ORIGINAL ARTICLES

Meta-analysis: Anticholinergics, but not β-agonists, Reduce Severe Exacerbations and Respiratory Mortality in COPD

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BACKGROUND: Anticholinergics and β2-agonists have generally been considered equivalent choices for bronchodilation in chronic obstructive pulmonary disease (COPD).

OBJECTIVE: To assess the safety and efficacy of anticholinergics and β2-agonists in COPD.

DESIGN: We comprehensively searched electronic databases from 1966 to December 2005, clinical trial websites, and references from selected reviews. We included randomized controlled trials of at least 3 months duration that evaluated anticholinergic or β2-agonist use compared with placebo or each other in patients with COPD.

MEASUREMENTS: We evaluated the relative risk (RR) of exacerbations requiring withdrawal from the trial, severe exacerbations requiring hospitalization, and deaths attributed to a lower respiratory event.

RESULTS: Pooled results from 22 trials with 15,276 participants found that anticholinergic use significantly reduced severe exacerbations (RR 0.67, confidence interval [CI] 0.53 to 0.86) and respiratory deaths (RR 0.27, CI 0.09 to 0.81) compared with placebo. β2-Agonist use did not affect severe exacerbations (RR 1.08, CI 0.61 to 1.95) but resulted in a significantly increased rate of respiratory deaths (RR 2.47, CI 1.12 to 5.45) compared with placebo. There was a 2-fold increased risk for severe exacerbations associated with β2-agonists compared with anticholinergics (RR 1.95, CI 1.39 to 2.93). The addition of β2-agonist to anticholinergic use did not improve any clinical outcomes.

CONCLUSION: Inhaled anticholinergics significantly reduced severe exacerbations and respiratory deaths in patients with COPD, while β2-agonists were associated with an increased risk for respiratory deaths. This suggests that anticholinergics should be the bronchodilator of choice in patients with COPD, and β2-agonists may be associated with worsening of disease control.

KEY WORDS: chronic obstructive pulmonary disease; COPD; adrenergic β-agonists; cholinergic antagonists; muscarinic antagonists; meta-analysis; clinical outcomes; mortality.
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Chronic obstructive pulmonary disease (COPD) is characterized by partially reversible chronic airflow obstruction caused by an abnormal inflammatory reaction in the airways and lung parenchyma to inhaled toxins, most notably cigarette smoke.[1,2] The clinical course is marked by a slow progressive decline in lung function, considered to be the stable phase of the disease, with episodic acute exacerbations presenting as an increase in dyspnea, cough, and/or sputum production.[1,3] Exacerbations requiring hospitalization are associated with 3% to 4% short-term mortality.[3] Half of those patients hospitalized will be readmitted at least once over the next 6 months.[3] Chronic obstructive pulmonary disease is the fourth leading cause of death in the United States.[4]

Treatment with inhaled corticosteroids has been shown to reduce local inflammatory cells and systemic markers such as C-reactive protein, improve respiratory symptoms, reduce COPD exacerbations, and slow the progression of lung function decline.[5–9] Anticholinergic bronchodilators inhibit bronchoconstriction as well as mucus secretion, and have been shown to improve symptoms and reduce exacerbations without producing tolerance to their effects over time.[10–16] Inhaled anticholinergics are poorly absorbed from the gastrointestinal tract and lung, so that systemic adverse effects are rare.[10,17] β2-Agonists are bronchodilators that relax bronchial smooth muscle and are effective in the short-term relief of COPD symptoms.[18] However, long-term use may be associated with tolerance to their effects.[11,14]

We are gradually accumulating evidence concerning the increased risk β2-agonists have for adverse respiratory and cardiovascular events in patients with asthma and COPD, and are now questioning whether long-acting β2-agonists such as salmeterol and formoterol should be taken off the market.[19–31] Pooled data from 19 randomized controlled trials showed that long-acting β2-agonists increase hospitalizations for asthma (odds ratio [OR] 2.6, confidence interval [CI] 1.6 to 4.3), life-threatening asthma exacerbations requiring intubation and ventilation (OR 1.8, CI 1.1 to 2.9) and asthma-related deaths (OR 3.5, CI, 1.3 to 9.3) compared with placebo.[32]

The 2 types of bronchodilators, anticholinergics and β2-agonists, have generally been considered to be equivalent choices for use in patients with COPD.[1,33,34] Despite the fact that anticholinergics have been shown to have equal or superior efficacy compared with β2-agonists,[15,35–39] surveys have shown that prescriptions for β2-agonists in COPD are 10 times more common than anticholinergics in the United States and 2 times more common in the United Kingdom and Europe.[40–42] The objective of this meta-analysis is to compare the effects of β2-agonists and anticholinergics on exacerbations requiring

None of the authors have had any relationships with a manufacturer of a β2-agonist or anticholinergic agent at any time.

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withdrawal from the trial, severe exacerbations requiring hospitalization, and respiratory deaths in patients with COPD.

MATERIALS AND METHODS

Search Strategy

We performed a comprehensive search of MEDLINE, EMBASE, and Cochrane databases to identify randomized controlled trials on β2-agonist or anticholinergic use in patients with COPD, published between 1966 and December 2005. The search was performed using the terms bronchodilator, sympathomimetic, adrenergic β-agonist, anticholinergic, cholinergic antagonist, muscarinic antagonist, albuterol, salbutamol, bitolterol, isoetharine, metaproterenol, salmeterol, terbutaline, fenoterol, formoterol, procaterol, isoproterenol, reproterol, eformoterol, bambuterol, ipratropium, tiotropium, or oxitropium and obstructive lung disease, obstructive airway disease, obstructive pulmonary disease, or COPD. Trials were not excluded on the basis of language. The search was augmented by scanning relevant files from the U.S. Food and Drug Administration (FDA) website and references of identified reviews.

Study Selection

Trials were included if they were randomized controlled trials of β2-agonists or anticholinergics compared with placebo or each other, were of at least 3 months duration and reported at least one COPD exacerbation requiring withdrawal from the trial or hospitalization, or any respiratory death. A minimum duration of 3 months was chosen to allow for the development of adverse events. Trials that did not report any included event were excluded from the primary analysis, but were evaluated separately in order to estimate absolute risk differences.

Assessment of Validity

Two reviewers assessed the methodological quality of each trial according to the following factors: (1) Was the randomization procedure adequate and was allocation concealment described?, (2) Were patients and providers blind to the interventions?, (3) Were dropouts and withdrawals reported?, and (4) Was analysis performed by intention-to-treat? Each of these quality domains was scored on a 3-point scale. The quality assessment was used for a sensitivity analysis.[43,44]

Data Extraction and Synthesis

Two reviewers extracted data from the selected articles, reconciling differences by consensus. In addition, attempts were made to contact the investigators to obtain additional information concerning exacerbations and deaths. The proportion of patients with COPD exacerbations, severe exacerbations, and respiratory deaths from each trial was pooled using the fixed-effects model, expressed as relative risk (RR) with corresponding 95% confidence intervals.[45] COPD exacerbations were those that required withdrawal from the study or hospitalization. Severe exacerbations were those requiring hospitalization. A respiratory death was defined as a death thought to be due to a lower respiratory tract event, such as a COPD exacerbation, pneumonia, or respiratory failure. Deaths thought to be due to a cardiorespiratory cause were included, if they were thought to be related to the underlying COPD. To test for interstudy heterogeneity, the chi-square value was calculated for the hypothesis of homogeneity, with statistical significant set at $\alpha=0.1$. The fixed-effects model was chosen as minimal heterogeneity was noted in the analyses.

Results were reported separately for placebo-controlled trials of anticholinergics and β2-agonists, and for trials comparing β2-agonists to anticholinergics. The analysis was performed using Cochrane Review Manager 4.2 (Cochrane Library Software, Oxford, UK). Only trials that reported at least 1 event were used in the estimation of RR. If more than 1 event occurred in the same patient, only the first event was counted. In a separate analysis, those trials that reported no respiratory deaths were evaluated in order to estimate an absolute risk difference. The number needed to treat (NNT) to prevent an event, and the number needed to harm (NNH) to cause an event, were calculated.

Role of the Funding Source

The funding for this analysis came from salary support for Dr. Salpeter. The institution had no role in the design, conduct, or reporting of the study. The investigators all had complete access to the data, and no sponsorship from the institution or the pharmaceutical industry was provided to conduct this analysis.

RESULTS

Search Results

Figure 1 shows the results of the search for articles. The MEDLINE search identified approximately 5,000 articles, of which 84 were potentially relevant trials of bronchodilator use in COPD. After scanning references from selected articles and the FDA website, an additional 4 trials were identified. The EMBASE and Cochrane databases provided no additional trials. Of these 88 trials, 22 met the inclusion criteria.[12,13,46–65]

Trials were excluded for the following reasons: 37 trials were of less than 3 months duration, 9 trials did not provide adequate information on exacerbations or respiratory deaths, 2 trials did not compare the 2 types of bronchodilators with placebo or each other, 4 trials were not randomized, 2 trials provided data for asthma and COPD combined, and 12 trials provided data on participants from other trials.

Trial Characteristics

The analysis included 22 trials, with a total of 15,276 participants followed for 25,460 patient-years (Table 1). The mean trial duration was 20 months (range 3 to 60 months), with a mean study size of 694 participants (62 to 3,923). The mean (SD) age of participants at baseline was 59.9 (7.7) years in the anticholinergic group, 63.5 (1.0) in the β2-agonist group and 59.6 (7.4) years in the placebo group. The dropout rate was 18.5% in the anticholinergic group, 19.0% in the β2-agonist group and 24.8% in the placebo group. From the available data, concomitant corticosteroids were used in 58.3% of the anticholinergic group, 56.5% of the β2-agonist group and 57.4% of the placebo group. β2-agonists used in the trials were albuterol, metaproterenol, formoterol, and salmeterol. Anticholinergic agents studied were ipratropium and tiotropium.

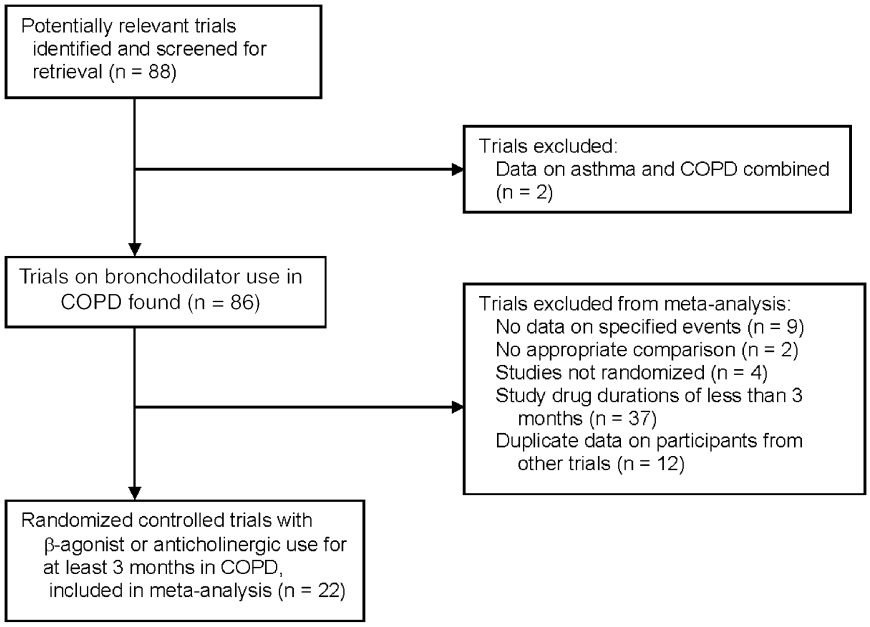

FIGURE 1. Flow chart of trials search.

Methodological Quality of Included Studies

All trials were randomized, double blind trials that performed analysis according to intention-to-treat and adequately described withdrawals. Thirteen trials described the method of randomization or allocation concealment, while 9 did not. No trial received the lowest quality score on any domain, so no sensitivity analysis was performed.

Quantitative Data Synthesis

Anticholinergics Compared with Placebo. Seven trials compared inhaled anticholinergics with placebo (Fig. 2). Anticholinergics reduced the risk of a COPD exacerbation requiring withdrawal from the trial by 40% (RR 0.60, CI 0.48 to 0.75) and a severe exacerbation requiring hospitalization by 33% (RR 0.67, CI 0.53 to 0.86). The absolute risk reduction for severe exacerbations was approximately 4 cases per 100 patient-years of treatment compared with placebo, with a NNT of 25.

The Lung Health Study[47] provided data on hospitalization for lower respiratory morbidity but not COPD exacerbations, so these were not included in the analysis. If data on lower respiratory morbidity were included as COPD exacerbations, the RR for hospitalization would be 0.75 (CI 0.61 to 0.93).

There were 2 reported respiratory deaths out of 4,036 participants in the anticholinergic group and 12 respiratory deaths out of 3,845 participants in the placebo group, with a reduction in risk of 73% (RR 0.27, CI 0.09 to 0.81). In order to assess absolute rates for respiratory deaths we included those trials that reported no deaths, thus adding to the denominator. The absolute risk reduction for respiratory deaths with anticholinergics was 0.36% per year (NNT of 278).

β2-Agonists Compared with Placebo. There were 13 trials that compared β2-agonist use with placebo (Fig. 3). All of the trials except for one[55] evaluated the long-acting β2-agonists salmeterol and formoterol. Of note, all trials allowed for as-needed β2-agonist use in both the treatment and placebo groups, so in effect were comparing regular β2-agonist use with as-needed use. Concomitant inhaled corticosteroids were used in 57% of participants.

The risk of withdrawal from the trial for COPD exacerbation was reduced by 19% (RR 0.81, CI 0.68 to 0.95), without a significant effect on hospitalization (RR 1.08, CI, 0.61 to 1.95). However, β2-agonist use was associated with a significant increase in respiratory deaths (RR 2.47, CI 1.12 to 5.45) compared with placebo, with 21 deaths out of 1,320 participants in the β2-agonist group and 8 deaths out of 1,084 participants in the placebo group. When trials without respiratory deaths were included in the analysis, thus adding to the denominator, the absolute risk increase with β2-agonists is 0.76% per year (NNH of 131).

One trial[66] provided 60% of the weight for respiratory deaths, with data provided from unpublished information and a published erratum.[67] This trial also studied combined treatment with budesonide plus formoterol and budesonide treatment alone, and reported 5 deaths out of 254 patients in the combined treatment group and 6 deaths out of 257 patients in the budesonide group (RR 0.84, CI, 0.26 to 2.73, P=.78).

β2-Agonists Compared with Anticholinergics. Seven trials directly compared β2-agonists with anticholinergics (Fig. 4). Three of the trials did not allow for any open-label β2-agonist use in either of the treatment groups (Table 1). Compared with anticholinergics, β2-agonists resulted in increased rates of exacerbations requiring withdrawal from the trial (RR 2.02, CI 1.39 to 2.93) as well as severe exacerbations requiring hospitalization (RR 1.95, CI 1.06 to 3.59). Only 2 trials reported on respiratory deaths, with a nonsignificant trend toward increased respiratory mortality associated with β2-agonists compared with anticholinergics (RR 6.91, CI 0.85 to 55.97, P=0.07).

Table 1. Table of Included Studies

Study Year	Design Duration (mo)	Number (*n*) in AC BA Placebo	Mean Age in AC BA Placebo	FEV_1 (L) in AC BA Placebo	Dropout (%) in AC BA Placebo	Treatment Groups	Concomitant Steroid Use (%) in AC BA Placebo	Comments
Aalbers 2002	Parallel	0	NA	NA	NA	Formoterol 4.5 mcg, 9 mcg, 18 mcg BID Placebo	NA	Rescue BA
	3	514	62.6	1.44	16.3		100	
		173	61.8	1.47	15.6		100	
Anthonisen 2002 Lung	Parallel	1,961	48.4	2.62	26	Ipratropium	Not stated	Unpublished information. Smoking intervention and usual care also studied
Health Study	60	0	NA	2.64	NA	36 mcg TID		
		1,962	48.6	NA	24	Placebo		
Boyd 1997	Parallel	0	NA	NA	NA	Salmeterol 50 mcg, 100 mcg BID Placebo	NA	Rescue BA
	4	447	62.5	1.27	11.2		62	
		227	61	1.31	9.3		69	
Brusasco 2003	Parallel	402	63.8	1.12	15.4	Tiotropium 18 mcg QD Salmeterol 50 mcg BID Placebo	Not stated	Rescue BA
	6	405	64.1	1.07	18.8			
		400	64.6	1.09	25.8			
Calverley 2003	Parallel	0	NA	NA	NA	Formoterol 9 mcg BID Placebo	NA	Unpublished information and erratum. Budesonide/Formoterol and Budesonide also studied
	12	255	63	1.00	43.5		0	
		256	65	0.98	41.4		0	
Casaburi 2000	Parallel	279	65	1.04	6.1	Tiotropium 18 mcg QD Placebo	Not stated	Rescue BA
	3	0	NA	NA	NA			
		191	65.5	1.00	10.9			
Casaburi 2002	Parallel	550	65	1.04	18.7	Tiotropium 18 mcg QD Placebo	50	Rescue BA. Two phase 3 trials. Information from FDA website
	12	0	NA	NA	NA		NA	
		371	65	1.00	27.8		49	
Chapman 2002	Parallel	0	NA	NA	NA	Salmeterol 50 mcg BID	NA	Rescue BA
	6	201	>40	1.19	9.9		68	
		207	>40	1.28	13.5		55	
Colice 1996	Parallel	113	63.7	1.02	13.3	Ipratropium 500 mcg TID Albuterol 2,500 mcg TID	49	Treatments nebulized. Rescue BA
	3	110	64.7	0.99	19		46	
		0	NA	NA	NA		NA	
Combivent 1997	Parallel	214	64.8	0.91	10.7	Ipratropium 500 mcg TID Albuterol 3,000 mcg TID	Not stated	Treatments nebulized. No rescue BA allowed
	3	216	64.6	0.91	11.6			
		0	NA	NA	NA			
Cook 2001	Cross-over	0	NA	NA	NA	Albuterol 200 mcg BID Placebo	NA	Rescue BA.
	3 each	62	69.9	0.98	0		100	
		62	69.9	0.98	5		100	
Donohue 2002	Parallel	209	64.5	1.11	12	Tiotropium 18 mcg QD Salmeterol 50 mcg BID Placebo	66	Rescue BA
	6	213	64.6	1.07	16.9		72	
		201	65.6	1.06	27.8		73	

Table 1 (continued)

Study Year	Design Duration (mo)	Number (*n*) in AC BA Placebo	Mean Age in AC BA Placebo	FEV_1 (L) in AC BA Placebo	Dropout (%) in AC BA Placebo	Treatment Groups	Concomitant Steroid Use (%) in AC BA Placebo	Comments
Friedman 1999	Parallel	362	64	0.93	18.2	Ipratropium 42 mcg QID Albuterol 240 mcg QID	48	No rescue BA allowed. Ipratropium + Albuterol studied
	3	347	64.6	0.95	14.1		41	
		0	NA	NA	NA		NA	
Mahler 2002	Parallel	0	NA	NA	NA	Salmeterol 50 mcg BID with and without fluticasone Placebo	NA	Rescue BA
	6	160	63.5	1.24	28.1		49	
		181	64	1.32	38.1		48	
Niewoehner 2005	Parallel	914	67.6	1.04	163	Tiotropium 18 mcg QD Placebo	71	Rescue BA
	6	0	NA	NA	NA		NA	
		915	68.1	1.04	26.7		69	
Rossi 2002	Parallel	0	NA	NA	NA	Formoterol 12 mcg, 24 mcg BID Placebo	NA	Rescue BA. Theophylline studied
	12	425	Not	1.38	21.6		47	
		220	stated	1.40	26.8		49	
Rutten-van Molken 1999	Parallel	0	NA	NA	NA	Salmeterol 50 mcg BID Placebo	NA	Rescue BA. Salmeterol+Ipratropium studied
	3	47	65.4	1.3	6.3		81	
		50	63.2	1.3	8		76	
Szafranski 2003	Parallel	0	NA	NA	NA	Formoterol 4.5 mcg BID with and without budesonide Placebo	NA	Rescue BA
	12	201	63	1.00	31.8		28	
		205	65	0.98	43.9		26	
Tashkin 1986	Parallel	132	61.9	1.09	10.6	Ipratropium 20 mcg QID Metaproterenol 750 mcg QID	31	No rescue BA allowed
	3	129	60.9	1.09	21.7		26	
		0	NA	NA	NA		NA	
Taylor 2001	Parallel	379	65.8	1.06	11.1	Ipratropium 42 mcg, 84 mcg QID Placebo	Not stated	Rescue BA
	3	0	NA	NA	NA			
		128	64.8	1.06	17.1			
Van Noord 2000	Parallel	0	NA	NA	NA	Salmeterol 50 mcg BID Placebo	NA	Rescue BA. Salmeterol+Ipratropium studied
	3	47	65	1.3	14.9		91	
		50	63	1.3	16		78	
Wadbo 2002	Parallel	62	64.8	Not	9.7	Ipratropium 80 mcg BID Formoterol 18 mcg BID Placebo	Not stated	Rescue BA
	3	61	63.6	listed	26.2			
		60	63.6		28.3			

AC, anticholinergic; BA, β2-agonist, NA, not applicable; mcg, micrograms; QD, daily; BID, twice a day; TID, 3 times a day; QID, 4 times a day; FEV_1, forced expiratory volume at 1 second.

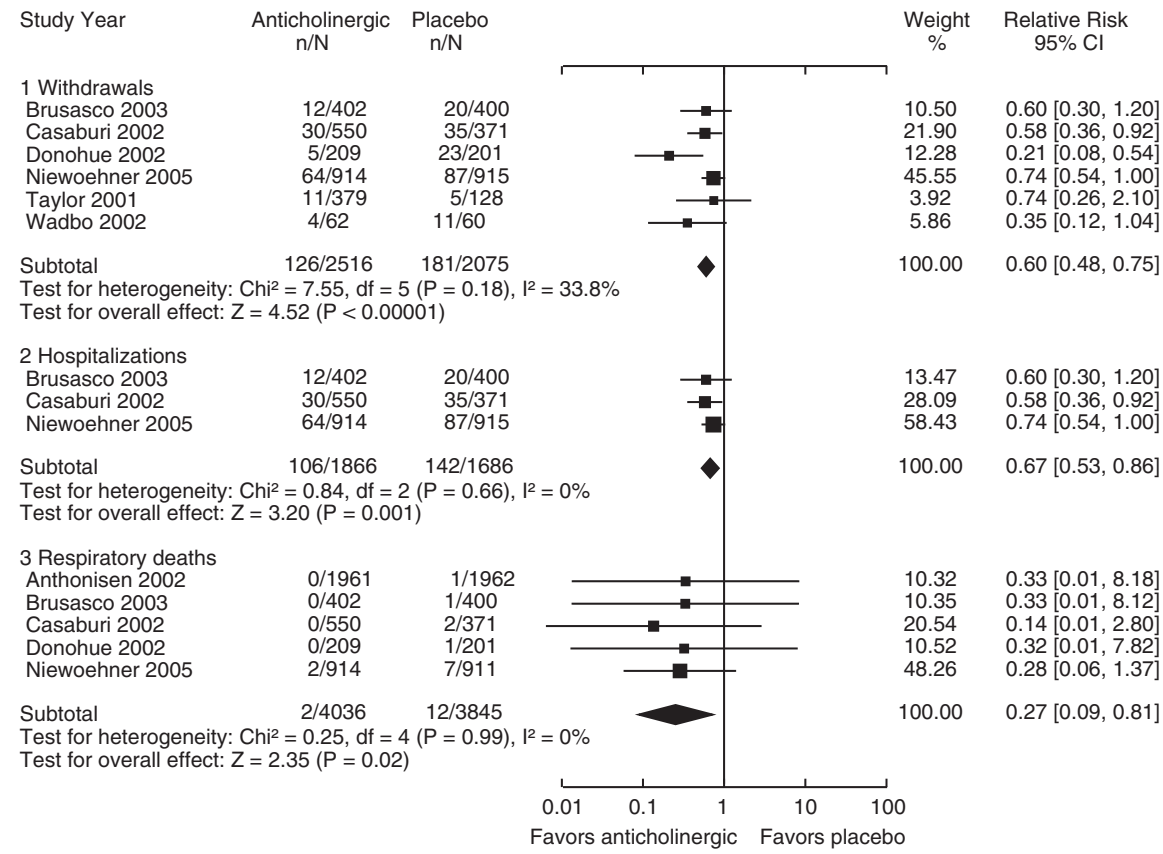

FIGURE 2. Effect of anticholinergics compared with placebo on chronic obstructive pulmonary disease withdrawals, hospitalizations, and respiratory deaths (relative risk).

Four trials compared anticholinergics alone to combination treatment with anticholinergic and β2-agonist.[52,54,55,57] Anticholinergic use alone was not associated with a significant difference in severe exacerbations (RR 0.83, CI 0.25 to 3.83) or deaths (RR 0.35, CI 0.04 to 3.3) compared with combination treatment.

Analysis of Interstudy Variance and Publication Bias. No evidence of significant heterogeneity was noted in any of the analyses, $P > .3$. Funnel plots of effect size versus standard error found no evidence for publication bias in the analysis.

DISCUSSION

Pooled results from 22 randomized trials of patients with COPD show that anticholinergics reduced severe exacerbations by 33% and respiratory deaths by 73% compared with placebo, while β2-agonists resulted in a 2-fold increase in respiratory deaths. The absolute risk reduction for respiratory deaths associated with anticholinergics is 0.36% per year (NNT of 278) and the absolute risk increase associated with β2-agonists is 0.76% per year (NNH of 131). The addition of a β2-agonist to an anticholinergic agent did not improve clinical outcomes. These results suggest that anticholinergics should be the bronchodilator of choice in COPD.

In order to put the risks of β2-agonists into perspective we must also understand the benefits. Pooled data from randomized trials have shown that β2-agonists are effective bronchodilators in patients with COPD, with some trials showing an improvement in symptom scores.[18,68] This meta-analysis indicates that β2-agonists can reduce withdrawals for symptomatic exacerbations by almost 20%. However, this improvement in symptoms may occur at the same time as a worsening of disease control, manifested by an increase in respiratory mortality. Tolerance to the bronchodilator effect of β2-agonists has been documented in patients with COPD over time, with a significant decline in strength of bronchodilation after 3 months of treatment compared with the first dose.[11–13,15,16,52,54] Evidence of tolerance to the bronchoprotective effect of β2-agonist use in COPD has also been demonstrated, with an increase in bronchial hyperresponsiveness seen with regular treatment.[14]

This meta-analysis shows that the anticholinergics, ipratropium and the newer long-acting tiotropium, reduced severe exacerbations and respiratory mortality compared with placebo. Unfortunately, in the United States only 5% of all prescriptions for COPD are anticholinergics.[40] Tiotropium has been shown to prevent the decline in trough FEV1 values that are seen with placebo use over the course of 1 year.[50,51,69] This finding suggests that anticholinergics, like inhaled corticosteroids, may slow the progressive decline in lung function that is seen in patients with COPD. Currently, a 4-year trial of tiotropium is under way to test this hypothesis.[17] Two trials have compared tiotropium with ipratropium; pooled results show that tiotropium is associated with fewer severe exacerbations than ipratropium (RR 0.56, CI 0.36 to 0.89).[69,70] A cost-

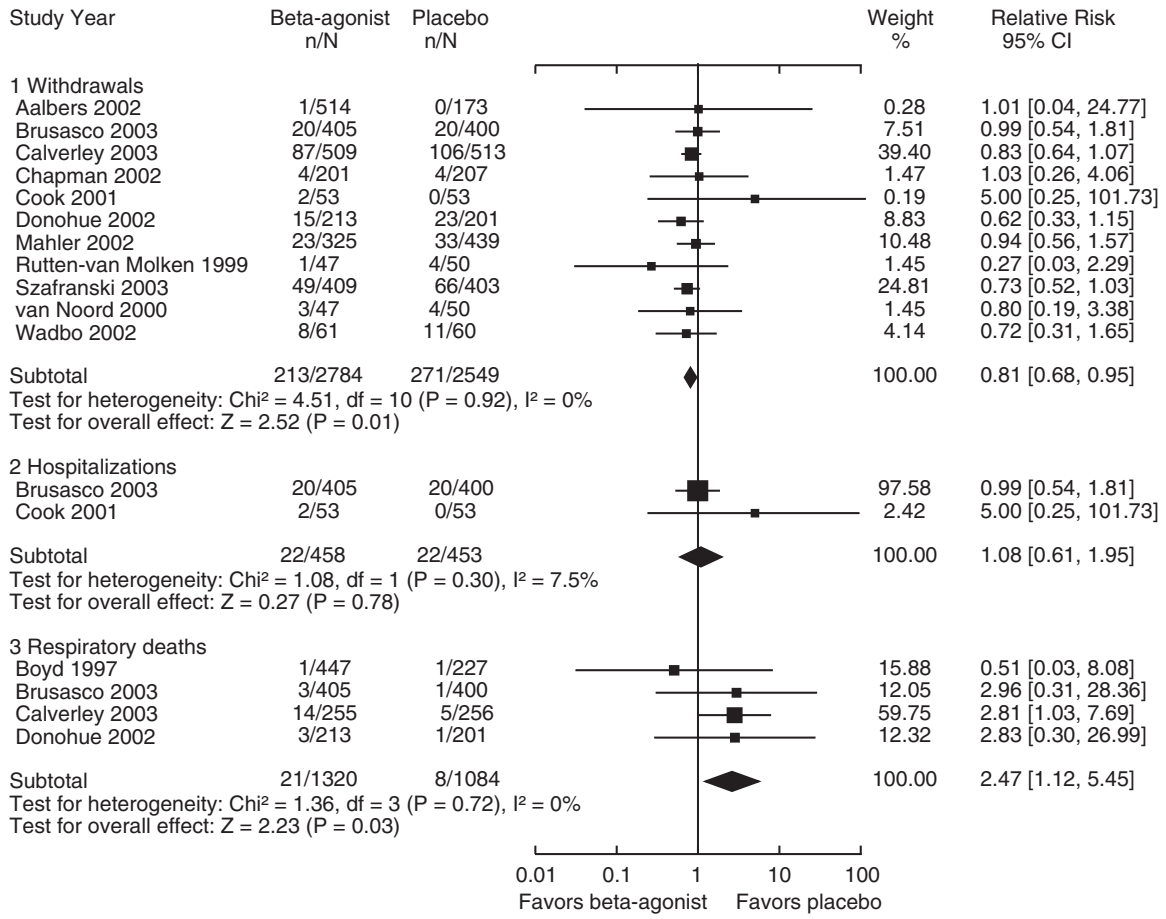

FIGURE 3. Effect of β2-agonists compared with placebo on chronic obstructive pulmonary disease withdrawals, hospitalizations, and respiratory deaths (relative risk).

effectiveness analysis found that costs associated with tiotropium are slightly higher than with ipratropium, but that the reduction in hospitalization is thought to be cost-effective.[71]

Current guidelines recommend that an inhaled bronchodilator (anticholinergic or β2-agonist) be used in the treatment of stable COPD, and if symptoms persist or there are frequent exacerbations the addition of an inhaled corticosteroid should be considered.[33] In this meta-analysis approximately one-half of the patients treated with β2-agonists had concomitant inhaled corticosteroid use. Three trials[49,58,62] provided data with and without inhaled corticosteroids, but only 1 provided information on severe exacerbations or respiratory deaths,[66] so subgroup analysis on the effect of concomitant inhaled corticosteroids could not be done.

This analysis has several limitations. Standard meta-analytic results can be uncertain when the numbers of events per study are small, as is the case with deaths. Some of the analyses in this study provided pooled data from only 2 trials, so may not provide meaningful results. There was not enough information available to assess the potential protective effect of concomitant inhaled corticosteroids on the adverse effects of β2-agonists, or the difference in results for long-acting and short-acting β2-agonists. The search revealed 9 trials that were excluded because no severe exacerbations or deaths were reported. It is difficult to tell if events occurred but were not reported. Other trials did not provide cause of death, so could not be included in the analysis of respiratory deaths. The accurate assessment of respiratory deaths was further hindered by the difficulty in ascertaining the true cause of death. For example, it is possible that the increase in respiratory deaths seen with β2-agonists may be due in part to an increase in cardiovascular risk.[30] Finally, it is unfortunate that no true placebo-controlled trials of β2-agonist use in COPD have been published. Despite these limitations, we believe that this meta-analysis provides valuable information on the comparative effects of anticholinergics and β2-agonists on clinical outcomes in COPD.

In summary, both anticholinergics and β2-agonists may be effective bronchodilators and improve symptoms in patients with COPD. Anticholinergics reduced severe exacerbations and respiratory deaths in patients with COPD. However, β2-agonists had no effect on severe exacerbations and resulted in an increased rate of respiratory deaths, possibly owing to a reduction in disease control. Concomitant corticosteroids were used in over one-half of patients treated with β2-agonists, but it is not clear if this provided some protection against the adverse effects. The results of this meta-analysis suggest that anticholinergics should be the bronchodilator of choice in patients with COPD. The long-term safety of β2-agonists in patients with COPD should be addressed.

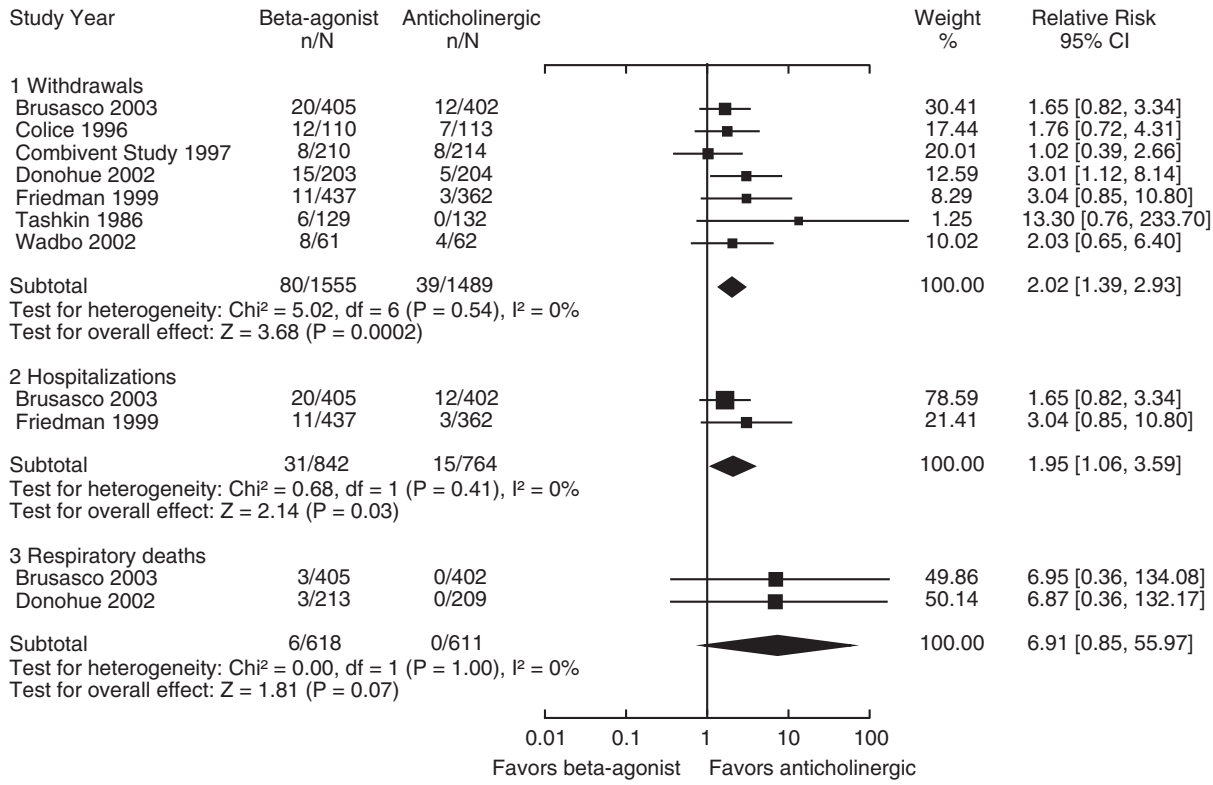

FIGURE 4. Effect of β2-agonists compared with anticholinergics on chronic obstructive pulmonary disease withdrawals, hospitalizations, and respiratory deaths (relative risk).

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