

Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice Guideline Update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society

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Description: This guideline is an official statement of the American College of Physicians (ACP), American College of Chest Physicians (ACCP), American Thoracic Society (ATS), and European Respiratory Society (ERS). It represents an update of the 2007 ACP clinical practice guideline on diagnosis and management of stable chronic obstructive pulmonary disease (COPD) and is intended for clinicians who manage patients with COPD. This guideline addresses the value of history and physical examination for predicting airflow obstruction; the value of spirometry for screening or diagnosis of COPD; and COPD management strategies, specifically evaluation of various inhaled therapies (anticholinergics, long-acting β -agonists, and corticosteroids), pulmonary rehabilitation programs, and supplemental oxygen therapy.

Methods: This guideline is based on a targeted literature update from March 2007 to December 2009 to evaluate the evidence and update the 2007 ACP clinical practice guideline on diagnosis and management of stable COPD.

Recommendation 1: ACP, ACCP, ATS, and ERS recommend that spirometry should be obtained to diagnose airflow obstruction in patients with respiratory symptoms (Grade: strong recommendation, moderate-quality evidence). Spirometry should not be used to screen for airflow obstruction in individuals without respiratory symptoms (Grade: strong recommendation, moderate-quality evidence).

Recommendation 2: For stable COPD patients with respiratory symptoms and FEV₁ between 60% and 80% predicted, ACP, ACCP, ATS, and ERS suggest that treatment with inhaled bronchodilators may be used (Grade: weak recommendation, low-quality evidence).

Recommendation 3: For stable COPD patients with respiratory symptoms and FEV₁ <60% predicted, ACP, ACCP, ATS, and ERS recom-

mend treatment with inhaled bronchodilators (Grade: strong recommendation, moderate-quality evidence).

Recommendation 4: ACP, ACCP, ATS, and ERS recommend that clinicians prescribe monotherapy using either long-acting inhaled anticholinergics or long-acting inhaled β -agonists for symptomatic patients with COPD and FEV₁ <60% predicted. (Grade: strong recommendation, moderate-quality evidence). Clinicians should base the choice of specific monotherapy on patient preference, cost, and adverse effect profile.

Recommendation 5: ACP, ACCP, ATS, and ERS suggest that clinicians may administer combination inhaled therapies (long-acting inhaled anticholinergics, long-acting inhaled β -agonists, or inhaled corticosteroids) for symptomatic patients with stable COPD and FEV₁ <60% predicted (Grade: weak recommendation, moderate-quality evidence).

Recommendation 6: ACP, ACCP, ATS, and ERS recommend that clinicians should prescribe pulmonary rehabilitation for symptomatic patients with an FEV₁ <50% predicted (Grade: strong recommendation, moderate-quality evidence). Clinicians may consider pulmonary rehabilitation for symptomatic or exercise-limited patients with an FEV₁ >50% predicted. (Grade: weak recommendation, moderate-quality evidence).

Recommendation 7: ACP, ACCP, ATS, and ERS recommend that clinicians should prescribe continuous oxygen therapy in patients with COPD who have severe resting hypoxemia (PaO₂ \leq 55 mm Hg or SpO₂ \leq 88%) (Grade: strong recommendation, moderate-quality evidence).

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† Former Clinical Guidelines Committee member who was active during the development of this guideline.

Chronic obstructive pulmonary disease (COPD) is a slowly progressive disease involving the airways or pulmonary parenchyma (or both) that results in airflow obstruction. Manifestations of COPD range from dyspnea, poor exercise tolerance, chronic cough with or without sputum production, and wheezing to respiratory failure or cor pulmonale. Exacerbations of symptoms and concomitant chronic diseases may contribute to the severity of COPD in individual patients. A diagnosis of COPD is confirmed when a patient who has symptoms of COPD is found to have airflow obstruction (generally defined as a postbronchodilator FEV₁-FVC ratio less than 0.70, but taking into account that age-associated decreases in FEV₁-FVC ratio may lead to overdiagnosis in elderly persons) in the absence of an alternative explanation for the symptoms (for example, left ventricular failure or deconditioning) or the airflow obstruction (for example, asthma). Clinicians should be careful to avoid attributing symptoms to COPD when common comorbid conditions, such as heart failure, are associated with the same symptoms.

In the United States, COPD affects more than 5% of the adult population; it is the third leading cause of death and the 12th leading cause of morbidity (1–3). The total economic costs of COPD in the United States were estimated to be \$49.9 billion in 2010, and the total direct cost of medical care is approximately \$29.5 billion per year (4).

The purpose of this guideline is to update the 2007 American College of Physicians guideline on diagnosis and management of stable COPD (5) and present new evidence on the diagnosis and management of stable COPD. This guideline update was developed through a joint collaboration among 4 organizations: the American College of Physicians (ACP), American College of Chest Physicians (ACCP), American Thoracic Society (ATS), and European Respiratory Society (ERS). In this guideline, we rephrased and clarified our 2007 guideline recommendations. We also added recommendations on when to consider pharmacotherapy in patients with stable COPD, clarified how to select among various monotherapies, reaffirmed our 2007 recommendations on when to use spirometry, and expanded on our recommendation for pulmonary rehabilitation. We also added a recommendation for treatment of patients with respiratory symptoms and FEV₁ between 60% and 80% predicted.

The target audience for this guideline includes all clinicians caring for patients with COPD, and the target pa-

tient population is comprised of patients with stable COPD. For the purpose of this guideline, we use the terms *COPD* and *airflow obstruction*, where COPD is defined by both physiologic and clinical criteria and airflow obstruction is defined by spirometric findings alone. This guideline does not address all components of management of a patient with COPD and is limited to pharmacologic management, pulmonary rehabilitation, and oxygen therapy. It does not cover smoking cessation, surgical options, palliative care, end-of-life care, or nocturnal ventilation.

METHODS

The guideline panel included representatives from each of the 4 collaborating organizations, and the resulting guideline represents an official and joint clinical practice guideline from those organizations. The guideline panel communicated via conference calls and e-mails. The members reached agreement and resolved any disagreements through facilitated discussion. The final recommendations were approved by unanimous vote. The key questions and scope for the guideline were developed with input from the joint guideline panel. Evidence reviews and tables were presented to the guideline panel for review and comments. The guideline panel evaluated the recommendations on the basis of the evidence.

The key questions and scope of the guideline were developed with input from the joint guideline panel. These questions were:

1. What is the value of the history and physical examination for predicting airflow obstruction?
2. What is the value of spirometry for screening and diagnosis of adults who are asymptomatic and have risk factors for developing airflow obstruction, or who are COPD treatment candidates?
3. What management strategies are effective for treating COPD?
 - a. mono- and combination inhaled therapies (anticholinergics, long-acting β -agonists, or corticosteroids);
 - b. pulmonary rehabilitation programs; or
 - c. supplemental long-term oxygen therapy (evidence not updated).

The Minnesota Evidence-based Practice Center performed an updated literature search that included studies from MEDLINE published between March 2007 and December 2009. Additional background material reviewed by the guideline panel included the 2007 systematic evidence review by Wilt and colleagues (6) and the 2004 Agency for Healthcare Research and Quality–sponsored Minnesota Evidence-based Practice Center evidence report (7).

The literature search focused on evidence for the value of spirometry for screening or diagnosis of COPD; the efficacy and comparative effectiveness of management strategies, such as inhaled monotherapies (anticholinergics, long-acting β -agonists, or corticosteroids), combination therapies, and pulmonary rehabilitation programs, for pa-

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tients with COPD. For diagnostic accuracy of the physical examination and spirometry, we used an updated systematic review from 2008 (8), because the guideline panel agreed that there is no reason to suspect that diagnostic accuracy of the physical examination or spirometry would have changed since the ACP guideline was published in 2007 (5). In addition, we did not update the search for the utility of supplemental oxygen for patients with COPD who have awake, resting hypoxemia because widespread consensus remains on this issue. The patient outcomes that were considered were exacerbations, hospitalizations, mortality, health-related quality of life, and dyspnea.

This guideline rates the evidence and recommendations by using the ACP guideline grading system, which is based on the system developed by the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) workgroup (Table). Details of the ACP guideline development process are found in the ACP methods paper (9).

PREDICTION OF AIRFLOW OBSTRUCTION ON THE BASIS OF HISTORY AND PHYSICAL EXAMINATION

The evidence evaluated for the 2007 ACP guideline (5) showed that findings on physical examination had high specificity (>90%) but poor sensitivity for airflow obstruction. The literature showed that combinations of findings in the history and clinical examination were more helpful than a single finding for predicting the presence or absence of airflow obstruction (10–15). A 70–pack-year history of smoking is the best predictor of airflow obstruction. The best combination to rule out airflow obstruction was absence of a smoking history and no evidence of wheezing on either history or physical examination.

In our guideline update, we relied on a recent systematic review by Simel and Rennie (8) that updated the previously published evidence on clinical examination and airflow obstruction (16). This update indicated that the single best variable for identifying adults with airflow obstruction (typically defined as postbronchodilator FEV₁–FVC ratio <0.70, with severity category based on the results of postbronchodilator FEV₁ reported as a percent of the predicted value) is a history of greater than 40 pack-years of smoking (positive likelihood ratio [LR], 12 [95% CI, 2.7 to 50]). A combination of findings was more helpful for diagnosing airflow obstruction than was any individual sign, symptom, or piece of historical information. The combination of all 3 of the following items—patient-reported smoking history greater than 55 pack-years, wheezing on auscultation, and patient self-reported wheezing—almost assures the presence of airflow obstruction (LR, 156). In addition, the absence of all 3 items practically rules out airflow obstruction (LR, 0.02) (8, 17).

A physician's "overall clinical impression" has been evaluated in only 2 studies with a total of 13 physicians. Based on a standardized history and physical examination,

Table. The American College of Physicians' Guideline Grading System*

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced With Risks and Burden
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

* Adopted from the classification developed by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) workgroup.

the "overall clinical impression" was useful for diagnosing airflow obstruction in patients with moderate to severe disease (LR, 5.6 [CI, 3.1-10]) but was of limited value in ruling out airflow obstruction (LR, 0.59 [CI, 0.51-0.68]) (10, 17). However, the sparseness of the data makes any conclusion about the value of "overall clinical impression" premature.

USING SPIROMETRY TO SCREEN FOR AIRFLOW OBSTRUCTION OR DIAGNOSE COPD

Spirometry is a pulmonary function test that measures the presence and severity of airflow obstruction. In symptomatic patients, spirometry is helpful for determining whether the symptoms are due to respiratory disease or other conditions. Chronic obstructive pulmonary disease is diagnosed when spirometry demonstrates airflow obstruction that is not fully reversible. Although a single spirometric test done without bronchodilators is relatively inexpensive, the aggregate economic and public health costs associated with screening all adults with risk factors for COPD in the absence of respiratory symptoms are large. Follow-up visits, repeated office spirometry, full pulmonary function tests with bronchodilator testing, lung imaging, and drug prescriptions would follow initial primary care–office spirometry in many patients (18).

As reported in the 2007 ACP guideline, regardless of exposure to COPD risk factors, our evidence update found no evidence of benefit of using spirometry to screen adults who have no respiratory symptoms. What constitutes "asymptomatic" with respect to patients with airflow obstruction on spirometry is not precisely defined in the literature, although wheezing, shortness of breath, chronic cough, or limitations on exertion, when due to the respiratory system disease, in most cases would classify a patient as having symptomatic COPD. Clinicians should be alert, however, that some patients may deny limitation on exertion because they have knowingly or unknowingly restricted their activities to those that do not cause symp-

toms. Patients with very low daily activities may be symptomatic if they tried to engage in the activities normal for someone of their age and health state.

Evidence for Treating At-Risk Asymptomatic Individuals With Mild to Moderate Airflow Obstruction (FEV_1 -FVC Ratio <0.70 and $FEV_1 \geq 50\%$ Predicted) or Without Airflow Obstruction (FEV_1 -FVC Ratio ≥ 0.70) to Prevent the Development of Symptomatic Airflow Obstruction

The evidence reviewed for the 2007 ACP guideline showed no beneficial effect of treatment of asymptomatic persons, with or without risk factors for airflow obstruction, to prevent future respiratory symptoms or reduce subsequent decline in lung function.

In our guideline update, we identified 1 study that provided subgroup data comparing smoking cessation plus ipratropium, smoking cessation plus placebo, and usual care (the control group that received no intervention) in asymptomatic adult smokers with mild to moderate airflow obstruction (19). In the smoking cessation plus ipratropium group, ipratropium did not prevent the development of symptoms, regardless of the presence of airflow obstruction at baseline.

No evidence from randomized, controlled trials (RCTs) has evaluated the effectiveness of long-acting inhaled bronchodilators (anticholinergics or β -agonists) or inhaled corticosteroids in at-risk asymptomatic persons who do not have airflow obstruction (7).

Thus, we reaffirm our 2007 guideline, which recommends against treating asymptomatic individuals with or without spirometric evidence of airflow obstruction, regardless of the presence or absence of risk factors for airflow obstruction.

Initiating, Monitoring, or Modifying Therapy in Symptomatic Patients on the Basis of Spirometric Findings

In the 2007 ACP clinical guideline (5), we did not find any evidence to support the use of routine periodic spirometry after initiation of therapy in order to monitor disease status or guide therapy modification.

In our guideline update, there is no new evidence to support the use of routine periodic spirometry after initiation of therapy to monitor disease status or to modify therapy in symptomatic patients. Improvements in clinical symptoms do not necessarily correlate with spirometric responses to therapy or reduction of long-term decline in FEV_1 . Spirometry is useful to identify symptomatic patients with airflow obstruction who may benefit from pharmacotherapy. The evidence supports the initiation of inhaled bronchodilator treatment (anticholinergics, long-acting β -agonists, or corticosteroids) in patients who have respiratory symptoms and FEV_1 less than 60% predicted. Because of the wide intraindividual variation, the spirometric decline of lung function cannot be used to measure individual long-term response to treatment.

Using Spirometry Results to Promote Smoking Cessation

In the 2007 ACP guideline, we did not find any high-quality evidence that the use of spirometry or the communication of spirometry results to patients improved smoking cessation. Updated evidence for this guideline supports our prior findings that obtaining and providing individuals with spirometry results does not independently improve smoking cessation or the likelihood of continued abstinence. Evidence from 1 RCT showed no benefit of spirometry in achieving smoking cessation success at 6, 12, or 24 months of follow-up (20). Another study showed a 7% statistically significant benefit of using spirometry results as part of a smoking cessation program over 12 months. However, it was not an independent effect, because individuals who received spirometric testing results that were translated into "lung age" also received additional counseling, encouragement, and advice on smoking cessation, whereas the control group received spirometry results were given as a raw FEV_1 figure (21). One study showed no difference at 36-month follow-up among individuals who received annual spirometry results in addition to smoking cessation information and advice and individuals who received spirometry results only at baseline and at year 3 (22).

COPD MANAGEMENT STRATEGIES

The goals of COPD treatment are to reduce long-term lung function decline, prevent and treat exacerbations, reduce hospitalizations and mortality, relieve disabling dyspnea, and improve exercise tolerance and health-related quality of life.

Effect of Inhaled Therapies on Long-Term Decline in Lung Function

Pooled results from 9 long-term trials (19, 23–30), some of which were not statistically significant, demonstrated that inhaled therapies (long-acting bronchodilators, inhaled corticosteroids, or combination bronchodilator and corticosteroid therapy) reduced the annual decline in mean FEV_1 more than placebo did. Monotherapy trials reported absolute decreases in the annual rate of FEV_1 decline associated with use of tiotropium (40 mL/y), inhaled corticosteroids (44 mL/y), and long-acting β -agonists (42 mL/y). The mean differences in decline compared with placebo, were -2 , -8 and -13 mL/y, respectively, and were not considered by most authorities to be clinically important differences (23–25, 28, 29). Other studies have demonstrated that combinations of inhaled agents are not more effective than monotherapy for slowing declines in lung function. Evidence is inadequate to predict in which patients inhaled therapies will have the greatest effect on long-term decline in lung function.

The largest clinically significant effect of combination therapy was observed in the TORCH (Towards a Revolution in COPD Health) trial, in which the mean annual decline in FEV_1 associated with a long-acting β -agonist

plus an inhaled corticosteroid was 39 mL/y compared with 55 mL/y for placebo (difference, -16 mL/y) (28). In the UPLIFT (Understanding the Potential Long-Term Impacts on Function with Tiotropium) trial, there was a non-significant difference in long-term lung function decline between long-term tiotropium plus usual care (in general, another inhaled therapy) and placebo plus usual care (40 mL/y and 42 mL/y, respectively) (23). Another trial of long-acting β -agonist plus inhaled corticosteroid compared with tiotropium alone showed no statistically significant mean change in FEV₁ decline over 2 years (30). In comparison, the effect of smoking cessation on FEV₁, as measured by the difference in mean FEV₁ decline among sustained quitters (13 mL/y) versus continuing smokers (60 mL/y), was -47 mL/y (19).

Comparison of the Benefits of Inhaled Therapies According to Baseline FEV₁

Updated evidence reconfirms our prior findings that the patients who benefit the most from inhaled therapies (anticholinergics, long-acting β -agonists, or corticosteroids) are those who have respiratory symptoms and air-flow obstruction with FEV₁ less than 60% predicted. Although some patients who were studied had an FEV₁ greater than 60% predicted, the mean FEV₁ of the included patients has been 60% predicted or less for most COPD treatment trials.

Effects of Monotherapy in COPD

Exacerbations, Hospitalizations, and Mortality

Evidence reviewed in the 2007 ACP guideline showed that monotherapy with a long-acting inhaled β -agonist, a long-acting inhaled anticholinergic (tiotropium), or an inhaled corticosteroid was superior to placebo and short-acting anticholinergics in reducing exacerbations (5). Annual rates of exacerbations with salmeterol and fluticasone were statistically significantly lower than with placebo (31). Tiotropium (relative risk [RR], 0.84 [CI, 0.78 to 0.90]), long-acting β -agonists (RR, 0.87 [CI, 0.82 to 0.93]), and inhaled corticosteroids (RR, 0.85 [CI, 0.75 to 0.96]) reduced the RR for at least one exacerbation compared with placebo (6). However, ipratropium, a short acting anticholinergic, was not superior to placebo (RR, 0.95 [CI, 0.78 to 1.15]) (6). In comparison studies, long-acting β -agonists were as effective in reducing exacerbations as ipratropium (RR, 0.89 [CI, 0.72 to 1.10]), inhaled corticosteroids (RR, 1.06 [CI, 0.84 to 1.34]), and the long-acting anticholinergic tiotropium (RR, 1.11 [CI, 0.93 to 1.33]) (6). Finally, tiotropium was more effective than ipratropium (RR, 0.77 [CI, 0.62 to 0.95]) in reducing exacerbations (6).

Tiotropium has been shown to statistically significantly reduce hospitalizations for COPD exacerbations compared with placebo (absolute risk difference, -2% [CI, -4% to -1%]) (32–35) but not compared with ipratropium (absolute risk difference, -4% [CI, -10% to 1%]) (36). The Lung Health Study (trials 1 and 2) found

no statistically significant differences in hospitalizations per 100 person-years of exposure between ipratropium and placebo or between inhaled corticosteroids and placebo (19, 25). The TORCH study found no difference in pulmonary-cause mortality with salmeterol, fluticasone, or the combination of these agents compared with placebo (31, 37). However, the annual hospitalization rate was 18% lower in the salmeterol group than the placebo group (31). A meta-analysis by Salpeter and colleagues (38) identified an increase in pulmonary-cause mortality associated with use of long-acting β -agonist (21 deaths among 1320 participants vs. 8 deaths per 1084 participants in the placebo group; RR, 2.47 [CI, 1.12 to 5.45]) and a 73% relative reduction in mortality associated with anticholinergics compared with placebo (2 deaths per 4036 participants vs. 12 deaths per 3845 participants, respectively; RR, 0.27 [CI, 0.09 to 0.82]).

In this guideline update, no new studies were identified during our initial search time frame that evaluated the effect of inhaled monotherapies (anticholinergics, long-acting β -agonists, or corticosteroids) on exacerbations, hospitalizations, or mortality. After the search date for the guideline had passed, a large randomized trial demonstrated that tiotropium compared with salmeterol reduced the time to first exacerbation (primary outcome), total number of exacerbations, and severe exacerbations in patients with moderate to very severe COPD (mean FEV₁, 52%). Adverse effects were similar between groups (39).

Health-Related Quality of Life and Dyspnea

One new trial (23) of at least 2 years' duration in addition to the 2 trials reviewed for the 2007 guideline (24, 31) provided information on respiratory health-related quality of life as measured by the St. George's Respiratory Questionnaire. All 3 studies demonstrated a statistically significant improved quality of life with monotherapy (tiotropium, salmeterol, or fluticasone) compared with placebo, but the mean absolute difference did not achieve the threshold of a minimal important difference (defined as at least a 4-point difference in the symptom scale scores).

Studies infrequently reported dyspnea scores, and when these were reported, a small improvement with monotherapies was typically demonstrated. Reasons for not reporting dyspnea scores include no acceptable and appropriate approach to assess dyspnea in a clinical trial setting and a lack of a uniform method. Two recent studies of at least 2 years' duration in addition to the Lung Health Study that were included in the 2007 review provided information on dyspnea (23, 25, 40). The Lung Health Study found a statistically significant benefit in reducing the frequency of dyspnea in patients who were assigned to receive inhaled corticosteroids versus placebo (68% vs. 62%, respectively, reported no dyspnea at 36 months; $P = 0.02$) (25). Another study reported that Medical Research Council dyspnea scores were reduced with fluticasone ther-

apy compared with placebo (-0.2 point/y [CI, -0.3 to -0.06 point/y]; $P = 0.003$) (40).

Adverse Effects

As reported in the 2007 guideline, potential adverse reactions include oropharyngeal candidiasis, dysphonia, and moderate to severe easy bruisability with inhaled corticosteroids (24, 26, 41); dry mouth with tiotropium (42); and increased cardiovascular events with long-acting inhaled β -agonists (43). On the basis of 2 RCTs, the incidence of fracture over 3 years was similar with inhaled corticosteroids and placebo (1.4% vs. 2.0%, respectively) (24, 26). However, in the Lung Health Study, lumbar spine and femur bone densities were statistically significantly lower in the inhaled triamcinolone group (25).

Two recent meta-analyses published after the 2007 review reported on adverse effects (44, 45). One meta-analysis of 11 RCTs of greater than 6 months' duration did not identify increased risks for pneumonia, 1-year mortality, or fracture associated with inhaled corticosteroids as monotherapy (44). Another recent meta-analysis of RCTs (45) found that short- or long-acting anticholinergics were associated with an increased risk for major cardiovascular events in 4 trials 48 weeks to 24 months in duration (RR, 2.12 [CI, 1.22 to 3.67]; absolute risk difference, 1.2) but not in 8 RCTs 6 weeks to 6 months in duration (RR, 0.82 [CI, 0.43 to 1.58]). However, a panel convened by the U.S. Food and Drug Administration noted the limitations of that meta analysis, which included potentially biased study selection, lack of assessment of patient follow-up time, lack of information on adverse events in patients who withdrew from many of the included trials, lack of patient-level data, and the combination of the trials on short-acting and long-acting anticholinergics in the main analysis (46).

Evidence for Using Monotherapies in Patients With FEV₁ Between 50% and 80% Predicted

Among symptomatic patients with FEV₁ greater than 50% predicted but less than 80% predicted or those with normal airflow but who have chronic sputum production (at-risk individuals), 7 large studies of inhaled corticosteroids or short- or long-acting anticholinergics that lasted at least 1 year (including 2 published since the 2007 review [47, 48]) found little to no improvement in exacerbations, health-related quality of life, COPD hospitalizations, or mortality (19, 24–27, 47, 48).

Effect of Combination Therapies for COPD

In the 2007 ACP guideline, the conclusion was that it cannot be clearly established when to use combination therapy instead of monotherapy. The evaluated evidence showed that combination therapies do not consistently demonstrate benefits over monotherapy.

This guideline update reprises the analysis of the 2007 ACP guideline by focusing on 9 trials of at least 2 years' duration. The outcome "exacerbations" was evaluated ac-

ording to "rates" (exacerbations per patient-year in patients who had at least 1 exacerbation). Two new large, long-term studies with data on combination therapy compared with monotherapy found a benefit of using combination therapy over monotherapy in symptomatic patients with an FEV₁ less than 60% predicted, because combination therapy was associated with a higher percentage of patients with clinically noticeable improvement in respiratory symptoms (23, 30). However, results of other studies did not support this benefit; the average change in respiratory symptoms was below a clinically noticeable threshold, and adverse events were increased (6). Because studies of various combination therapies are lacking, there is little evidence to support the identification of any preferred combination therapy. A recent Cochrane review concluded that the relative efficacy and safety of combination inhalers remains uncertain because the authors found that the proportion of missing outcome data compared with the observed outcome data in the current studies may be sufficient to induce a clinically relevant bias in the intervention effect (49).

Exacerbations, Hospitalizations, and Mortality

One study compared combination therapy (salmeterol plus fluticasone) with monotherapy (tiotropium) for 2 years in 1323 patients with a mean FEV₁ of 39% predicted (30). The results for secondary end points showed that compared with monotherapy, combination therapy reduced overall mortality (hazard ratio [HR], 0.48 [CI, 0.27 to 0.85]) and increased the percentage of patients who had a clinically significant improvement in respiratory health status scores (32% with combination therapy vs. 27% with monotherapy at year 2) (30). The absolute risk difference in mortality was approximately 1%. There were no differences between monotherapy and combination therapy in the overall rates of exacerbations, exacerbations requiring hospitalization, the percentage of patients who had at least 1 exacerbation, or mean change in FEV₁ at 2 years.

In the TORCH trial, the mean FEV₁ was 44% predicted among 6112 patients, and fewer than 15% of patients had an FEV₁ greater than 60% predicted. Combination therapy (salmeterol plus fluticasone) reduced the annual rate of exacerbations compared with monotherapy (salmeterol alone, fluticasone alone, or placebo) (31). Although mortality with combination therapy was reduced in this trial compared with monotherapy, the reduction did not reach the predetermined level of statistical significance.

Another randomized trial showed that addition of fluticasone-salmeterol to tiotropium therapy compared with tiotropium plus placebo did not influence exacerbation rates but did improve lung function, health-related quality of life, and hospitalization in patients with moderate or severe COPD (postbronchodilator FEV₁ <65% predicted) (50).

The UPLIFT study included 5993 patients and compared tiotropium plus any other nonanticholinergic

respiratory medications with placebo plus any other nonanticholinergic respiratory medications over 4 years. This study was not a true comparison of combination versus placebo because more than 90% of the patients in the placebo group were using another (nonstudy) inhaled medication throughout the trial; approximately two thirds were receiving long-acting β -agonists, inhaled corticosteroids, or both agents). Inclusion in the study required an FEV₁ less than 70% predicted; the mean FEV₁ of enrollees was 48% predicted. The study authors concluded that in patients with severe symptomatic airflow obstruction the addition of tiotropium reduced the rate of exacerbations (HR, 0.86 [CI, 0.81 to 0.91]), increased the delay in time to first exacerbation (16.7 months vs. 12.5 months; $P < 0.05$), and reduced the incidence of respiratory failure compared with placebo. The percentage of patients who experienced at least 1 exacerbation differed between study groups, although all patients experienced at least 1 exacerbation (23). Addition of tiotropium also prolonged the time to first hospitalization for exacerbations (HR, 0.86 [CI, 0.78 to 0.95]) but not the number of exacerbations per patient-year leading to hospitalization (RR, 0.94 [CI, 0.82 to 1.07]). There was no statistically significant difference in overall mortality (HR, 0.89 [CI, 0.79 to 1.02]).

Health-Related Quality of Life and Dyspnea

Two trials (30, 31) of at least 2 years' duration provided information on health-related quality of life as measured by the St. George's Respiratory Questionnaire. In a study published after the 2007 review, Wedzicha and colleagues (30) noted a statistically significant improvement among symptomatic patients with severe airflow obstruction (mean FEV₁, 39% predicted) who were assigned to receive inhaled combined long-acting β -agonist and corticosteroid therapy compared with tiotropium alone. In the TORCH trial (31), the average change in score over 3 years was statistically significantly better in the combination therapy group than in the salmeterol-alone group, the fluticasone-alone group, and the placebo group (averaged over 3 years, the difference of the difference between combination and placebo group in the score for the St. George's Respiratory Questionnaire was 3.1 units).

Two new studies provide an update to the 2007 review. The UPLIFT study (23) assessed the effect of tiotropium on the incidence of dyspnea and found a decrease of 39% in patients receiving tiotropium compared with those receiving placebo (RR, 0.61 [CI, 0.40 to 0.94]; 0.38 vs. 0.62 per 100 patient-years, respectively). Lapperre and colleagues (40) found that use of inhaled corticosteroids alone or in combination with a long-acting β -agonist was associated with a small, non-clinically significant improvement over baseline dyspnea compared with placebo

(change in Medical Research Council dyspnea score of approximately 0.2 to 0.3).

Adverse Effects

The 2007 literature was updated with 2 studies of the adverse effects of combination therapy. One study of 2 years' duration that included 1323 patients with a mean FEV₁ 39% predicted found that the percentage of patients with serious adverse events was greater with combination therapy (salmeterol-fluticasone) than with monotherapy (tiotropium) (30% vs. 24%; $P = 0.02$) (30). Salmeterol-fluticasone therapy was also associated with more cases of patient- and investigator-reported pneumonia than was therapy with tiotropium alone (8% vs. 4%; $P = 0.008$) (30). In contrast, the UPLIFT trial (tiotropium plus any other nonanticholinergic respiratory medications compared with placebo plus any other nonanticholinergic respiratory medications) found a reduced risk for myocardial infarction with long-acting inhaler tiotropium compared with placebo (RR, 0.73 [CI, 0.53 to 1.00]) and no difference in risk for stroke (23).

Evidence to Use Combination Therapy in Patients With FEV₁ Between 50% and 80% Predicted

One study of patients with FEV₁ between 50% and 80% predicted who were treated with the combination of a long-acting β -agonist and inhaled corticosteroid showed little improvement in exacerbations, mortality, or health-related quality of life compared with placebo recipients (48). Subgroup data from another trial showed that the time to first exacerbation and the time to exacerbation resulting in hospital admission were longer in the tiotropium group than in the control group (HR, 0.82 [CI, 0.75 to 0.90] and 0.74 [CI, 0.62 to 0.88], respectively) (47).

Pulmonary Rehabilitation

Results reported in the 2007 ACP guideline suggest that pulmonary rehabilitation programs provide improvements in respiratory symptoms, quality of life, and the 6-minute walk test, at least in the short term following the program, among persons with baseline respiratory symptoms and a mean FEV₁ of approximately 50% predicted.

Most studies have historically enrolled patients with a mean FEV₁ of 50% predicted or lower. Although the generalizability of these data to patients with less severe airflow obstruction is less clear, evidence reviewed in this guideline update suggests that patients with moderate COPD also experience benefit (49). We found no new information on the effectiveness of pulmonary rehabilitation programs in severe COPD. However, a recently published RCT (outside our inclusion criteria) that included 252 patients with moderate to severe COPD who were monitored over 8 weeks compared outpatient hospital-based pulmonary rehabilitation with home-based pulmonary rehabilitation (51). Study inclusion required a diagnosis of COPD and an FEV₁ less than 70% predicted. The mean FEV₁ was

43% predicted, and approximately one third of individuals had moderate COPD (Global Initiative for Chronic Obstructive Lung Disease stage II). More than 99% of patients had self-reported shortness of breath. Results showed that both interventions produced similar improvements in the dyspnea domain of the Chronic Respiratory Questionnaire and total score on St. George's Respiratory Questionnaire. The improvement in dyspnea from baseline in both groups was statistically significant and greater for both scale scores than the previously determined minimally important difference at 3 months. However, only the home-based program reached the minimum clinically important difference at 12 months. The main components of most reported pulmonary rehabilitation programs included endurance and exercise training, education, behavioral modification, and outcome assessment.

One study used a multidisciplinary pulmonary rehabilitation program that included a 4-month clinic-based program followed by 20 months of community-based maintenance among symptomatic adults, among whom approximately 68% had an FEV₁ greater than 50%. Participants showed clinically significant benefits in St. George's Respiratory Questionnaire scores at 4 months but not at 12 months (52). There were no statistically significant differences in moderate to severe exacerbations (co-primary outcome with St. George's Respiratory Questionnaire score) at 4 or 12 months and no clinically important differences in the 6-minute walk test after 4 months or 2 years. One small study showed that there were no differences in 18-month mortality between the outpatient rehabilitation group and the control group ($P = 0.79$) (53). Evidence reviewed by Puhan and colleagues (54) from small studies of moderate-quality evidence showed that pulmonary rehabilitation is an effective intervention to reduce hospital readmissions and to improve health-related quality of life in patients with COPD after an exacerbation. Another systematic review showed that inspiratory muscle training with targeted hyperventilation increases muscle strength and endurance, and it improves exercise capacity and decreases dyspnea for adults with stable COPD (55).

Supplemental Long-Term Oxygen Therapy

We did not update the search to evaluate the utility of long-term oxygen therapy because widespread consensus remains on this point. To summarize the evidence presented in the 2007 ACP guideline (5), 2 trials (56, 57) showed that supplemental oxygen used 15 or more hours daily to maintain a PaO₂ greater than 60 mm Hg reduced mortality in patients with COPD who have severe resting hypoxemia (mean resting PaO₂ \leq 55 mm Hg) (RR, 0.61 [CI, 0.46 to 0.82]). Two other studies (58, 59) showed no effect on relative risk for mortality with use of supplemental oxygen (9 to 13 hours daily) during the day or at night in patients with similar severity of airflow obstruction but daytime PaO₂ greater than 60 mm Hg. In addition, studies

showed no effect of ambulatory oxygen on respiratory health-related quality of life measures (60, 61). Physiologic indications for the use of long-term oxygen therapy include cor pulmonale or polycythemia with PaO₂ between 55 and 59 mm Hg (62).

SUMMARY

Evidence shows that history and physical examination are poor predictors of airway obstruction and its severity. However, combination of all 3 of the following findings in an individual—greater than 55-pack-year history of smoking, wheezing on auscultation, and patient self-reported wheezing—can be considered predictive of airflow obstruction, defined as postbronchodilator FEV₁-FVC ratio less than 0.70.

Spirometry is a pulmonary function test that is useful to identify airflow obstruction in symptomatic patients who may benefit from pharmacotherapy, long-term oxygen, or pulmonary rehabilitation (or all of these strategies). Symptomatic patients with FEV₁ less than 60% predicted will benefit from inhaled treatments (anticholinergics, long-acting β -agonists, or corticosteroids). The evidence does not support treating asymptomatic persons, regardless of the presence or absence of airflow obstruction or risk factors for airflow obstruction.

Currently, evidence does not support the use of spirometry as a screening strategy for airflow obstruction in persons without respiratory symptoms, even in the presence of risk factors. In addition, spirometry does not seem to have an independent influence on the likelihood of quitting smoking or maintaining abstinence. The routine use of spirometry in asymptomatic patients in primary care settings may potentially lead to unnecessary testing, increased costs and resource utilization, unnecessary disease labeling, and the harms of long-term treatment with no known preventive effect on avoiding future symptoms.

Most trials that compared the efficacy or effectiveness of various inhaled monotherapies did not show any differences among these medications. Monotherapy with a long-acting inhaled agent (long-acting anticholinergic, long-acting β -agonist, or corticosteroid) was superior to placebo or short-acting anticholinergic therapy in reducing exacerbations. The evidence is not conclusive in linking inhaled monotherapies with reductions in hospitalizations or mortality. In some studies, combination therapy with various inhaled agents (anticholinergics, long-acting β -agonists, or corticosteroids) was shown to reduce exacerbations, hospitalizations, mortality, and improve health-related quality of life compared with monotherapy. Other studies have not identified these benefits, however, and a few studies have identified a modest increase in the risk for adverse events. Finally, on the basis of studies that showed benefit, it remains unclear when combination therapy is preferred over monotherapy.

Pulmonary rehabilitation improves symptoms in patients with an FEV₁ less than 50% predicted. However, the generalizability of pulmonary rehabilitation benefits to all patients is not clear. We did not update the search to evaluate the utility of long-term oxygen therapy. Evidence evaluated for our 2007 guideline showed a reduction in mortality associated with use of long-term supplemental oxygen therapy for patients with severe resting hypoxemia (PaO₂ ≤55 mm Hg).

RECOMMENDATIONS

Recommendation 1: ACP, ACCP, ATS, and ERS recommend that spirometry should be obtained to diagnose airflow obstruction in patients with respiratory symptoms (Grade: strong recommendation, moderate-quality evidence). Spirometry should not be used to screen for airflow obstruction in individuals without respiratory symptoms (Grade: strong recommendation, moderate-quality evidence).

Targeted use of spirometry for diagnosis of airflow obstruction is beneficial for patients with respiratory symptoms, particularly dyspnea. Existing evidence does not support the use of spirometry to screen for airflow obstruction in individuals without respiratory symptoms, including those with current or past exposure to risk factors for COPD. Evidence is insufficient to support the use of inhaled therapies in asymptomatic individuals who have spirometric evidence of airflow obstruction, regardless of the presence or absence of risk factors for airflow obstruction. There is no difference in the annual rate of FEV₁ decline or prevention of symptoms in these individuals with treatment. No evidence from RCTs supports treating asymptomatic individuals, with or without risk factors for airflow obstruction, who do not have spirometric evidence of airflow obstruction. In addition, evidence does not show any independent benefit of obtaining and providing spirometry results on success rates in smoking cessation. No study evaluated the use of periodic spirometry after initiation of therapy to monitor ongoing disease status or modify therapy.

Recommendation 2: For stable COPD patients with respiratory symptoms and FEV₁ between 60% and 80% predicted, ACP, ACCP, ATS, and ERS suggest that treatment with inhaled bronchodilators may be used (Grade: weak recommendation, low-quality evidence).

There is limited and conflicting evidence of health benefits resulting from initiation of inhaled bronchodilators (anticholinergics or long-acting β -agonists) in symptomatic patients with FEV₁ between 60% and 80% predicted as documented by spirometry. Individual patients may benefit from the therapy and may show improvement in their respiratory symptoms. However, the duration of maintenance therapy and the frequency of reevaluation once a patient is receiving therapy are unknown because evidence is limited. Further research is needed to evaluate the health benefits of inhaled therapies (anticholinergics or

long-acting β -agonists) in symptomatic patients with FEV₁ between 60% and 80% predicted.

This recommendation does not address the occasional use of short-acting inhaled bronchodilators for acute symptom relief.

Recommendation 3: For stable COPD patients with respiratory symptoms and FEV₁ <60% predicted, ACP, ACCP, ATS, and ERS recommend treatment with inhaled bronchodilators (Grade: strong recommendation, moderate-quality evidence).

Patients who benefit the most from inhaled bronchodilators (anticholinergics or long-acting β -agonists) seem to be those who have respiratory symptoms and airflow obstruction with an FEV₁ less than 60% predicted. The mean FEV₁ was less than 60% predicted in the majority of the trials that evaluated the management of COPD.

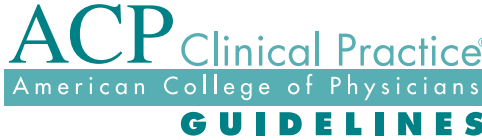
This recommendation does not address the occasional use of short-acting inhaled bronchodilators for acute symptom relief.

Recommendation 4: ACP, ACCP, ATS, and ERS recommend that clinicians prescribe monotherapy using either long-acting inhaled anticholinergics or long-acting inhaled β -agonists for symptomatic patients with COPD and FEV₁ <60% predicted. (Grade: strong recommendation, moderate-quality evidence). Clinicians should base the choice of specific monotherapy on patient preference, cost, and adverse effect profile.

Monotherapy with a long-acting inhaled β -agonist or a long-acting inhaled anticholinergic is beneficial in reducing exacerbations and improving health-related quality of life. Evidence was inconclusive regarding the effect of inhaled agents (anticholinergics and long-acting β -agonists) on mortality, hospitalizations, and dyspnea. Although data support that inhaled corticosteroids are superior to placebo in reducing exacerbations, concerns about their side effect profile (thrush, potential for bone loss, and moderate to severe easy bruisability) and less biologic rationale, in contrast to the rationale that supports the use of inhaled steroids as anti-inflammatory monotherapy in asthma, led to our recommendation that inhaled corticosteroids are not a preferred monotherapy for patients with stable COPD. Adverse effects related to inhaled long-acting anticholinergics or long-acting β -agonists range from mild (for example, dry mouth) to potentially serious (for example, cardiovascular events). Pooled analyses of results from trials of monotherapy show no statistically significant differences in outcomes among various monotherapies. However, some of the large recent trials have shown that different monotherapies may have a greater effect on certain outcomes. These observed effects need to be confirmed with further comparative effectiveness studies. Clinicians should base selection of treatment from among various monotherapies on individual patient preferences, cost, and adverse effect profile.

Recommendation 5: ACP, ACCP, ATS, and ERS suggest that clinicians may administer combination inhaled therapies (long-acting inhaled anticholinergics, long-acting inhaled

Figure. Summary of the American College of Physicians guideline on diagnosis and management of stable chronic obstructive pulmonary disease.

 Summary of the American College of Physicians Guideline on Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease	
Disease or condition	Stable COPD
Target audience	Internists, family physicians, and other clinicians
Target patient population	Adults with stable COPD
Interventions	History and physical examination Spirometry Management strategies, including smoking cessation, inhaled therapies (anticholinergics, long-acting β -agonists, or corticosteroids), pulmonary rehabilitation programs, and supplemental long-term oxygen therapy
Outcomes	Exacerbations Hospitalizations and mortality Health-related quality-of-life dyspnea Adverse effects
Recommendations	<p><i>Recommendation 1: ACP, ACCP, ATS, and ERS recommend that spirometry should be obtained to diagnose airflow obstruction in patients with respiratory symptoms (Grade: strong recommendation, moderate-quality evidence). Spirometry should not be used to screen for airflow obstruction in individuals without respiratory symptoms (Grade: strong recommendation, moderate-quality evidence).</i></p> <p><i>Recommendation 2: For stable COPD patients with respiratory symptoms and FEV₁ between 60% and 80% predicted, ACP, ACCP, ATS, and ERS suggest that treatment with inhaled bronchodilators may be used (Grade: weak recommendation, low-quality evidence).</i></p> <p><i>Recommendation 3: For stable COPD patients with respiratory symptoms and FEV₁ <60% predicted, ACP, ACCP, ATS, and ERS recommend treatment with inhaled bronchodilators (Grade: strong recommendation, moderate-quality evidence).</i></p> <p><i>Recommendation 4: ACP, ACCP, ATS, and ERS recommend that clinicians prescribe monotherapy using either long-acting inhaled anticholinergics or long-acting inhaled β-agonists for symptomatic patients with COPD and FEV₁ <60% predicted (Grade: strong recommendation, moderate-quality evidence). Clinicians should base the choice of specific monotherapy on patient preference, cost, and adverse effect profile.</i></p> <p><i>Recommendation 5: ACP, ACCP, ATS, and ERS suggest that clinicians may administer combination inhaled therapies (long-acting inhaled anticholinergics, long-acting inhaled β-agonists, or inhaled corticosteroids) for symptomatic patients with stable COPD and FEV₁ <60% predicted (Grade: weak recommendation, moderate-quality evidence).</i></p> <p><i>Recommendation 6: ACP, ACCP, ATS, and ERS recommend that clinicians should prescribe pulmonary rehabilitation for symptomatic patients with an FEV₁ <50% predicted (Grade: strong recommendation, moderate-quality evidence). Clinicians may consider pulmonary rehabilitation for symptomatic or exercise-limited patients with an FEV₁ >50% predicted (Grade: weak recommendation, moderate-quality evidence).</i></p> <p><i>Recommendation 7: ACP, ACCP, ATS, and ERS recommend that clinicians should prescribe continuous oxygen therapy in patients with COPD who have severe resting hypoxemia (PaO₂ \leq55 mm Hg or SpO₂ \leq88%) (Grade: strong recommendation, moderate-quality evidence).</i></p>
Clinical considerations	<ul style="list-style-type: none"> • This guideline refers to patients with stable COPD. • Treatment benefits for COPD are primarily related to prevention and treatment of exacerbations among patients who have or are likely to have exacerbations, reduce hospitalizations and mortality, relieve dyspnea that limits activity, and improve exercise tolerance and health-related quality of life. • Respiratory symptom status is not a reliable indicator of the presence of airflow obstruction. Individuals with normal spirometric values may report respiratory symptoms, whereas individuals who have severe to very severe airflow obstruction by spirometry may report no symptoms. • The best combination to exclude COPD includes never having smoked, no reported wheezing, and no wheezing on clinical examination. Three of the following findings in a patient can be considered predictive of airflow obstruction (defined as postbronchodilator FEV₁-FVC ratio <70): history of smoking >55 pack-years, wheezing on auscultation, and patient self-report of wheezing.

ACP = American College of Physicians; ACCP = American College of Chest Physicians; ATS = American Thoracic Society; COPD = chronic obstructive pulmonary disease; ERS = European Respiratory Society.

β -agonists, or inhaled corticosteroids) for symptomatic patients with stable COPD and FEV₁ <60% predicted (Grade: weak recommendation, moderate-quality evidence).

Many symptomatic patients with stable COPD and an FEV₁ less than 60% predicted may benefit from combination therapy, but when to use combination therapy instead

of monotherapy has not been clearly established. The long-term benefit of combination therapy compared to monotherapy in 2 recent large clinical trials (TORCH and UPLIFT) was moderate for COPD exacerbations and of borderline statistical significance for mortality, but was not consistently seen in earlier trials. In some studies, combination therapy has been associated with a modest increase in the risk for adverse events, whereas other studies have not found this. Thus, the evidence is insufficient to support a strong recommendation for the broad use of combination therapy, and clinicians will need to weigh the potential benefits and harms of combination therapy on a case-by-case basis. The combination therapy that has been most studied to date is long-acting inhaled β -agonists plus inhaled corticosteroids.

Recommendation 6: ACP, ACCP, ATS, and ERS recommend that clinicians should prescribe pulmonary rehabilitation for symptomatic patients with an FEV₁ <50% predicted (Grade: strong recommendation, moderate-quality evidence). Clinicians may consider pulmonary rehabilitation for symptomatic or exercise-limited patients with an FEV₁ >50% predicted. (Grade: weak recommendation, moderate-quality evidence).

Evidence supports the use of pulmonary rehabilitation for symptomatic patients who have severe COPD (FEV₁ <50% predicted). This is based on the fact that controlled trials of pulmonary rehabilitation have had a mean FEV₁ of less than 50% predicted. The generalizability of the benefits of pulmonary rehabilitation in patients with less severe airflow obstruction is less clear. Physicians may consider prescribing pulmonary rehabilitation for patients with an FEV₁ greater than 50% predicted if they remain symptomatic or have exercise limitation despite maximal medical therapy.

Recommendation 7: ACP, ACCP, ATS, and ERS recommend that clinicians should prescribe continuous oxygen therapy in patients with COPD who have severe resting hypoxemia (PaO₂ ≤55 mm Hg or SpO₂ ≤88%) (Grade: strong recommendation, moderate-quality evidence).

To accurately evaluate oxygen status, the assessment should ideally occur when patients are stable rather than during or immediately after an exacerbation. Use of supplemental oxygen for 15 or more hours daily can help improve survival in patients with COPD who have severe resting hypoxemia (PaO₂ ≤55 mm Hg or SpO₂ ≤88%).

Because pulse oximetry has essentially supplanted arterial blood gases as a measure of oxygenation in nonhospitalized patients, it is reasonable to use oxygen saturation measured by pulse oximetry (SpO₂) as a surrogate for PaO₂. On the basis of the typical relationship between PaO₂ and SpO₂ as defined by the oxyhemoglobin dissociation curve, PaO₂ of 55 mm Hg or less correlates approximately with SpO₂ 88% or less.

See the **Figure** for a summary of the recommendations and clinical considerations.

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Note: Clinical practice guidelines are “guides” only and may not apply to all patients and all clinical situations. Thus, they are not intended to over-ride clinicians’ judgment. All ACP clinical practice guidelines are considered automatically withdrawn or invalid 5 years after publication, or once an update has been issued.

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(money to institution): Novartis; Grants/grants pending (money to institution): GlaxoSmithKline, Novartis, Chiesi, AstraZeneca, Johnson & Johnson; Payment for lectures including service on speakers bureaus: Boehringer Ingelheim, GlaxoSmithKline, Pfizer, Bayer, Nycomed, Chiesi; Travell/accommodations/meeting expenses unrelated to activities listed: Boehringer Ingelheim. Dr. Shekelle: Employment: Veterans Affairs Medical Center; Grants/grants pending (money to institution): Agency for Healthcare Research and Quality, National Institutes of Health, Veterans Administration; Royalties: UpToDate; Travell/accommodations/meetings expenses unrelated to activities listed: Travel to meetings sponsored by AHRQ, the Health Foundation, the University of Michigan, VA, Italian regional health authority, and RAND. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M11-0925.

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