

Management of Stable Chronic Obstructive Pulmonary Disease: A Systematic Review for a Clinical Practice Guideline

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Background: Chronic obstructive pulmonary disease (COPD) is a common and disabling condition in adults. Information about therapeutic effectiveness and adverse effects of common treatment options and how clinical and spirometric characteristics affect outcomes is not well known but is important for clinicians caring for patients with stable COPD.

Purpose: To evaluate the effectiveness of COPD management strategies.

Data Sources: English-language publications in MEDLINE and the Cochrane Library through March 2007.

Study Selection: Randomized, controlled trials (RCTs) and previous systematic reviews of inhaled therapies, pulmonary rehabilitation, disease management, and supplemental oxygen in adults with COPD.

Data Extraction: Participant, study, and intervention characteristics; exacerbations; deaths; respiratory health status; exercise capacity; hospitalizations; and adverse effects.

Data Synthesis: Eight meta-analyses and 42 RCTs examined inhaled therapies: short-acting anticholinergics ($n = 7$), long-acting anticholinergics ($n = 10$), long-acting β_2 -agonists ($n = 22$), corticosteroids ($n = 14$), dual D_2 dopamine receptor- β_2 -agonist ($n = 3$), or short-acting β_2 -agonist plus ipratropium ($n = 3$). Evidence for nonpharmacologic therapies included 3 reviews of 39 RCTs plus 6 additional RCTs of pulmonary rehabilitation, 2 reviews of 13 RCTs plus 2 additional RCTs of disease management, and 8 RCTs of

oxygen. Overall, long-acting inhaled therapies, used alone or in combination, reduced exacerbations more than placebo by 13% to 25% and had similar effectiveness to each other. Average improvements in health status scores were less than what is considered to be clinically noticeable. Inhaled monotherapy did not reduce mortality rates. Inhaled corticosteroids plus long-acting β_2 -agonists reduced deaths in relative terms compared with placebo (relative risk, 0.82 [95% CI, 0.69 to 0.98]) and inhaled corticosteroids alone (relative risk, 0.79 [CI, 0.67 to 0.94]) but not compared with long-acting β_2 -agonists alone (relative risk, 0.82 [CI, 0.52 to 1.28]). Absolute reductions were 1% or less and were not statistically significant. Pulmonary rehabilitation improved health status and dyspnea but not walking distance. Neither disease management nor ambulatory oxygen improved measured outcomes. Supplemental oxygen reduced mortality rates among symptomatic patients with resting hypoxia (relative risk, 0.61 [CI, 0.46 to 0.82]). Insufficient evidence supports using spirometry to guide therapy.

Limitations: Articles were limited to those in the English language. Treatment adherence, adverse effects, and effectiveness may differ among clinical settings. Short-acting inhalers for "rescue therapy" were not evaluated.

Conclusion: Long-acting inhaled therapies, supplemental oxygen, and pulmonary rehabilitation are beneficial in adults who have bothersome respiratory symptoms, especially dyspnea, and FEV₁ less than 60% predicted.

Ann Intern Med. 2007;147:639-653.

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In the United States, more than 5% of adults have symptomatic chronic obstructive pulmonary disease (COPD), which is a leading cause of morbidity and mortality (1, 2). Treatment options include inhaled pharmacologic therapy with short- or long-acting bronchodilators or corticosteroids, pulmonary rehabilitation, disease management, and supplemental oxygen (3). Long-acting inhaled bronchodilators and pulmonary rehabilitation have been recommended for patients with spirometrically detected obstruction, even without symptoms (3). Addition of inhaled corticosteroids to long-acting bronchodilators (combination therapy) has been recommended for individuals with repeated exacerbations and an FEV₁ less than 50% predicted. Information about therapeutic effectiveness and adverse effects of common treatment options and how clinical and spirometric characteristics affect outcomes is not well known but is important for clinicians caring for patients with stable COPD.

This review updates a report prepared for the Agency for Healthcare Research and Quality (AHRQ) and serves as the background paper for an American College of Physician's Clinical Practice Guideline (4). It addresses the

following questions: Which inhaled therapies are effective for treatment and maintenance of stable COPD? When should clinicians consider pulmonary rehabilitation and disease management? When should clinicians prescribe oxygen therapy? Should clinicians base treatment decisions on spirometric results, symptoms, or both?

Detailed information on the use of spirometry for diagnosis and case finding is available in the original AHRQ report at www.ahrq.gov/clinic/tp/spirotp.htm. Spirometry

See also:

Print

Related article 633
Summary for Patients I-41

Web-Only

Appendix Tables
CME quiz
Conversion of graphics into slides
Audio summary

for case finding and management would be useful if it identified individuals who were not clinically detected as candidates for COPD treatments, excluded individuals with false-positive clinical presentations for COPD, or independently identified thresholds to guide initiation or modification of therapies. Our previous report identified insufficient evidence to support these conditions.

METHODS

Data Sources and Selection

For our previous report, we searched PubMed and the Cochrane Library for articles published in English from 1966 through May 2005. The current review extends the search related to COPD therapies through March 2007 by using search terms used in a 2003 review by Sin and colleagues (5) to identify randomized, controlled trials (RCTs), controlled clinical trials, meta-analyses, and reviews published since the completion of their search in 2002. To supplement our search, we examined the Cochrane Database of Systematic Reviews of Effectiveness, examined bibliographies of published articles, and contacted experts. We categorized interventions as 1) inhaled medications (β_2 -agonists, anticholinergics, combination β_2 -agonists and anticholinergics, inhaled corticosteroids, and combination inhaled corticosteroids and long-acting β_2 -agonists or anticholinergics), 2) pulmonary rehabilitation, 3) disease management programs, and 4) oxygen therapy.

Two reviewers used standardized data abstraction sheets to examine titles and abstracts of newly identified references. If both reviewers agreed on eligibility, we included the article. Disagreement among reviewers, although rare, was resolved by discussion, with final decision by the lead author. Trials were eligible if they were randomized; involved persons with COPD that was defined clinically or by spirometry; and measured clinical outcomes, including exacerbations, standardized respiratory health status measures, hospitalizations, and deaths. Studies reporting only spirometry outcomes were ineligible. Inhaled therapy trials had to include 50 or more participants per treatment group and at least 3 months of follow-up. Trials of pulmonary rehabilitation programs had to include at least 6 weeks of follow-up and a usual care comparison group. We excluded studies that compared different types of pulmonary rehabilitation, and we included systematic reviews and meta-analyses of COPD therapies.

Data Extraction

Two individuals extracted data onto standardized forms. The lead author resolved any disagreements. Main outcomes for all interventions were the percentage of participants experiencing at least 1 exacerbation, mean change in respiratory health status, hospitalization, and death. Respiratory health status was assessed by the validated St. George Respiratory Questionnaire (SGRQ) or the Chronic Respiratory Disease Questionnaire (CRDQ). A 4-unit re-

duction (out of 100) on the SGRQ and a 0.5-unit increase per question on the 7-question CRDQ are defined as clinically noticeable improvements (6). For pulmonary rehabilitation, we collected information on the 6-minute walk test and defined a minimally clinically significant effect size as 53 meters or more.

We collected data on adverse effects of long-acting inhaled therapies (including specifically described adverse effects, "serious adverse effects," treatment adherence, study withdrawals, and withdrawals due to adverse effects) from trials that lasted at least 1 year and from systematic reviews that specifically addressed adverse effects. We assessed whether these studies used placebo or active control run-in periods, as well as the number and reasons for exclusion of potentially eligible patients from randomization during the run-in period.

Study Quality Assessment

We used the methods of Schulz and colleagues (7) to assess the quality of randomized trials on the basis of allocation concealment. We assessed blinding, intention-to-treat analysis, length of follow-up, withdrawals or loss to follow-up, and funding source. We rated the quality of systematic reviews or meta-analysis according to the Strength of Recommendation Taxonomy (8). An RCT was considered high quality if it had allocation concealment, blinding (if possible), intention-to-treat analysis, adequate size, and adequate follow-up (>80%). Systematic reviews or meta-analysis with high-quality studies and consistent findings are indicated as good-quality, patient-oriented evidence.

Data Synthesis and Analysis

Intervention effectiveness was described according to baseline respiratory symptom status, spirometrically defined level of airflow obstruction, acute change in spirometry, or spirometric change over time (inhaled medications and use of spirometry to guide therapy). The magnitude of effect across interventions (inhaled therapies and oxygen) was based on relative risks and absolute risk differences, as well as comparison with previously determined, minimally important clinical differences in respiratory health status and exercise capacity. Study results were combined, if appropriate, to produce pooled estimates. We calculated relative risks and 95% CIs for categorical variables and weighted mean differences and 95% CIs for continuous variables. We conducted analyses by using a DerSimonian-Laird random-effects model in Review Manager software, version 4.2 (The Cochrane Collaboration, Oxford, United Kingdom) (9). We assessed heterogeneity by using a chi-square test and the I^2 test. An I^2 statistic of 50 or greater indicates substantial heterogeneity (10). If heterogeneity existed, we conducted sensitivity analyses to explore potential causes of heterogeneity.

Role of the Funding Source

This project was funded by the AHRQ, U.S. Department of Health and Human Services. The updated synthe-

sis was conducted in collaboration with the American College of Physicians' Clinical Efficacy Assessment Subcommittee. Panel members assisted in the formulation of questions and reviewing drafts of this report. The funding source had no role in the design, conduct, or reporting of the study or in the decision to submit the manuscript for publication.

RESULTS

Yield of the Literature Search

Figure 1 shows that 42 RCTs involving short- or long-acting inhaled monotherapy or combination therapy (ipratropium [11–17], tiotropium [14, 15, 18–25]), long-acting β_2 -agonists (11, 13, 14, 17, 18, 21, 26–41), corticosteroids (28, 29, 32, 33, 38–47), dual D₂ dopamine receptor- β_2 -agonist (sibena det) (30, 48, 49), short-acting β_2 -agonists, and ipratropium (50–52) versus placebo or active control and 8 meta-analyses of RCTs (5, 53–59) were included for assessment of COPD inhaled therapies. We have identified 10 RCTs and 5 systematic reviews since our AHRQ report. Our updated search yielded an additional 16 RCTs and 2 systematic reviews of nonpharmacologic treatments. Three systematic reviews of 39 unique RCTs and 6 additional RCTs evaluated pulmonary rehabilitation (6 RCTs and 1 systematic review were added for our review) (5, 60–90). Two systematic reviews of 13

unique RCTs and 2 additional trials evaluating disease management, education, and follow-up were eligible (2 RCTs and 1 systematic review were added for our review) (5, 91–106). Supplemental oxygen therapy was not addressed in our original report. We included 8 RCTs and 1 systematic review evaluating 7 of these 8 trials (5, 107–114).

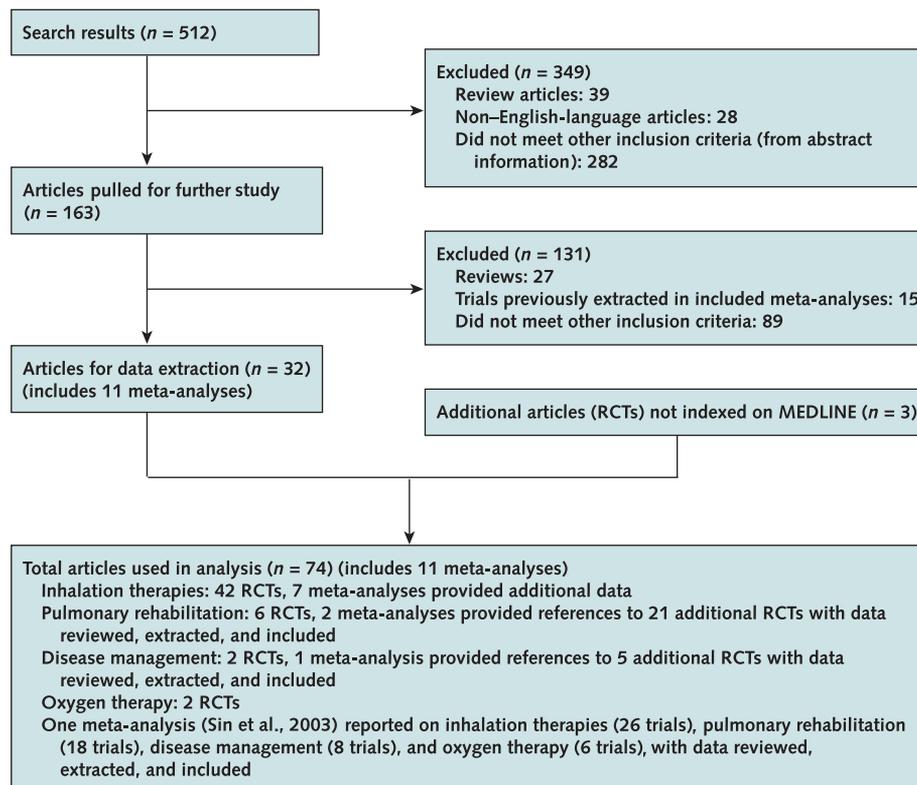
Quality Assessment

Appendix Table 1 (available at www.annals.org) and other systematic reviews (5, 60, 61, 91) describe the included randomized trials. We identified no study quality differences according to type of inhaled medication.

Concealment of treatment allocation for inhaled therapies was adequate in 17 studies (12, 22, 25, 26, 29–31, 36–40, 42, 44, 46, 47, 49). All trials were double-blind, and nearly all used intention-to-treat analyses. Several included only participants who were taking at least 1 dose or who had 1 valid postbaseline measurement (17, 23, 30, 32, 38, 42, 44, 48, 49) or excluded participants because of noneligibility after randomization or good practice or ethics violations by individual study sites (26, 39). All but 7 studies were funded by pharmaceutical companies. All trials had adequate participant follow-up (>80%). Six trials lasted 3 years or longer (12, 39, 42, 44, 45, 47).

Concealment of treatment allocation for trials of pulmonary rehabilitation and oxygen therapy was adequate in

Figure 1. Data search and selection.



1 and 4 studies, respectively (87, 107, 109, 111, 113). One disease management trial adequately randomly assigned practice centers but did not use individual randomization (106). Among nonpharmacologic trials, 7 used intention-to-treat analysis (86, 107–112). Five trials reported double-blinding (87, 89, 111, 112, 114), and 4 trials indicated blinded assessment of outcomes (85, 89, 107, 113). Four oxygen therapy trials lasted 2 years or longer (76–79).

Almost all COPD treatment trials involved participants who were prone to exacerbations, had previous diagnoses of COPD, had disabling respiratory symptoms, had mean FEV₁ less than 50% predicted, and used inhaled therapies. Only 4 RCTs used population-based recruitment and enrolled participants similar to those likely to be identified by spirometric case finding of “at-risk” individuals (11, 42, 44, 46), although some trials provided additional analysis according to spirometric status.

The Table summarizes the strength of the evidence for each question addressed in our review.

Which Inhaled Therapies Are Effective for Treatment and Maintenance of Stable COPD?

Exacerbations

Monotherapies with inhaled long acting β_2 -agonists, a long-acting anticholinergic, or corticosteroids were of similar effectiveness and were superior to placebo or short-acting anticholinergics in reducing exacerbations (Figures 2 and 3). Compared with placebo, inhaled corticosteroids, long-acting bronchodilators (tiotropium, β_2 -agonists), or both reduced the relative risk for having at least 1 exacerbation by 13% to 17% and the absolute risk by 4% to 6%. Ipratropium, a short-acting anticholinergic, was not superior to placebo. In active comparator studies, long-acting β_2 -agonists were of similar effectiveness to corticosteroids or the short- or long-acting anticholinergics, ipratropium, or tiotropium.

The incremental effect of combination therapy with inhaled corticosteroids and long-acting β_2 -agonists versus monotherapy using these agents was of borderline statistical significance, as assessed in 6 multigroup trials lasting 6 to 36 months (mean baseline FEV₁ <50%) (Figures 2 and 3). The pooled absolute risk differences in the percentage of participants having at least 1 exacerbation for long-acting β_2 -agonists, corticosteroids, and combination therapy were -4% [95% CI, -8% to -1%], -5% [CI, -11% to 1%], and -6% [CI, -12% to -1%], respectively, compared with placebo (28, 29, 34, 41). Combination therapy did not reduce the value compared with monotherapy with either inhaled corticosteroids or long-acting β_2 -agonists (relative risk, 0.88 [CI, 0.75 to 1.17] vs. β_2 -agonists and 0.96 [CI, 0.85 to 1.08] vs. inhaled corticosteroids) (28, 29, 34, 41). A large 3-year RCT (TORCH [Towards a Revolution in COPD Health] [39]) of combination long-acting β_2 -agonist plus inhaled corticosteroid (fluticasone, 500 μg twice daily) versus placebo, long-acting β_2 -agonist, or inhaled corticosteroid monotherapy evaluated the annual rate

of moderate to severe exacerbations in symptomatic adults with severe airflow obstruction. Pooling these results was not possible because the study (39) reported only annual rates of exacerbations (rather than proportions). The study investigators observed a statistically significant relative risk reduction of nearly identical magnitude to our pooled findings (relative risk, 0.75 [CI, 0.69 to 0.81] vs. placebo; 0.88 [CI, 0.81 to 0.95] vs. β_2 -agonists; and 0.91 [CI, 0.84 to 0.99] vs. inhaled corticosteroids). However, another trial found no difference in the annual rate of moderate to severe exacerbations or time to first exacerbation ($P = 0.15$) regardless of baseline FEV₁ among participants randomly assigned to continue combination therapy with salmeterol–fluticasone compared with those in whom fluticasone therapy (500 μg twice daily) was withdrawn (40).

One 3-group trial lasting for 1 year evaluated combination therapy with all 3 classes of inhalers. The proportion of participants who experienced an exacerbation did not differ among those receiving monotherapy with a long-acting anticholinergic (tiotropium) (62.8%), those receiving combination tiotropium plus a long-acting β_2 -agonist (salmeterol) (64.8%), or those receiving all 3 therapies (tiotropium plus corticosteroid plus a long-acting β_2 -agonist [salmeterol–fluticasone]) (60.0%) (25) (Figure 3). The combination of a short-acting β_2 -agonist (albuterol) plus ipratropium reduced exacerbations compared with albuterol alone (absolute risk difference, -6%) (50–52).

Respiratory Health Status Measures and Hospitalizations

Twenty trials, including the largest (38), reported SGRQ or CRDQ outcomes, but published results often did not permit pooling. Except for 5 trials (11, 25, 28, 33, 36), the average improvement in health status because of monotherapy or combination therapy was not considered clinically significant (6) (Appendix Table 2, available at www.annals.org). In secondary analyses of 2 trials of tiotropium (18, 19), the percentage of individuals achieving a clinically significant difference in the SGRQ was greater with tiotropium than with placebo (49% vs. 35%).

Few RCTs reported hospitalization results. When reported, reductions were not consistently observed and do not permit definitive conclusions on the relative effectiveness of inhaled therapies. Monotherapy with a long-acting β_2 -agonist and combination therapy of long-acting β_2 -agonists and corticosteroids reduced the relative annual rate of severe exacerbations requiring hospitalizations by 17% and 18%, respectively, versus placebo in the TORCH study (39). The 12% relative reduction with inhaled corticosteroids did not achieve statistical significance (rate ratio, 0.88 [CI, 0.74 to 1.03]). Combination therapy was not superior to β_2 -agonists (rate ratio, 1.02 [CI, 0.87 to 1.20]) or inhaled corticosteroids (rate ratio, 0.95 [CI, 0.82 to 1.12]) used as monotherapy. Combination therapy with tiotropium plus salmeterol–fluticasone (but not tiotropium plus salmeterol) reduced hospitalizations for acute COPD

Table. Summary of Evidence and Conclusions Related to Each Clinical Question*

Question	Available Evidence	Conclusion
Which inhaled therapies are effective for treatment and maintenance of stable COPD?	42 RCTs Almost all RCTs enrolled exacerbation-prone, symptomatic participants with mean FEV ₁ <50%	Good evidence supports long-acting inhaled anticholinergics, β_2 -agonists, and corticosteroids as having similar effectiveness in reducing exacerbations. Fair evidence supports the conclusion that monotherapy or combination therapy generally fails to achieve clinically significant improvements in respiratory health status. Fair evidence supports the conclusion that reductions in hospitalizations are inconsistent and does not permit definitive conclusions about relative effectiveness. Good evidence supports the conclusion that monotherapies do not reduce mortality rates.
When should clinicians consider pulmonary rehabilitation and disease management?	Pulmonary rehabilitation: 6 RCTs and 3 meta-analyses of 39 additional RCTs Disease management: 2 RCTs and 2 meta-analysis of 13 additional RCTs	Pulmonary rehabilitation: Exacerbations, hospitalizations, and standardized health status measures were infrequently reported. During the program, dyspnea improved. Improvements in health status, but not exercise capacity, were clinically significant. Disease management: One systematic review of 6 small RCTs ($n = 230$) found that respiratory rehabilitation after acute COPD exacerbations in patients with severe airflow obstruction reduced hospital admissions (relative risk, 0.26 [95% CI, 0.12 to 0.54]) and produced a clinically significant improvement in health status and exercise capacity. There was no improvement in deaths, hospital readmissions, length of stay, or health status. Exacerbations were only reported in 1 trial.
When should clinicians prescribe oxygen therapy?	9 RCTs ($n = 723$)	Good evidence supports the conclusion that supplemental oxygen used ≥ 15 hours daily to maintain a $P_{aO_2} > 60$ mm Hg reduces deaths in participants with an FEV ₁ of approximately <30% predicted and a mean resting $P_{aO_2} \leq 55$ mm Hg. Exacerbations or hospitalizations were rarely reported. Good evidence supports that ambulatory oxygen does not improve respiratory health status measures, exercise capacity, or hospitalizations over the short term.
Should clinicians base treatment decisions on spirometric results, symptoms, or both?	7 large inhaled therapy RCTs ≥ 1 year in duration among participants with FEV ₁ >50% but <80% No RCTs evaluated spirometry for monitoring or modifying therapy No RCTs of long-acting β -agonists in adults with mean FEV ₁ >60% No RCTs evaluated effectiveness of therapies among adults with FEV ₁ <60% but without respiratory symptoms	Good evidence demonstrates that treatment benefits are limited to individuals with both bothersome respiratory symptoms (especially dyspnea and frequent exacerbations) and FEV ₁ <60% predicted. Good evidence demonstrates no improvement in respiratory outcomes or deaths among persons with mild to moderate airflow obstruction (FEV ₁ >50% but <80%) or those with normal airflow but chronic sputum production. Fair evidence suggests that modifying therapy according to spirometric results is unlikely to be beneficial because 1) clinical improvement is not closely associated with an individual's spirometric response to therapy 2) pharmacologic treatments provide only a small change in long-term decline in lung function 3) wide intraindividual variation exists in spirometric decline 4) higher doses (compared with lower doses) or combination inhaled therapies (compared with monotherapy) have not been shown to provide clinically significant benefits 5) limited evidence suggests that interventions are not effective in asymptomatic individuals.

* COPD = chronic obstructive pulmonary disease; RCT = randomized, controlled trial.

exacerbations (rate ratio, 0.53 [CI, 0.33 to 0.86]) and all-cause hospitalizations versus tiotropium alone (25). Three trials lasting 3 to 12 months of long-acting β_2 -agonist therapy in participants with a mean FEV₁ less than 60% predicted demonstrated a 2% reduction (CI, -5% to 1%) compared with placebo that was not statistically significant (11, 18, 34). The Lung Health Study (LHS) I and II enrolled persons with mild to moderate airflow obstruction (mean FEV₁, 75% and 64% predicted, respectively; trial duration, 5 years) (12, 43). The LHS I showed no statistically significant differences in hospitalizations per 100 person-years of exposure between ipratropium and placebo (12). In LHS II, inhaled corticosteroids resulted in a small and nonsignificant decrease in hospitalizations per 100 per-

son-years of exposure for respiratory conditions ($P = 0.07$) and no difference in nonrespiratory hospitalizations (43). The proportion of participants requiring hospitalization for COPD was lower with tiotropium than with placebo (absolute risk difference, -2% [CI, -4% to -1%]) (18, 19, 22, 24) and with ipratropium (absolute risk difference, -4% [CI, -10% to 1%]) (mean FEV₁ <60%; trial duration, 6 months to 1 year) (14).

Deaths

Death was the primary end point in only 1 trial (39). Mortality rates did not statistically differ in any trial or in pooled analyses of monotherapies (Figure 4). In a retro-

spective individual-patient data meta-analysis published before the TORCH study (56), inhaled corticosteroids resulted in a 1% absolute reduction in all-cause mortality compared with placebo (hazard ratio, 0.75 [CI, 0.57 to 0.99]). The mortality rate was not reduced among participants with a baseline FEV₁ of 60% predicted or more (hazard ratio, 0.90 [CI, 0.54 to 1.53]). Combination therapy with long-acting β_2 -agonists plus inhaled corticosteroids reduced the relative but not the absolute risk for death compared with placebo (relative risk, 0.82 [CI, 0.69 to 0.98]; absolute risk difference, -0.01 [CI, -0.03 to 0.01]) and inhaled corticosteroids (relative risk, 0.79 [CI, 0.67 to 0.94]; absolute risk difference, -0.01 [CI, -0.03 to 0.02]). Neither the relative nor the absolute risk for death improved with combination long-acting β_2 -agonists plus inhaled corticosteroids compared with long-acting β_2 -agonists (relative risk, 0.90 [CI, 0.76 to 1.08]).

Withdrawals and Adverse Events

Appendix Table 3 shows withdrawals and adverse events with long-acting inhaled therapies compared with placebo. An additional active comparator study evaluated combining the long-acting anticholinergic tiotropium with the β_2 -agonists salmeterol or salmeterol-fluticasone versus tiotropium alone (25). All but the tiotropium combination study (25) used a run-in period before randomization of initially eligible participants. The duration (10 days to 3 months), interventions allowed or provided (placebo, study drug, nonstudy chronic COPD medications, or rescue therapies), and reasons for exclusion (adherence, adverse events, and additional eligibility criteria) varied across studies. The mean percentage of persons who were enrolled in the run-in period but were not subsequently randomly assigned was 23% and ranged from 10% to 29% in the 12 trials that reported this information (25, 28, 29, 35, 36, 39–43, 45, 47). In the 7 trials that reported reasons for exclusions, 19% were mainly due to adverse events, followed by inadequate adherence to run-in medications (28, 36, 39–42, 47). None of the trials adequately described how the cause, severity, or duration of an adverse event was assessed, with the exception of fractures. Inconsistencies in adverse events reporting limited quantitative synthesis.

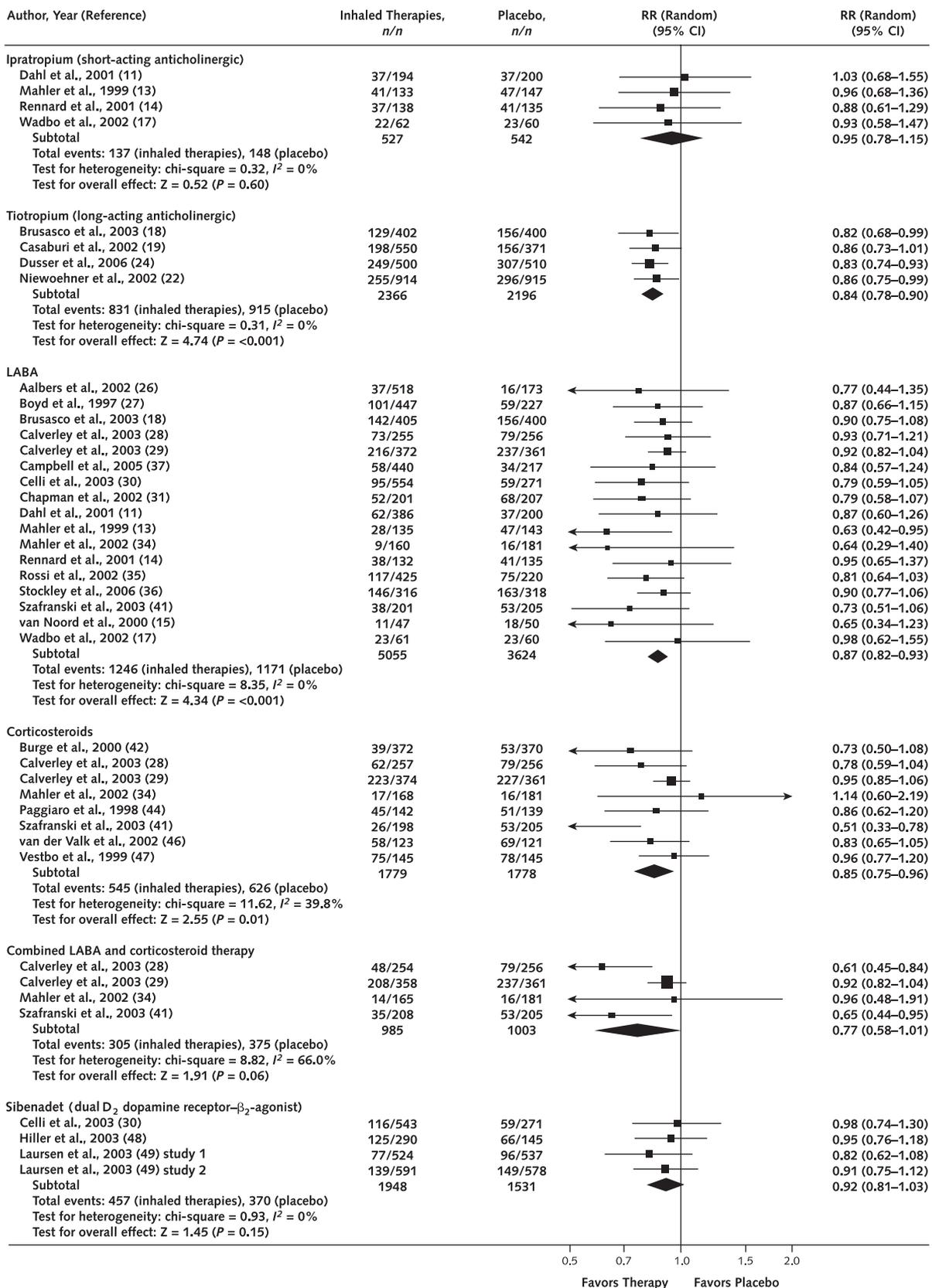
“All study withdrawals” occurred less frequently among persons randomly assigned to tiotropium (21%) (19, 24), long-acting β_2 -agonists (33%) (28, 29, 35, 36, 39, 41), corticosteroids (31%) (28, 29, 35, 36, 39, 41), or combination long-acting β_2 -agonists plus corticosteroids (32%) compared with placebo (28% to 44%). All study withdrawals were less likely to occur with combination therapy than with long-acting β_2 -agonist monotherapy (32% vs. 37%; relative risk, 0.82 [CI, 0.71 to 0.96]) or corticosteroid monotherapy (32% vs. 37%; relative risk, 0.87 [CI, 0.80 to 0.94]) (28, 29, 39, 41). Fewer withdrawals occurred with the combination of all 3 classes of long-acting inhaled agents (anticholinergics, β_2 -agonists, and

corticosteroids) versus long-acting anticholinergic monotherapy (relative risk, 0.54 [CI, 0.30 to 0.96]) (25). “Withdrawals due to adverse effects” were similar or lower with inhaled therapies than with placebo. About 50% of enrollees remained adherent to therapy as prescribed. Adverse events during follow-up were usually minor and were seldom more than with placebo. “Serious adverse events” did not statistically significantly differ with inhaled treatment used as monotherapy or in combination therapy versus placebo. “Serious adverse events” occurred in 10% of participants receiving inhaled corticosteroids as monotherapy or combination therapy in the TORCH trial compared with 6% of participants receiving placebo or long-acting β_2 -agonists (39). Compared with placebo, adverse events that were considered to be related to treatment were more common with tiotropium and corticosteroids but not with long-acting β_2 -agonists. The frequencies of serious adverse events did not differ between combination therapy and long-acting β_2 -agonists or corticosteroids used as monotherapy (28, 39, 40).

The most common specific adverse effects of tiotropium were dry mouth, occurring in 10.3% of participants (relative risk, 4.4 [CI, 2.2 to 8.8] vs. placebo) (19, 24), and urine retention (odds ratio, 2.5 [CI, 0.5 to 14] vs. placebo) (53). Respiratory infections and pneumonia were similar with long-acting β_2 -agonists and with placebo (28, 35, 36, 38). A meta-analysis of 20 RCTs assessed the cardiovascular effects of inhaled β_2 -agonists (primarily salmeterol and formoterol) in patients with asthma or COPD. β_2 -Agonists were associated with an increase in cardiovascular events compared with placebo (2.7% vs. 0.7%) (56). Of these events, 87% were due to sinus tachycardia. Major cardiovascular events were higher compared with placebo, although they did not statistically differ (relative risk, 1.66 [CI, 0.76 to 3.60]). Another pooled analysis concluded that respiratory deaths increased with long-acting β_2 -agonists and decreased with anticholinergics (59). However, their conclusions were based on very few events; were not verified in our review of the published primary literature; included findings from duplicate publications; and did not incorporate the TORCH study, which found no difference in deaths due to pulmonary causes between placebo and salmeterol (5% in each group) (39).

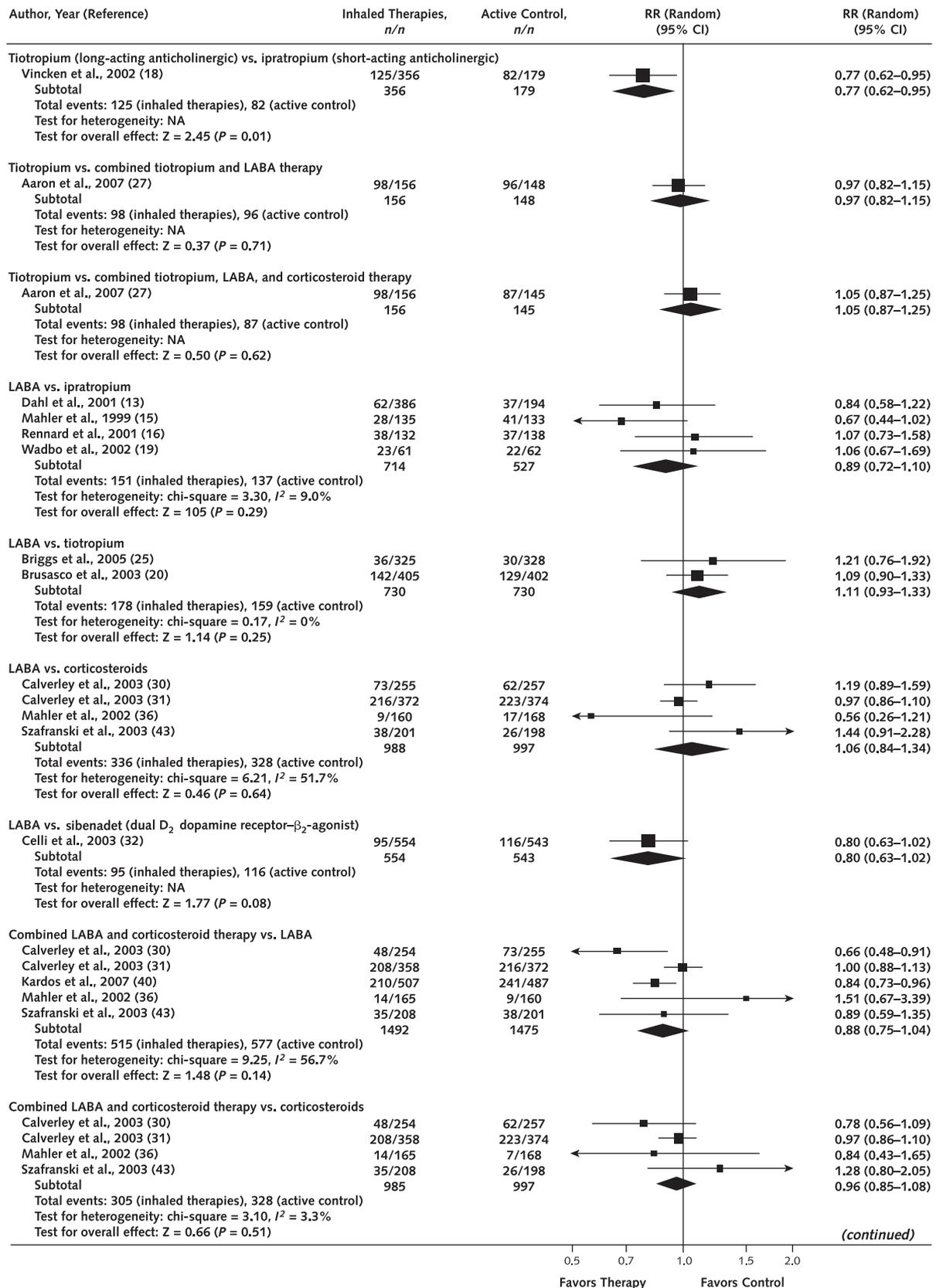
Three trials provided information about the risk for pneumonia with inhaled corticosteroid use lasting up to 3 years. Pooled analysis showed significant heterogeneity ($P = 0.02$; $I^2 = 74\%$), which disappeared ($P = 0.56$; $I^2 = 0\%$) when the smallest trial that enrolled younger patients with mild airflow obstruction was excluded. In 2 trials, inhaled corticosteroids were associated with an increased risk for pneumonia compared with placebo (relative risk, 1.55 [CI, 1.33 to 1.80]). Inhaled corticosteroids were associated with an increased frequency of oropharyngeal candidiasis (28, 29, 42, 43, 45), throat irritation (28, 29, 42, 45), and a moderate to severe degree of easy bruising (29, 42, 45). After 3 years, lumbar spine and femur bone min-

Figure 2. Number of participants who had at least 1 exacerbation: inhalation treatments versus placebo.



LABA = long-acting β_2 -agonist; RR = relative risk.

Figure 3. Number of participants who had at least 1 exacerbation: inhalation treatments versus active control.

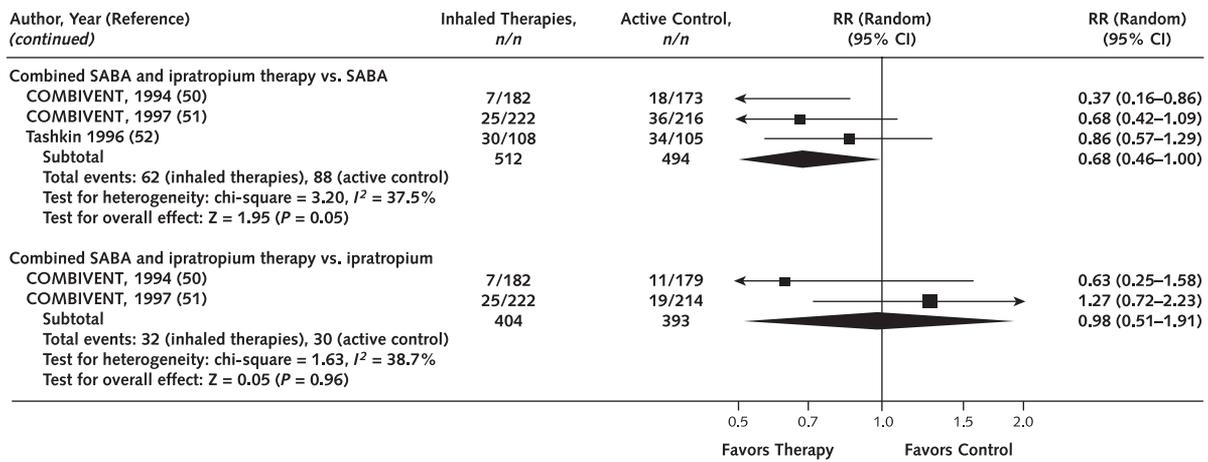


(continued)

0.5 0.7 1.0 1.5 2.0
Favors Therapy Favors Control

Continued

Figure 3—Continued.



LABA = long-acting β_2 -agonist; NA = not applicable; RR = relative risk; SABA = short-acting β_2 -agonist.

eral density were lower in the LHS II triamcinolone group (43), but not in a small subset evaluated in TORCH (39). Pooled results from 3 RCTs indicated that fracture incidence was similar for inhaled corticosteroids used alone or in combination with long-acting β_2 -agonists for up to 3 years versus placebo (pooled relative risk, 0.96 [CI, 0.55 to 1.68]) (39, 42, 45). In the trial evaluating all 3 classes of long-acting inhaled therapies, 47% of patients in the tiotropium plus placebo group discontinued study medications compared with 43% in the tiotropium plus salmeterol group and 26% in the tiotropium plus salmeterol-fluticasone group ($P < 0.001$) (25). Serious adverse events were similar across the 3 treatment groups.

When Should Clinicians Consider Pulmonary Rehabilitation and Disease Management?

Pulmonary rehabilitation but not disease management may improve health status and exercise capacity during the program in symptomatic adults with severe airflow obstruction. Conclusions based on published findings are problematic because exacerbations, hospitalizations, standardized health status measures, and exercise capacity were infrequently reported (Appendix Tables 4 and 5, available at www.annals.org) (60–90). Most pulmonary rehabilitation programs contained 4 major components: endurance or exercise training, education, behavioral modification, and outcome assessment. Programs primarily emphasized endurance training and enrolled patients with severe to very severe COPD (mean FEV₁, 31% to 54% predicted). Only 6 trials identified in the systematic review by Sin and colleagues (57) reported mean differences in SGRQ scores versus controls (pooled difference, 4.4 [CI, 0.3 to 8.4]), and 3 studies observed the average improvement between control and intervention greater than the 4-point minimally important difference (62, 67, 72). The average effect for the CRDQ dyspnea subscale was clinically significant (mean difference [vs. control] ranged from 0.2 to 14), but

the increase in exercise tolerance measured by distance walked in 6 minutes was less than the 53-meter threshold that was determined to be clinically significant. Pulmonary rehabilitation did not reduce deaths, although sample size and study duration were insufficient to adequately evaluate this end point (5). A review of 6 small RCTs ($n = 230$) found that respiratory rehabilitation after acute COPD exacerbations in patients with severe airflow obstruction (baseline FEV₁ <40% predicted) reduced hospitalizations (relative risk, 0.26 [CI, 0.12 to 0.54]; 3 trials reporting) and produced a clinically significant improvement in exercise capacity, as measured by the increased distance walked during the 6-minute walk test (64 to 215 meters; 4 trials reporting) and the SGRQ and CRDQ dyspnea subscales compared with usual care (3 trials reporting) (61).

Studies evaluating disease management used patient education, self-management with development of a treatment action plan, or enhanced follow-up with a respiratory health worker or pharmaceutical care coordinator (91–106). Appendix Tables 4 and 5 (available at www.annals.org) shows details of these studies. A total of 2911 patients with COPD were enrolled in 15 studies that lasted from 3 months to 1 year (5, 91, 105, 106). Average baseline FEV₁ was less than 50% predicted, and all patients were taking inhaled bronchodilators. The only trial reporting exacerbations noted fewer episodes in the self-management plus telephone follow-up group (92). Pooled mortality rates from trials lasting at least 9 months and providing results did not differ between intervention and control (relative risk, 0.88 [CI, 0.66 to 1.18]) (Table 4). The RCTs of brief interventions found no evidence for a reduction in all-cause readmissions, and data from long-term or more intensive intervention RCTs were equivocal about health care utilization outcomes (91). The pooled difference in SGRQ health status scores versus usual care was less than clinically noticeable (weighted mean difference, -2.5 [CI,

Figure 4. Mortality: inhalation treatments versus placebo or combination long-acting β_2 -agonists and corticosteroid therapy versus monotherapy.

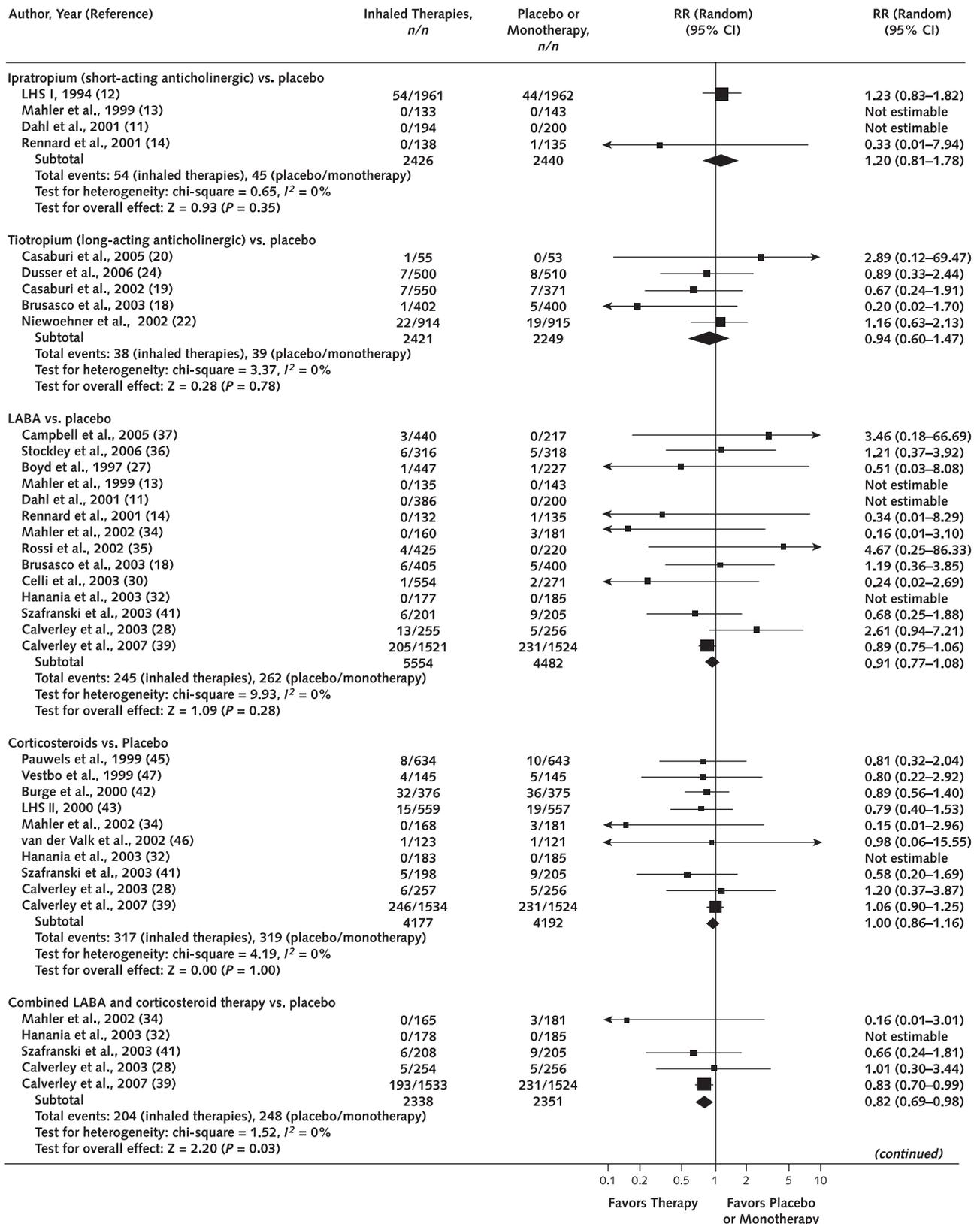
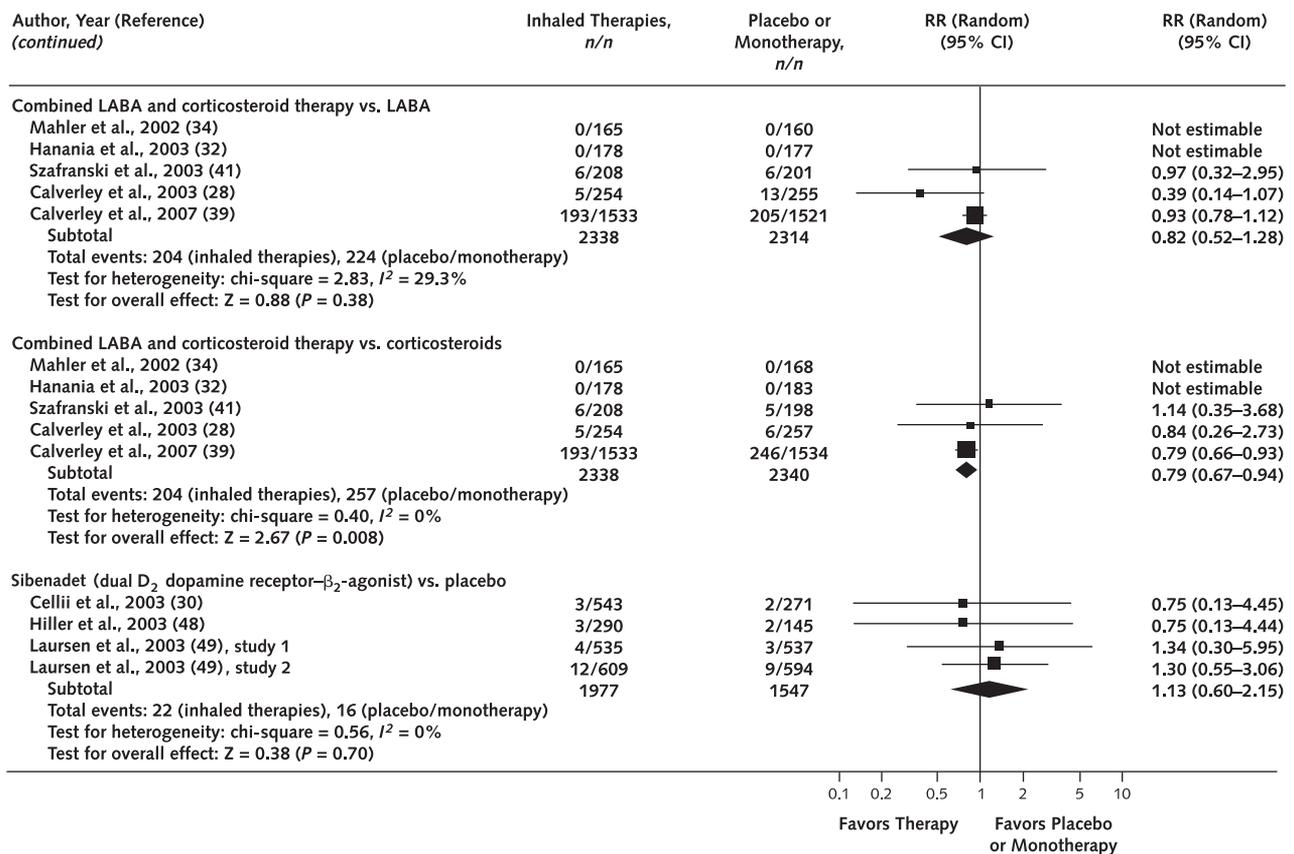


Figure 4—Continued.



LABA = long-acting β_2 -agonist; LHS = Lung Health Study; RR = relative risk.

–4.8 to –0.1]). The relative risk and number of hospital readmissions did not differ (relative risk, 0.86 [CI, 0.68 to 1.08]).

When Should Clinicians Prescribe Oxygen Therapy?

Supplemental oxygen used during most of the daytime each day reduced deaths in patients with very severe airflow obstruction and daytime hypoxemia (107–114). Four trials had follow-up of 2 to 5 years (107–110). Baseline PaO₂ ranged from 51 to 75 mm Hg. Interventions included using fixed doses of supplemental nocturnal oxygen for resting hypoxemia, titrating supplemental oxygen to maintain daytime arterial PaO₂ between 60 and 80 mm Hg, using as-needed ambulatory oxygen in addition to home oxygen, and using short-burst oxygen therapy for activity-limiting dyspnea among patients with COPD who were not hypoxemic at rest.

Exacerbations or hospitalizations were rarely reported. Supplemental oxygen used for 15 or more hours daily to maintain a PaO₂ greater than 60 mm Hg reduced deaths in 2 studies (n = 290) that enrolled persons with mean baseline FEV₁ less than 30% and mean resting PaO₂ of 55 mm Hg or less (relative risk, 0.61 [CI, 0.46 to 0.82]) (108, 109). In 2 additional trials (n = 211), supplemental oxygen (mean use, 9 to 13 hours per day) did not reduce

deaths among individuals with similar spirometric values but daytime PaO₂ greater than 60 mm Hg (relative risk, 1.16 [CI, 0.85 to 1.58]) (109, 110).

Three small short-term studies assessed the effect of ambulatory oxygen on respiratory health status (111–113). Mean changes in CRDQ scores and exercise tolerance did not achieve clinically detectable improvement. The number of hospitalizations over 6 to 12 months and urgent care visits did not differ among cylinder oxygen (mean, 2.2 hospitalizations [SD, 2.4]), cylinder air (mean, 1.8 hospitalizations [SD, 1.5]), and usual care (mean, 1.4 hospitalizations [SD, 1.0]) (112).

Should Clinicians Base Treatment Decisions on Spirometric Results, Symptoms, or Both?

Evidence of intervention effectiveness was limited to individuals with both bothersome respiratory symptoms (especially dyspnea and frequent exacerbations) and an FEV₁ less than 60% predicted. Almost all treatment trials enrolled participants with symptomatic COPD who were prone to exacerbations and had a mean FEV₁ less than 50% predicted. No data were available to determine whether long-acting β_2 -agonists were effective in symptomatic individuals with FEV₁ greater than 60% or prevented symptoms among asymptomatic individuals.

No treatment trial evaluated modifying therapy, instituting combination inhaled therapy, or monitoring disease status according to spirometric results. However, these are unlikely to be beneficial because earlier findings (www.ahrq.gov/clinic/tp/spirotp.htm) demonstrated that 1) clinical improvement is not closely associated with an individual's spirometric response to therapy; 2) treatments other than smoking cessation provide only a small change in long-term decline in lung function; 3) wide intraindividual variation exists in spirometric decline; 4) higher doses of inhaled therapies have not been shown to provide clinically significant improvement compared with lower doses; 5) combination therapy provided little to no benefit compared with monotherapy; and 6) interventions were not effective in asymptomatic persons.

DISCUSSION

Current evidence suggests that COPD treatment benefits are primarily related to reduced exacerbations among exacerbation-prone adults with activity-limiting dyspnea and FEV₁ less than 60% predicted. Inhaled corticosteroids and long-acting bronchodilators seem to be of similar effectiveness in reducing exacerbations compared with short-acting bronchodilators, but they differ in their adverse effects. Evidence indicates that average improvement in respiratory health status is clinically insignificant, but some individuals achieve a noticeable improvement. Mortality reduction occurs with long-term supplemental oxygen in symptomatic patients with severe airflow obstruction and resting hypoxemia. Studies of oxygen inconsistently reported other outcomes. When reported, treatment-related improvements were typically small. Studies of pulmonary rehabilitation showed improvements in health status and dyspnea but not in walking distance during the program. Neither disease management nor ambulatory oxygen seem to have benefits.

Combination therapy with inhaled corticosteroids and long-acting β_2 -agonists was of borderline statistical significance in reducing exacerbations and improving health status compared with monotherapy. Compared with long-acting β_2 -agonists alone, combination therapy did not reduce mortality. Compared with corticosteroids alone, combination therapy produced a 1% to 2% absolute mortality benefit that was of borderline statistical significance. Reductions in hospitalizations versus long-acting monotherapies were generally small and were not consistently observed. Health status improvements were generally not clinically significant. Tiotropium, added to a long-acting β_2 -agonist or corticosteroid plus long-acting β_2 -agonist, did not reduce exacerbations or improve dyspnea versus tiotropium monotherapy (25).

Adverse effects of long-acting inhaled therapies were usually mild, although pneumonia may be more common with inhaled corticosteroids. There was no association with fractures, but trials were short in duration. Most trials used

a treatment run-in period and enrolled exacerbation-prone persons who were previously receiving and tolerating long-acting inhaled therapy. Consequently, adverse effects, treatment adherence, and effectiveness may be different in clinical practice than in published trials. All-cause withdrawals and withdrawals due to adverse effects were fewer with long-acting inhaled therapies and combination therapies than with placebo and monotherapies, respectively, suggesting that the perceived benefits of long-acting inhalers outweigh harms.

In adults with mild to moderate airflow obstruction who did not report respiratory symptoms, treatment with ipratropium did not prevent symptom development. No studies evaluated treatment of asymptomatic individuals with severe airflow obstruction. Among symptomatic participants with FEV₁ greater than 50% but less than 80% or those with normal airflow but having chronic sputum production, 7 large studies of inhaled corticosteroids or anticholinergics that lasted at least 1 year found little to no improvement in exacerbations, health status, hospitalizations, or deaths (12, 29, 40, 43, 45, 47; www.ahrq.gov/clinic/tp/spirotp.htm).

Respiratory symptoms are common, clinical examination has poor accuracy for determining airflow obstruction severity (www.ahrq.gov/clinic/tp/spirotp.htm), and few adults have airflow obstruction severe enough that treatments have demonstrated effectiveness. Therefore, adopting a strategy that targets use of long-acting inhaled corticosteroids or bronchodilators as monotherapy to individuals reporting activity-limiting respiratory symptoms (especially dyspnea) and having an FEV₁ less than 60% would maintain benefits and minimize unnecessary testing or ineffective treatment. Pulmonary rehabilitation in these individuals may be beneficial, and long-term nocturnal supplemental oxygen in the presence of resting hypoxemia can reduce mortality. Spirometry to monitor disease status or modify therapy has not been evaluated in randomized trials. Studies are required to determine whether the relative effectiveness among therapies varies according to an individual's baseline or follow-up spirometry findings.

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Disclaimer: The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the AHRQ or the U.S. Department of Health and Human Services.

Acknowledgment: The authors thank Indy Rutks, who assisted in the literature search and creation of some figures.

Grant Support: Prepared by the Minnesota AHRQ Evidence-based Practice Center, Minneapolis, Minnesota, under AHRQ contract no. 290-02-0009 and a contract with the American College of Physicians.

Potential Financial Conflicts of Interest: *Consultancies:* D. Niewoehner (Boehringer Ingelheim, AstraZeneca, GlaxoSmithKline, Sanofi Aventis,

Schering-Plough, Adams Respiratory Therapeutics). *Honoraria*: D. Niewoehner (Pfizer Inc., Boehringer Ingelheim). *Grants received*: D. Niewoehner (Boehringer Ingelheim, GlaxoSmithKline).

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Appendix Table 1. Treatments, Baseline Characteristics, and Study Quality of Individual Trials of Treatments for Chronic Obstructive Pulmonary Disease*

Author, Year (Reference)	Study Duration	Treatment	Control	Range of FEV ₁	Demographic Information	Study Quality†
Inhaled therapies						
Dahl et al., 2001 (11)	12 wk	1) Ipratropium bromide, 40 µg tid (n = 194); 2) formoterol, 12 µg bid (n = 194); 3) formoterol 24 µg bid (n = 192)	Placebo (n = 200)	44%–46% predicted	780 European and North American men and women (25%); mean age, 64 y	Allocation concealed: NR Blinding: double Intention-to-treat: yes Funding: pharmaceutical Lost to follow-up/withdrawals: NR
Anthonisen et al., 1994 (12)	5 y	Ipratropium bromide tid plus smoking intervention (n = 1961)	1) Smoking intervention and placebo (n = 1962); 2) UC (n = 1964)	75% predicted	U.S. men and women (37%); mean age, 48 y	Allocation concealed: adequate Blinding: double Intention-to-treat: unclear (2 analyses; 1 with valid follow-up and 1 with missing data) Funding: government Lost to follow-up/withdrawals: 0.4%
Mahler et al., 1999 (13)	12 wk	1) Ipratropium, 36 µg qid (n = 133); 2) salmeterol, 42 µg bid (n = 135)	Placebo (n = 143)	37%–42% predicted	U.S. men and women (26%); mean age, 63 y; white, 91%; black, 7%; Hispanic, 1%; Asian/other, 1%	Allocation concealed: NR Blinding: double Intention-to-treat: yes Funding: pharmaceutical Lost to follow-up/withdrawals: <1%
Rennard et al., 2001 (14)	12 wk	1) Ipratropium, 36 µg tid (n = 138); 2) salmeterol, 42 µg bid (n = 132)	Placebo (n = 135)	1.22–1.30 L	U.S. men and women (37%); mean age, 63 y; white, 94%; black, 5%; Hispanic, 1%	Allocation concealed: NR Blinding: double Intention-to-treat: yes Funding: pharmaceutical Lost to follow-up/withdrawals: 2.7%
van Noord et al., 2000 (15)	13 wk	Tiotropium, 18 µg qid (n = 191)	Ipratropium, 40 µg qid (n = 97)	40%–42% predicted	Dutch men and women (16%); mean age, 64 y	Allocation concealed: NR Blinding: double Intention-to-treat: yes Funding: pharmaceutical Lost to follow-up/withdrawals: NR
Vincken et al., 2002 (16)‡	1 y	Tiotropium, 18 µg qid (n = 356)	Ipratropium bromide, 40 µg qid (n = 179)	39%–42% predicted	Dutch/Belgian men and women (15%); mean age, 64 y	Allocation concealed: NR Blinding: double Intention-to-treat: yes Funding: pharmaceutical Lost to follow-up/withdrawals: <1%
Wadbo et al., 2002 (17)	12 wk	1) Ipratropium bromide, 80 µg tid (n = 62); 2) formoterol, 18 µg bid (n = 61)	Placebo (n = 60)	33%–34% predicted	Swedish men and women (47%); mean age, 64 y	Allocation concealed: NR Blinding: double Intention-to-treat: partial, had to take 1 dose Funding: NR Lost to follow-up/withdrawals: NR, but not >1%
Brusasco et al., 2003 (18)‡	6 mo	1) Tiotropium, 18 µg qid (n = 402); 2) salmeterol, 50 µg bid (n = 405)	Placebo (n = 400)	38%–39% predicted	European and Canadian men and women (24%); mean age, 64 y	Allocation concealed: NR Blinding: double Intention-to-treat: yes Funding: pharmaceutical Lost to follow-up/withdrawals: NR, withdrawals mostly due to AEs
Casaburi et al., 2002 (19)‡	1 y	Tiotropium, 18 µg qid (n = 550)	Placebo (n = 371)	38%–39% predicted	U.S. men and women (44%); mean age, 67 y	Allocation concealed: NR Blinding: double Intention-to-treat: yes Funding: pharmaceutical Lost to follow-up/withdrawals: NR, withdrawals mostly due to AEs
Casaburi et al., 2005 (20)	25 wk	Tiotropium, 18 µg qid (n = 55)	Placebo (n = 53)	33%–36% predicted	U.S. men and women (1.5%); mean age, 68 y; white, 91%	Allocation concealed: NR Blinding: double Intention-to-treat: no Funding: pharmaceutical Lost to follow-up/withdrawals: NR
Niewoehner et al., 2005 (22)	6 mo	Tiotropium, 18 µg qid (n = 914)	Placebo (n = 915)	36% predicted	U.S. men and women (34%); mean age, 64 y	Allocation concealed: adequate Blinding: double Intention-to-treat: yes Funding: pharmaceutical Lost to follow-up/withdrawals: <1%
Briggs et al., 2005 (23)	12 wk	Tiotropium, 18 µg qid (n = 328)	Salmeterol, 50 µg bid (n = 325)	38% predicted	U.S. men and women (34%); mean age, 64 y	Allocation concealed: NR Blinding: double Intention-to-treat: partial, had to take 1 dose Funding: pharmaceutical Lost to follow-up/withdrawals: NR, withdrawals mostly due to AEs
Dusser et al., 2006 (24)	1 y	Tiotropium, 18 µg qid (n = 500)	Placebo (n = 510)	48% predicted	1010 French men and women (12%); mean age, 65 y	Allocation concealed: NR Blinding: double Intention-to-treat: yes Funding: pharmaceutical Lost to follow-up/withdrawals: NR
Aaron et al., 2007 (25)	1 y	Tiotropium, 18 µg qid, plus salmeterol, 25 µg bid, plus fluticasone, 250 µg bid (n = 145)	1) Tiotropium, 18 µg qid (n = 156); 2) tiotropium, 18 µg qid, plus salmeterol, 25 µg bid (n = 148)	38%–39% predicted	449 Canadian men and women (44%); mean age, 68 y; white, 98%	Allocation concealed: adequate Blinding: double Intention-to-treat: yes Funding: government/private Lost to follow-up/withdrawals: 1.8%

Appendix Table 1—Continued

Author, Year (Reference)	Study Duration	Treatment	Control	Range of FEV ₁	Demographic Information	Study Quality†
Hanania et al., 2003 (32)	24 wk	1) Salmeterol, 50 µg bid (n = 177); 2) fluticasone, 250 µg bid (n = 183); 3) salmeterol, 50 µg, plus fluticasone, 250 µg bid (n = 178)	Placebo (n = 185)	41%–42% predicted	723 U.S. men and women (37%); mean age, 64 y; white, 93%; black, 4%; Asian/other, 3%	Allocation concealed: NR Blinding: double Intention-to-treat: partial, last valid measure used Funding: pharmaceutical Lost to follow-up/withdrawals: 1.8%
Jones et al., 1997 (33)	16 wk	1) Salmeterol, 50 µg bid (n = 94); 2) salmeterol, 100 µg bid (n = 94)	Placebo (n = 95)	45%–47% predicted	326 international men and women (14%); mean age, 63 y	Allocation concealed: NR Blinding: double Intention-to-treat: yes Funding: pharmaceutical Lost to follow-up/withdrawals: NR
Mahler et al., 2002 (34)	24 wk	1) Salmeterol, 50 µg bid (n = 160); 2) fluticasone, 500 µg bid (n = 168); 3) salmeterol, 50 µg, plus fluticasone, 500 µg bid (n = 165)	Placebo (n = 181)	40%–41% predicted	691 U.S. men and women (34%); mean age, 63 y; white, 93%; black, 5%; Asian/other, 2%	Allocation concealed: NR Blinding: double Intention-to-treat: no Funding: pharmaceutical Lost to follow-up/withdrawals: NR
Rossi et al., 2002 (35)	1 y	1) Formoterol, 12 µg bid (n = 211); 2) formoterol, 24 µg bid (n = 214)	1) Placebo (n = 220); 2) oral slow-release theophylline, 200/300 mg bid (n = 209)	46%–49% predicted	854 European men and women (17%); mean age, 63 y	Allocation concealed: NR Blinding: double Intention-to-treat: yes Funding: pharmaceutical Lost to follow-up/withdrawals: 3.0%
Stockley et al., 2006 (36)	1 y	Salmeterol, 50 µg bid (n = 316)	Placebo (n = 318)	46% predicted	634 international men and women (24%); mean age, 62 y	Allocation concealed: adequate Blinding: double Intention-to-treat: yes Funding: pharmaceutical Lost to follow-up/withdrawals: 2.2%
Campbell et al., 2005 (37)	26 wk	1) Formoterol, 9 µg bid (n = 215); 2) formoterol, 9 µg bid, plus formoterol, 4.5 µg as needed (n = 225)	Placebo (n = 217)	54% predicted	657 international men and women (32%); mean age, 60 y	Allocation concealed: adequate Blinding: double Intention-to-treat: yes Funding: pharmaceutical Lost to follow-up/withdrawals: <1%
Kardos et al., 2007 (38)	44 wk	Salmeterol, 50 µg, plus fluticasone, 500 µg bid (n = 507)	Salmeterol, 50 µg bid (n = 487)	40% predicted (postbronchodilator)	994 German men and women (24%); mean age, 64 y	Allocation concealed: adequate Blinding: double Intention-to-treat: partial, had to take 1 dose Funding: pharmaceutical Lost to follow-up/withdrawals: <1%
Aalbers et al., 2002 (26)	12 wk	1) Formoterol, 4.5 µg bid (n = 171); 2) formoterol, 9 µg bid (n = 166); 3) formoterol, 18 µg bid (n = 177)	Placebo (n = 173)	53%–55% predicted	692 European men and women (32%); mean age, 62 y	Allocation concealed: adequate Blinding: double Intention-to-treat: partial, except participants withdrawn within 14 days of randomization Funding: pharmaceutical Lost to follow-up/withdrawals: NR
Boyd et al., 1997 (27)	16 wk	1) Salmeterol, 50 µg bid (n = 229); 2) salmeterol, 100 µg bid (n = 218)	Placebo (n = 227)	1.23–1.31 L	674 European men and women (21%); mean age, 62 y	Allocation concealed: NR Blinding: double Intention-to-treat: yes Funding: pharmaceutical Lost to follow-up/withdrawals: NR
Calverley et al., 2003 (28)	1 y	1) Formoterol, 4.5 µg bid (n = 171); 2) budesonide, 200 µg bid (n = 257); 3) formoterol, 4.5 µg, plus budesonide, 160 µg bid (n = 254)	Placebo (n = 256)	36% predicted	1022 international men and women (25%); mean age, 64 y	Allocation concealed: NR Blinding: double Intention-to-treat: yes Funding: NR Lost to follow-up/withdrawals: 0.8%
Calverley et al., 2003 (29)	1 y	1) Salmeterol, 50 µg bid (n = 372); 2) fluticasone, 500 µg bid (n = 374); 3) salmeterol, 50 µg, plus fluticasone, 500 µg bid (n = 358)	Placebo (n = 361)	44%–45% predicted	1465 international men and women (28%); mean age, 63 y	Allocation concealed: adequate Blinding: double Intention-to-treat: NR Funding: pharmaceutical Lost to follow-up/withdrawals: 2.0%
Calverley et al., 2007 (39)	3 y	1) Salmeterol, 50 µg bid (n = 1542); 2) fluticasone, 500 µg bid (n = 1551); 3) salmeterol, 50 µg, plus fluticasone, 500 µg bid (n = 1546)	Placebo (n = 1545)	44% predicted (postbronchodilator)	6184 international men and women (24%); mean age, 65 y	Allocation concealed: adequate Blinding: double Intention-to-treat: partial Funding: pharmaceutical Lost to follow-up/withdrawals: 1.5%
Celli et al., 2003 (30)	12 wk	1) Salmeterol, 50 µg bid (n = 554); 2) sibenadet, 500 µg tid (n = 543)	Placebo (n = 271)	42%–44% predicted	1368 international men and women (25%); mean age, 64 y; white, 96%; black, 1%; Oriental, 2%; other, 1%	Allocation concealed: adequate Blinding: double Intention-to-treat: partial, had to take 1 dose Funding: pharmaceutical Lost to follow-up/withdrawals: NR
Chapman et al., 2002 (31)	24 wk	Salmeterol, 50 µg bid (n = 201)	Placebo (n = 207)	44%–46% predicted	408 international men and women (36%); age ≥40 y	Allocation concealed: adequate Blinding: double Intention-to-treat: yes Funding: pharmaceutical Lost to follow-up/withdrawals: NR, withdrawals mostly due to AEs

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Appendix Table 1—Continued

Author, Year (Reference)	Study Duration	Treatment	Control	Range of FEV ₁	Demographic Information	Study Quality†
Wouters et al., 2005 (40)	1 y	Salmeterol, 50 μg, plus fluticasone, 500 μg bid (n = 189)	Salmeterol, 50 μg bid (n = 184)	48% predicted	373 Dutch men and women (26%); mean age, 63 y	Allocation concealed: adequate Blinding: double Intention-to-treat: no Funding: pharmaceutical Lost to follow-up/withdrawals: NR
Szafranski et al., 2003 (41)	1 y	1) Formoterol, 4.5 μg bid (n = 201); 2) budesonide, 200 μg bid (n = 198); 3) formoterol, 4.5 μg, plus budesonide, 160 μg bid (n = 208)	Placebo (n = 205)	36%–37% predicted	812 international men and women (21%); mean age, 64 y	Allocation concealed: NR Blinding: double Intention-to-treat: yes Funding: pharmaceutical Lost to follow-up/withdrawals: NR, withdrawals mostly due to AEs
Burge et al., 2000 (42)	3 y	Fluticasone, 500 μg bid (n = 376)	Placebo (n = 375)	50% predicted	751 British men and women (25%); mean age, 64 y	Allocation concealed: adequate Blinding: double Intention-to-treat: partial, 1 valid measure Funding: pharmaceutical Lost to follow-up/withdrawals: 9.0%
Lung Health Study II, 2000 (43)	4.5 y	Triamcinolone, 600 μg bid (n = 559)	Placebo (n = 557)	63%–65% predicted	1116 North American men and women (37%); mean age, 56 y; white, 95%; nonwhite, 5%	Allocation concealed: NR Blinding: double Intention-to-treat: yes Funding: government Lost to follow-up/withdrawals: NR, withdrawals mostly due to AEs
Paggiaro et al., 1998 (44)	6 mo	Fluticasone propionate, 500 μg bid (n = 142)	Placebo (n = 139)	55%–59% predicted	281 international men and women (23%); mean age, 63 y	Allocation concealed: adequate Blinding: double Intention-to-treat: partial, had to take 1 dose Funding: NR Lost to follow-up/withdrawals:
Pauwels et al., 1999 (45)	3 y	Budesonide, 400 μg bid (n = 634)	Placebo (n = 643)	77% predicted	1277 European men and women (27%); mean age, 52 y	Allocation concealed: NR Blinding: double Intention-to-treat: yes Funding: pharmaceutical Lost to follow-up/withdrawals: 2.7%
van der Valk et al., 2002 (46)	6 mo	Fluticasone, 500 μg bid (n = 123)	Placebo (n = 121)	56%–58% predicted (postbronchodilator)	244 Dutch men and women (16%); mean age, 64 y	Allocation concealed: adequate Blinding: double Intention-to-treat: yes Funding: private/pharmaceutical Lost to follow-up/withdrawals: 0%
Vestbo et al., 1999 (47)	3 y	Budesonide, 800 μg plus 400 μg bid for 6 mo, then 400 μg bid for 30 mo (n = 145)	Placebo (n = 145)	86%–87% predicted (postbronchodilator)	290 Danish men and women (40%); mean age, 59 y	Allocation concealed: adequate Blinding: double Intention-to-treat: yes Funding: pharmaceutical/government Lost to follow-up/withdrawals: NR
Hiller et al., 2003 (48)	1 y	Sibenalet, 500 μg tid (n = 290)	Placebo (n = 145)	41% predicted	435 U.S. men and women (43%); mean age, 64 y	Allocation concealed: NR Blinding: double Intention-to-treat: partial, had to take 1 dose Funding: pharmaceutical Lost to follow-up/withdrawals: NR
Laursen et al., 2003 (49), study 1	12 wk	Sibenalet, 50 μg tid (n = 524)	Placebo (n = 526)	39%–40% predicted	1072 European men and women (27%); mean age, 65 y	Allocation concealed: adequate Blinding: double Intention-to-treat: partial, had to take 1 dose Funding: pharmaceutical Lost to follow-up/withdrawals: NR
Laursen et al., 2003 (49), study 2	6 mo	Sibenalet, 500 μg tid (n = 591)	Placebo (n = 578)	40%–41% predicted	1203 European (3 countries) men and women (26%); mean age, 63 y	Allocation concealed: adequate Blinding: double Intention-to-treat: partial, had to take 1 dose Funding: pharmaceutical Lost to follow-up/withdrawals: NR
COMBIVENT, 1994 (50)	12 wk	Ipratropium, 21 μg, plus albuterol, 120 μg tid (n = 182)	1) Ipratropium, 21 μg tid (n = 179); 2) albuterol, 100 μg tid (n = 173)	37% predicted	534 U.S. men and women (35%); mean age, 63 y; white, 94%; black, 5%; other, 1%	Allocation concealed: NR Blinding: double Intention-to-treat: yes Funding: pharmaceutical Lost to follow-up/withdrawals: 2.8%
COMBIVENT, 1997 (51)	12 wk	Ipratropium, 0.5 mg, plus albuterol, 3.0 mg qid (n = 222)	1) Ipratropium bromide, 0.5 mg qid (n = 214); 2) albuterol sulfate, 3.0 mg qid (n = 216)	34% predicted	652 U.S. men and women (35%); mean age, 65 y; white, 93%; black, 6%; other, 1%	Allocation concealed: unclear Blinding: double Intention-to-treat: yes Funding: pharmaceutical Lost to follow-up/withdrawals: 0.6%
Tashkin et al., 1986 (52)	12 wk	Ipratropium, 40 μg bid (n = 132)	Metaproterenol, 1500 μg bid (n = 129)	37% predicted	213 U.S. men and women (16%); mean age, 61 y	Allocation concealed: NR Blinding: double Intention-to-treat: yes Funding: pharmaceutical Lost to follow-up/withdrawals: NR, withdrawals mostly due to AEs

Appendix Table 1—Continued

Author, Year (Reference)	Study Duration	Treatment	Control	Range of FEV ₁	Demographic Information	Study Quality†
Pulmonary rehabilitation‡						
Koopers et al., 2006 (85)	5 wk	Respiratory muscle endurance training by means of tube breathing (<i>n</i> = 18)	Sham by means of tube breathing (<i>n</i> = 18)	50%–58% predicted	36 Dutch men and women (53%); mean age, 56 y	Allocation concealed: NR Blinding: outcome assessor Intention-to-treat: no Funding: unclear Lost to follow-up/withdrawals: 0%
Lindsay et al., 2005 (86)	3 mo	Pulmonary rehabilitation program (6 weekly sessions of psychoeducation, including motivating participants to build up exercise habits) and tiotropium, 18 µg qid (<i>n</i> = 25)	UC and tiotropium, 18 µg qid (<i>n</i> = 25)	0.8–0.9 L	50 Chinese men and women (24%); mean age, 70 y	Allocation concealed: NR Blinding: NR Intention-to-treat: yes Funding: academic Lost to follow-up/withdrawals: 0%
Hill et al., 2006 (87)	8 wk	High-intensity inspiratory training using an inspiratory threshold device (<i>n</i> = 18)	Sham inspiratory training (<i>n</i> = 17)	37% predicted	35 Australian men and women (31%); mean age, 68 y	Allocation concealed: adequate Blinding: double Intention-to-treat: no Funding: government Lost to follow-up/withdrawals: 0%
Güell et al., 2006 (88)	16 wk	Pulmonary rehabilitation (relaxation and breathing exercises for the first 2 mo followed by exercise training (five 30-min sessions on a cycle ergometer for 2 mo) (<i>n</i> = 20)	UC (<i>n</i> = 20)	32%–38% predicted	40 Spanish men and women (6%); mean age, 65 y	Allocation concealed: no Blinding: no Intention-to-treat: no Funding: unclear Lost to follow-up/withdrawals: unclear
Carrieri-Kohlman et al., 2005 (89)	1 y	1) Dyspnea self-management program (education, home walking prescription, biweekly monitoring calls) plus exposure (4 supervised treadmill sessions once weekly for 2 mo) (<i>n</i> = 33); 2) dyspnea self-management training as above, except there were 24 supervised treadmill sessions 3 times weekly for 2 mo (<i>n</i> = 34)	Dyspnea self-management program (<i>n</i> = 36)	45% predicted	115 U.S. men and women (55%); mean age, 66 y	Allocation concealed: NR Blinding: outcome assessor Intention-to-treat: no Funding: government Lost to follow-up/withdrawals: unclear
Beckerman et al., 2005 (90)	1 y	Inspiratory muscle training using an inspiratory threshold device (<i>n</i> = 21)	Inspiratory muscle training with a very low load (<i>n</i> = 21)	42%–43% predicted	42 Israeli men and women (24%); mean age, 67 y	Allocation concealed: unclear Blinding: double Intention-to-treat: unclear Funding: NR Lost to follow-up/withdrawals: unclear
Disease management‡						
McGeoch et al., 2006 (105)	1 y	Structured education from nurse or respiratory educator on the use of a written self-management plan (methods of early recognition of exacerbations and a range of appropriate self-initiated interventions, including antibiotics and corticosteroids) plus usual care (<i>n</i> = 86)	UC (<i>n</i> = 73)	53%–55% predicted	159 New Zealand men and women (41%); mean age, 71 y; New Zealand European, 89%; New Zealand Maori, 3%; other, 8%	Allocation concealed: unclear Blinding: no Intention-to-treat: no Funding: none from pharmaceutical Lost to follow-up/withdrawals: 1%
Wood-Baker et al., 2006 (106)	1 y	Structured education from nurse (range of topics, including COPD pathology, smoking cessation, nutrition, breathing control, medications, and inhaler use). Participants received a COPD information booklet and written self-management plan (listing patient medications and an individualized action plan based on early recognition of exacerbations) (<i>n</i> = 67)	UC (<i>n</i> = 72)	44%–46% predicted	139 Australian men and women (42%); mean age, 70 y	Allocation concealed: adequate, but only practice centers were blinded, not patients Blinding: no Intention-to-treat: no Funding: pharmaceutical Lost to follow-up/withdrawals: 1.4%
Oxygen therapy						
Eaton et al., 2006 (112)	6 mo	Short-burst cylinder oxygen therapy (<i>n</i> = 25)	1) Short-burst cylinder air (<i>n</i> = 26); 2) UC (<i>n</i> = 27)	39%–45% predicted	78 New Zealand men and women (54%); mean age, 77 y	Allocation concealed: adequate Blinding: double Intention-to-treat: yes Funding: NR Lost to follow-up/withdrawals: 0%
Lacasse et al., 2005 (113)	1 y	1) Concentrator alone (home oxygen with an oxygen concentrator) (<i>n</i> = NR); 2) concentrator plus as-needed ambulatory oxygen (<i>n</i> = NR)	Concentrator plus as-needed ambulatory air (<i>n</i> = NR)	38% predicted	40 Canadian men and women (54%); mean age, 68 y	Allocation concealed: adequate Blinding: outcome assessor Intention-to-treat: NR Funding: government Lost to follow-up/withdrawals: 0%
NOTT Group, 1980 (107)	3 y	1) Continuous oxygen therapy (<i>n</i> = 101); 2) nocturnal oxygen therapy (<i>n</i> = 102)		30% predicted	203 British men and women (21%); mean age, 65 y; white, 78%	Allocation concealed: adequate Blinding: outcome assessor Intention-to-treat: yes Funding: government Lost to follow-up/withdrawals: <1%
MRC, 1981 (108)	5 y	Oxygen therapy (<i>n</i> = 42)	UC (<i>n</i> = 45)	0.58–76 L	87 British men and women (21%); mean age, 58 y; white, 78%	Allocation concealed: unclear Blinding: NR Intention-to-treat: yes Funding: government Lost to follow-up/withdrawals: 0%

Continued on following page

Appendix Table 1—Continued

Author, Year (Reference)	Study Duration	Treatment	Control	Range of FEV ₁	Demographic Information	Study Quality†
Górecka et al., 1997 (109)	3 y	Long-term oxygen therapy (n = 68)	UC (n = 67)	30% predicted	135 Polish men and women (24%); mean age, 61 y	Allocation concealed: adequate Blinding: NR Intention-to-treat: yes Funding: NR Lost to follow-up/withdrawals: 0%
Chaouat et al., 1999 (110)	2.5 y	Nocturnal oxygen therapy (n = 41)	UC (n = 35)	36%–39% predicted	76 international persons (sex NR); mean age, 64 y	Allocation concealed: inadequate (odd–even) Blinding: NR Intention-to-treat: yes Funding: none from industry Lost to follow-up/withdrawals: 2.6%
Eaton et al., 2002 (111), crossover study	12 wk	Oxygen therapy, crossing over to air	Cylinder air, crossing over to oxygen	26% predicted	50 New Zealand men and women (30%); mean age, 67 y	Allocation concealed: NR Blinding: double Intention-to-treat: yes Funding: government Lost to follow-up/withdrawals: 0%
McDonald et al., 1995 (114), crossover study	12 wk	Oxygen therapy, crossing over to air	Cylinder air, crossing over to oxygen	0.9 L	36 Australian persons (sex NR); mean age, 73 y	Allocation concealed: NR Blinding: double Intention-to-treat: no Funding: private/industry Lost to follow-up/withdrawals: 0%

* AE = adverse event; bid = twice daily; COPD = chronic obstructive pulmonary disease; MRC = Medical Research Council; NOTT = Nocturnal Oxygen Therapy Trial; NR = not reported; qid = 4 times daily; tid = 3 times daily; UC = usual care.

† Based on Strength of Recommendation Taxonomy criteria (8). Randomized, controlled trials are considered high quality if they have allocation concealment, blinding (if possible), intention-to-treat analysis, adequate size, and adequate follow-up (>80%).

‡ Information on randomized, controlled trials identified in previously published systematic reviews is available in those reviews (pulmonary rehabilitation [60, 61]; disease management [91]).

Appendix Table 2. Inhaled treatments for Chronic Obstructive Pulmonary Disease versus Placebo and Control: Improvement in the St. George Respiratory Questionnaire or Chronic Respiratory Disease Questionnaire at Study End Point*

Measure	References	Participants, n	Study Duration, mo	Mean (SD) Improvement		WMD (95% CI)	Pooled WMD (95% CI)	Baseline FEV ₁ , % predicted
				Treatment Group	Control Group			
Versus placebo								
Ipratropium								
SGRQ	11, 17	516	3	-0.5 to -2.7	1.50 to -1.5	1.50 to -1.5	-	33 to 45
CRDQ	13, 14	549	3	6.8 to 9.2	2.1 to 6.8	2.4 to 4.7	-	37 to 41
Tiotropium								
SGRQ	18, 19	1723	6 to 12	-3.2 to -4.2	0.5 to -1.5	-2.7 to -3.7	-	38 to 39
LABA								
SGRQ	17, 18, 30, 31, 33, 36	2720	3 to 12	0.0 to -6.8	1.5 to -3.2	-1.3 to -5.4	-4.25 (-4.42 to -4.08)	33 to 47
SGRQ	11, 28, 29, 37, 39, 41	2893	3 to 12	0.8 to -6.6	4.9 to -4.3	-1.1 to -5.1	-	36 to 54
CRDQ	13, 14, 34	856	3 to 6	6.4 to 10.3	2.1 to 6.8	2.0 to 5.0	-	41 to 42
Corticosteroids								
SGRQ	28, 29, 39-41, 46	2637	6 to 36	1.9 to -4.3	4.9 to -0.8	-0.8 to -3.5	-	36 to 58
CRDQ	32, 34	709	709	4.8 to 10.4	5.0	-1.8 to 5.8	-1.8 to 5.8	41 to 42
Combination corticosteroid and LABA therapy								
SGRQ	28, 29, 39, 41	1642	12	-2.6 to -4.5	4.9 to -2.3	-2.2 to -7.5	-	36 to 46
CRDQ	32, 34	709	6	10.0	5.0	5.0 to 5.2	-	40 to 42
Sibenaedet								
SGRQ	30, 49	1886	3	-4.2 to -8.2	-3.2 to -5.9	-1.0 to -2.3	-1.55 (-3.45 to 0.35)	39 to 44
SGRQ	49	1203	6	-5.2	-5.0	-0.2	-	40 to 41
Versus other monotherapy								
Ipratropium vs. tiotropium								
SGRQ	16	535	12	-0.4	-3.74	-3.30 (-5.51 to -1.09)	-	39 to 42
LABA vs. ipratropium								
SGRQ	11, 17	509	3	0.0 to -6.6	-0.5 to -2.7	0.5 to -3.9	-	33 to 45
CRDQ	13, 14	538	3	7.1 to 10.3	6.8 to 9.2	0.30 to 1.1	-	37 to 42
LABA vs. tiotropium								
SGRQ	18	807	6	-2.8 (0.7)	-4.2 (0.7)	1.40 (-0.54 to 3.34)	-	39
LABA vs. corticosteroids								
SGRQ	28, 29, 39, 41	1657	12	0.8 to -3.6	1.9 to -3.1	-0.3 to -1.7	-	36 to 45
CRDQ	32, 34	690	6	6.4 to 8.0	4.8 to 10.4	-3.2 to -4.0	-	40 to 42
LABA vs. sibenaedet								
SGRQ	30	1097	3	-5.3 (0.8)	-4.2 (0.8)	-1.10 (-3.32 to 1.12)	-	42
Combination corticosteroid and LABA therapy vs. corticosteroid or LABA monotherapy								
Versus LABA								
SGRQ	28, 29, 38, 39, 41	2642	12	-2.6 to -4.5	0.8 to -3.6	-0.3 to -3.4	-	36 to 45
CRDQ	32, 34	680	6	10.0	6.4 to 8.0	2.0 to 3.2	-	40 to 42
Versus corticosteroids								
SGRQ	28, 29, 39, 41	1656	12	-2.6 to -4.5	1.9 to -3.6	-1.4 to -4.5	-	36 to 45
CRDQ	32, 34	694	6	10.0	4.8 to 10.4	-0.6 to 5.2	-	41 to 42
Combination corticosteroid and LABA therapy vs. LABA monotherapy after withdrawal of inhaled corticosteroid therapy after 3-mo run-in period								
SGRQ	40	373	12	2.4	3.2	0.89 (adjusted)	-	48
Combination tiotropium and LABA therapy vs. tiotropium								
SGRQ	25	304	12	-6.3	-4.5	-1.8	-	38 to 39
Combination tiotropium, corticosteroid, and LABA therapy vs. tiotropium								
SGRQ	25	301	12	-8.6	-4.5	-4.1	-	39

* Not all studies reported mean change by individual treatment or control. CRDQ = Chronic Respiratory Disease Questionnaire; LABA = long-acting β_2 -agonist; SGRQ = St. George Respiratory Questionnaire; WMD = weighted mean difference.

Appendix Table 3. Study Withdrawals and Adverse Effects for Trials Lasting 1 Year or More: Inhaled Treatment versus Placebo*

Withdrawals or Effect (Reference)	Treatment Group, n/n (%)	Placebo Group, n/n (%)	Relative Risk Ratio (95% CI)	Change in Absolute Risk (95% CI)
Tiotropium (2 trials)				
All study withdrawals (19, 24)	220/1050 (21.0)	250/881 (28.4)	0.75 (0.62 to 0.89)	-7 (-11 to -3)
Withdrawals due to adverse effect (19, 24)	68/1050 (6.5)	69/881 (7.8)	0.73 (0.53 to 1.01)	-2 (-6 to 2)
Adverse effect considered treatment-related (19)	104/550 (18.9)	34/371 (9.2)	2.06 (1.43 to 2.97)	10 (5 to 14)
Serious adverse effect (19)	99/550 (18.0)	78/371 (21.0)	0.86 (0.66 to 1.12)	-3 (-8 to 2)
Dry mouth (19, 24)	108/1050 (10.3)	17/881 (1.9)	4.40 (2.19 to 8.82)	8 (-4 to 20)
LABA (6 trials)				
All study withdrawals (28, 29, 35, 36, 39, 41)	1024/3111 (32.9)	1164/2905 (40.1)	0.84 (0.77 to 0.92)	-6 (-9 to -4)
Withdrawals due to adverse effect (28, 29, 35, 36, 39, 41)	521/2990 (17.4)	607/2788 (21.8)	0.83 (0.70 to 0.98)	-4 (-6 to -1)
Serious adverse effect (28, 35, 36, 39, 41)	886/2639 (33.6)	851/2447 (34.8)	0.97 (0.85 to 1.12)	-1 (-4 to 3)
Adverse effect considered treatment-related (29, 36, 39)	242/2130 (11.4)	264/2172 (12.2)	0.91 (0.78 to 1.08)	-1 (-3 to 1)
Respiratory infection (28, 35, 36)	85/896 (9.5)	64/698 (9.2)	1.08 (0.78 to 1.51)	1 (-2 to 4)
Pneumonia (28, 39)	212/1797 (11.8)	192/1800 (10.7)	1.50 (0.53 to 4.20)	1 (0 to 3)
Corticosteroids (8 trials)				
All study withdrawals (28, 29, 39, 41-43, 45, 47)	1280/4094 (31.3)	1508/4087 (36.9)	0.84 (0.79 to 0.90)	-6 (-9 to -3)
Withdrawals due to adverse effect (28, 29, 39, 41-43, 45, 47)	723/4073 (17.8)	779/4061 (19.2)	0.91 (0.78 to 1.08)	-2 (-4 to 1)
Serious adverse effect (28, 39, 41, 42, 47)	926/2524 (36.7)	923/2520 (36.6)	0.93 (0.74 to 1.17)	-2 (-9 to 5)
Adverse effect considered treatment-related (29, 39)	365/1926 (19.0)	250/1905 (13.1)	1.44 (1.25 to 1.67)	6 (4 to 8)
Severe cardiovascular disorder (42, 45)	68/1006 (6.8)	76/1013 (7.5)	0.90 (0.66 to 1.23)	-1 (-3 to 1)
Severe lower respiratory disorder (42, 45)	104/1006 (10.3)	115/1013 (11.4)	0.89 (0.71 to 1.13)	-1 (-8 to 5)
Pneumonia (28, 39, 47)	305/1954 (15.6)	216/1945 (11.1)	1.18 (0.61 to 2.29)	2 (-4 to 7)
Candidiasis (28, 29, 42, 43, 45)	104/2196 (4.7)	41/2187 (1.9)	2.55 (1.64 to 3.98)	3 (0 to 5)
Bruising (29, 42, 45)	116/1380 (8.4)	64/1374 (4.7)	1.73 (1.11 to 2.68)	3 (1 to 6)
Throat or mouth irritation (28, 29, 42, 45)	110/1637 (6.7)	64/1630 (3.9)	1.70 (1.26 to 2.29)	2 (1 to 3)
Fractures (39, 42, 45)	98/2558 (3.8)	99/2557 (3.9)	0.92 (0.56 to 1.53)	0 (-1 to 1)
Combination LABA and corticosteroid therapy (4 trials)				
All study withdrawals (28, 29, 39, 41)	757/2366 (32.0)	1030/2367 (43.5)	0.72 (0.66 to 0.80)	-12 (-14 to -9)
Withdrawals due to adverse effect (28, 29, 39, 41)	419/2353 (17.8)	565/2346 (24.1)	0.74 (0.66 to 0.83)	-6 (-9 to -4)
Serious adverse effect (28, 39, 41)	776/2008 (38.6)	741/2005 (37.0)	1.05 (0.97 to 1.13)	2 (-1 to 5)
Adverse effect considered treatment-related (29, 39)	336/1904 (17.6)	250/1905 (13.1)	1.34 (1.16 to 1.56)	5 (2 to 7)
Pneumonia (28, 39)	311/1800 (17.3)	192/1800 (10.7)	1.83 (0.96 to 3.48)	5 (-1 to 11)
Candidiasis (28, 29)	26/612 (4.2)	5/617 (<1)	4.76 (1.91 to 11.84)	3 (-1 to 7)
Bruising (29, 42)	29/358 (8.1)	22/361 (6.1)	1.33 (0.78 to 2.27)	2 (-2 to 6)
Throat or mouth irritation (28, 29)	20/612 (3.3)	9/617 (1.5)	2.16 (0.98 to 4.74)	2 (0 to 3)
Fractures (39)	97/1546 (6.3)	79/1544 (5.1)	1.23 (0.92 to 1.64)	1 (0 to 3)

* LABA = long-acting β_2 -agonist.

Appendix Table 4. Summary of Outcomes for Clinical Trials of Pulmonary Rehabilitation*

Author, Year (Reference)	Participants, n	Study Duration	FEV ₁	Control	Mean Difference in SGRQ Score (95% CI)	Mean Difference in CRDQ Dyspnea Score (95% CI)	Mean Difference in 6-Minute Walking Test (95% CI), m
From Sin et al., 2005 (57), systematic review							
Finnerty et al., 2001 (62)	65	6 wk	1.03 L	UC	-8.1 (-14.7 to -1.4)	-	-
Hernández et al., 2000 (63)	60	12 wk	41% predicted	UC	-	3.9 (0.5 to 7.3)	-
Stulbarg et al., 2002 (64)	103	8 wk	1.04 L	ED	-	3.3 (0.7 to 5.9)	30.7 (3.0 to 58.3)
Behnke et al., 2000 (65)	46	24 wk	35% predicted	UC	-	11.3 (4.6 to 18.0)	210 (88.6 to 331.4)
Güell et al., 2000 (66)	60	52 wk	35% predicted	UC	-	0.9 (0.4 to 1.5)	95 (58 to 133)
Griffiths et al., 2000 (67)	200	6 wk	0.90 L	UC	-9.4 (-12.3 to -6.5)	6.1 (4.6 to 7.5)	-
Ringbaek et al., 2000 (68)	45	8 wk	47% predicted	Placebo	0.1 (-9.8 to 10.0)	-	29.0 (-8.1 to 66.1)
Ries et al., 2003 (69)	172	52 wk	1.06 L	UC	-	3.6 total score (-7.7 to 14.9)	24.3 (0.1 to 48.6)
Engström et al., 1999 (70)	55	52 wk	32% predicted	UC	-1.8 (-7.8 to 4.2)	-	40.2 (10.2 to 70.2)
Larson et al., 1999 (71)	53	16 wk	50% predicted	ED	-	2.1 (-0.7 to 4.9)	-
Wedzicha et al., 1998 (moderate) (72)	66	8 wk	0.98 L	ED	-5.4 (-10.7 to 0.0)	8.9 (2.1 to 15.7)	-
Wedzicha et al., 1998 (severe) (72)	60	8 wk	0.92 L	ED	0.9 (-3.9 to 5.8)	0.2 (-5.0 to 5.4)	-
Bendstrup et al., 1997 (73)	47	12 wk	1.03 L	UC	-	8.0 (-2.4 to 18.4)	74.8 (36.3 to 119.3)
Goldstein et al., 1994 (74)	89	24 wk	35% predicted	UC	-	3.0 (0.7 to 5.3)	37.9 (10.8 to 65)
Wijkstra et al., 1994 (75)	45	12 wk	1.3 L	UC	-	4.5 (1.9 to 7.1)	-
Lake et al., 1990 (76)	28	8 wk	32% predicted	UC	-	-	121.0 (40.3 to 201.7)
Simpson et al., 1992 (77)	34	8 wk	39% predicted	UC	-	6.0 (-2.4 to 18.4)	29.0 (-5.07 to 63.07)
Troosters et al., 2000 (78)	100	24 wk	42% predicted	UC	-	14.0 (6.0 to 22.0)	52 (15 to 89)
Pooled data					-4.4 (-0.3 to -8.4)	4.1 (2.2 to 6.0)	50.3 (32.5 to 68.0)
Trials identified from most recent search							
Güell et al., 2006 (88)	40	16 wk	35% predicted	UC	-	1.0 (change in PR vs. change in control; $P \leq 0.01$)	85 (change in PR vs. change in control; $P \leq 0.01$)
Hill et al., 2006 (87)	35	8 wk	37% predicted	placebo	-	0.6 (change in PR vs. change in control; $P < 0.05$); total score, $P = NS$	21.9 (change in PR vs. change in control; $P < 0.05$)
Koopers et al., 2005 (85)	36	5 wk	54% predicted	placebo	-	5.3 (total score) (change in PR vs. change in control; $P = 0.07$)	28 (change in PR vs. change in control; $P = 0.02$)
Beckerman et al., 2005 (90)	42	52 wk	43% predicted	"Low load" ET	Significant differences ($P < 0.01$) in changes between groups 6 mo onward until end of study period	-	72 (change from baseline for PR vs. "almost no change" for control; $P < 0.05$)
Carrieri-Kohlman et al., 2005 (89)	103	52 wk	45% predicted	ED	-	ED: 4.5 (1.8 to 7.3) ED/4 ET sessions: 4.2 (1.2 to 7.2) ED/24 ET sessions: 3.2 (1.2 to 7.2) No significant differences between groups	Values not reported, but changes did not significantly differ between groups over the year
Lindsay et al., 2005 (86)	50	12 wk	<80% predicted	UC	-	-0.09 (change in PR vs. change in control; $P = NS$)	-25.4 (change in PR vs. change in control; $P = NS$)
From Puhan et al., 2005 (61), systematic review†							
Behnke et al., 2003 (79) (follow-up to Behnke et al., 2000 [65])	46	18 mo	35% predicted	UC	-	2.44 (1.42 to 3.48)	215 (160 to 270)
Kirsten et al., 1998 (80)	29	11 d	36% predicted	UC	-	1.09 (0.88 to 1.30)	158 (103 to 213)
Man et al., 2004 (81)	42	12 wk	39% predicted	UC	-12.7 (-20.4 to -5.0)	-	-
Murphy et al., 2005 (82)	26	26 wk	40% predicted	UC	-8.8 (-18.2 to 0.6)	-	-
Nava, 1998 (83)	70	6 wk	32% predicted	UC	-	-	68 (30 to 106)

* CRDQ = Chronic Respiratory Disease Questionnaire; ED = education; ET = exercise training; NS = not significant; PR = pulmonary rehabilitation; SGRQ = St. George Respiratory Questionnaire; UC = usual care.

† Systematic review of persons undergoing pulmonary rehabilitation after an exacerbation.

Appendix Table 5. Summary of Outcomes for Clinical Trials of Disease Management*

Author, Year (Reference)	Participants, n	Study Duration	FEV ₁	Mean Difference in SGRQ Score (95% CI)	Relative Risk for Hospitalization (95% CI)	Relative Risk for Death (95% CI)
From Sin et al., 2005 (57), systematic review						
Bourbeau et al., 2003 (92)	191	52 wk	0.99 L	-2.0 (-5.9 to 1.8)	0.64 (0.45 to 0.91)	0.55 (0.19 to 1.58)
Hermiz et al., 2002 (93)	177	12 wk	-	-1.3 (-5.6 to 3.0)	1.27 (0.66 to 2.43)	1.00 (0.43 to 2.33)
Weinberger et al., 2002 (94)	453	52 wk	48% predicted	-	0.98 (0.65 to 1.47)	-
Watson et al., 1997 (95)	69	26 wk	37% predicted	-4.0 (-8.1 to 0.1)	-	-
Gallefoss and Bakke, 2000 (96)	62	52 wk	58% predicted	-	0.78 (0.19 to 3.15)	-
Littlejohns et al., 1991 (97)	166	52 wk	47% predicted	-	0.93 (0.46 to 1.87)	0.36 (0.10 to 1.28)
Cockcroft et al., 1987 (98)	79	36 wk	0.82 L	-	-	0.56 (0.20 to 1.61)
Weinberger et al., 1996 (99)	583	26 wk	-	-	-	-
Pooled summary				WMD, -2.5 (-4.8 to -0.1) (vs. UC only)	0.86 (0.68 to 1.08)	0.63 (0.38 to 1.04)
From Taylor et al., 2005 (91), systematic review						
Bergner et al., 1998 (100)	301	52 wk	-	-	-	1.02 (0.47 to 2.22)
Smith et al., 1999 (101)	96	52 wk	0.87 L	-	No difference between groups	1.17 (0.39 to 3.53)
Farrero et al., 2001 (102)	122	52 wk	28% predicted	-	-0.79 (-1.33 to -0.25)†	1.21 (0.58 to 2.54)
Egan et al., 2001 (103)	66	6 wk; 3-mo follow-up	<35% predicted for 19% of participants	DM: median change, 0.6 Control: median change, -3.2 (P = 0.367)	-	-
Monninkhof et al., 2003 (104)	248	52 wk	-	-0.6 (-2.8 to 1.7)	-	0.95 (0.19 to 4.81)
McGeoch et al., 2006 (105)	159	52 wk	54% predicted	-1.27 (-5.71 to 3.17)‡	8% vs. 9% (P = 0.91)	0.42 (0.04 to 4.59)
Wood-Baker et al., 2006 (106)	139	52 wk	45% predicted	1.7 (-2.43 to 5.83)‡	0.20 (-0.08 to 0.48)†	1.34 (0.38 to 4.79)
Overall pooled summary				WMD, -2.5 (-4.8 to -0.1) (vs. UC only)	0.86 (0.68 to 1.08) (5 trials)	0.88 (0.66 to 1.18) (9 trials)§
				WMD, 0.32 (-2.70 to 3.35) (2 trials)‡	WMD, -0.1 (-0.26 to 0.24) (2 trials)†	-

* DM = disease management; SGRQ = St. George Respiratory Questionnaire; UC = usual care; WMD = weighted mean difference.

† Mean difference in number of hospitalizations.

‡ Difference in changes from baseline for intervention and control groups.

§ Long-term trials only (≥36 wk).