Bronchodilators in COPD: Impact of β-agonists and anticholinergics on severe exacerbations and mortality

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Abstract: This review summarizes the long-term clinical outcomes associated with β-agonist and anticholinergic bronchodilator use in patients with chronic obstructive pulmonary disease (COPD). Pooled data from randomized placebo-controlled trials of at least three months duration were used to evaluate the risk for COPD hospitalizations, respiratory mortality, and total mortality. The results show that anticholinergic use is associated with a 30% reduction in COPD hospitalizations, a 70% reduction in respiratory mortality, and without a significant effect on total mortality. In contrast, β-agonist use had no effect on COPD hospitalizations and was associated with a two-fold increased risk for respiratory death compared with placebo. When the two bronchodilators were directly compared with each other, β-agonists were associated with a two-fold increased risk for COPD hospitalization and a five-fold increased risk for total mortality compared with anticholinergics. When β-agonists were added to either anticholinergic use or inhaled corticosteroid use alone, there was no significant improvement in any long-term clinical outcome. These results indicate that anticholinergics should be the bronchodilator of choice in COPD, while β-agonists may be associated with poorer disease control.

Keywords: chronic obstructive pulmonary disease, COPD, adrenergic beta-agonists, cholinergic antagonists, bronchodilator, systematic review, clinical outcomes, mortality.

Long-term clinical outcomes in COPD

Chronic obstructive pulmonary disease (COPD) is characterized by partially reversible chronic airflow obstruction, caused by inflammatory reactions in the airways and lung parenchyma to inhaled toxins such as tobacco smoke (Celli and MacNee 2004). The airflow obstruction is progressive over time, and is often accompanied by some degree of airway hyperreactivity, which may be partially reversible (ATS 1995). Acute exacerbations of COPD occur, defined loosely as an episode of increased dyspnea, cough, and sputum production (McCrory et al 2001). Exacerbations severe enough to require hospitalization are associated with 3% to 4% short-term mortality, and half of those hospitalized will be readmitted within 6 months (McCrory et al 2001). COPD is a major cause of morbidity and mortality worldwide, and the prevalence of the disease continues to rise (Sullivan et al 2000; Michaud et al 2001).

The main therapeutic options for the management of COPD are inhaled corticosteroids and bronchodilators. Inhaled corticosteroids significantly reduce inflammatory cells in the lungs, as well as systemic inflammatory markers such as C-reactive protein, compared with placebo (Sin et al 2004; Gan et al 2005). However, there is some evidence that corticosteroids have no antiinflammatory effects in COPD patients who are still smoking (Van Overveld et al 2006). The use of systemic corticosteroids in acute COPD exacerbations have been shown to improve lung function and reduce hospital stays and treatment failures (Wood-Baker et al 2001; Niewoehner 2002; Singh et al 2002). Outpatient treatment with systemic corticosteroids can improve

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symptoms and reduce the relapse rate (Aaron et al 2003). Meta-analyses have shown that long-term treatment with inhaled corticosteroids reduce the rate of COPD exacerbations by 30% and slow the progression of airway function decline (van Grunsven et al 1999; Alsaeedi et al 2002; Sutherland et al 2003; Salpeter and Buckley 2006). One meta-analysis of randomized controlled trials found a 25% reduction in all-cause mortality for inhaled corticosteroids compared with placebo (Sin et al 2005). However, pooled data from another meta-analysis did not show a reduction in respiratory or total mortality compared with placebo (Salpeter and Buckley 2006).

The two types of bronchodilators, β-agonists and anticholinergics, are generally considered to be equivalent choices in the treatment of COPD (Pauwels et al 2001; Celli and MacNee 2004; NCCC 2004). Many trials of these agents have concentrated on short-term physiological endpoints, such as the forced expiratory volume at 1 second (FEV_1), quality of life, or symptoms. Anticholinergics have been shown to have equal or superior efficacy as β-agonists in the improvement of lung function parameters (Karpel 1991; Rennard et al 1996; McCrory and Brown 2001; Sin et al 2003; Tashkin and Cooper 2004). However, surveys show that prescriptions for β-agonists are two times more common than anticholinergics in the UK and Europe, and ten times more common in the US (Ramsey 2000; Rudolf 2000; Roche et al 2001).

This review summarizes the effect of β-agonists and anticholinergics on severe exacerbations and mortality, compared with placebo and with each other. The effects of inhaled corticosteroids on these outcomes are also evaluated. The results of two meta-analyses are presented (Salpeter and Buckley 2006; Salpeter, Buckley, Salpeter 2006) that pooled long-term randomized placebo-controlled trials of anticholinergic or β-agonist use and evaluated COPD hospitalizations, respiratory mortality, and total mortality. Of note, after these meta-analyses were published it was revealed that data from one of the included trials was also reported in another trial (Brusasco et al 2006). We now provide the analysis with the duplicated data excluded. Information on the trials included in the meta-analysis is shown in Table 1.

Anticholinergic bronchodilators

Anticholinergic bronchodilators include the short-acting ipratropium and oxtropium (not available in the US), and the long-acting tiotropium that has been recently introduced to the market (Barnes 2004). They work by inhibiting bronchoconstriction as well as mucus secretion, and have been shown in clinical trials to reduce symptoms and exacerbations, without the development of tolerance to their effects over time (Ashutosh and Lang 1984; Tashkin et al 1986; van Schayck et al 1990; Rennard et al 1996; Donohue et al 2003; Barnes 2004).

Anticholinergics compared with placebo

The pooled results of 9 randomized placebo-controlled trials (Table 1) that ranged from three months to five years in duration (Salpeter, Buckley, Salpeter 2006) showed that anticholinergics reduced the risk of COPD hospitalizations by 30% and reduced respiratory deaths by 70%, compared with placebo (Figure 1). No significant effect on total mortality was seen (Salpeter and Buckley 2006). It is estimated that 58% of the participants were also taking concomitant inhaled corticosteroids.

Long-acting compared with short-acting anticholinergics

When trials that compared the long-acting tiotropium with the short-acting ipratropium were pooled together, tiotropium was associated with 40% less severe exacerbations than ipratropium (Barr et al 2005; Salpeter and Buckley 2006). A cost-effective analysis that was funded by Boehringer Ingelheim found that the mean healthcare costs for tiotropium, including medications and hospital visits, was slightly higher than with ipratropium (Oostenbrink et al 2004). However the benefit of reducing hospitalizations was considered cost-effective. Tiotropium has also been shown to prevent the decline in trough FEV_1 values, compared with placebo, over the course of one year (Casaburi et al 2000, 2002; FDA 2002; Barr et al 2005).

β-agonist bronchodilators

β-agonist bronchodilators work by relaxing bronchial smooth muscle, and have been shown to be effective in the short-term relief of COPD symptoms (Sestini et al 2002). However, β-agonists have adverse cardiovascular effects and increase the risk of adverse cardiac events by over two-fold compared with placebo (Salpeter et al 2004). This risk may be highest in patients with COPD and concomitant heart disease. In addition, significant tolerance to the respiratory effects of β-agonists develops with long-term use (Donohue et al 2003).

Controversy has raged over the past 50 years concerning the safety of β-agonists in asthma and COPD (Lipworth 1992; Fahy and Boushey 1995; Taylor et al 1996). Regular β-agonist use in reactive airway disease results in tolerance to the drug's bronchodilator and bronchoprotective effects, and is associated with poorer disease control (Sears et al 1990; Salpeter et al

Table 1 Included studies in COPD meta-analysis

Study year Duration (months)	Number (n)	Active intervention	Concomitant corticosteroid use (%)
Anthonisen 2002 60	3923	Ipratropium	Not stated
Boyd 1997 4	674	Salmeterol	65
Brusasco 2003 6	1207	Tiotropium Salmeterol	Not stated
Calverley 2003 12	511	Formoterol with and without budesonide	50
Casaburi 2000 3	470	Tiotropium	Not stated
Casaburi 2002 12	921	Tiotropium	50
Colice 1996 3	223	Ipratropium Albuterol	48
Combivent 1997 3	430	Ipratropium Albuterol and combination	Not stated
Cook 2001 3	124	All on ipratropium with and without albuterol	100
Friedman 1999 3	709	Ipratropium Albuterol and combination	45
Mahler 2002 6	341	Salmeterol with and without fluticasone	49
Niewoehner 2005 6	1829	Tiotropium	70
Rennard 2001 3	273	Salmeterol Ipratropium	Not stated
Rossi 2002 12	645	Formoterol	48
Spiriva NDA (FDA 2002) 12	921	Tiotropium	Not stated
Szafranski 2003 12	406	Formoterol with and without budesonide	27
Taylor 2001 3	507	Ipratropium	Not stated
Wadbo 2002 3	183	Ipratropium Formoterol	Not stated

Abbreviations: COPD, chronic obstructive pulmonary disease.

2004). A recent meta-analysis pooled results from 19 asthma trials with 33,826 participants and found that the long-acting β-agonists salmeterol and formoterol increased asthma hospitalizations, life-threatening asthma attacks, and asthma deaths by two-fold to four-fold, compared with placebo (Nelson et al 2006; Salpeter, Buckley, Ormiston, et al 2006). Statistically significant increases in asthma hospitalizations were seen for salmeterol and formoterol, and for children and adults. It was recently questioned whether the long-acting β-agonists should be taken off the market (FDA 2005).

β-agonists compared with placebo

The pooled results of 9 randomized-placebo controlled trials (Table 1) lasting from three to 12 months (Salpeter and Buckley 2006; Salpeter, Buckley, Salpeter 2006) showed that β-agonist use increased respiratory deaths by over two-fold compared with placebo, without significantly affecting hospitalizations or total mortality (Figure 2). It was estimated that 56% of the participants were on concomitant inhaled corticosteroids.

β-agonists compared with anticholinergics

Seven trials directly compared β-agonists with anticholinergics in COPD (Table 1) and reported on hospitalizations or deaths (Salpeter and Buckley 2006; Salpeter, Buckley, Salpeter 2006). β-agonist use was associated with a two-fold increased risk for hospitalizations and a five-fold increased risk for total mortality compared with anticholinergic use

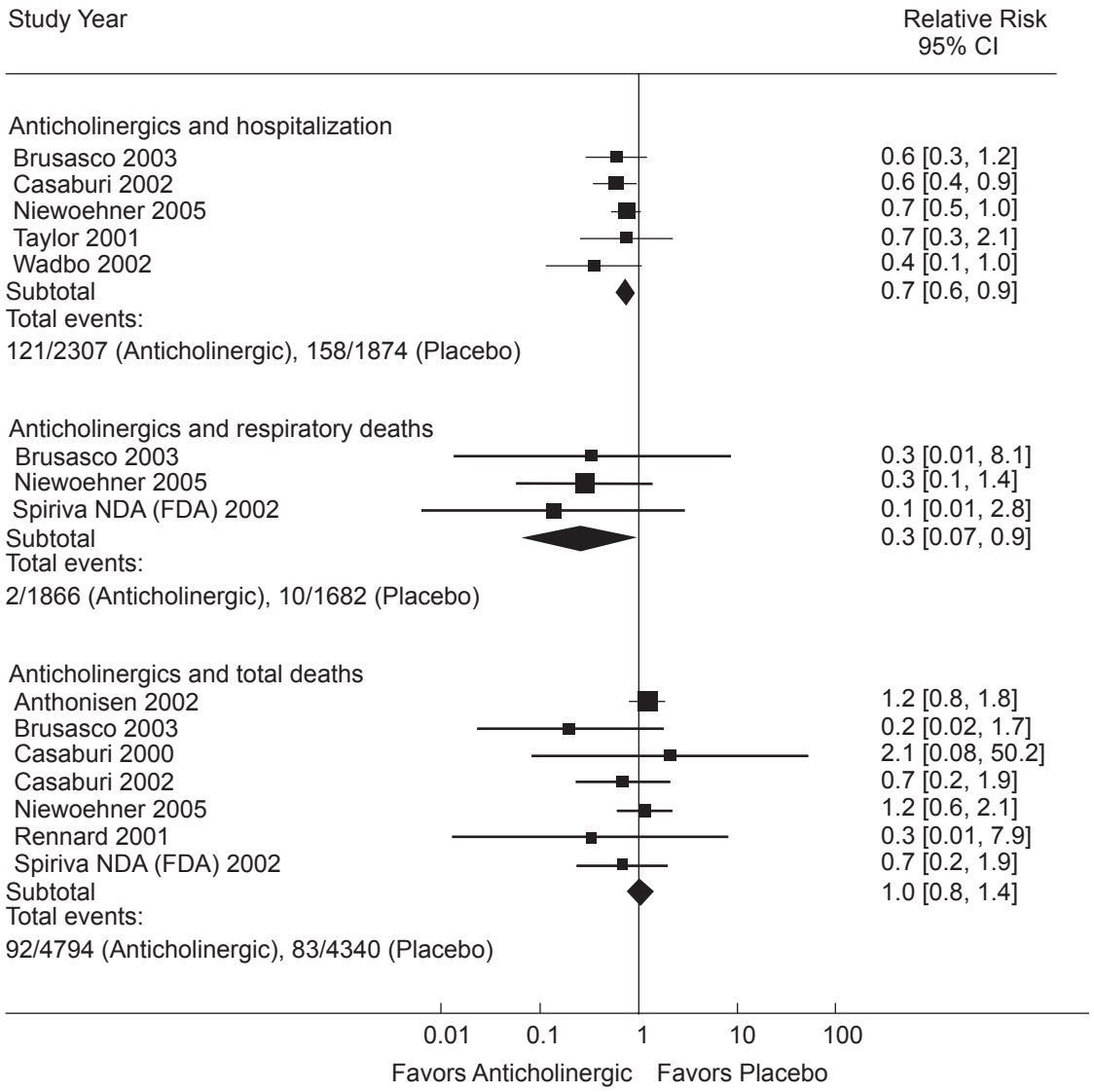

Figure 1 Effect of anticholinergics compared with placebo on COPD hospitalizations, respiratory deaths and total deaths.
Abbreviations: CI, confidence internal; COPD, chronic obstructive pulmonary disease; NDA, new drug application.

(Figure 3). Four additional trials evaluated the combination of anticholinergics and β-agonists (Table 1); pooled results found that the combination was not better than anticholinergic use alone on these long-term clinical outcomes (Salpeter and Buckley 2006).

β-agonists compared with inhaled corticosteroids

Only three trials (Table 1) directly compared β-agonists with inhaled corticosteroids (Salpeter and Buckley 2006). Pooled results found that β-agonists were associated with a two-fold increased risk for total mortality compared with corticosteroids, with marginal significance.

One meta-analysis has evaluated combined corticosteroid and long-acting β-agonist treatment compared with placebo and either modality alone (Nannini et al 2004). Combination treatment reduced severe COPD exacerbations by 25% compared with placebo and by 22% compared with β-agonist alone. However, the combination treatment had no significant effect on severe exacerbations compared with corticosteroid alone. Recently, an additional trial that lasted three years have been performed, but the results have not been presented (GlaxoSmithKline 2006). Preliminary results show that combined treatment reduced total mortality compared with placebo, but the results compared with inhaled corticosteroids alone and β-agonist alone are not available at present.

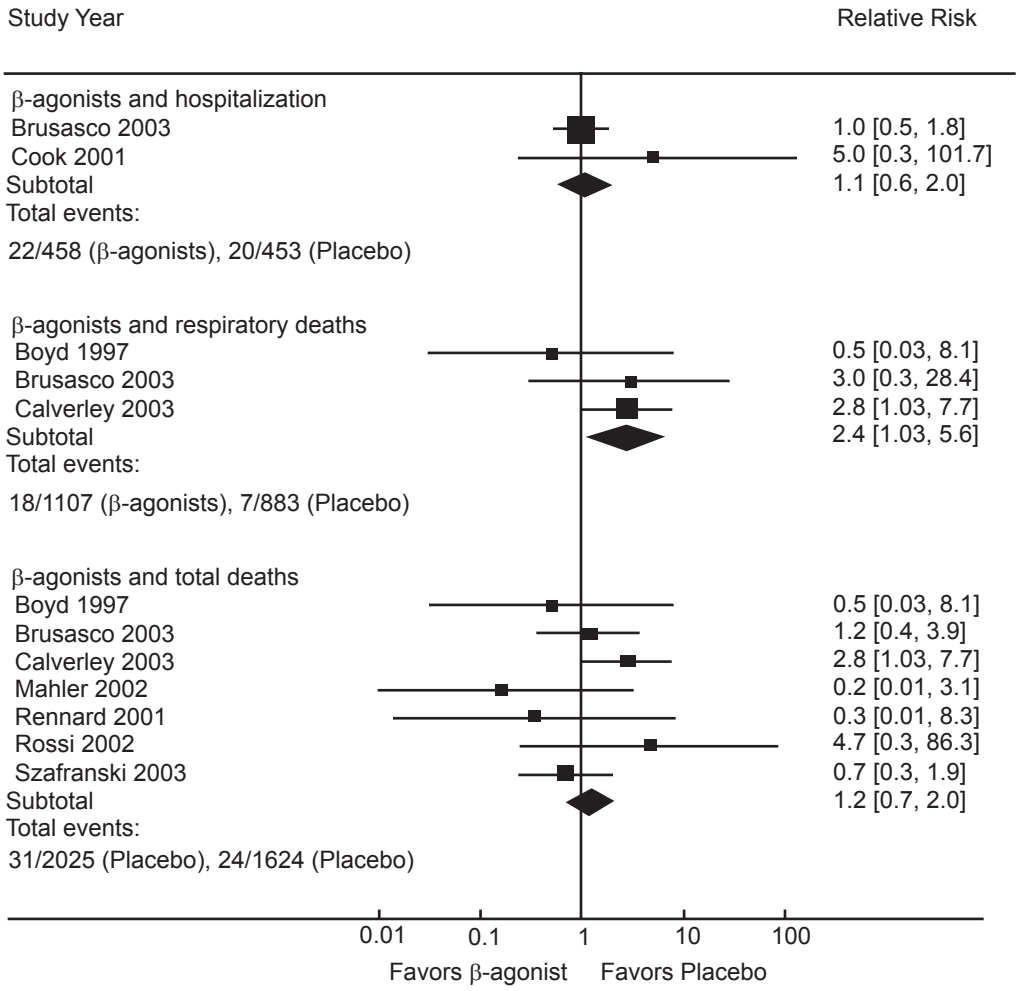

Figure 2 Effect of β-agonists compared with placebo on COPD hospitalizations, respiratory deaths and total deaths.
Abbreviations: COPD, chronic obstructive pulmonary disease.

Summary

The main therapeutic options in the treatment of COPD have been bronchodilators in combination with inhaled corticosteroid. Guidelines presently state that both bronchodilators, anticholinergics and β-agonists, are equivalent choices for use in COPD, while in practice β-agonists are prescribed 2–10 times more often than anticholinergics. This systematic review has summarized the available data on long-term clinical outcomes associated with β-agonist and anticholinergic bronchodilators in COPD. Anticholinergic inhalers reduce COPD hospitalizations by 30% and respiratory deaths by 70% compared with placebo, while β-agonists increase respiratory mortality by over two-fold compared with placebo. When compared with each other, β-agonists are associated with a two-fold increased risk for COPD hospitalization and a five-fold increased risk for total mortality compared with anticholinergics. When β-agonists are added to anticholinergics or corticosteroids, there was no improvement in long-term clinical outcomes.

This meta-analysis has several limitations. Meta-analytic results can be uncertain when the numbers of events per study are small, as is the case with respiratory deaths. Another limitation is that most of the studies did not report deaths as a primary outcome, so the ascertainment of cause of death may be uncertain. It is unfortunate that there was not enough information to evaluate the protective effect of concomitant inhaled corticosteroids on the adverse effects of β-agonists. Furthermore, it was not possible to perform subgroup analysis to compare the differences in results between long-acting and short-acting β-agonists, or between the two long-acting agents, salmeterol and formoterol. Despite these limitations, this pooled analysis provides valuable information on the comparative effects of anticholinergics and β-agonists on clinical outcomes in COPD.

These results indicate that anticholinergics are superior to β-agonists in improving long-term clinical outcomes, and that guidelines should be changed so that anticholinergics are the bronchodilator of choice in COPD. Tiotropium is more

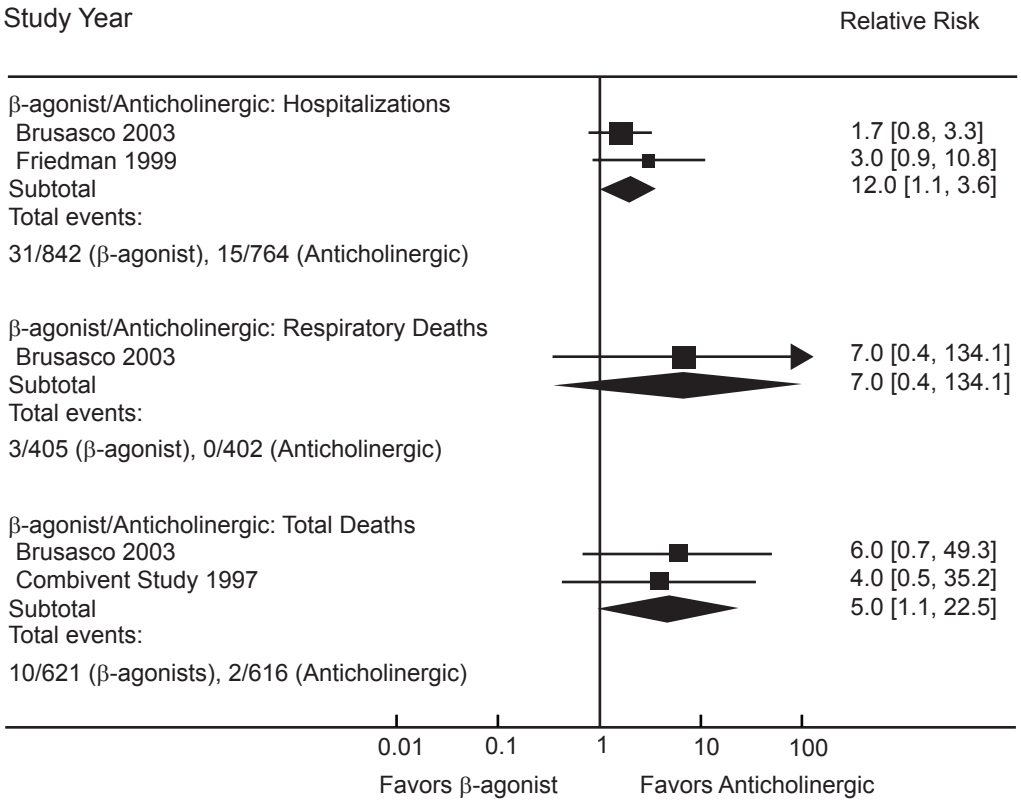

Figure 3 Effect of β-agonists compared with anticholinergics on COPD hospitalizations, respiratory deaths and total deaths
Abbreviations: COPD, chronic obstructive pulmonary disease..

effective than ipratropium for long-term clinical outcomes, but at a slightly greater cost. We provide evidence that β-agonists may actually increase respiratory mortality by over two-fold compared with placebo. More studies are needed to evaluate the long-term clinical benefit of the long-acting β-agonists, salmeterol and formoterol, in combination with inhaled corticosteroids, compared with the long-acting anticholinergic agent, tiotropium, combined with inhaled corticosteroids.

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