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 (McCory 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 (McCory 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
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 FEV₁ 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...


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

References
Aaron SD, Vandemheen KL, Hebert P, et al. 2003. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. N Engl J Med, 348:2618–25.
Alsaeedi A, Sin DD, McAlister FA. 2002. The effects of inhaled corticosteroids in chronic obstructive pulmonary disease: a systematic review of randomized placebo-controlled trials. Am J Med, 113:59–65.
Anthonisen NR, Connell JE, Enright PL, et al. 2002. Hospitalizations and mortality in the Lung Health Study. Am J Crit Care Med, 166:333–9.
Ashutosh K, Lang H. 1984. Comparison between long-term treatment of chronic bronchitic airway obstruction with ipratropium bromide and metaproterenol. Ann Allergy, 53:401–6.
[ATP] American Thoracic Society. 1995. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 152(5 Pt 2):S77–121.
Barnes PJ. 2004. The role of anticholinergics in chronic obstructive pulmonary disease. Am J Med, 117(Suppl 12A):24S–32S.
Barr RG, Bourbeau J, Camargo CA, et al. 2005. Inhaled tiotropium for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev, 2:CD002876.
Boyd G, Morice AH, Pounsford JC, et al. 1997. An evaluation of salmeterol in the treatment of chronic obstructive pulmonary disease (COPD). Eur Respir J, 10:815–21.
Brusasco B, Hodder R, Miravitlles M, et al. 2003. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax, 58:399–404.
Brusasco V, Hodder R, Miravitlles M, et al. 2006. Letter to the editor. Health outcomes following treatment for 6 months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax, 61:91.
Calverley PM, Boonsawat W, Cseke Z, et al. 2003. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J, 22:912–19.
Casaburi R, Briggs DD, Jr., Donohue JF, et al. 2000. The spirometric efficacy of once-daily dosing with tiotropium in stable COPD: a 13-week multicenter trial. The US Tiotropium Study Group. Chest, 118:1294–302.
Casaburi R, Mahler DA, Jones PW, et al. 2002. A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. Eur Respir J, 19:217–24.
Celli BR, MacNee W. 2004. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J, 23:932–46.
Combivent Inhalation Solution Study Group. 1997. Routine nebulized ipratropium and albuterol are better than either alone in COPD. The Combivent Inhalation Solution Study Group. Chest, 112:1514–21.
Cook D, Guyatt G, Wong E, et al. 2001. Regular versus as-needed short-acting inhaled beta-agonist therapy for chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 163:85–90.
Donohue JF, Menjoge S, Kesten S. 2003. Tolerance to bronchodilating effects of salmeterol in COPD. Respir Med, 97:1014–20.
Fahy JV, Boushey HA. 1995. Controversies involving inhaled beta-agonists and inhaled corticosteroids in the treatment of asthma. Clin Chest Med, 16:715–33.

[FDA] US Food and Drug Administration Advisory Committee. 2005. Serevent, Advair, Foradil withdrawals to be considered by Advisory Committee [online]. 8 August 2005. URL: http://www.fdaadvisory-committee.com/FDCAdvisoryCommittee/Committees/Pulmonary-Allergy%20Drugs/071305_betasesafety/071305_BroncoP.htm.

[FDA] US Food and Drug Administration. 2002. NDA 21–395 Spiriva (Tiotropium bromide) inhalation powder for COPD [online]. Accessed on 10 August 2005. URL: http://www.fda.gov/OHRMS/DOCKETS/ac/02/briefing/3890B1_05_Clinical%20Briefing.doc.

Friedman M, Serby CW, Menjoge SS, et al. 1999. Pharmacoeconomic evaluation of a combination of ipratropium plus albuterol compared with ipratropium alone and albuterol alone in COPD. Chest, 115:635–41.

Gan WQ, Man SF, Sin DD. 2005. Effects of inhaled corticosteroids on sputum cell counts in stable chronic obstructive pulmonary disease: a systematic review and a meta-analysis. BMC Pulm Med, 5:3.

GlaxoSmithKline. 2006. GSK announces positive results of Seretide study in patients with chronic obstructive pulmonary disease (COPD) [online]. Accessed on 18 August 2006. URL: http://www.gsk.com/ControllerServlet/appId=4&pageId=402&kwesid=780.

Karpel JP. 1991. Bronchodilator responses to anticholinergic and beta-adrenergic agents in acute and stable COPD. Chest, 99:871–6.

Lipworth BJ. 1992. Risks versus benefits of inhaled beta 2-agonists in the management of asthma. Drug Saf, 7:54–70.

Mahler DA, Wire P, Horstman D, et al. 2002. Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 166:1084–91.

McCrorry DC, Brown CD, Gelfand SE, et al. 2001. Management of acute exacerbations of COPD. A summary and appraisal of published evidence. Chest, 119:1190–209.

McCrorry DC, Brown CD. 2001. Inhaled short-acting beta2-agonists versus ipratropium for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev, 2:CD002984.

Michaud CM, Murray CJ, Bloom BR. 2001. Burden of disease—implications for future research. JAMA, 285:535–9.

Nannini L, Cates CJ, Lasserson TJ, et al. 2004. Combined corticosteroid and long acting beta-agonist in one inhaler for chronic obstructive pulmonary disease. Cochrane Database Syst Rev, 3:CD003794.

[NCCC] National Collaborating Centre for Chronic Conditions. 2004. Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. Thorax, 59(Suppl) 1:1–232.

Nelson HS, Weiss ST, Bleecker ER, et al. 2006. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest, 129:15–26.

Niewoehner DE. 2002. The role of systemic corticosteroids in acute exacerbation of chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 1:243–8.

Niewoehner DE, Rice K, Cote C, et al. 2005. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily, inhaled anticholinergic bronchodilator: a randomized trial. Ann Intern Med, 143:317–26.

Oostenbrink JB, Rutten-van Molken MP, Al MJ, et al. 2004. One-year cost-effectiveness of tiotropium versus ipratropium to treat chronic obstructive pulmonary disease. Eur Respir J, 23:241–9.

Panwels RA, Buist AS, Calverley PM, et al. 2001. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. Am J Respir Crit Care Med, 163:1256–76.

Ramsey SD. 2000. Suboptimal medical therapy in COPD: exploring the causes and consequences. Chest, 117(2 Suppl):338–78.

Rennard SI, Serby CW, Ghafouri M, et al. 1996. Extended therapy with ipratropium is associated with improved lung function in patients with COPD. A retrospective analysis of data from seven clinical trials. Chest, 110:62–70.

Rennard SI, Anderson W, Zuwallack R, et al. 2001. Use of a-long-acting inhaled beta-2-adrenergic agonist, salmeterol xinafoate, in Patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 163:1087–92.

Roche N, Lepage T, Bourcereau J, et al. 2001. Guidelines versus clinical practice in the treatment of chronic obstructive pulmonary disease. Eur Respir J, 18:903–8.

Rossi A, Kristufek P, Levine BE, et al. 2002. Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD. Chest, 121:1058–69.

Rudolf M. 2000. The reality of drug use in COPD: the European perspective. Chest, 117(2 Suppl):295–325.

Salpeter SR, Buckley NS, Ormiston TM, et al. 2006. Long-acting beta-agonists increase severe asthma exacerbations and asthma-related deaths: meta-analysis of randomized controlled trials. Ann Intern Med, 144:904–12.

Salpeter SR, Buckley NS, Salpeter EE. 2006. Meta-analysis: Anticholinergics, but not beta-agonists, reduce severe exacerbations and respiratory mortality in COPD. J Gen Intern Med, 21:1011–19.

Salpeter SR, Buckley NS. 2006. Systematic review of clinical outcomes in chronic obstructive pulmonary disease: β-Agonist use compared with anticholinergics and inhaled corticosteroids. Clin Rev Allergy Immuno, 31:219–30.

Salpeter SR, Ormiston TM, Salpeter EE. 2004. Cardiovascular effects of beta-agonists in patients with asthma and COPD: a meta-analysis. Chest, 125:2309–21.

Salpeter SR, Ormiston TM, Salpeter EE. 2004. Meta-analysis: respiratory tolerance to regular beta2-agonist use in patients with asthma. Ann Intern Med, 140:802–13.

Sears MR, Taylor DR, Print CG, et al. 1990. Regular inhaled beta-agonist treatment in bronchial asthma. Lancet, 336:1391–6.

Sestini P, Renzoni E, Robinson S, et al. 2002. Short-acting beta 2 agonists for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev, 4:CD001495.

Sin DD, Lacy P, York E, et al. 2004. Effects of fluticasone on systemic markers of inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med, 170:760–5.

Sin DD, McAlister FA, Man SF, et al. 2003. Contemporary management of chronic obstructive pulmonary disease: scientific review. JAMA, 290:2301–12.

Sin DD, Wu L, Anderson JA, et al. 2005. Inhaled corticosteroids and mortality in chronic obstructive pulmonary disease. Thorax, 60:992–7.

Singh JM, Palda VA, Stanbrook MB, et al. 2002. Corticosteroid therapy for patients with acute exacerbations of chronic obstructive pulmonary disease: a systematic review. Arch Intern Med, 162:2527–36.

Sullivan SD, Ramsey SD, Lee TA. 2000. The economic burden of COPD. Chest, 117(2 Suppl):SS–95.

Sutherland ER, Almers H, Ayas NT, et al. 2003. Inhaled corticosteroids reduce the progression of airflow limitation in chronic obstructive pulmonary disease: a meta-analysis. Thorax, 58:937–41.

Szafranski W, Cukier A, Ramirez A, et al. 2003. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. Eur Respir J, 21:74–81.

Tashkin DP, Ashutosh K, Bleecker ER, et al. 1986. Comparison of the anticholinergic bronchodilator ipratropium bromide with metaproterenol in chronic obstructive pulmonary disease. A 90-day multi-center study. Am J Med, 81(5A):81–90.

Tashkin DP, Cooper CB. 2004. The role of long-acting bronchodilators in the management of stable COPD. Chest, 125:249–59.

Taylor DR, Sears M, Cockcroft DW. 1996. The beta-agonist controversy. Med Clin N Am, 80:719–48.

Taylor J, Kotch A, Rice K, et al. 2001. Ipratropium bromide hydrofluoro-alkane inhalation aerosol is safe and effective in patients with COPD. Chest, 120:1253–61.

van Grunsven PM, van Schayck CP, Derenne JP, et al. 1999. Long term effects of inhaled corticosteroids in chronic obstructive pulmonary disease: a meta-analysis. Thorax, 54:7–14.
Van Overveld FJ, Demkow U, Gorecka D, et al. 2006. Differences in responses upon corticosteroid therapy between smoking and non-smoking patients with COPD. *J Physiol Pharmacol*, 57(Suppl 4): 273–82.

van Schayck CP, Graafsmaj S, Visch MB, et al. 1990. Increased bronchial hyperresponsiveness after inhaling salbutamol during 1 year is not caused by subsensitization to salbutamol. *J Allergy Clin Immunol*, 86:793–800.

Wadbo M, Lofdahl CG, Larsson K, et al. 2002. Effects of formoterol and ipratropium bromide in COPD: a 3-month placebo-controlled study. *Eur Respir J*, 20:1138–46.

Wood-Baker R, Walters EH, Gibson P. 2001. Oral corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 2:CD001288.