Annals of Internal Medicine | Clinical Guidelines

Screening for Chronic Obstructive Pulmonary Disease Using Spirometry: Summary of the Evidence for the U.S. Preventive Services Task Force

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Background: Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States. Fewer than half of the estimated 24 million Americans with airflow obstruction have received a COPD diagnosis, and diagnosis often occurs in advanced stages of the disease.

Purpose: To summarize the evidence on screening for COPD using spirometry for the U.S. Preventive Services Task Force (USPSTF).

Data Sources: English-language articles identified in PubMed and the Cochrane Library through January 2007, recent systematic reviews, expert suggestions, and reference lists of retrieved articles.

Study Selection: Explicit inclusion and exclusion criteria were used for each of the 8 key questions on benefits and harms of screening. Eligible study types varied by question.

Data Extraction: Studies were reviewed, abstracted, and rated for quality by using predefined USPSTF criteria.

Data Synthesis: Pharmacologic treatments for COPD reduce acute exacerbations in patients with severe disease. However, severe COPD is uncommon in the general U.S. population. Spirometry has not been shown to independently increase smoking cessation rates. Potential harms from screening include false-positive results and adverse effects from subsequent unnecessary therapy. Data on the prevalence of airflow obstruction in the U.S. population were used to calculate projected outcomes from screening groups defined by age and smoking status.

Limitation: No studies provide direct evidence on health outcomes associated with screening for COPD.

Conclusion: Screening for COPD using spirometry is likely to identify a predominance of patients with mild to moderate airflow obstruction who would not experience additional health benefits if labeled as having COPD. Hundreds of patients would need to undergo spirometry to defer a single exacerbation.

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Chronic obstructive pulmonary disease is defined as airflow limitation that is not fully reversible, is gradually progressive, and is associated with an abnormal inflammatory lung response to noxious particles or gases (1). It currently affects more than 5% of the adult population and is the fourth leading cause of death in the United States. Direct medical and total economic costs of COPD in 1993 were estimated to be $15 billion and $24 billion, respectively (2).

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) specifies 4 stages of COPD, based on impairment in FEV_1 as measured with spirometry: mild (stage I), moderate (stage II), severe (stage III), and very severe (stage IV) (1). Patients with stage I disease have FEV_1 of at least 80% of predicted, whereas those with stage IV disease have FEV_1 less than 30% of predicted or FEV_1 less than 50% of predicted and chronic respiratory failure.

Fewer than half of the estimated 24 million Americans with airflow obstruction have actually received a diagnosis of COPD, and diagnosis often occurs in advanced stages of the disease (2). Because 4 in 5 patients with COPD are current or former smokers, some groups have advocated mass screening of asymptomatic smokers by using office spirometry (3). Early detection could in theory improve health outcomes by increasing smoking cessation rates; prioritizing administration of influenza and pneumococcal vaccines; and permitting earlier initiation of pharmacologic treatments, oxygen therapy, or pulmonary rehabilitation.

In 2005, the Agency for Healthcare Research and Quality (AHRQ) published a systematic review (2) from the Minnesota Evidence-based Practice Center of the utility of spirometry for case finding, diagnosis, and management of COPD. The report created an opportunity for the U.S. Preventive Services Task Force (USPSTF) to make a timely recommendation on screening for COPD using spirometry. In consultation with the USPSTF, we developed an analytic framework (**Figure 1**) to guide this summary of the evidence on the benefits and harms associated with

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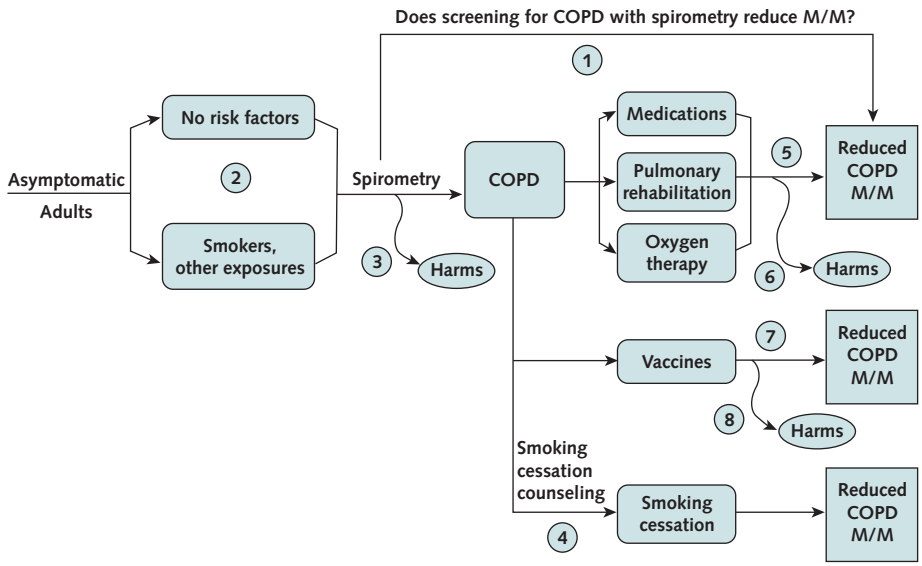
Figure 1. **Analytic framework for screening for chronic obstructive pulmonary disease (*COPD*) using spirometry.**



M/M = morbidity and mortality.

screening for COPD using spirometry. The key questions were as follows:

1. Does screening for COPD with spirometry reduce morbidity and mortality?

2. What is the prevalence of COPD in the general population? Do risk factors reliably discriminate between high-risk and average-risk populations?

3. What are the adverse effects of screening for COPD with spirometry?

4. Do individuals with COPD detected by screening spirometry have improved smoking cessation rates compared with usual smokers?

5. Does pharmacologic treatment, oxygen therapy, or pulmonary rehabilitation for COPD reduce morbidity and mortality?

6. What are the adverse effects of COPD treatments?

7. Do influenza and pneumococcal immunizations reduce COPD-associated morbidity and mortality?

8. What are the adverse effects of influenza and pneumococcal immunizations in patients with COPD?

METHODS

In addition to summarizing evidence previously synthesized in the 2005 AHRQ report (2) and in 2 subsequent updated reviews (4, 5), we performed, at the request of the USPSTF, supplemental literature searches for evidence that COPD screening programs reduce morbidity and mortality, evidence of harms from spirometry and COPD treatments, and new evidence on spirometry's use as an independent motivational tool for smoking cessation.

Data Sources

Supplemental searches were limited to English-language articles identified in PubMed and the Cochrane Library. We searched for studies from 1966 through December 2006 that addressed key questions 1 and 3. We searched for studies published in 2005 and 2006 that addressed key question 4. We searched for systematic reviews published from 1997 through January 2007 that addressed key questions 6, 7, and 8. The **Appendix** (available at www.annals.org) provides detailed search terms. We identified additional potentially relevant studies by reviewing the reference lists of retrieved articles and consulting with experts.

Study Selection

Two authors independently reviewed all titles, abstracts, and full articles by using explicit inclusion and exclusion criteria for each key question (**Appendix**, available at www.annals.org). Abstracts that were selected by fewer than 2 reviewers were discussed and selected on the basis of consensus. We considered studies of spirometry regardless of whether the testing was performed in a pulmonary function laboratory or in an office setting.

For questions on benefits of screening and treatment, we included randomized, controlled trials (RCTs); systematic reviews; and meta-analyses. For questions on harms, we also included nonrandomized studies that were generalizable to primary care populations.

Data Extraction and Quality Assessment

Two authors independently reviewed the text of studies selected for full article review to determine whether the studies met eligibility criteria for inclusion. Two authors

rated the quality of studies that met inclusion criteria by using established USPSTF methods (**Appendix Table 1**, available at www.annals.org). Disagreements in quality rating were resolved by consensus.

Data Synthesis and Statistical Analysis

With 1 exception, data were synthesized qualitatively in narrative and tabular format because of the heterogeneity of patient characteristics, study methods, and/or outcome assessments. Selected health outcomes of COPD treatments were synthesized quantitatively in the 2007 review by Wilt and colleagues (5) but were not further meta-analyzed for this review.

Projected outcomes of population-based screening for COPD using spirometry were estimated by using data on the prevalence of airflow obstruction in the general U.S. population (2) and pooled effectiveness of inhaled therapies at reducing the absolute risk for COPD exacerbations (5).

Role of the Funding Source

The work of the USPSTF is supported by the AHRQ. This review did not receive separate funding.

RESULTS

Does Screening for COPD with Spirometry Reduce Morbidity and Mortality?

We did not identify any published controlled studies that addressed this question.

What Is the Prevalence of COPD in the General Population? Do Risk Factors Reliably Discriminate between High-Risk and Average-Risk Populations?

The 2005 AHRQ report (2) identified population-based surveys from 7 countries that reported overall prevalence of COPD ranging from 4.5% to 21.1%, depending on the definition used (symptoms necessary or sufficient; American Thoracic Society vs. GOLD criteria) and the population studied.

The National Health and Nutrition Examination Surveys (NHANES) I and III characterized the general U.S. population (6, 7). In NHANES III, 16 084 participants had spirometry; reported detailed medical history information, including previous COPD or an equivalent diagnosis (chronic bronchitis, emphysema); and answered specific questions about the presence of COPD-associated symptoms of cough, phlegm, wheezing, and dyspnea. Among the participants, 7.2% had objectively measured airflow obstruction consistent with the GOLD definition of COPD and 63.3% with airflow obstruction did not report having received a previous diagnosis of COPD. On the other hand, only 17.4% who reported a previous COPD diagnosis had abnormal spirometry result.

The prevalence of COPD increased in older adults and current or past smokers. In NHANES I, the prevalence of severe airflow obstruction not reversible by bronchodilators (corresponding to GOLD stages III or IV) increased from 2.6% in adults age 50 to 59 years to 4.2% in adults age 70 to 74 years. Among current smokers, 2.1% had severe airflow obstruction compared with fewer than 1% of never smokers. Among current smokers, mild or moderate airflow obstruction was nearly 10 times as prevalent as severe airflow obstruction (19.8% vs. 2.1%). Respiratory symptoms did not correlate with the presence or degree of obstruction; 21% of participants with FEV_1 less than 50% of predicted reported no symptoms.

In summary, about 1 in 14 adults in the general U.S. population has objectively measured airflow obstruction consistent with COPD. Evidence suggests that airflow obstruction consistent with COPD is underdiagnosed in primary care; however, basing a COPD diagnosis on symptoms alone leads to overdiagnosis in patients who do not have airflow obstruction. Older adults and current or past smokers are at increased risk for severe disease, but age and smoking status do not reliably discriminate between high- and average-risk populations.

What Are the Adverse Effects of Screening for COPD with Spirometry?

We identified 3 articles containing information relevant to this key question. One article evaluated the frequency of cardiac ectopy during spirometry. Two articles examined the theoretical rate of false-positive spirometry results in patients at low risk for airflow obstruction. None of these studies used portable office spirometers.

Fields and colleagues (8) measured the incidence of premature atrial and ventricular contractions during the performance of spirometric flow-volume loops on 42 patients referred to a pulmonary function laboratory. More than half of the patients had a measured FEV_1–FVC ratio less than 75%, and 18 patients had known cardiac disease. Patients had ambulatory electrocardiographic monitoring for 60 minutes before spirometry, 30 minutes during spirometry, and 60 minutes after spirometry. Cardiac ectopy did not increase during or after spirometry, regardless of patients' histories of pulmonary or cardiac disease.

Hardie and colleagues (9) surveyed a sample of the general population age 70 to 100 years living in Bergen, Norway. Current or former smokers, individuals with previous physician-diagnosed respiratory disease, and individuals with heart disease associated with severe dyspnea were excluded. A randomly selected sample of 208 of the 612 remaining "healthy" persons were invited to participate in a clinical examination that included spirometry. Seventy-one participants completed acceptable spirometry. Results indicated that roughly 35% of healthy elderly (age >70 years) participants tested would receive a diagnosis of at least GOLD stage I COPD (FEV_1–FVC ratio <70% and FEV_1 >80% predicted). This number increased to 50% in participants older than age 80 years. Although the absence of a reference standard made it impossible to determine how many of these apparently healthy persons actually had COPD, Hardie and colleagues concluded that applying

strict criteria for airflow obstruction would potentially result in increasing COPD overdiagnosis with increasing age.

Vedal and Crapo (10) recruited 314 healthy adults with characteristics similar to those used to determine reference spirometry values. A total of 251 participants who met inclusion criteria for normal pulmonary function (no history of heart, lung, or chest-wall disease; no history of cigarette smoking; normal chest radiography; and normal heart and lung examinations) had pulmonary function tests, including simple spirometry (FVC, FEV_1, and FEV_1–FVC ratio). Ten percent had at least 1 abnormal spirometric result. These findings were used to develop COPD diagnostic criteria requiring 2 abnormal spirometry measurements that do not differ from each other by more than 5%; currently, therefore, only 1 abnormal spirometry measurement would not result in a COPD diagnosis.

In summary, no evidence suggests that spirometry causes any clinically significant adverse effects. However, data suggest that a baseline percentage of false-positive results occurs in asymptomatic healthy persons.

Do Individuals with COPD Detected by Screening Spirometry Have Higher Smoking Cessation Rates Than Usual Smokers?

The 2005 AHRQ report (2) systematically reviewed RCTs that evaluated spirometry as a motivational tool for smoking cessation, independently or in combination with behavioral and pharmacologic therapies. Wilt and colleagues (4) updated their literature search through October 2005 in a subsequent article. Seven RCTs containing 6052 participants met inclusion criteria. Outcomes included self-reported and biologically verified abstinence rates, sustained abstinence over the course of the study, and number of quit attempts. Follow-up ranged from 9 to 36 months. In general, participants in both the intervention and control groups received smoking cessation counseling.

Absolute improvements in abstinence rates in the included trials varied from 1% to 33%. Although 4 trials showed statistically significant results in favor of the smoking cessation intervention, the independent effect of spirometry could not be assessed. Only 1 trial evaluated spirometry independently from pharmacologic therapies proven to increase cessation rates (nicotine replacement, bupropion). This trial, which required a separate appointment outside of the primary care setting for spirometry, showed a statistically insignificant 1% improvement in patient-reported abstinence at 12 months (11).

Our supplemental literature search identified 1 systematic review and 1 fair-quality RCT in addition to the 2005 AHRQ report (2). Bize and associates (12) reviewed RCTs on the efficacy of "biomedical risk assessment and feedback" to improve smoking cessation rates. Measurements included exhaled carbon monoxide, spirometry, genetic testing, and carotid and femoral ultrasonography. The initial literature search retrieved 4049 references. Eight trials met inclusion criteria; 4 of these used spirometry as one of the elements. The only RCT not included in the 2005 AHRQ report used spirometry in combination with exhaled carbon monoxide measurements and found a statistically insignificant improvement (odds ratio, 2.45 [95% CI, 0.73 to 8.25]) in biochemically measured abstinence in the intervention group after 6 months (13).

Buffels and colleagues (14) recruited 221 adult smokers from 16 general practices in Belgium. Willingness to quit smoking, assessed by their primary care physician, was required for study eligibility. Comparability of study groups was not clear, because patient characteristics other than sex and smoking status were not reported. All participants were prescribed nicotine replacement therapy, bupropion, or both and were then randomly assigned to a group that had spirometry in the office or to a control group that did not have spirometry. Participants were contacted at 6, 12, and 24 months thereafter to determine whether they had or had not resumed smoking. Those who reported sustained abstinence after 2 years had urine testing to verify cessation. Differences in quit rates between the intervention and control groups were not statistically significant.

In summary, the evidence on spirometry as an independent motivational tool for smoking cessation is inconclusive. Most studies have at least 1 of the following important limitations: did not evaluate spirometry independently from other therapies known to improve smoking cessation rates, insufficient sample size to detect a statistically significant effect, and heterogeneity of interventions and outcome measures that precludes pooling of data in a meta-analysis.

Does Pharmacologic Treatment, Oxygen Therapy, or Pulmonary Rehabilitation for COPD Reduce Morbidity and Mortality?

Pharmacologic Treatment

Wilt and colleagues (5) recently updated the 2005 AHRQ report to include RCTs or meta-analyses of inhaled COPD therapies published through March 2007. Eligible treatments included long-acting β-agonists, short- and long-acting anticholinergics, inhaled corticosteroids, and combinations of these medications. "Rescue" treatments, such as short-acting β-agonists, were not reviewed. Included studies enrolled patients with COPD; had more than 50 participants in each group (intervention therapy vs. placebo or active control); had a duration of at least 3 months; and provided outcomes data on COPD exacerbations, health status, and hospitalizations and/or mortality.

A total of 43 RCTs and 10 meta-analyses met inclusion criteria. Most trials involved patients with disabling respiratory symptoms and severe or very severe airflow obstruction (FEV_1 <50% predicted). Because of the very limited number of patients with mild or moderate COPD and the trial designs, treatment effectiveness by severity of disease could not be evaluated.

Of the outcomes reviewed, the evidence that inhaled therapies for COPD decreased exacerbations was most complete and compelling. Monotherapy with any of 3 of the 4 major classes of inhaled COPD therapies (long-acting β-agonists, long-acting anticholinergics, and corticosteroids) decreased the risk for at least 1 exacerbation more than placebo (relative risk reduction, 13% to 17%; absolute risk reduction, 4% to 6%). Short-acting anticholinergics did not reduce exacerbations more than placebo.

Nine trials evaluated combination therapy. Six trials compared inhaled corticosteroids plus long-acting β-agonists with placebo or monotherapy with 1 of the component medications. In a pooled analysis of the 5 published studies, the absolute risk reduction in patients having at least 1 exacerbation for combination therapy was 6% (CI, 1% to 12%). Combination therapy was not statistically significantly more beneficial than inhaled corticosteroids (relative risk, 0.96 [CI, 0.85 to 1.08]) or long-acting β-agonists alone (relative risk, 0.88 [CI, 0.75 to 1.17]). Albuterol plus ipratropium reduced exacerbations more than albuterol alone (absolute risk reduction, 6%).

Health status measures were assessed in 19 studies that administered the St. George Respiratory Questionnaire or the Chronic Respiratory Disease Questionnaire. Only 4 trials demonstrated clinically significant improvements with inhaled therapies; 3 of these were limited to patients with either severe or very severe airflow obstruction (mean FEV_1 <50% predicted).

Long-acting anticholinergics reduced the proportion of patients who required hospitalization for COPD more than placebo (absolute risk reduction, 2% [CI, 1% to 4%]). On the other hand, 3 trials that evaluated long-acting β-agonists versus placebo did not find a statistically significant difference in the proportion. Similarly, the Lung Health Studies I and II (which enrolled patients with mild to moderate disease) found no difference in hospitalizations per 100 person-years of exposure in patients receiving ipratropium or inhaled corticosteroids (15).

A meta-analysis of retrospective patient-level data from trials of inhaled corticosteroids versus placebo demonstrated an absolute reduction of 1% in all-cause mortality after 1 year (16). This effect was most pronounced in subgroups of women and former smokers but was not present in patients with mild to moderate disease (FEV_1 >60% predicted).

Subsequent to this meta-analysis, Calverley and colleagues (17) conducted a fair-quality RCT that compared all-cause mortality in patients taking combination salmeterol–fluticasone, salmeterol alone, fluticasone alone, or placebo over 3 years in patients with COPD who had FEV_1 less than 60% of predicted. A total of 6112 current or former smokers between 40 and 80 years of age were recruited from outpatient centers in 42 countries. Whether recruitment occurred in primary care settings, referral centers, or a combination of both was not clear. Patients had had 1 previous COPD exacerbation on average; data on length of time since COPD diagnosis and duration of previous pharmacologic therapy were not provided. The relative risk reduction in all-cause mortality in the combination therapy group approached but did not reach statistical significance (odds ratio, 0.825 [CI, 0.681 to 1.002]) compared with the placebo group.

Oxygen Therapy

Two trials of patients with very severe COPD (FEV_1 <30% predicted) and resting hypoxia (Pa_{O_2} ≤55 mm Hg) demonstrated reductions in mortality (relative risk, 0.61 [CI, 0.46 to 0.82]) with supplemental oxygen. In 2 other trials in similar patients with less severe hypoxia, supplemental oxygen did not affect mortality (18, 19). No trials to date have evaluated the effect of supplemental oxygen on any health outcome in patients with less severe disease.

Pulmonary Rehabilitation

Two previous systematic reviews (20, 21) of rehabilitation programs incorporating exercise training, education, behavioral modification, and outcome assessment found improvements of borderline clinical significance in health status but no effect on mortality in patients with severe COPD. A more recent systematic review and meta-analysis (22) of 31 RCTs found clinically significant improvements in dyspnea, fatigue, emotional function, and patients' sense of control over their condition on the Chronic Respiratory Disease Questionnaire and statistically significant improvements on the St. George Respiratory Questionnaire that did not reach clinical significance.

Summary

Pharmacologic treatments modestly reduce exacerbations in patients with symptomatic severe COPD and may have a small absolute effect on all-cause mortality. However, the strongest evidence for a mortality benefit comes from an RCT involving patients with a previous exacerbation who would not have received a diagnosis with screening. Oxygen therapy reduces mortality in patients with very severe COPD and resting hypoxia. Pulmonary rehabilitation improves health status measures in selected patients.

These conclusions are limited by the absence of patients with mild or moderate COPD in most therapeutic trials. In addition, none of these therapies has been tested in patients with airflow obstruction who do not recognize or report symptoms.

What Are the Adverse Effects of COPD Treatments?

Wilt and colleagues (5) reported on adverse effects of COPD medications that occurred in RCTs. Inhaled corticosteroids increased the frequency of oropharyngeal candidiasis, throat irritation, and easy bruising and decreased lumbar spine and femur bone density. Tiotropium increased the frequency of dry mouth. A meta-analysis of 20 RCTs (23, 24) found that β-agonists increased the preva-

Table 1. **Projected Outcomes of Screening 10 000 Asymptomatic Adults for Chronic Obstructive Pulmonary Disease Using Spirometry***

Variable	Current Smoker	Never Smoker	Age 40–49 y	Age 50–59 y	Age 60–69 y	Age 70–74 y
Patients screened, *n*	10 000	10 000	10 000	10 000	10 000	10 000
Patients with FEV_1 <50% of predicted, *n*†	207	95	80	260	370	420
Patients prevented from having ≥1 COPD exacerbation, *n*	12	5	4	15	22	25
NNS to prevent 1 COPD exacerbation over 6–36 mo	833	2000	2500	667	455	400

* Screening and treatment assumptions were as follows: 1) The true prevalence of FEV_1 <50% of predicted, in subgroups of the general primary care population, is that measured in the Third National Health and Nutrition Examination Survey (7); 2) inhaled therapies only benefit patients with FEV_1 <50% of predicted; 3) treatment consists of the combination of an inhaled β-agonist and an inhaled corticosteroid; 4) patients who do not recognize or report symptoms have similar benefit to that of symptomatic patients; 5) treatment produces a 6% absolute risk reduction in patients having ≥1 COPD exacerbation over 6–36 mo (as in the 2007 review by Wilt et al. [5]); 6) because a COPD exacerbation causes a patient to seek medical care, leading to a clinical diagnosis, the incremental benefit of screening over clinical detection is limited to avoidance of a single exacerbation. COPD = chronic obstructive pulmonary disease; NNS = number needed to screen.
† These patients were therefore eligible to receive inhaled therapies.

lence of sinus tachycardia and major and minor cardiovascular events. A large recent RCT of COPD therapy found no differences in cardiovascular events between patients using a long-acting β-agonist and control participants; this trial also found no differences in fractures between patients using an inhaled corticosteroid and control participants (17). Using these known adverse effects to inform our literature search, we identified 12 systematic reviews of fair to good quality published since 1997 (**Appendix Table 2**, available at www.annals.org). **Appendix Table 3** (available at www.annals.org) summarizes their findings by drug class.

For short-acting inhaled β_2-agonists, no adverse events have been reliably noted in RCTs because of short duration and small sample sizes (25). Long-acting inhaled β_2-agonists have several cardiovascular effects. A single dose increases heart rate and serum potassium concentration (24). One review of RCTs found a statistically significant higher risk for cardiovascular events (24), whereas another showed no statistically significant difference in incidence or time to first cardiovascular event (26). In case–control studies, long-acting inhaled β_2-agonist use has been associated with an increased risk for myocardial infarction, heart failure, cardiomyopathy, and unstable angina (23). One review of RCTs found an increased risk for respiratory death with long-acting inhaled β_2-agonist use compared with placebo (27); however, Wilt and colleagues could not reproduce these findings in their 2007 review (5). A subsequent large RCT did not find a statistically significant difference in mortality in patients taking a long-acting β-agonist (17).

Reviews of inhaled anticholinergics compared with placebo found statistically significant increases in dry mouth, urinary tract infections, and urinary retention (28, 29). Results for cardiovascular events varied. In 1 review, the evidence could not be reliably summarized because of the heterogeneity of RCT results (29). Another review found no statistically significant difference in incidence of cardiac arrest or myocardial infarction; however, risks for tachycardia and dysrhythmias were higher (28). In comparisons of placebo, ipratropium, and salmeterol, no statistically significant difference in cardiovascular or all-cause mortality was observed (28–30).

Reviews of inhaled corticosteroids compared with placebo found statistically significant increased risks for oropharyngeal candidiasis and skin bruising (31, 32). Bone mineral density effects varied. One review reported no effect (33), whereas other reviews were inconclusive because of short study duration and small sample sizes. Case–control studies suggested an increased risk for fractures, open-angle glaucoma, and cataracts; these effects seemed to be small and infrequent. A large RCT found a statistically significant increased risk for pneumonia in patients using fluticasone after 3 years (17).

In summary, minor adverse effects are commonly associated with inhaled COPD treatments. The evidence regarding major adverse effects (such as fractures, cardiovascular events, and mortality) is mixed and inconclusive.

Do Influenza and Pneumococcal Immunizations Reduce COPD-Associated Morbidity and Mortality? What Are the Adverse Effects of Influenza and Pneumococcal Immunizations in Patients with COPD?

Two systematic reviews in the Cochrane Library (34, 35) provided information on these key questions. Both reviews identified RCTs of the respective vaccines in patients with COPD from the Cochrane Airways Group specialized register of trials (derived from systematic searches of the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, and CINAHL databases) and hand searches of respiratory journals and meeting abstracts. The influenza vaccination reviewers searched for trials through May 2006, and the pneumococcal vaccination reviewers searched through April 2006. Trials recruited patients with a representative range of COPD severity from mild to very severe, but few trials stratified results by disease severity.

The influenza vaccination review (34) included 11 fair- to good-quality RCTs that reported exacerbation rates, hospitalizations, mortality, lung function, and adverse effects. Six trials involved only patients with COPD. Data comparing exacerbation rates between vaccinated and unvaccinated patients were extracted from 2 studies involv-

ing a total of 180 patients. Compared with placebo, influenza vaccination reduced the total number of exacerbations (weighted mean difference, −0.37 exacerbation per vaccinated person [CI, −0.64 to −0.11 exacerbations per vaccinated person]). When data were stratified into "early" (within 4 weeks of vaccination) and "late" (after 4 weeks) exacerbations, decreases in the latter were responsible for almost the entire effect. Vaccinated and unvaccinated groups did not statistically significantly differ in lung function, hospitalizations, or mortality.

Influenza vaccination, compared with placebo, was associated with a statistically significant increase in local reactions at the injection site across all included studies. Other adverse effects, including increases in wheezing, upper respiratory tract symptoms, malaise, and myalgia, were generally mild and transient and were not consistently observed.

The pneumococcal vaccination review (35) included 4 RCTs of varying quality with a total of 937 patients. Only studies limited to patients with COPD were included. One study of 49 patients provided data on exacerbations; this study did not show a statistically significant difference in this outcome between vaccinated and unvaccinated patients (odds ratio, 1.43 [CI, 0.31 to 6.69]). No statistically significant benefits of pneumococcal vaccination in patients with COPD were observed for secondary end points of pneumonia, emergency department visits, hospitalizations, or mortality. One of the included studies showed a trend toward pneumonia protection in a subgroup of vaccinated patients with FEV_1 less than 40% predicted (odds ratio, 0.47 [CI, 0.22 to 1.01]) (36). The other 3 studies did not report data by COPD severity.

None of the studies on pneumococcal vaccine reported quantitative data on disability, change in lung function, or adverse effects.

In summary, influenza vaccination reduces exacerbations in patients with COPD; evidence regarding benefits of pneumococcal vaccination is insufficient. Whether benefits vary according to severity of COPD is uncertain, and these data do not support prioritizing vaccination on the basis of spirometric measurements. Both vaccines seem to be well tolerated.

Projected Outcomes from Screening for COPD Using Spirometry

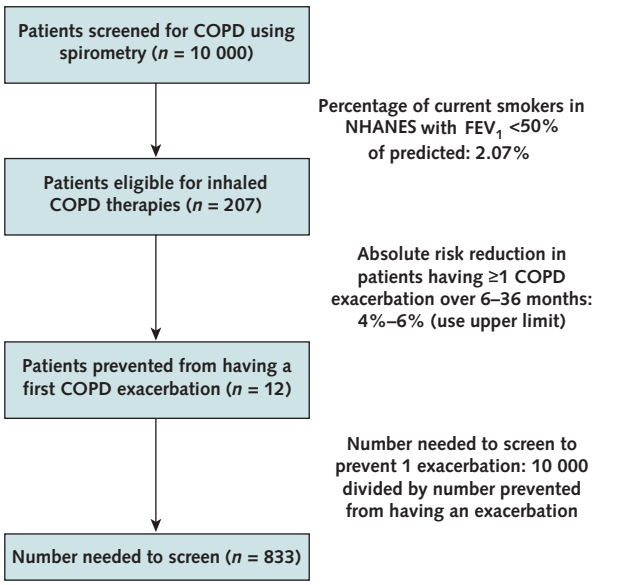
Table 1 shows the hypothetical outcomes of a spirometry screening program targeting various U.S. population subgroups, defined by smoking status and age. These cal-

Table 2. **Summary of Evidence***

Key Question	Studies Identified	Summary of Evidence
Does screening for COPD with spirometry reduce morbidity and mortality?	No RCTs directly address this question	No evidence is available to answer this question.
What is the prevalence of COPD in the general population? Do risk factors reliably discriminate between high-risk and average-risk populations?	Population-based surveys (including NHANES) from 7 countries NHANES I and III (6, 7)	Prevalence is 4.5% to 21.1%, depending on COPD definition, and is 7.2% in the U.S. population using the GOLD definition. Severe airflow obstruction is higher in older adults and in current and past smokers.
What are the adverse effects of screening for COPD with spirometry?	3 small studies of spirometry performed in pulmonary function laboratories	Spirometry seems to be physically safe; some false-positive test results occur in asymptomatic patients.
Do individuals with COPD detected by screening spirometry have improved smoking cessation rates compared with usual smokers?	8 RCTs and 2 systematic reviews with up to 36 months of follow-up; only 2 RCTs evaluated the independent motivational effect of spirometry	Spirometry does not seem to increase smoking cessation rates, but further studies may be needed.
Does pharmacologic treatment, oxygen therapy, or pulmonary rehabilitation for COPD reduce morbidity and mortality?	43 RCTs and 10 meta-analyses identified in 2007 systematic review by Wilt et al. (5)	Pharmacologic treatments reduce exacerbations in patients with symptomatic severe COPD and have a small effect on all-cause mortality. Oxygen therapy reduces mortality in patients with resting hypoxia. Pulmonary rehabilitation improves some health status measures. None of these therapies has been tested in patients with airflow obstruction who do not recognize or report symptoms.
What are the adverse effects of COPD treatments?	12 fair- to good-quality systematic reviews	Common minor adverse effects include dry mouth, urinary retention, tachycardia, oropharyngeal candidiasis, and easy bruising. Major adverse effects seem rare.
Do influenza and pneumococcal immunizations reduce COPD-associated morbidity and mortality? What are the adverse effects of influenza and pneumococcal immunizations in patients with COPD?	2 Cochrane systematic reviews, 1 including 11 RCTs and 1 including 4 RCTs	Influenza vaccination reduced COPD exacerbations occurring >4 weeks after vaccination. Pneumococcal vaccination had no statistically significant effect on health outcomes. Local reactions occurred at the injection site.

* COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; NHANES = National Health and Nutrition Examination Survey; RCT = randomized, controlled trial.

Figure 2. **Projected outcomes of population-based screening for chronic obstructive pulmonary disease (*COPD*) using spirometry in current smokers age 40 years or older.**



NHANES = National Health and Nutrition Examination Survey.

culations were based on NHANES data on the prevalence of FEV_1 less than 50% of predicted and on the absolute risk reduction in COPD exacerbations from inhaled treatments, as reported in Wilt and colleagues' review (5). We made an untested assumption that patients with airflow obstruction who do not recognize or report symptoms would benefit to the same degree as patients with symptoms studied in the clinical trials. Making this assumption allowed the USPSTF to estimate the upper bound, or maximum benefit, that might be achieved through early detection and treatment of these patients. **Figure 2** shows a sample calculation of the number of patients needed to screen if population-based screening were applied to current smokers older than age 40 years, as some groups (3) have advocated.

DISCUSSION

No direct evidence indicates that screening patients for COPD using spirometry improves long-term health outcomes (**Table 2**). An evaluation of the potential benefits of such screening depends on piecing together a coherent chain of evidence. One impetus for screening has been data from population surveys showing that a substantial number of smokers with severe airflow obstruction do not recognize or report respiratory symptoms to a physician. However, these prevalence data also show that more than 90% of patients with undetected airflow obstruction have FEV_1 50% of predicted or greater. This information is important because the efficacy of COPD pharmacologic treatments has been established only in symptomatic patients with FEV_1 less than 50% of predicted.

Pharmacologic treatments for COPD have been demonstrated to reduce the absolute risk for 1 or more COPD exacerbations by 4% to 6% in pooled analyses. Although a recent RCT suggested that these treatments also reduce mortality to a smaller degree, that trial was conducted in a sample of symptomatic patients, most of whom had already experienced exacerbations and would have received a diagnosis clinically rather than with screening. No studies to date permit an estimate of the incremental mortality benefit from treating patients who would not have received a diagnosis clinically.

The hypothesis that knowing one's spirometry results might provide extra motivation for a smoker to quit has not been tested adequately. Previous trials have not assessed the independent effect of spirometry as part of a comprehensive smoking cessation program that includes proven pharmacologic therapies. However, data suggest that even if spirometry provides an incremental benefit over other cessation strategies, the benefit is likely to be small.

Individuals with mild to moderate airflow obstruction may benefit from receiving an annual influenza vaccine, although how much of the overall reduction in COPD exacerbations applies to this subgroup is uncertain. The incremental benefit is likely to be small because most patients with COPD are older than 50 years of age and would already be targeted to receive the vaccine.

These potential benefits must be weighed against potential harms. Although studies conducted in pulmonary function laboratories have demonstrated little risk of spirometry causing physical harm, widespread screening of adult smokers (most of whom do not have airflow obstruction) is likely to produce some false-positive results. Pharmacotherapy is commonly associated with minor adverse effects and, rarely, with major events.

In conclusion, screening for COPD using spirometry is likely to identify a predominance of patients with mild to moderate airflow obstruction who would not experience additional health benefits if labeled as having COPD. A few individuals with severe airflow obstruction (FEV_1 <50% of predicted) might benefit from pharmacologic treatments that reduce exacerbations. Hundreds of patients would need to have screening spirometry to identify 1 person with COPD whose incremental health benefit over clinical diagnosis would probably be limited to the avoidance of a first exacerbation.

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Appendix: Details of Supplemental Literature Searches

Key Question 1

We searched PubMed to identify English-language RCTs or meta-analyses published from 1966 through December 2006, using combinations of the Medical Subject Heading (MeSH) terms *pulmonary disease/chronic obstructive*, *spirometry*, *smoking*, and *mass screening*. Articles were eligible for inclusion if they had a randomized or quasi-randomized study design, compared a screened sample with an unscreened sample, and included morbidity and/or mortality outcomes. The literature search returned 1 abstract, which was excluded because it was a study of lung cancer screening with computed tomography rather than COPD screening with spirometry.

Key Question 3

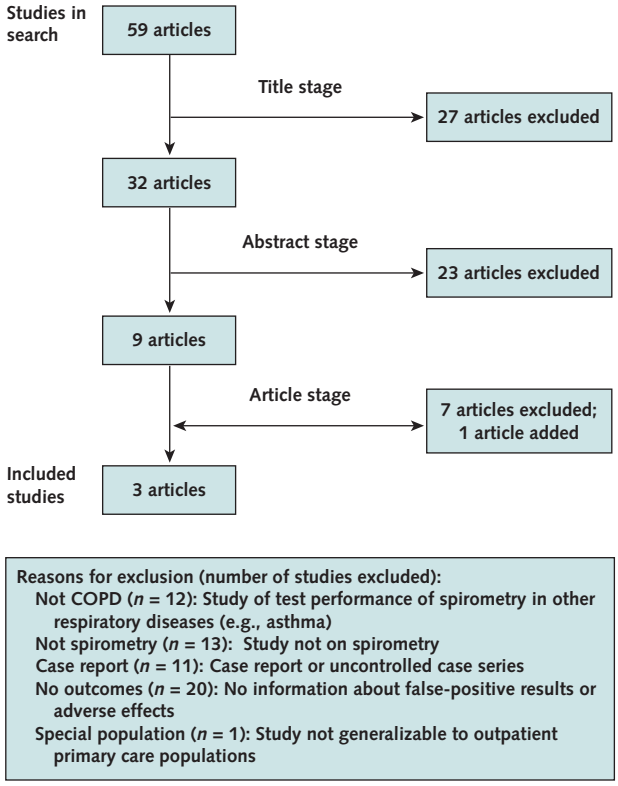
We searched OVID MEDLINE to identify English-language studies published from 1966 through December 2006, using combinations of the MeSH terms *spirometry*, *diagnostic errors*, and *adverse effects*. We considered studies of spirometry regardless of whether the testing was performed in a pulmonary function laboratory or in an office setting. We excluded articles that were narrative reviews, letters, or editorials; included only a sample that did not have COPD (for example, children with cystic fibrosis); or did not address harms or test characteristics of spirometry. We also excluded isolated case reports documenting spirometry-induced pneumomediastinum, bronchial obstruction, or incarcerated inguinal hernia.

We had determined a priori to exclude articles that compared the diagnostic accuracy of spirometry performed in primary care settings with that performed in referral settings (with referral settings serving as the "gold standard"). No articles of this type were retrieved by the search.

Two reviewers independently reviewed the title lists, abstracts, and full articles. Disagreements were resolved by consensus.

The initial literature search retrieved 59 articles, which were entered into an EndNote database (Thomson ResearchSoft, Philadelphia, Pennsylvania). We excluded 27 articles at the title stage; after a review of the remaining abstracts, we excluded 23 additional articles. The remaining 9 articles were obtained for full-text review; 7 more articles were excluded at this stage. One article was identified from reviewing the reference list from an excluded article, leaving 3 articles included in this review. **Appendix Figure 1** shows the flow of the literature search.

Appendix Figure 1. **Study flow diagram: key question 3.**



COPD = chronic obstructive pulmonary disease.

Key Question 4

We searched PubMed for systematic reviews and RCTs of spirometry as a motivational tool for smoking cessation published in 2005 and 2006, using a search strategy identical to that of the 2005 AHRQ report (2). We excluded studies that had follow-up less than 6 months or had fewer than 25 participants per treatment group or if the control group received spirometric results. Two reviewers independently reviewed the title lists, abstracts, and full articles. Disagreements were resolved by consensus.

The initial literature search returned 42 articles, which were entered into an EndNote database. We excluded 36 articles at the title or abstract stage; the remaining 6 articles were obtained for full-text review. We excluded 3 more articles at this stage. One of the remaining 3 articles was the 2005 AHRQ report (5); the other 2 articles are included in this review. **Appendix Figure 2** shows the flow of the literature search.

Key Question 6

We searched PubMed to identify English-language systematic reviews of adverse effects of COPD medications published from January 1997 through January 2007, using the MeSH terms *pulmonary disease* and *chronic obstructive/drug therapy*, and combinations of MeSH terms and text words representing adverse effects noted in the RCTs of therapy included in Wilt and colleagues' 2007 systematic review (5). Two reviewers reviewed the titles. Studies were excluded if they were not systematic re-

views; discussed medications other than β-agonists, anticholinergics, or inhaled corticosteroids; were older versions of the same publication (such as Cochrane reviews); or had no relevant outcomes.

The initial literature search returned 50 articles, which were entered into an EndNote database. We excluded 38 articles at the title stage. Two reviewers independently reviewed the full text of the remaining 12 articles, all of which met inclusion criteria for this review. **Appendix Figure 3** shows the flow of the literature search.

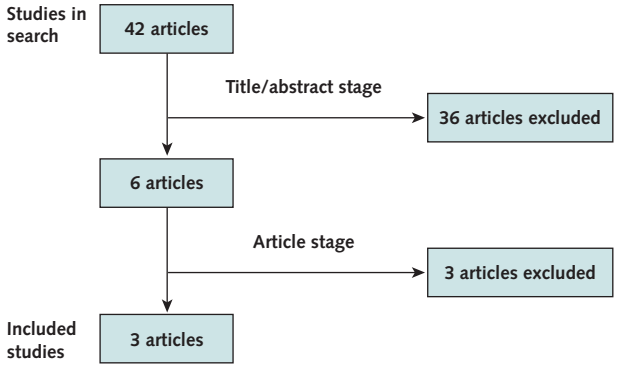
Key Question 7

We searched the Cochrane Database of Systematic Reviews for completed reviews of the benefits of influenza and pneumococcal vaccinations in patients with COPD. One review on each vaccination was identified and included in the review.

Key Question 8

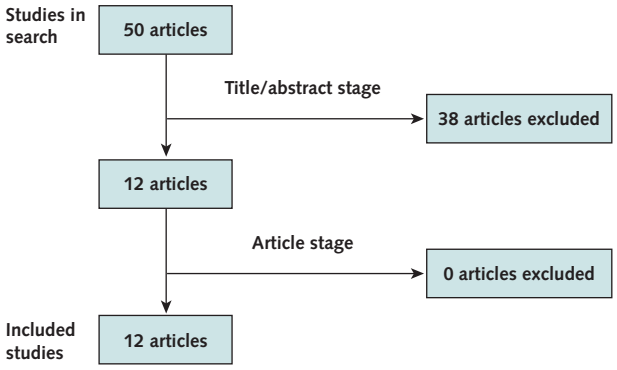
We searched PubMed to identify English-language systematic reviews published from January 1997 through January 2007, using combinations of the MeSH terms and text words *pneumococcal vaccine*, *influenza vaccine*, *adverse effects*, *harms*, and *safety*. The initial literature search returned 3 articles. Two of these articles had already been retrieved for key question 7, and the third article was a previous version of 1 of these articles.

Appendix Figure 2. **Study flow diagram: key question 4.**



Reasons for exclusion (number of studies excluded):
- Study design (*n* = 39): Narrative review or study design not meeting inclusion criteria
- No outcomes: No information on smoking cessation outcomes
- Not spirometry: Spirometry not a component of smoking cessation intervention

Appendix Figure 3. **Study flow diagram: key question 6.**



Reasons for exclusion (number of studies excluded):
- Wrong drug (*n* = 21): Study of a medication not meeting inclusion criteria
- Not chronic disease (*n* = 6): Therapy for acute exacerbations rather than chronic disease
- Study design (*n* = 11): Not a systematic review

Appendix Table 1. **U.S. Preventive Services Task Force Hierarchy of Research Design and Quality Rating Criteria***

Hierarchy of research design

I: Properly conducted RCT
II-1: Well-designed controlled trial without randomization
II-2: Well-designed cohort or case–control analytic study
II-3: Multiple time series with or without the intervention; dramatic results from uncontrolled experiments
III: Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees

Design-specific criteria and quality category definitions

Systematic reviews
- Criteria
  - Comprehensiveness of sources considered/search strategy used
  - Standard appraisal of included studies
  - Validity of conclusions
  - Recency and relevance are especially important for systematic reviews
- Definition of ratings based on above criteria
  - Good: Recent, relevant review with comprehensive sources and search strategies; explicit and relevant selection criteria; standard appraisal of included studies; and valid conclusions
  - Fair: Recent, relevant review that is not clearly biased but lacks comprehensive sources and search strategies
  - Poor: Outdated, irrelevant, or biased review without systematic search for studies, explicit selection criteria, or standard appraisal of studies

Case–control studies
- Criteria
  - Accurate ascertainment of cases
  - Nonbiased selection of cases/controls, with exclusion criteria applied equally to both
  - Response rate
  - Diagnostic testing procedures applied equally to each group
  - Measurement of exposure accurate and applied equally to each group
  - Appropriate attention to potential confounding variables
- Definition of ratings based on above criteria
  - Good: Appropriate ascertainment of cases and nonbiased selection of case and control participants; exclusion criteria applied equally to cases and controls; response rate ≥80%; diagnostic procedures and measurements accurate and applied equally to cases and controls; and appropriate attention to confounding variables
  - Fair: Recent, relevant, without major apparent selection or diagnostic work-up bias but with response rates <80% or attention to some but not all important confounding variables
  - Poor: Major section or diagnostic work-up biases, response rates <50%, or inattention to confounding variables

RCTs and cohort studies
- Criteria
  - Initial assembly of comparable groups
    - For RCTs: Adequate randomization, including first concealment and whether potential confounders were distributed equally among groups
    - For cohort studies: Consideration of potential confounders with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
  - Maintenance of comparable groups (includes attrition, crossovers, adherence, contamination)
  - Important differential loss to follow-up or overall high loss to follow-up
  - Measurements: equal, reliable, and valid (includes masking of outcome assessment)
  - Clear definition of the interventions
  - All important outcomes considered
- Definition of ratings based on above criteria
  - Good: Evaluates relevant available screening tests; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (>100) of broad-spectrum patients
  - Fair: Evaluates relevant available screening tests; uses reasonable although not best standard; interprets reference standard independently of screening test; moderate sample size (50–100 participants) and a "medium" spectrum of patients
  - Poor: Has fatal flaw, such as uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size or very narrow selected spectrum of patients

Diagnostic accuracy studies
- Criteria
  - Screening test relevant, available for primary care, adequately described
  - Study uses a credible reference standard, performed regardless of test results
  - Reference standard interpreted independently of screening test
  - Handles indeterminate result in a reasonable manner
  - Spectrum of patients included in study
  - Sample size
  - Administration of reliable screening test
- Definition of ratings based on above criteria
  - Good: Evaluates relevant available screening test; uses a credible reference standard; interprets reference standard independently of screening test; reliability of test assessed; has few or handles indeterminate results in a reasonable manner; includes large number (>100) of broad-spectrum patients with and without disease
  - Fair: Evaluates relevant available screening test; uses reasonable although not best standard; interprets reference standard independently of screening test; moderate sample size (50–100 participants) and a "medium" spectrum of patients
  - Poor: Has fatal flaw, such as uses inappropriate reference standard; screening test improperly administered; biased ascertainment of reference standard; very small sample size or very narrow selected spectrum of patients

* From Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, et al. Current methods of the U.S. Preventive Services Task Force: a review of the process. Am J Prev Med. 2001;20:21–35. [PMID: 11306229] RCT = randomized, controlled trial.

Appendix Table 2. **Systematic Literature Reviews on Adverse Effects of Pharmacologic Therapies for Chronic Obstructive Pulmonary Disease***

Study	COPD Drug Class	Selected Studies	Literature Search Method: Search Strategy, Inclusion Criteria	Outcomes of Interest	Results	Sponsor
Sestini et al., 2002 (25)	β_2-Agonist: short-acting	13 RCTs Crossover High quality	Cochrane Airways Group, reference list from review articles and RCTs; no language restriction RCTs on inhaled short-acting β_2-agonist treatment compared with placebo, with 1-wk minimum treatment duration in patients with stable COPD	Symptoms, QOL, lung function, patient preference, adverse effects, study withdrawals, mortality, exercise capacity, sick-days	No adverse events reliably noted; may be because of insufficient data, small sample size, or short duration of studies. No data reported on hospital admissions or mortality. FEV_1 and FVC are significantly higher with use compared with placebo. Postbronchodilator morning and evening PEFR are significantly increased with use compared with placebo. Patients preferred β_2-agonists 10 times more than placebo. Sparse trials and nonuniform methods of measurement gave variable results for symptoms, QOL, and exercise capacity.	None noted
Ferguson et al., 2003 (26)	β_2-Agonist: salmeterol	7 RCTs Pooled analysis	Trials selected by availability of individual patient data; sponsorship by GSK; randomized, double-blind, parallel-group, multiple-dose studies; and salmeterol, 50 μg bid in arm via MDI, to patients with COPD diagnosis	Incidence of CV adverse events†	No significant difference of incidence for CV adverse events (RR, 1.03 [95% CI, 0.8–1.3]; $P = 0.796$), or time to first CV adverse event ($P = 0.944$) between salmeterol, 50 μg bid, and placebo among patients with COPD. Significant interaction with age: increasing incidence of CV adverse events with age ($P = 0.027$).	GSK Research & Development
Salpeter et al., 2004 (24)	β_2-Agonist	33 RCTs: 13 single-dose trials, 20 of longer duration (3–365 d) Meta-analysis Quality: 15 longer-duration trials were parallel-group trials; all single-dose and 5 longer-duration trials were crossover trials	EMBASE, MEDLINE, CINAHL, scanned references of identified articles and reviews; published 1966–June 2003; no language restriction RCTs on β_2-agonist use in asthma or COPD that allowed open-label "rescue" β_2-agonist use in both treatment groups, providing extractable data on heart rate or potassium concentrations or reporting ≥1 adverse CV event	Short-term effects on heart rate and potassium concentration Long-term CV adverse events‡	Short-term use (single dose) increased heart rate by 9.12 beats/min (CI, 5.32–12.92 beats/min) and reduced potassium concentration by 0.36 mmol/L (CI, 0.18–0.54 mmol/L) compared with placebo. Long-term use significantly increased CV adverse event risk (RR, 2.54 [CI, 1.59–4.09]; $P < 0.001$) compared with placebo and significantly increased sinus tachycardia (RR, 3.06 [CI, 1.7–5.5]). All other CV events showed no statistical difference (RR, 1.66 [CI, 0.76–3.6]).	None noted
Salpeter, 2004 (23)	β_2-Agonist	8 case–control studies by systematic review 33 RCTs by meta-analysis (see detail in previous row: Salpeter et al., 2004 [24])	EMBASE, MEDLINE, CINAHL, scanned references of identified articles and reviews; published 1966–June 2003; no language restriction RCTs and case–control studies on CV safety of β_2-agonist use in asthma or COPD	CV adverse events†	Case–control: Use associated with increased CV adverse effects, degree of risk may be dose-dependent. Two studies demonstrated increased risk for MI: One found it higher among new users and those with concomitant cardiac conditions; the other found significantly higher risk for hospitalization with unstable angina or MI with inhaled β_2-agonist use over 3 mo. A third study found no significant association with short-acting β_2-agonist use and risk for MI. Three studies found increased risk for heart failure or cardiomyopathy. Finally, 2 studies showed higher risks for cardiac arrest and acute cardiac death with nebulized and oral treatment vs. MDI. RCT: β_2-Agonist use increases CV adverse effects >2-fold when compared with placebo (see details in previous row: Salpeter et al., 2004 [24]).	None noted
Salpeter et al., 2006 (27)	β_2-Agonist: albuterol, metaproterenol, formoterol, salmeterol Anticholinergic: ipratropium, tiotropium	22 RCTs Pooled analysis Quality: No study received the lowest quality score on the 4 measurements (randomization and allocation concealment, double-blinding, withdrawals, and intention-to-treat analysis)	EMBASE, MEDLINE, Cochrane, scanned relevant articles from FDA Web site and references of identified reviews; published 1966–December 2005; no language restriction RCTs on β_2-agonist or anticholinergic use in COPD compared with placebo, 3-mo minimum duration, reporting ≥1 COPD exacerbation leading to study withdrawal, hospitalization, or respiratory death	Safety and efficacy; RR for exacerbations leading to study withdrawal, hospitalization, or respiratory death	Anticholinergics, compared with placebo, decreased study withdrawals (RR, 0.60 [CI, 0.48–0.75]), hospitalizations (RR, 0.67 [CI, 0.53–0.86]), and respiratory deaths (RR, 0.27 [CI, 0.09–0.81]); NNT = 25. β_2-Agonists, compared with placebo, decreased withdrawal (RR, 0.81 [CI, 0.68–0.95]) and had no significant effect on hospitalization (RR, 1.08 [CI, 0.61–1.95]) but significantly increased respiratory deaths (RR, 2.47 [CI, 1.12–5.45]); NNH = 131. (Note: 57% of participants had concomitant inhaled corticosteroid use.) β_2-Agonist, compared with anticholinergics, increased withdrawals (RR, 2.02 [CI, 1.39–2.93]) and hospitalizations (RR, 1.95 [CI, 1.06–3.59]). There was a nonsignificant upward trend toward respiratory deaths associated with β_2-agonist compared with anticholinergics (RR, 6.91 [CI, 0.85–55.97]; $P = 0.07$).	None noted
Barr et al., 2005 (30)	Anticholinergic: tiotropium	12 RCTs; 6584 patients (3 trials reported combined results of separate pairs of trials) Quality: Concealment of allocation not described in 9 trials; adequately described in 3 trials By the Jadad criteria, trials scored between 3 and 5 on a 5-point scale	Cochrane Airways Group, Cochrane Central Register of Controlled Trials, LILACS, hand searches of 20 respiratory journals and conference abstracts, requests for unpublished studies from tiotropium manufacturer and identified RCT authors, and search of bibliographies for included trials and reviews; no language restriction RCTs comparing tiotropium with placebo, ipratropium, or long-acting β_2-agonist in patients with stable COPD, for ≥1 mo	Exacerbations, hospitalization, all-cause mortality, symptom scales, pulmonary function, anticholinergic adverse events§	Tiotropium reduced exacerbations (OR, 0.74; $P = 0.85$; NNT = 14) and hospitalizations (OR, 0.64; $P = 0.83$; NNT = 30) compared with placebo or ipratropium. No significant difference in all-cause mortality when tiotropium was compared with placebo, ipratropium, or salmeterol. Significant increase in dry mouth compared with placebo (OR, 5.4 [CI, 3.3–8.8]), ipratropium (OR, 2.1 [CI, 1.05–4.2]), or salmeterol (OR, 5.1 [CI, 2.2–12]). Tiotropium improved QOL and symptom scores and may slow decline of FEV_1.	NIH grant
Barr et al., 2006 (29)	Anticholinergic: tiotropium	9 RCTs; 8002 patients Meta-analysis Quality: Concealment of allocation was described in 1 study By the Jadad criteria, trials scored between 3 and 5 on a 5-point scale	Cochrane Airways Group, hand searches of 20 respiratory journals and conference abstracts, requests for unpublished trials from tiotropium manufacturer and RCT authors, and search of reference lists for included trials and reviews; no language restriction RCTs comparing tiotropium with placebo, ipratropium, or long-acting β_2-agonist in patients with stable COPD, for ≥3 mo	Exacerbations, hospitalizations, all-cause mortality, symptom scales, pulmonary function, anticholinergic adverse events§	Tiotropium significantly decreases COPD exacerbation (OR, 0.73 [CI, 0.66–0.81]; NNT = 13) and hospitalizations (OR, 0.68 [CI, 0.54–0.84]; NNT = 38) compared with placebo and ipratropium. No significant differences noted in CV (OR, 1.17 [CI, 0.54–2.51], pulmonary (OR, 0.50 [CI, 0.19–1.29]), and all-cause mortality (OR, 0.38 [CI, 0.09–1.66]) for the same comparison. No significant differences noted in exacerbation (OR, 0.86 [CI, 0.67–1.11]) and hospitalization (OR, 0.54 [CI, 0.29–1.01]) when tiotropium is compared with salmeterol. Tiotropium improved QOL and symptom scores and may slow decline of FEV_1. Dry mouth is significantly increased with use compared with placebo (OR, 4.6 [CI, 3.0–7.1]), ipratropium (OR, 2.1 [CI, 1.05–4.2]), and salmeterol (OR, 4.7 [CI, 2.4–9.2]); summary estimate OR, 3.9 (CI, 2.8–5.5). Urinary tract infections are significantly increased with use compared with placebo (OR, 1.6 [CI, 0.97–2.6]) and ipratropium (OR, 1.8 [CI, 0.97–2.6]); summary estimate OR, 1.6 (CI, 1.03–2.6). Urinary retention and constipation were consistently found but were not statistically significant. The significant heterogeneity of arrhythmia and AF events could not provide a reliable summary estimate.	NIH grants
Kesten et al., 2006 (28)	Anticholinergic: tiotropium	19 RCTs; 7819 patients (mean age, 64 y) Pooled analysis	No published trials met inclusion criteria: Completed trials of 18-g/d tiotropium, placebo-controlled, parallel-group RCTs on tiotropium use in obstructive lung disease in the HandiHaler (Boehringer Ingelheim) project database as of May 2004	Incidence rates and RR for all adverse events	There are significantly increased risks for dry mouth (RR, 3.60 [CI, 2.56–5.05]) and urinary retention (RR, 10.93 [CI, 1.26–94.88]) with tiotropium use compared with placebo, whereas risks are significantly decreased for dyspnea (RR, 0.64 [CI, 0.50–0.81]), COPD exacerbation (RR, 0.72 [CI, 0.64–0.82]), and pneumonia (RR, 0.64 [CI, 0.42–0.98]). No significant difference noted in incidence of CV mortality (RR, 0.57 [CI, 0.26–1.26]), cardiac arrest (RR, 0.90 [CI, 0.26–3.15]), or MI (RR, 0.74 [CI, 0.26–2.07]). Increased risk noted for any tachycardia (RR, 1.68 [CI, 0.69–4.10]). Risk for dysrhythmias, other than VT, VF, and AF, were increased (RR, 2.71 [CI, 1.10–6.65]) with tiotropium use compared with placebo, although no excess of dysrhythmias was classified as serious. No significant differences noted in respiratory mortality (RR, 0.71 [CI, 0.29–1.74]), CV mortality (RR, 0.57 [CI, 0.26–1.26]), and all-cause mortality (RR, 0.76 [CI, 0.50–1.16]) when tiotropium was compared with placebo.	Boehringer Ingelheim Pharmaceutical (Ridgefield, CT)

Continued on following page

Appendix Table 2—**Continued**

Study	COPD Drug Class	Selected Studies	Literature Search Method: Search Strategy, Inclusion Criteria	Outcomes of Interest	Results	Sponsor
Alsaeedi et al., 2002 (31)	Corticosteroid	9 RCTs; 3976 patients Quality: By the Jadad criteria, 6 trials scored between 3 and 5 on a 5-point scale	EMBASE, MEDLINE, CINAHL, SIGLE, Cochrane Central Register of Controlled Trials, reference lists of identified trials, and request for unpublished trials from content experts; restricted to human participants, no language restrictions RCTs of inhaled corticosteroids for at least 6 mo in stable COPD	Long-term effects of inhaled corticosteroid on COPD; RRs for rate of decline in FEV_1, exacerbation, and all-cause mortality	Pulmonary function tests results varied among the trials. Inhaled corticosteroid use reduced exacerbations (RR, 0.70 [CI, 0.58–0.84]) compared with placebo. There was no significant difference in all-cause mortality (RR, 0.84 [CI, 0.60–1.18]) associated with use compared with placebo. Adverse events included significantly increased risk for oropharyngeal candidiasis (RR, 2.1 [CI, 1.5–3.1]) and skin bruising (RR, 2.1 [CI, 1.6–2.8]) for inhaled corticosteroid use compared with placebo. There were variable effects on BMD. Trials were short, leading to inadequate follow-up time and evidence on BMD, fractures, cataracts, and adrenal insufficiency.	None noted
Halpern et al., 2004 (33)	Corticosteroid	14 studies; prospective cohort and randomized trials Meta-analysis, random effects Quality: Unpublished study not rated Others rated according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001): 4 studies rated 1b (individual RCT [with narrow CI]) and 9 studies rated 2b (individual cohort study [including low-quality RCT]; e.g., <80% follow-up)	EMBASE, MEDLINE, reference lists from product literature, and unpublished studies from pharmaceutical companies that produce the drug; language restricted to English, French, Spanish, Italian, German, Russian, or Polish Studies using ≥1 inhaled corticosteroid, providing inclusion/exclusion criteria for participants, presented adult data separately from pediatric patients or adults only, 12-mo minimum duration, defined treatment protocol, presented primary results, included ≥1 desired outcome measures	BMD	Long-term use of inhaled corticosteroid is not significantly associated with changes in BMD of the lumbar spine (mean, −0.23% [CI, −1.84% to 1.38%]), femoral neck (mean, −0.17% [CI, −1.88% to 1.54%]), or trochanter major (mean, 1.46% [CI, −3.26% to 6.19%]). There are no significant differences in lumbar BMD among asthmatics (mean, 0.13% [CI, −2.60% to 2.86%]) and patients with COPD (mean, −0.42% [CI, −2.41% to 1.58%]). No significant differences were found for lumbar BMD among patients treated with fluticasone propionate (mean, −0.20% [CI, −2.74% to 2.33%]), beclomethasone dipropionate (mean, −0.73% [CI, −3.01% to 1.54%]), or budesonide (mean, −0.39% [CI, −3.46% to 2.69%]).	None noted
Sin et al., 2005 (16)	Corticosteroid	7 RCTs; 5085 patients Pooled analysis, based on intention-to-treat analysis	The Inhaled Steroid Effects Evaluation in COPD study: randomized trials on effects of inhaled corticosteroid vs. placebo for at least 12 mo in patients with stable COPD	Effect on all-cause mortality	Inhaled corticosteroid use reduces risk for mortality significantly compared with placebo (adjusted HR, 0.73 [CI, 0.55–0.96]). Patients with GOLD stages III and IV disease showed a significantly reduced mortality with inhaled corticosteroids (HR, 0.66 [CI, 0.45–0.96]). Subgroup analysis found women (adjusted HR, 0.46 [CI, 0.24–0.91]), former smokers (adjusted HR, 0.60 [CI, 0.39–0.93]), and people with baseline postbronchodilator FEV_1 <60% (adjusted HR, 0.67 [CI, 0.48–0.94]) had increased beneficial effect, although not statistically significant.	None noted
Gartlehner et al., 2006 (32)	Corticosteroid	13 RCTs, 11 observational studies Meta-analysis; fixed effects Quality: Most studies given a rating of "fair," according to the USPSTF criteria	EMBASE, MEDLINE, Cochrane Library, International Pharmaceutical Abstracts, reference lists of identified studies and request for unpublished studies from content experts; restricted to human studies, English language, and 1970–2005 RCTs, 6-mo minimum duration and outpatient sample, for efficacy of corticosteroids in obstructive airway disease; observational studies, 12-mo minimum duration with >100 patients, were added for safety assessment	Overall mortality, exacerbations, QOL, functional capacity, and symptoms	No significant difference in all-cause mortality (RR, 0.81 [CI, 0.60–1.08]) was associated with inhaled corticosteroid use compared with placebo. Risk for exacerbation was significantly reduced (RR, 0.67 [CI, 0.59–0.77]). NNT for 17.7 months in patients with moderate or severe COPD is 12. Heterogeneous results are seen for QOL, functional capacity, and symptoms. Adverse events: The short duration and small sample sizes of RCTs limited validity of adverse events analysis. Observational studies showed mixed results for inhaled corticosteroids' effects on BMD; however, 2 case studies showed an increased risk for fractures. A COPD subgroup analysis of a case–control study found increased risk for cataracts with longer duration of use (adjusted OR, 1.03 [CI, 0.94–1.13]). The risk for open-angle glaucoma increased in a case–control study and a cross-sectional study, with associated dose-related increase.	None noted

* AF = atrial fibrillation; bid = twice daily; BMD = bone mineral density; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; FDA = U.S. Food and Drug Administration; GOLD = Global Initiative for Chronic Obstructive Lung Disease; GSK = GlaxoSmithKline; HR = hazard ratio; MDI = metered-dose inhaler; MI = myocardial infarction; NIH = National Institutes of Health; NNH = number needed to harm; NNT = number needed to treat; OR = odds ratio; PEFR = peak expiratory flow rate; QOL = quality of life; RCT = randomized, controlled trial; RR = relative risk; USPSTF = U.S. Preventive Services Task Force; VF = ventricular fibrillation; VT = ventricular tachycardia.
† May include hypertension, angina pectoris, palpitations, tachyarrhythmias, tachycardia, syncope, cardiac failure, MI, coronary artery disorders, thrombosis.
‡ May include sinus tachycardia and VT, syncope, AF, congestive heart failure, MI, cardiac arrest, and sudden death.
§ Palpitations, dry mouth, blurred vision, urinary tract obstruction, and constipation.

Appendix Table 3. **Adverse Effects of Pharmacologic Treatments for Chronic Obstructive Pulmonary Disease***

COPD Drug Class	Adverse Effect: Detail	Mortality Effect	Comment
β_2-Agonists			
Short-acting inhaled (albuterol or salbutamol, isoproterenol, terbutaline)	None: No adverse events reliably noted—may be because of insufficient data, small size, or short duration of RCTs (25). A case–control study found no significant association with short-acting β_2-agonist use and risk for MI (24).	No data.	
Long-acting inhaled (salmeterol, formoterol)	Increased heart rate: Short-term use (single dose) increased heart rate by 9 beats/min (95% CI, 5.32–12.92 beats/min) compared with placebo (23). Reduced potassium: Short-term use reduced potassium concentration by 0.36 mmol/L (CI, 0.18–0.54 mmol/L) compared with placebo (24). CV events†: Long-term use increased CV adverse event risk (RR, 2.54 [CI, 1.59–4.09]) compared with placebo and increased sinus tachycardia (RR, 3.06 [CI, 1.7–5.5]). All other CV events showed no statistical difference (RR, 1.66 [CI, 0.76–3.6]) (24). No significant difference in incidence for CV adverse events (RR, 1.03 [CI, 0.8–1.3]; $P = 0.796$), or time to first CV adverse event ($P = 0.944$) between salmeterol and placebo in patients with COPD. Incidence of CV adverse events increased with age ($P = 0.027$) (26). In case–control studies, inhaled β_2-agonist use was associated with increased CV adverse effects. Two studies demonstrated increased risk for MI: One found it higher among new users and those with concomitant cardiac conditions, and the other found significantly higher risk for hospitalization with unstable angina or MI with inhaled β_2-agonist use over 3 mo. Three additional case–control studies found increased risk for heart failure or cardiomyopathy (24).	β_2-Agonists, compared with placebo, had significantly increased respiratory deaths (RR, 2.47 [CI, 1.12–5.45]); NNH = 131 (27). β_2-Agonists, compared with anticholinergics, had a nonsignificant upward trend toward respiratory deaths (RR, 6.91 [CI, 0.85–55.97]; $P = 0.07$) (27). 2 case–control studies showed higher risks for cardiac arrest and acute cardiac death with nebulized and oral treatment vs. metered-dose inhaler (23).	–
Anticholinergics			
Inhaled (tiotropium, ipratropium)	Dry mouth: Significant increase in dry mouth when tiotropium was compared with placebo (OR, 5.4 [CI, 3.3–8.8]), ipratropium (OR, 2.1 [CI, 1.05–4.2]), or salmeterol (OR, 5.1 [CI, 2.2–12]) (30). Dry mouth was increased with tiotropium compared with placebo (OR, 4.6 [CI, 3.0–7.1]), ipratropium (OR, 2.1 [CI, 1.05–4.2]), and salmeterol (OR, 4.7 [CI, 2.4–9.2]); summary estimate OR, 3.9 (CI, 2.8–5.5) (29). Risks for dry mouth (RR, 3.60 [CI, 2.56–5.05]) were significantly increased with tiotropium use compared with placebo (28). Urinary retention and constipation: Increased risk for urinary retention (RR, 10.93 [CI, 1.26–94.88]) with tiotropium compared with placebo (28). Urinary retention (OR, 2.6 [CI, 0.6–12]) and constipation (OR, 1.7 [CI, 0.8–3.7]) were consistently found, but not statistically significant (29). Urinary tract infections were significantly increased with tiotropium use compared with placebo (OR, 1.6 [CI, 0.97–2.6]) and ipratropium (OR, 1.8 [CI, 0.97–2.6]); summary estimate OR, 1.6 (CI, 1.03–2.6) (29). CV events: No reliable summary estimate of arrhythmias because of significant heterogeneity of data (29). No significant difference in incidence of cardiac arrest (RR, 0.90 [CI, 0.26–3.15]) or MI (RR, 0.74 [CI, 0.26–2.07]). Increased risk for any tachycardia (RR, 1.68 [CI, 0.69–4.1]). Risk for dysrhythmias, other than VT, VF, and AF, was increased (RR, 2.71 [CI, 1.10–6.65]) with tiotropium use compared with placebo, although no excess of dysrhythmias was classified as serious (28).	Anticholinergics, compared with placebo, decreased respiratory deaths (RR, 0.27 [CI, 0.09–0.81]); NNT = 25 (27). No significant difference in all-cause mortality when tiotropium was compared with placebo, ipratropium, or salmeterol (30). No significance differences in CV, pulmonary, and all-cause mortality when tiotropium was compared with placebo and ipratropium (28, 29).	–
Corticosteroids			
Inhaled (flunisolide, triamcinolone acetate, budesonide, fluticasone propionate, beclomethasone dipropionate)	Oropharyngeal candidiasis: Significantly increased risk for oropharyngeal candidiasis (RR, 2.1 [CI, 1.5–3.1]) compared with placebo (31). Skin bruising: Significantly increased risk for skin bruising (RR, 2.1 [CI, 1.6–2.8]) compared with placebo (31). BMD: Long-term use of inhaled corticosteroids was not significantly associated with changes in BMD of the lumbar spine (mean, −0.23% [CI, −1.84% to 1.38%]), femoral neck (mean, −0.17% [CI, −1.88% to 1.54%]), or trochanter major (mean, 1.46% [CI, −3.26% to 6.19%]). No significant differences were found for lumbar BMD among patients treated with fluticasone propionate, beclomethasone dipropionate, and budesonide (33). Observational studies showed mixed results for inhaled corticosteroids' effects on BMD (32). Fractures: Case–control studies showed an increased risk for fractures (32). Open-angle glaucoma: Risk for open-angle glaucoma was increased in 1 case–control study and 1 cross-sectional study, with associated dose-related increase (32). Cataracts: A COPD subgroup analysis of a case–control study found an increased risk for cataracts with longer duration of use (adjusted OR, 1.03 [CI, 0.94–1.13]) (32).	No significant difference in all-cause mortality associated with use compared with placebo (31, 32). Significantly reduced risk for death compared with placebo (adjusted HR, 0.73 [CI, 0.55–0.96]), especially in patients with GOLD stages III and IV disease (HR, 0.66 [CI, 0.45–0.96]) (16).	The short duration and small sample sizes of RCTs led to inadequate data to document valid differences in BMD, fractures, cataracts, and adrenal insufficiency (31, 32).

* AF = atrial fibrillation; BMD = bone mineral density; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HR = hazard ratio; MI = myocardial infarction; NNH = number needed to harm; NNT = number needed to treat; OR = odds ratio; RCT = randomized, controlled trial; RR = relative risk; VF = ventricular fibrillation; VT = ventricular tachycardia.
† Hypertension, angina pectoris, palpitations, AF, tachyarrhythmia, sinus tachycardia and VT, syncope, cardiac failure, MI, coronary artery disorders, thrombosis, cardiac arrest, or sudden death.