shortness of breath) | 3 (941) | –0.07 (–0.1 to –0.03) |
| Use of rescue medication (puffs/d) | 4 (253) | –0.99 (–1.4 to –0.6) |
| Withdrawals for lack of efficacy | 5 (1581) | 0.3 (0.2 to 0.5) |
| | | Odds ratio (CI) |
| Exacerbations | 4 (1741) | 0.7 (0.6 to 0.9) |

*SGRQ = St. George's Respiratory Questionnaire; CDRQ = Chronic Respiratory Diseases Questionnaire; TDI = transition dyspnea index. CI defined in Glossary; a fixed-effects model was used.
†Lower scores indicate better quality of life.
‡Not significant.

## COMMENTARY

COPD is a major cause of morbidity and mortality with a rising incidence worldwide. Large RCTs and meta-analyses show that currently available pharmacotherapy may improve symptoms and perhaps even survival.

Appleton and colleagues provided an indepth systemic review of the role of LABAs in the management of stable COPD. LABAs led to small statistically significant increases in lung function ($FEV_1$) and improvement in some measures of health status compared with placebo. These findings further support current guideline recommendations for use of LABAs in stable moderate-to-severe COPD. However, the story does not end here. In light of recent concerns and the continued debate about LABAs and increased asthma-related deaths (1), is it possible that LABAs also increase deaths in patients with COPD?

The meta-analysis by Salpeter and colleagues shows the effectiveness of anticholinergics in reducing COPD exacerbations and hospitalizations. Interestingly, compared with placebo, anticholinergics reduced respiratory-related deaths while $\beta_2$-agonists increased mortality in patients with COPD. A closer look at the data, however, reveals major limitations of the combined respiratory mortality results. No trials were designed to study mortality as a primary endpoint and the numbers of respiratory deaths reported in individual trials were small, rendering the pooling of respiratory deaths less certain. In addition, differential dropout rates in the treatment and placebo groups (more patients withdrawing from the placebo group) may have biased the accurate accounting of deaths. Therefore, any firm conclusions about the negative role of LABAs on COPD survival or the positive survival effect of anticholinergics are premature. Encouragingly, preliminary reports from

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# Review: Anticholinergics, but not $\beta_2$-agonists, reduce exacerbations requiring hospitalization and respiratory deaths in COPD

Salpeter SR, Buckley NS, Salpeter EE. **Meta-analysis: anticholinergics, but not beta-agonists, reduce severe exacerbations and respiratory mortality in COPD.** J Gen Intern Med. 2006;21:1011-9.

**Clinical impact ratings:** GIM/FP/GP ★★★★★★☆ Pulmonology ★★★★★★☆

## QUESTION

How effective are anticholinergics and $\beta_2$-agonists for chronic obstructive pulmonary disease (COPD)?

## METHODS

**Data sources:** MEDLINE, EMBASE/Excerpta Medica, and Cochrane databases (to December 2005); U.S. Food and Drug Administration web site; and references of identified reviews.

**Study selection and assessment:** Randomized controlled trials (RCTs) in any language that compared anticholinergics or $\beta_2$-agonists with placebo or with each other, had ≥ 3-month follow-up, and reported COPD exacerbations requiring study withdrawal or hospitalization, or respiratory death. 22 RCTs ($n$ = 15 276, mean age range 60 to 64 y) with mean 20-month follow-up (range 3 to 60 mo) met the selection criteria. Methodologic quality of individual studies was based on randomization procedure and allocation concealment, blinding of patients and providers, reporting of withdrawals and dropouts, and intention-to-treat analysis.

**Outcomes:** Exacerbations causing withdrawal from the study, severe exacerbations requiring hospitalization, and respiratory death.

## MAIN RESULTS

Anticholinergics used were ipratropium and tiotropium. $\beta_2$-agonists used were albuterol, metaproterenol, formoterol, and salmeterol. Compared with placebo, anticholinergics reduced withdrawals, hospitalizations, and respiratory deaths (Table). $\beta_2$-agonists reduced withdrawals, but did not have an effect on hospitalizations and increased respiratory deaths (Table). Compared with anticholinergics, $\beta_2$-agonists increased withdrawals and hospitalizations, and were associated with a nonsignificant increase in respiratory deaths (Table).

## CONCLUSIONS

In patients with chronic obstructive pulmonary disease, anticholinergics are superior to $\beta_2$-agonists for reducing exacerbations. $\beta_2$-agonists increase risk for respiratory deaths compared with placebo.

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**Anticholinergics, $\beta_2$-agonists, and placebo for chronic obstructive pulmonary disease at mean 20 months***

| Comparisons | Outcomes | Number of trials ($n$) | RRR (95% CI) | NNT (CI) |
|---|---|---|---|---|
| Anticholinergics vs placebo | Withdrawals | 6 (4591) | 40% (25 to 52) | 29 (23 to 46) |
| Hospitalizations | 3 (3552) | 33% (14 to 47) | 36 (26 to 85) | |
| Respiratory death | 5 (7881) | 73% (19 to 91) | 442 (355 to 1698) | |
| $\beta_2$-agonists vs placebo | Withdrawals | 11 (5333) | 19% (5 to 32) | 50 (30 to 189) |
| | | | RRI (CI) | NNH (CI) |
| Hospitalizations | 2 (911) | 8.0% (–39 to 95) | Not significant | |
| Respiratory death | 4 (2404) | 147% (12 to 445) | 92 (31 to 1127) | |
| $\beta_2$-agonists vs anticholinergics | Withdrawals | 7 (3044) | 102% (39 to 193) | 38 (20 to 98) |
| Hospitalizations | 2 (1606) | 95% (6 to 259) | 54 (20 to 851) | |
| Respiratory death | 2 (1229) | 591% (–15 to 5497) | Not significant | |

*Abbreviations defined in Glossary; RRR, RRI, NNT, NNH, and CI calculated from control event rates in article using a fixed-effects model.

## COMMENTARY

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a large multicenter RCT (2) of 6112 patients with moderate-to-severe COPD who received combination therapy (salmeterol and fluticasone) or each component alone, do not portend increased all-cause mortality in patients receiving salmeterol.

Salpeter and colleagues chose to combine results from both short- and long-acting anticholinergics (tiotropium) in their analysis. Several RCTs have shown that, compared with ipratropium, tiotropium leads to greater improvement in symptoms and fewer COPD exacerbations and hospitalizations (3). Perhaps even greater improvements in outcomes would have been noted if only the results for the tiotropium studies were combined. A recent meta-analysis by Barr and colleagues (3) showed reductions in COPD symptoms, exacerbations, and hospitalizations with tiotropium compared with placebo and ipratropium. Unlike Salpeter and colleagues, Barr and colleagues did not show a reduction in all-cause or respiratory-specific mortality in patients using tiotropium, nor did they show a difference between tiotropium and LABAs for any of the outcomes studied. The latter comparisons were limited to 2 trials.

In conclusion, we have good evidence for the use of anticholinergics and LABAs in reducing symptoms and exacerbations in patients with COPD. More studies are needed to determine whether anticholinergics are better than LABAs. The possibility of increased mortality in patients given LABAs is important to note, but at present, insufficient evidence exists to confirm this hypothesis. The effect of combination therapies is not yet fully understood but represents hope for the future of patients with COPD.

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***References***

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