CHEST™

Prevention of Acute Exacerbations of COPD

American College of Chest Physicians and Canadian Thoracic Society Guideline

Gerard J. Criner, MD, FCCP; Jean Bourbeau, MD, FCCP; Rebecca L. Diekemper, MPH; Daniel R. Ouellette, MD, FCCP; Donna Goodridge, RN, PhD; Paul Hernandez, MDCM; Kristen Curren, MA; Meyer S. Balter, MD, FCCP; Mohit Bhutani, MD, FCCP; Pat G. Camp, PhD, PT; Bartolome R. Celli, MD, FCCP; Gail Dechman, PhD, PT; Mark T. Dransfield, MD; Stanley B. Fiel, MD, FCCP; Marilyn G. Foreman, MD, FCCP; Nicola A. Hanania, MD, FCCP; Belinda K. Ireland, MD; Nathaniel Marchetti, DO, FCCP; Darcy D. Marciniuk, MD, FCCP; Richard A. Mularski, MD, MSHS, MCR, FCCP; Joseph Ornelas, MS; Jeremy D. Road, MD; and Michael K. Stickland, PhD

PODCAST

BACKGROUND: COPD is a major cause of morbidity and mortality in the United States as well as throughout the rest of the world. An exacerbation of COPD (periodic escalations of symptoms of cough, dyspnea, and sputum production) is a major contributor to worsening lung function, impairment in quality of life, need for urgent care or hospitalization, and cost of care in COPD. Research conducted over the past decade has contributed much to our current understanding of the pathogenesis and treatment of COPD. Additionally, an evolving literature has accumulated about the prevention of acute exacerbations.

METHODS: In recognition of the importance of preventing exacerbations in patients with COPD, the American College of Chest Physicians (CHEST) and Canadian Thoracic Society (CTS) joint evidence-based guideline (AECOPD Guideline) was developed to provide a practical, clinically useful document to describe the current state of knowledge regarding the prevention of acute exacerbations according to major categories of prevention therapies. Three key clinical questions developed using the PICO (population, intervention, comparator, and outcome) format addressed the prevention of acute exacerbations of COPD: nonpharmacologic therapies, inhaled therapies, and oral therapies. We used recognized document evaluation tools to assess and choose the most appropriate studies and to extract meaningful data and grade the level of evidence to support the recommendations in each PICO question in a balanced and unbiased fashion.

RESULTS: The AECOPD Guideline is unique not only for its topic, the prevention of acute exacerbations of COPD, but also for the first-in-kind partnership between two of the largest thoracic societies in North America. The CHEST Guidelines Oversight Committee in partnership with the CTS COPD Clinical Assembly launched this project with the objective that a systematic review and critical evaluation of the published literature by clinical experts and researchers in the field of COPD would lead to a series of recommendations to assist clinicians in their management of the patient with COPD.

CONCLUSIONS: This guideline is unique because it provides an up-to-date, rigorous, evidence-based analysis of current randomized controlled trial data regarding the prevention of COPD exacerbations.

CHEST 2015; 147(4):894-942

ABBREVIATIONS: AECOPD = acute exacerbation of COPD; CB = consensus based; CDC = US Centers for Disease Control and Prevention; CHEST = American College of Chest Physicians; CRGC = Canadian Respiratory Guidelines Committee; CTS = Canadian Thoracic Society; GIN = Guidelines International Network; GOC = Guidelines Oversight Committee; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HR = hazard ratio; NAC = N-acetylcysteine; PICO = population, intervention, comparator, outcome; RCT = randomized controlled trial; RR = rate ratio; S-CMC-lys = S-carboxymethylcysteine lysine salt; SGRQ = St. George's Respiratory Questionnaire; WHO = World Health Organization; WMD = weighted mean difference

Summary of Recommendations

PICO 1: Do Nonpharmacologic Treatments and Vaccinations Prevent/Decrease Acute Exacerbations of COPD?

1. In patients with COPD, we suggest administering the 23-valent pneumococcal vaccine as part of overall medical management but did not find sufficient evidence that pneumococcal vaccination prevents acute exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places high value on the benefits of pneumococcal vaccine for general health, and we endorse existing guidelines that recommend it for patients with COPD. Although evidence does not specifically support using the vaccine for the prevention of acute exacerbations, multiple bodies, including the US Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO), recommend the use of pneumococcal vaccine for all adults aged ≥ 65 years and in those aged 19 to 64 years with underlying medical conditions such as COPD that put them at greater risk of serious pneumococcal infection.

2. In patients with COPD, we recommend administering the influenza vaccine annually to prevent acute exacerbations of COPD (Grade 1B).

Underlying Values and Preferences: This recommendation places high value on the benefits of influenza vaccination for general health, the low risk of side effects, and the existing guidelines that recommend it for patients with COPD. Although the effect and evidence are moderate for the prevention of acute exacerbations of COPD, multiple bodies, including the CDC and WHO, recommend the use of a yearly influenza vaccine for all adults, including those with COPD.

3. In patients with COPD, we suggest including smoking cessation counseling and treatment using best practices as a component of a comprehensive clinical strategy to prevent acute exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places high value on the benefits of smoking cessation for all individuals. In particular, it is the only evidence-based intervention that improves COPD prognosis by mitigating lung function decline and reduces symptoms. Although the effect and evidence for smoking cessation in the prevention of acute exacerbations of COPD are low, evidence supports smoking cessation for many reasons: smokers with mild COPD who produce cough and phlegm achieve substantial symptom reductions in the first year after smoking cessation with less lung function decline and less symptoms upon sustained cessation; cigarette smoking may be associated with infections such as pneumonia; among other general health benefits. The benefit from smoking cessation outweighs the risks, and a myriad of strategies have been summarized by other guidelines and reviews. In general, effective smoking cessation programs include behavioral, physiologic, and psychologic components comprising an acknowledgment of current smoking followed by advice to quit, pharmacologic therapies (nicotine replacement therapy, antidepressants, nicotine receptor modifier therapy), and counseling (in-person or telephone

Manuscript received July 10, 2014; revision accepted September 17, 2014; originally published Online First October 16, 2014.

AFFILIATIONS: From the Temple University School of Medicine (Dr Criner), Philadelphia, PA; Respiratory Epidemiology and Clinical Research Unit (Dr Bourbeau), Montreal Chest Institute, McGill University Health Centre, Montreal, QC, Canada; American College of Chest Physicians (Ms Diekemper and Mr Ornelas), Glenview, IL; Henry Ford Health System (Dr Ouellette), Detroit, MI; College of Medicine (Dr Goodridge), University of Saskatchewan, Saskatoon, SK, Canada; Department of Medicine (Dr Hernandez), and School of Physiotherapy (Dr Dechman), Dalhousie University, Halifax, NS, Canada; Canadian Thoracic Society (Ms Curren), Ottawa, ON, Canada; Division of Respirology (Dr Balter), University of Toronto, Toronto, ON, Canada; University of Alberta (Dr Bhutani), Edmonton, AB, Canada; Department of Physical Therapy (Dr Camp), University of British Columbia, Vancouver, BC, Canada; Harvard Medical School (Dr Celli), Brigham and Women's Hospital, Boston, MA; University of Alabama at Birmingham and Birmingham VA Medical Center (Dr Dransfield), Birmingham, AL; Medical Center/Atlantic Health System (Dr Fiel), Morristown, NJ; Morehouse School of Medicine (Dr Foreman), Atlanta, GA; Baylor College of Medicine (Dr Hanania), Houston, TX; TheEvidenceDoc, LLC (Dr Ireland), Pacific, MO; Temple University School of Medicine (Dr Marchetti), Philadelphia, PA; Division of Respirology, Critical Care and Sleep Medicine (Dr Marciniuk), Royal University Hospital, University of Saskatchewan, Saskatoon, SK, Canada; Kaiser Permanente Center for Health Research (Dr Mularski), Portland, OR; Department of Medicine (Dr Road), University of British Columbia, Vancouver, BC, Canada; and Division of Pulmonary Medicine (Dr Stickland), University of Alberta, Edmonton, AB, Canada.

FUNDING/SUPPORT: The American College of Chest Physicians and the Canadian Thoracic Society supported the development this article and the innovations addressed within.

CORRESPONDENCE TO: Gerard J. Criner, MD, FCCP, Department of Pulmonary and Critical Care Medicine, Temple University School of Medicine, 745 Parkinson Pavilion, 3401 N Broad St, Philadelphia, PA 19140; e-mail: gerard.criner@tuhs.temple.edu

DOI: 10.1378/chest.14-1676

counseling), with cessation rates ranging from 8.8% to 34.5%. Smoking cessation that includes counseling and pharmacologic interventions are cost-effective.

4. In patients with moderate, severe, or very severe COPD who have had a recent exacerbation (ie, ≤ 4 weeks), we recommend pulmonary rehabilitation to prevent acute exacerbations of COPD (Grade 1C).

Underlying Values and Preferences: The pulmonary rehabilitation recommendations place high value on pulmonary rehabilitation reducing the risk of hospitalizations in patients with COPD who have had a recent COPD exacerbation (ie, ≤ 4 weeks posthospitalization). Although it has been well established that pulmonary rehabilitation improves quality of life, exercise tolerance, and dyspnea, these recommendations do not support pulmonary rehabilitation for the prevention of rehospitalizations in patients with COPD greater than 4 weeks after a recent hospitalization.

5. In patients with moderate, severe, or very severe COPD who have had an exacerbation greater than the past 4 weeks, we do not suggest pulmonary rehabilitation to prevent acute exacerbations of COPD (Grade 2B).

Underlying Values and Preferences: The pulmonary rehabilitation recommendations place high value on pulmonary rehabilitation reducing the risk of hospitalizations in patients with COPD who have had a recent COPD exacerbation (ie, ≤ 4 weeks posthospitalization). Although it has been well established that pulmonary rehabilitation improves quality of life, exercise tolerance, and dyspnea, these recommendations do not support pulmonary rehabilitation for the prevention of rehospitalizations in patients with COPD greater than 4 weeks after a recent hospitalization.

6. In patients with COPD, we suggest that education alone should not be used for prevention of acute exacerbations of COPD (Ungraded Consensus-Based Statement).

Underlying Values and Preferences: This recommendation places high value on reducing hospitalizations for COPD exacerbations, as these are associated with increased morbidity and mortality. A lower value was placed on the motivational educational intervention because it is labor intensive compared with traditional education techniques.

7. In patients with COPD, we suggest that case management alone should not be used for prevention of acute exacerbations of COPD (Ungraded Consensus-Based Statement).

Underlying Values and Preferences: This recommendation places high value on reducing hospitalizations for COPD exacerbations, as these are associated with increased morbidity and mortality. A lower value was placed on the lack of change in quality of life in either group because this information was present for only a small proportion of the entire sample.

8. In patients with COPD with a previous or recent history of exacerbations, we recommend education and case management that includes direct access to a health-care specialist at least monthly to prevent severe acute exacerbations of COPD, as assessed by decreases in hospitalizations (Grade 1C).

Underlying Values and Preferences: This recommendation places high value on reducing hospitalizations for COPD exacerbations, as these are associated with increased morbidity and mortality.

9. In patients with moderate to severe COPD, we suggest education together with an action plan but without case management does not prevent severe acute exacerbations of COPD, as assessed by a decrease in ED visits or hospitalizations over a 12-month period (Grade 2C).

Underlying Values and Preferences: This recommendation places high value on reducing hospitalizations for COPD exacerbations, as these are associated with increased morbidity and mortality.

10. For patients with COPD, we suggest education with a written action plan and case management for the prevention of severe acute exacerbations of COPD, as assessed by a decrease in hospitalizations and ED visits (Grade 2B).

Underlying Values and Preferences: This recommendation places high value on reducing COPD-related hospitalizations, as these are associated with increased morbidity and mortality. Hospitalizations were believed to best reflect exacerbations because increased physician visits or increased medication use could be a result of the intervention to prevent an exacerbation. High value was also placed on changes in individuals with a history of exacerbations and on outcomes that specifically identified COPD-related hospitalizations. The recommendation reflects the fact that one study reported increased mortality in the intervention group. Although we do not know the reason for increased mortality in this one study, patients with underlying severe disease and clinical instability need close attention and careful follow-up. This point emphasizes that a specially trained

staff is required to supervise this intervention and that patient selection must be individualized.

11. For patients with COPD, we suggest that telemonitoring compared with usual care does not prevent acute exacerbations of COPD, as assessed by decreases in emergency room visits, exacerbations, or hospitalizations over a 12-month period (Grade 2C).

Underlying Values and Preferences: There is insufficient evidence at this time to support the contention that telemonitoring prevents COPD exacerbations.

PICO 2: Does Maintenance Inhaled Therapy Prevent/Decrease Acute Exacerbations of COPD?

12. In patients with moderate to severe COPD, we recommend the use of long-acting β_2-agonist compared with placebo to prevent moderate to severe acute exacerbations of COPD (Grade 1B).

Underlying Values and Preferences: This recommendation places high value on long-acting β_2-agonist therapy reducing the risk of acute exacerbations of COPD, both moderate (required course of oral steroids, antibiotics, or both) and severe (required hospitalization), together with the comparative benefit of long-acting β_2-agonist therapy improving quality of life and lung function compared with placebo. This recommendation also acknowledges that there are no significant differences in serious adverse events or incidence of mortality between long-acting β_2-agonist therapy and placebo in this patient group.

13. In patients with moderate to severe COPD, we recommend the use of a long-acting muscarinic antagonist compared with placebo to prevent moderate to severe acute exacerbations of COPD (Grade 1A).

Underlying Values and Preferences: This recommendation places high value on long-acting muscarinic antagonists reducing the risk of acute exacerbations of COPD, both moderate (required course of oral steroids, antibiotics, or both) and severe (required hospitalization), together with the comparative benefit of a long-acting muscarinic antagonist improving quality of life and lung function compared with placebo. Although pooled analyses show a reduction in COPD hospitalization with the use of a long-acting muscarinic antagonist compared with placebo, it does not reach statistical significance for all-cause hospitalization. This recommendation also acknowledges that there are no significant differences in serious adverse events or incidence of mortality between long-acting muscarinic antagonists and placebo in this patient group.

14. In patients with moderate to severe COPD, we recommend the use of long-acting muscarinic antagonists compared with long-acting β_2-agonist to prevent moderate to severe acute exacerbations of COPD (Grade 1C).

Underlying Values and Preferences: This recommendation places high value on long-acting muscarinic antagonists reducing the risk of acute exacerbations of COPD, both moderate (required course of oral steroids, antibiotics, or both) and severe (required hospitalization), together with the comparative benefit of long-acting muscarinic antagonists having a lower rate of nonfatal serious adverse events compared with long-acting β_2-agonists. This comparative benefit may not apply with the new ultralong-acting β_2-agonists that are a once-daily medication. Although pooled analyses show a reduction in COPD hospitalization with the use of a long-acting muscarinic antagonist compared with placebo, it does not reach statistical significance for all-cause hospitalization. A lower value was placed on the lack of statistically significant differences in changes in lung function, quality of life, and patient symptoms between the two drug groups.

15. In patients with moderate to severe COPD, we suggest the use of a short-acting muscarinic antagonist compared with short-acting β_2-agonist monotherapy to prevent acute mild-moderate exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places value on a short-acting muscarinic antagonist to reduce the risk of acute exacerbations of COPD together with the comparative benefit of a short-acting muscarinic antagonist improving quality of life and lung function compared with short-acting β_2-agonist monotherapy. No data favor one therapy over the other in terms of COPD hospitalizations. This recommendation also acknowledges that medication-related adverse events were fewer in the short-acting muscarinic antagonist than in the short-acting β_2-agonist group.

16. In patients with moderate to severe COPD, we suggest the use of short-acting muscarinic antagonist plus short-acting β_2-agonist compared with short-acting β_2-agonist alone to prevent acute moderate exacerbations of COPD (Grade 2B).

Underlying Values and Preferences: This recommendation places value on a short-acting muscarinic antagonist plus short-acting β_2-agonist reducing the risk of acute exacerbations of COPD together with the comparative small benefits of a short-acting muscarinic

antagonist plus a short-acting β_2-agonist improving quality of life, exercise tolerance, and lung function compared with short-acting β_2-agonist alone. This recommendation also acknowledges that there are no significant differences in serious adverse events with the use of a short-acting muscarinic antagonist plus a short-acting β_2-agonist vs a short-acting β_2-agonist alone.

17. In patients with moderate to severe COPD, we suggest the use of long-acting β_2-agonist monotherapy compared with short-acting muscarinic antagonist monotherapy to prevent acute exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places value on long-acting β_2-agonist therapy reducing the risk of acute exacerbations of COPD in patients treated with long-acting β_2-agonist monotherapy over short-acting muscarinic antagonist monotherapy and the comparative value of long-acting β_2-agonist monotherapy improving lung function, quality of life, and dyspnea scores compared with short-acting muscarinic antagonist monotherapy. No data favor one therapy over the other in terms of COPD hospitalizations. This recommendation also acknowledges that there are no significant differences in serious adverse events with the use of long-acting β_2-agonist monotherapy over short-acting muscarinic antagonist monotherapy.

18. In patients with moderate to severe COPD, we recommend the use of a long-acting muscarinic antagonist compared with a short-acting muscarinic antagonist to prevent acute moderate to severe exacerbations of COPD (Grade 1A).

Underlying Values and Preferences: This recommendation places high value on a long-acting muscarinic antagonist reducing the risk of acute exacerbations of COPD, both moderate (required course of oral steroids, antibiotics, or both) and severe (required hospitalization), together with the comparative benefit of a long-acting muscarinic antagonist improving quality of life and lung function compared with a short-acting muscarinic antagonist. This recommendation also acknowledges that there were fewer nonfatal serious adverse events in subjects treated with a long-acting muscarinic antagonist than in those treated with a short-acting muscarinic antagonist.

19. In patients with moderate to severe COPD, we suggest the combination use of a short-acting muscarinic antagonist plus long-acting β_2-agonist compared with long-acting β_2-agonist monotherapy to prevent acute mild to moderate exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places value on the combination of short-acting muscarinic antagonist plus long-acting β_2-agonist therapy reducing the risk of acute exacerbations of COPD compared with the use of long-acting β_2-agonist therapy alone and the comparative value of short-acting muscarinic antagonist plus long-acting β_2-agonist therapy improving lung function, quality of life, and dyspnea scores compared with long-acting β_2-agonist monotherapy. No data favor one therapy over the other in terms of COPD hospitalizations. This recommendation also acknowledges that there are no significant differences in serious adverse events with the combined use of short-acting muscarinic antagonist plus long-acting β_2-agonist therapy vs long-acting β_2-agonist therapy alone.

20. For patients with stable moderate, severe, and very severe COPD, we recommend maintenance combination inhaled corticosteroid/long-acting β_2-agonist therapy (and not inhaled corticosteroid monotherapy) compared with placebo to prevent acute exacerbations of COPD (Grade 1B).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD together with slowing the rate of decline in health-related quality of life and a relatively lower value on the risks and consequences of oral candidiasis, hoarseness and dysphonia, bruising, and pneumonia.

21. For patients with stable moderate, severe, and very severe COPD, we recommend maintenance combination inhaled corticosteroid/long-acting β_2-agonist therapy compared with long-acting β_2-agonist monotherapy to prevent acute exacerbations of COPD (Grade 1C).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD together with improved health-related quality of life, reduced dyspnea, less rescue medication use, and improved lung function and a relatively lower value on the risks and consequences of oral candidiasis, upper respiratory tract infections, and pneumonia.

22. For patients with stable moderate to very severe COPD, we recommend maintenance combination inhaled corticosteroid/long-acting β_2-agonist therapy compared with inhaled corticosteroid monotherapy to prevent acute exacerbations of COPD (Grade 1B).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD together with the comparative mortality benefit of combination inhaled corticosteroid/long-acting β_2-agonist therapy, acknowledging that there were no significant differences in serious adverse events or incidence of pneumonia between the groups. This recommendation does not support the use of inhaled corticosteroid monotherapy in COPD.

23. For patients with stable COPD, we recommend inhaled long-acting anticholinergic/long-acting β_2-agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 1C).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD.

24. For patients with stable COPD, we recommend maintenance combination of inhaled corticosteroid/long-acting β_2-agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 1C).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD and a relatively lower value on the risks and consequences of pneumonia.

25. For patients with stable COPD, we suggest maintenance combination of inhaled long-acting anticholinergic/corticosteroid/long-acting β_2-agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD.

PICO 3: In Patients Aged > 40 Years Who Are Previous or Current Smokers With COPD, Does Oral Therapy Prevent/Decrease Acute Exacerbations of COPD?

26. For patients with moderate to severe COPD, who have a history of one or more moderate or severe COPD exacerbations in the previous year despite optimal maintenance inhaler therapy, we suggest the use of a long-term macrolide to prevent acute exacerbations of COPD (Grade 2A).

Underlying Values and Preferences: This recommendation places high value on the prevention of COPD exacerbations. However, clinicians prescribing macrolides need to consider in their individual patients the potential for prolongation of the QT interval and hearing loss as well as bacterial resistance. The duration and exact dosage of macrolide therapy are unknown.

27. For patients with an acute exacerbation of COPD in the outpatient or inpatient setting, we suggest that systemic corticosteroids be given orally or intravenously to prevent hospitalization for subsequent acute exacerbations of COPD in the first 30 days following the initial exacerbation (Grade 2B).

Underlying Values and Preferences: We place high value on reducing recurrent exacerbations in the first 30 days following an initial acute exacerbation of COPD by treating the exacerbation with systemic corticosteroids. This recommendation takes into consideration the risks associated with the short-term use of systemic corticosteroids, which include hyperglycemia, weight gain, and insomnia, but the benefits of this intervention are believed to outweigh the risks. The use of systemic corticosteroids to treat an acute exacerbation has not been shown to reduce acute exacerbations beyond the 30-day window. Furthermore, no evidence supports the use of long-term corticosteroids to reduce acute exacerbations of COPD, and the risks of hyperglycemia, weight gain, infection, osteoporosis, and adrenal suppression far outweigh any benefits.

28. For patients with an acute exacerbation of COPD in the outpatient or inpatient setting, we recommend that systemic corticosteroids not be given orally or intravenously for the sole purpose of preventing hospitalization due to subsequent acute exacerbations of COPD beyond the first 30 days following the initial acute exacerbation of COPD (Grade 1A).

Remark: This does not preclude the use of systemic corticosteroids for the treatment of acute exacerbations of COPD.

Underlying Values and Preferences: We place high value on reducing recurrent exacerbations in the first 30 days following an initial acute exacerbation of COPD by treating the exacerbation with systemic corticosteroids. This recommendation takes into consideration the risks associated with short-term use of systemic corticosteroids, which include hyperglycemia, weight gain, and insomnia, but the benefits of this intervention are believed to outweigh the risks. The use of systemic corticosteroids to treat an acute exacerbation has not been shown to reduce acute exacerbations beyond the 30-day window. Furthermore, no evidence supports the use of long-term

corticosteroids to reduce acute exacerbations of COPD, and the risks of hyperglycemia, weight gain, infection, osteoporosis, and adrenal suppression far outweigh any benefits.

29. For patients with moderate to severe COPD with chronic bronchitis and a history of at least one exacerbation in the previous year, we suggest the use of roflumilast to prevent acute exacerbations of COPD (Grade 2A).

Underlying Values and Preferences: Clinicians prescribing roflumilast need to advise their patients of the potential side effects of weight loss and diarrhea. Patients may have to discontinue the therapy because of side effects. The decision to prescribe this medication should also be informed by the fact that there are limited data for supplemental effectiveness in patients concurrently using inhaled therapies.

30. For stable patients with COPD, we suggest treatment with oral slow-release theophylline twice daily to prevent acute exacerbations of COPD (Grade 2B).

Underlying Values and Preferences: Physicians should inform their patients with COPD who are being treated with maintenance bronchodilator therapy and inhaled corticosteroids and who continue to have periodic exacerbations that theophylline may reduce the number of exacerbations. Patient decisions may also be informed by the relatively narrow therapeutic window with respect to adverse effects of treatment with theophylline. Physicians should use the lowest effective dose in prescribing theophylline in order to avoid adverse effects. Theophylline use requires vigilance on the part of the physician in order to avoid serious drug interactions, which lead to changes in serum theophylline levels. Patients should be advised that changes in tobacco use habits will affect serum theophylline levels and that they should inform their physicians if they stop smoking while taking theophylline.

31. For patients with moderate to severe COPD and a history of two or more exacerbations in the previous 2 years, we suggest treatment with oral N-acetylcysteine to prevent acute exacerbations of COPD (Grade 2B).

Underlying Values and Preferences: Physicians should inform their patients with COPD who are being treated with maintenance bronchodilator therapy and inhaled corticosteroids and who continue to have periodic exacerbations that N-acetylcysteine may reduce the number of exacerbations. Patient decisions may also be informed by the low risk of adverse effects from treatment with N-acetylcysteine.

32. For stable outpatients with COPD who continue to experience acute exacerbations of COPD despite maximal therapy designed to reduce acute exacerbations of COPD, we suggest that oral carbocysteine could be used to prevent acute exacerbations where this therapy is available (Ungraded Consensus-Based Statement).

Underlying Values and Preferences: This suggestion places high value on preventing acute exacerbations of COPD, with minimal risks associated with carbocysteine. The main adverse events reported in studies were mild GI symptoms.

33. For patients with moderate to severe COPD who are at risk for COPD exacerbations, we do not recommend using statins to prevent acute exacerbations of COPD (Grade 1B).

Underlying Values and Preferences: We place high value on reducing exacerbations in patients with COPD and, thus, do not recommend statins for preventing acute exacerbations. However, patients with COPD may meet accepted criteria for initiating statins because of the presence of cardiovascular risk factors.

Introduction

COPD is a common disease with substantial associated morbidity and mortality. Patients with COPD usually have a progression of airflow obstruction that is not fully reversible and can lead to a history of progressively worsening breathlessness, that can impact daily activities and health-related quality of life.[1-3] COPD is the fourth leading cause of death in Canada[4] and the third leading cause of death in the United States where it claimed 133,965 lives in 2009.[5] In 2011, 12.7 million US adults were estimated to have COPD.[6] However, approximately 24 million US adults have evidence of impaired lung function, indicating an underdiagnosis of COPD.[7] Although 4% of Canadians aged 35 to 79 years self-reported having been given a diagnosis of COPD, direct measurements of lung function from the Canadian Health Measures Survey indicate that 13% of Canadians have a lung function score indicative of COPD.[4]

COPD is also costly. In 2009, COPD caused 8 million office visits, 1.5 million ED visits, 715,000 hospitalizations, and 133,965 deaths in the United States.[8] In 2010, US costs for COPD were projected to be approximately $49.9 billion, including $29.5 billion in direct health-care expenditures, $8.0 billion in indirect morbidity costs, and $12.4 billion in indirect mortality costs.[9] Exacerbations account for most of the morbidity, mortality, and costs associated with COPD. The economic burden associated

with moderate and severe exacerbations in Canada has been estimated to be in the range of $646 million to $736 million per annum.[10] This value may be an underestimate given that the prevalence of moderate exacerbations is not well documented, COPD is underdiagnosed, and the rate of hospitalization due to COPD is increasing.[11]

Exacerbations are to COPD what myocardial infarctions are to coronary artery disease: They are acute, trajectory-changing, and often deadly manifestations of a chronic disease. Exacerbations cause frequent hospital admissions, relapses, and readmissions[12]; contribute to death during hospitalization or shortly thereafter[12]; reduce quality of life dramatically[12,13]; consume financial resources[12,14]; and hasten a progressive decline in pulmonary function, a cardinal feature of COPD. Hospitalization due to exacerbations accounts for > 50% of the cost of managing COPD in North America and Europe.[15,16]

COPD exacerbation has been defined as

> an event in the natural course of the disease characterized by a baseline change in the patient's dyspnea, cough, and/or sputum that is beyond the normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD.[17,18]

Exacerbation in clinical trials has been defined for operational reasons on the basis of whether an increase in treatment beyond regular or urgent care is required in an ED or a hospital. Exacerbation treatment in clinical trials usually is defined by the use of antibiotics, systemic corticosteroids, or both.[19] The severity of the exacerbation is then ranked or stratified according to the outcome: mild, when the clinical symptoms are present but no change in treatment or outcome is recorded; moderate, when the event results in a change in medication such as the use of antibiotics and systemic corticosteroids; or severe, when the event leads to a hospitalization.[1]

Two-thirds of exacerbations are associated with respiratory tract infections or air pollution, but one-third present without an identifiable cause.[17] Exacerbations remain poorly understood in terms of not only cause but also treatment and prevention. Although the management of an acute exacerbation has been the primary focus of clinical trials, the prevention of acute exacerbations has not been a major focus until recently. Most current COPD guidelines focus on the general diagnosis and evaluation of the patient with COPD, the management of stable disease, and the diagnosis and management of acute exacerbations.[1,20] Although current COPD guidelines state that prevention of exacerbations is possible, little guidance is provided to the clinician regarding current available therapies for the prevention of COPD exacerbations.[1,20] Moreover, recent new therapies have promise in preventing acute exacerbations of COPD (AECOPDs) and would benefit from critical review of their efficacy in the exacerbation prevention management.[21-23] The American College of Chest Physicians (CHEST) and Canadian Thoracic Society (CTS) jointly commissioned this evidence-based guideline on the prevention of COPD exacerbations to fill this important void in COPD management.

The overall objective of this CHEST and CTS joint evidence-based guideline (AECOPD Guideline) was to create a practical, clinically useful document describing the current state of knowledge regarding the prevention of acute exacerbations of COPD according to major categories of prevention therapies. We accomplished this by using recognized document evaluation tools to assess and choose the most appropriate studies and evidence to extract meaningful data and to grade the level of evidence supporting the recommendations in a balanced and unbiased fashion. The AECOPD Guideline is unique not only for its topic, but also for the first-in-kind partnership between two of the largest thoracic societies of North America. The CHEST Guidelines Oversight Committee (GOC) in partnership with the CTS COPD Clinical Assembly launched this project with the objective that a systematic review and critical evaluation of the published literature by clinical experts and researchers in the field of COPD would lead to a series of recommendations to assist clinicians in their management of the patient with COPD. This guideline is unique because a group of interdisciplinary clinicians who have special expertise in COPD clinical research and care led the development of the guideline process with the assistance of methodologists.

Materials and Methods

Expert Panel Composition

Members from CHEST and CTS were selected to participate on the AECOPD Guideline panel based on their expertise in the field. CTS representatives were members of the CTS COPD Clinical Assembly. Members who were interested in serving on the guideline panel were asked to submit their curriculum vitae, statement of interest, and conflict of interest disclosure form to the CHEST GOC for review. The final panel comprised a chair from CHEST and vice-chair from CTS as well as eight panelists from CHEST and nine from CTS who are experts in pulmonology and respiratory therapy. Panelists were assigned to one of three writing groups that addressed each key question. The groups were referred to as PICO groups because the key questions were developed using the PICO format, which defines the population, intervention, comparator, and outcome of interest.

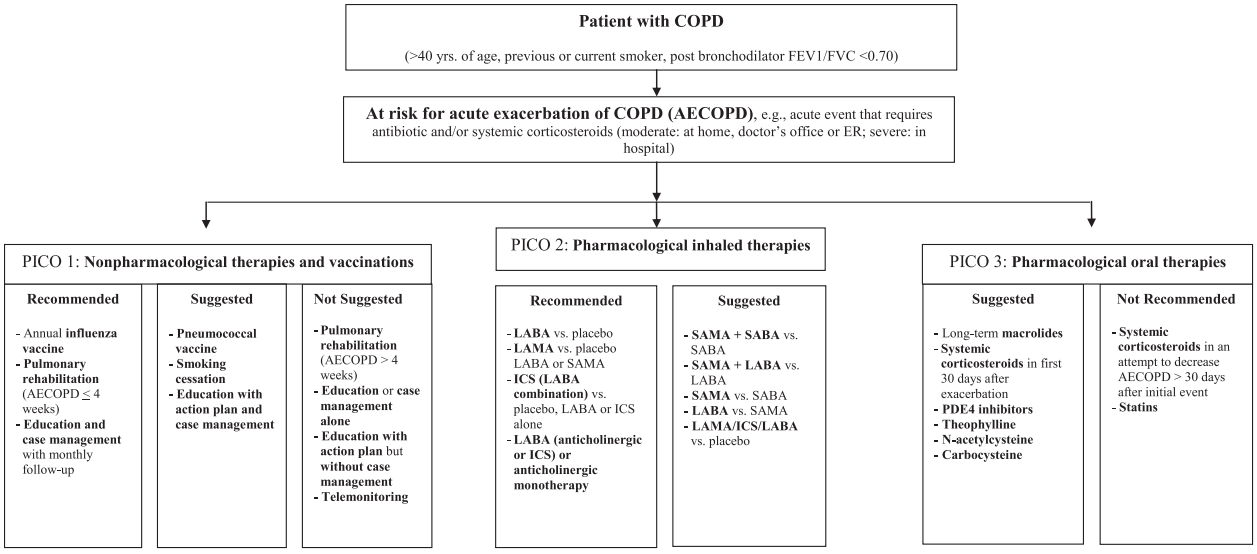

Figure 1 – *Decision tree for prevention of AECOPD according to three key clinical questions using the PICO format: nonpharmacologic therapies, inhaled therapies, and oral therapies. Note that the wording used is "recommended or not recommended" when the evidence was strong (level 1) or "suggested or not suggested" when the evidence was weak (level 2). AECOPD = acute exacerbation of COPD; ER = emergency room; ICS = inhaled corticosteroid; LABA = long-acting* β_2*-agonist; LAMA = long-acting muscarinic antagonist; PDE4 = phosphodiesterase 4; PICO = population, intervention, comparator, outcome; SABA = short-acting* β_2*-agonist; SAMA = short-acting muscarinic antagonist.*

Conflicts of Interest

The CHEST GOC reviewed all panel nominees, including the three methodologists, for their conflicts of interest. After review, nominees who reported no substantial conflicts of interest were approved, and nominees with potential conflicts of interest deemed to be manageable were "approved with management." Panelists approved with management were prohibited from writing and voting on treatment-related recommendations. They were allowed to contribute to writing the background sections of the guidelines and to participate in discussions of controversial recommendations. The chair was charged with reviewing any writing submitted by panelists who were approved with management. A grid tracking the conflicts of interest for each recommendation was created for each PICO writing group at the time of voting on the controversial recommendations. The three conflict of interest grids can be found in e-Tables 1 to 3.

Formulation of Key Questions

The AECOPD Guideline Executive Committee developed three key questions using the PICO format, which were then reviewed and revised by each PICO writing group. The three PICO questions that addressed the prevention of acute exacerbations of COPD were nonpharmacologic therapies, inhaled therapies, and oral therapies (Table 1). The outcome of interest was preventing acute exacerbations, including those requiring change in medication (antibiotic, prednisone, or both), ED visits and hospital admissions and readmissions, unscheduled physician visits, change in location of care, time to first exacerbation, or exacerbation rate. Systematic reviews were conducted for interventions identified in each PICO question, starting with a search for guidelines and systematic reviews. A further explanation of these processes was published separately.[24]

Definitions of Exacerbations

Exacerbation and COPD severity is noted when data were available to characterize the level of impairment or exacerbation severity. Exacerbations were defined as events that required a medication intervention with antibiotics, systemic corticosteroids, or both, and the severity of exacerbations was characterized by the location of care (home, ED, or hospital). Mild exacerbations were defined by adjustments in bronchodilator or inhaled corticosteroid therapy; moderate exacerbations were lower respiratory tract events treated with antibiotics, corticosteroids, or both agents; and severe exacerbations required ED visits or hospitalization. For the purpose of these guidelines, COPD was defined as a postbronchodilator $FEV_1/FVC < 0.7$. Mild COPD was further stratified by an $FEV_1 \geq 80\%$ predicted, moderate COPD by an FEV_1 50% to < 79% predicted, severe COPD by an FEV_1 30% to 49% predicted, and very severe COPD by an $FEV_1 < 30\%$ predicted.

Literature Searches

All panelists reviewed the PICO questions and finalized the search terms, inclusion and exclusion criteria, and databases that would be searched (Table 2). The Guidelines International Network (GIN) Library and National Guideline Clearinghouse were used to search for guidelines on COPD, and PubMed and the Cochrane Library were used to search for systematic reviews and primary literature.

The searches for guidelines were conducted on January 30, 2013, and included all guidelines published up to that date. The GIN search netted 26 guidelines, whereas the National Guidelines Clearinghouse search netted 24; only six of these were not found in the GIN search. In total, eight guidelines were considered relevant and were assessed for quality using the AGREE (Appraisal of Guidelines Research & Evaluation) II instrument.[25] Guidelines were excluded if they did not cover one of the three interventions (nonpharmacologic therapies, inhaled therapies, and oral therapies), did not cover the outcome of interest (prevention of acute exacerbations of COPD), or were not an evidence-based guideline.

The Cochrane search for systematic reviews took place on April 25, 2013, and was limited to systematic reviews published between 2007 and 2013. The PubMed search was conducted on April 29, 2013, and was limited to reviews published between 2008 and 2013. The search of the Cochrane Library resulted in 127 systematic reviews, and an additional 14 systematic reviews were found in the PubMed search. The systematic reviews were categorized by topic and sent to the three PICO groups for study selection. Relevant systematic reviews were assessed for quality using the DART (Documentation and Appraisal Review Tool)[26] to further determine whether they would be used to directly inform the evidence base for recommendations. Any fair- or good-quality

TABLE 1] PICO Questions

Section	Population	Intervention	Comparator	Outcome
Key question 1: In patients aged>40 y who are previous or current smokers with COPD, do nonpharmacologic treatments and vaccinations prevent acute exacerbations?				
Nonpharmacologic treatment and vaccinations	• Adults with COPD aged>40 y • Previous or current smoker • Diagnosis confirmed by spirometry $FEV_1/FVC<0.70$	• Nonpharmacologic treatment and vaccinations (includes self-management, intensive education, vaccinations, rehabilitation, telemedicine, and integration of information technology platforms) • Education: educational sessions on COPD without support intervention other than physician visits • Self-management: —Educational sessions on COPD with ongoing support/empowerment from a case manager or COPD educator through visits, telephone calls, or information technology —Educational sessions on COPD with telemedicine-based programs without support intervention, such as the presence of a case manager (telemonitoring, teleintervention), that include stationary and mobile device applications —In-home monitoring without an educational component • Pulmonary rehabilitation (inpatient and outpatient): educational sessions on COPD with an exercise training program (home, community, outpatient, or inpatient) for minimum of 4 wk or 12 sessions • Vaccinations: influenza and pneumococcal vaccination • Smoking cessation	• Usual care and community standard of care at that time	• Exacerbations requiring change in medication (antibiotics, prednisone, or both) • ED visits and hospital admissions and readmissions • Unscheduled physician visits • Change in location of care • Time to first exacerbation • Exacerbation rate

(Continued)

TABLE 1] *(continued)*

Section	Population	Intervention	Comparator	Outcome
Key question 2: In patients aged > 40 y who are previous or current smokers with COPD, does maintenance inhaled therapy prevent acute exacerbations?				
Maintenance inhaled therapy	• Adults with COPD aged > 40 y • Previous or current smoker • Diagnosis confirmed by spirometry $FEV_1/FVC < 0.70$	Maintenance inhaled therapy: • Long-acting anticholinergics • Short-acting anticholinergics alone and in combination with short-acting β_2-agonists • ICSs • Long-acting β_2-agonists (formoterol, salmeterol, indacaterol) • Combination of long-acting anticholinergics, ICSs, and long-acting β_2-agonists • Should not include short-acting reliever medications (short-acting β_2-agonists alone)	• Short-acting bronchodilators • Combination therapies compared with single modality • Studies where control arm includes treatment • Head-to-head comparison	• Exacerbations requiring change in medication (antibiotics, prednisone, or both) • ED visits and hospital admissions and readmissions • Unscheduled physician visits • Change in location of care • Time to first exacerbation • Exacerbation rate
Key question 3: In patients aged > 40 y who are previous or current smokers with COPD, does oral therapy prevent acute exacerbations?				
Oral therapy	• Adults with COPD aged > 40 y • Previous or current smoker • Diagnosis confirmed by spirometry $FEV_1/FVC < 0.70$	Oral therapy: • Chronic antibiotic therapy • Phosphodiesterase 4 inhibitors • Statins • Oral or systemic corticosteroid therapy • Mucolytics (erdosteine, carbocysteine, N-acetylcysteine) • Theophyllines	• Study-defined placebo	• Exacerbations requiring change in medication (antibiotics, prednisone, or both) • ED visits and hospital admissions and readmissions • Unscheduled physician visits • Change in location of care • Time to first exacerbation • Exacerbation rate

ICS = inhaled corticosteroid; PICO = population, intervention, comparator, outcome.

TABLE 2] Study Methods

Section	Type of Study	Search Terms	Inclusion/Exclusion Criteria	Databases Searched
Key question 1: In patients aged > 40 y who are previous or current smokers with COPD, do nonpharmacologic treatments and vaccinations prevent acute exacerbations?				
Nonpharmacologic treatment and vaccinations	• Systematic reviews/ meta-analyses • RCTs (if available) • Otherwise cohort studies, case series studies, prospective studies, retrospective studies	• Acute exacerbations • COPD, chronic obstructive lung disease, emphysema, chronic bronchitis, lung diseases (obstructive) • Chronic disease management, prevention • Nonpharmacologic therapies, education • Self-management • Case management • Action plans • In-home monitoring • Tele-intervention, telehealth, tele-health, Ehealth, e-health, telehealthcare, telecare, telemedicine, tele-monitoring, Emedicine, telecommunications and medicine, teleconsult • Respiratory rehabilitation pulmonary rehabilitation, (exercise, exercise training, activity, physical activity, exercise movement techniques, muscle training, kinesiotherapy, strength, training, walking, ambulation, mobilization, mobility, fitness exercise)—only if exercise is included • Immunizations, vaccination, influenza prevention, pneumococcal prevention • Smoking cessation	• English-language studies • No date restrictions • Studies included based on PICO • Included studies with follow-up duration ≥ 3 mo and studies with follow-up duration ≥ 6 mo • Primary and secondary outcomes included. If studies included that examined an outcome of interest as a secondary outcome, the assessment of the secondary outcomes was carefully examined and the body of evidence downgraded for risk of bias, if deemed necessary.	• National Guidelines Clearinghouse • Guidelines International Network • PubMed • Cochrane Library
Key question 2: In patients aged > 40 y who are previous or current smokers diagnosed with COPD, does maintenance inhaled therapy prevent acute exacerbations?				

(Continued)

TABLE 2] *(continued)*

Section	Type of Study	Search Terms	Inclusion/Exclusion Criteria	Databases Searched
Maintenance inhaled therapy	• Systematic reviews/ meta-analyses • RCTs (if available) • Otherwise cohort studies, case series studies, prospective studies, retrospective studies	• Acute exacerbations • COPD, chronic obstructive lung disease, emphysema, chronic bronchitis, lung diseases (obstructive) • Chronic disease management, prevention • Inhaled therapy • Long acting β agonists • Long acting anticholinergics • Short acting anticholinergics • Inhaled corticosteroids	• English-language studies • No date restrictions • Studies included based on PICO • Included studies with follow-up duration ≥ 3 mo and studies with follow-up duration ≥ 6 mo • Primary and secondary outcomes included. If studies included that examined an outcome of interest as a secondary outcome, the assessment of the secondary outcomes was carefully examined and the body of evidence downgraded for risk of bias, if deemed necessary.	• National Guidelines Clearinghouse • Guidelines International Network • PubMed • Cochrane Library
Key question 3: In patients aged > 40 y who are previous or current smokers with COPD, does oral therapy prevent acute exacerbations?				
Oral therapy	• Systematic reviews/ meta-analyses • RCTs (if available) • Otherwise cohort studies, case series studies, prospective studies, retrospective studies	• Acute exacerbations • COPD, chronic obstructive lung disease, emphysema, chronic bronchitis, lung diseases (obstructive) • Chronic disease management, prevention • Oral therapy • Antibiotics • Erdosteine • Carbocisteine • N-acetylcysteine • Phosphodiesterase-4 inhibitors • Statins • Oral or systemic corticosteroids • Mucolytics • Theophyllines	• English-language studies • No date restrictions • Studies included based on PICO • Included studies with follow-up duration ≥ 3 mo and studies with follow-up duration ≥ 6 mo • Primary and secondary outcomes included. If included studies examined an outcome of interest as a secondary outcome, the assessment of the secondary outcomes was carefully examined and the body of evidence downgraded for risk of bias, if deemed necessary.	• National Guidelines Clearinghouse • Guidelines International Network • PubMed • Cochrane Library

RCT = randomized controlled trial. See Table 1 legend for expansion of other abbreviation.

systematic reviews used in this manner were updated through the search strategies used by the review authors. Systematic reviews were also scanned for references that could further inform the primary literature searches.

Literature Searches by PICO Group

The PICO 1 nonpharmacologic therapies group reviewed 49 systematic reviews and determined that 15 were relevant. Of the 15 systematic reviews, four were used to directly inform the evidence base. The PICO 1 group conducted primary literature searches and reviews for the questions on education, action plans, case management, and smoking cessation because existing systematic reviews did not meet the predefined definitions for these interventions. The PICO 2 inhaled therapies group reviewed 49 systematic reviews and determined that 30 were relevant. Of the 30 systematic reviews, 11 were used to directly inform the evidence base. The PICO 3 oral therapies group reviewed 27 systematic reviews and determined that eight were potentially relevant. The PICO 3 group also conducted primary literature reviews because the extracted systematic reviews did not sufficiently address all the drug classes. Additional details on literature searches and study selection can be found in e-Appendix 1.

Study Selection and Data Extraction

A methodologist assigned to each PICO group conducted the initial literature searches and the first-round title and abstract review to exclude studies not related to COPD based on the inclusion and exclusion criteria shown in Table 2. The panelists reviewed the studies identified for exclusion and divided into pairs to apply the inclusion and exclusion criteria to the studies initially screened for inclusion. All recommendations were made independently in parallel and then compared. Disagreements were resolved through discussion and further consultation with the methodologist if needed. Panelists were divided into pairs for data extraction, with one performing data extraction and the other independently reviewing the initial data extraction. The methodologists assisted in building evidence tables and added data necessary for conducting any meta-analyses. Data from new studies identified in updated searches of published systematic reviews and data from de novo reviews were extracted into evidence tables (e-Tables 4, 5).

Quality Assessment

The methodologists assessed the quality of the guidelines using AGREE II[25] and DART.[26] Randomized controlled trials (RCTs) were assessed using the Cochrane Risk of Bias tool.[27] R. D. developed a quality assessment tool for intervention studies, including RCTs and observational studies, that was used to assess the quality of any observational studies included in the evidence reviews.[28,29] As the methodologists were assessing the quality of the studies, they also considered how exacerbations were counted[30] and whether the outcomes were treated as primary or secondary outcomes.

Meta-analyses and Evidence Profiles

Upon completion of the evidence tables and quality assessment, Review Manager version 5.1 software (The Cochrane Collaboration) was used to create meta-analyses on topics where data were homogeneous and poolable based on the measured outcomes. Studies with a shorter follow-up period (ie, 3-4 months) were examined separately from those with a longer follow-up period (ie, $\geq$ 6 months). When possible, meta-analyses included studies from published systematic reviews as well as new studies identified through updated searches. Meta-analyses were also used for data compiled from de novo reviews. Heterogeneity of the pooled results was assessed using a χ^2 test and Higgins I^2, and a forest plot was examined for consistency of the results. A Higgins $I^2 \geq 50\%$ and $P < .05$ indicated statistically significant heterogeneity. The random-effects model was chosen a priori as the appropriate model for pooling data. Results from the meta-analyses can be found in e-Tables 6 and 7.

Grading the Evidence Profiles

Evidence profiles were produced using GRADEpro software (GRADE Working Group). The GRADEpro software ranked the quality of the body of evidence using four categories: high, moderate, low, and very low (Table 3).[31] The quality of the evidence was then used to determine the strength of the supporting evidence that informed a recommendation (see the next section, Recommendations, for more information on grading recommendations). Additional information on grading the body of evidence can be found in "Methodologies for the Development of CHEST Guidelines and Expert Panel Reports."[24] Evidence profiles can be found in e-Tables 8 to 10.

Recommendations

Evidence tables, meta-analyses, evidence profiles, and all the studies included in the evidence review informed the recommendations and their associated grades. Recommendations were graded using the CHEST grading system (Table 4).[24,32] Values and preferences statements are considered part of a recommendation, and they appear with the recommendation in the main text of the guideline as well as in the summary of recommendations and executive summary. Panelists who were approved with management refrained from writing treatment-related recommendations and were assigned to drafting supporting text. Only one panelist in the PICO 1 nonpharmacologic therapies group was prohibited from writing treatment-related recommendations. Two panelists in the PICO 2 inhaled therapies group were permitted to write recommendations, and they worked with the other panelists in the group to draft supporting text. Three panelists in the PICO 3 oral therapies group were permitted to write recommendations, and they worked with the other panelists to draft the supporting text. Recommendations were not made in instances where the panelists believed the data insufficient or inconclusive to warrant a recommendation. In instances where there was insufficient evidence but a recommendation was still warranted, a weak suggestion was developed, and consensus based (CB) replaced the grade. Completed recommendations/suggestions and supporting text were reviewed by each PICO group and revised before shared with the entire panel.

Recommendations/suggestions and supporting text were sent to the panelists along with a survey of the recommendations/suggestions asking panelists to identify any recommendations deemed controversial based on wording, grade, or both. Any recommendations identified as

TABLE 3] Rating the Confidence in the Estimate of the Effect

Quality of the Evidence	Level of Confidence in the Estimate of the Effect
High	Very confident that the true effect lies close to that of the estimate of the effect
Moderate	Moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low	Very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect

Definitions adapted from Balshem et al.[31]

TABLE 4] American College of Chest Physicians Grading System

Grade of Recommendation	Balance of Benefit vs Risk and Burdens (Strength of the Recommendation: Level 1 or 2)	Methodological Strength of Supporting Evidence (Quality of Body of Evidence: A, B, C, or CB)	Implications
Graded evidence-based guideline recommendations			
Strong recommendation, high-quality evidence (1A)	Benefits clearly outweigh risk and burdens or vice versa	Consistent evidence RCTs without important limitations or exceptionally strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Further research is very unlikely to change confidence in the estimate of effect.
Strong recommendation, moderate-quality evidence (1B)	Benefits clearly outweigh risk and burdens or vice versa	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or very strong evidence from observational studies	Recommendation can apply to most patients in most circumstances. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate.
Strong recommendation, low- or very-low-quality evidence (1C)	Benefits clearly outweigh risk and burdens or vice versa	Evidence for at least one critical outcome from observational studies, case series, or RCTs with serious flaws or indirect evidence	Recommendation can apply to most patients in many circumstances. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate.
Weak recommendation, high-quality evidence (2A)	Benefits closely balance with risks and burden	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies	The best action may differ, depending on circumstances or patient or societal values. Further research is very unlikely to change confidence in the estimate of effect.
Weak recommendation, moderate-quality evidence (2B)	Benefits closely balance with risks and burden	Evidence from RCTs with important limitations (inconsistent results, methodologic flaws, indirect, or imprecise) or very strong evidence from observational studies	Best action may differ, depending on circumstances or patient or societal values. Higher-quality research may well have an important impact on confidence in the estimate of effect and may change the estimate.
Weak recommendation, low- or very-low-quality evidence (2C)	Uncertainty in the estimates of benefits, risks, and burden; benefits, risk, and burden may be closely balanced	Evidence for at least one critical outcome from observational studies, case series, or RCTs with serious flaws or indirect evidence	Other alternatives may be equally reasonable. Higher-quality research is likely to have an important impact on confidence in the estimate of effect and may well change the estimate.
Nongraded consensus-based suggestions			
Consensus based	Uncertainty due to lack of evidence but expert opinion that benefits outweigh risk and burdens or vice versa	Insufficient evidence for a graded recommendation	Future research may well have an important impact on confidence in the estimate of effect and may change the estimate.

CB = consensus based. See Table 2 legend for expansion of abbreviation.

controversial in the survey as well as any CB suggestions were presented and discussed during a live webinar. Panelists were then sent an additional survey with the revised statements resulting from the discussions and asked to vote on the recommendations/suggestions. The conflict of interest grids were sent with the voting survey, and panelists approved with management were on the honor system to refrain from voting on any treatment-related recommendations. Based on CHEST policy, 75% participation and 80% consensus were required for recommendations/suggestions to pass. Any recommendations/suggestions that did not pass were revised based on feedback included in the voting survey, and a new survey was sent with the incorporated changes.

Review Process

After the AECOPD Guideline Executive Committee provided final approval, the manuscript was sent to the Executive of the Canadian Respiratory Guidelines Committee (CRGC), CTS Executive, and CHEST reviewers representing the GOC, Board of Regents, and NetWorks. The CHEST NetWorks of interested members in the areas of airways disorders and clinical pulmonary medicine reviewed the manuscript content. All reviewed both content and methods for consistency, accuracy, and completeness. The *CHEST* Journal peer-review process was integrated with these reviews. All ideas for modification were marked as mandatory or suggested by the GOC, responded to or justified by the authors, and tracked through multiple rounds of review.

Dissemination, Implementation, and Knowledge Translation

After publication, the guidelines were promoted by both CHEST and CTS to a wide audience of physicians, other health-care providers, and the public through multiple avenues. Joint press releases were made to both the lay and the medical media, with major outreach efforts to all relevant print, broadcast, and Internet media. Panelists located in various large media markets were identified as potential spokespersons for interviews. In addition to the guidelines, a companion article was prepared to help with implementation.

American College of Chest Physicians: Social media promotion was facilitated over Twitter, Facebook, CHEST e-Communities, internal and external blogs, and other communication routes. Blast communications were sent to CHEST members with links to the publication and postings on the CHEST website.

In addition to publication in *CHEST*, other derivative products were prepared to help with implementation, including slide sets, algorithms, and other clinical tools. These derivative products were posted on the CHEST website and made available in CHEST Guidelines expected to launch at a later date. CHEST Guidelines will be the repository for the most current recommendations/suggestions from all CHEST guidelines, consensus statements, and hybrid documents. This online repository will also house a collection of related resources.

Canadian Thoracic Society: The knowledge translation plan was developed by (1) identifying key messages from the guideline recommendations, (2) determining the target audiences for each message, (3) seeking out the most credible messenger and engaging his or her interest in becoming involved in the communication, and (4) launching a knowledge translation strategy grounded in the best available research evidence. The CTS has a framework for guideline dissemination and implementation, with concurrent evaluation led by the CRGC based on the Knowledge-to-Action Framework.[33] Traditional knowledge diffusion avenues, such as presentations at scientific meetings and publication in peer-reviewed journals, will be used. The guideline was promoted through the CRGC website (www.respiratoryguidelines.ca). Targeted promotional communications were sent to provincial lung associations across Canada and distributed through CTS e-bulletins to individuals and organizations with an interest in this topic area.

CTS used other modes of communication such briefing notes, websites, creative media, and emerging online technologies (eg, podcasting, accredited webinars). To disseminate more broadly to the general public, traditional media and social media were engaged. Point-of-care tools for implementation of guideline recommendations were developed, including a trifold pocket brochure (Slim Jim) and electronic versions of the guideline for the smart phone and tablet. A slide kit for teaching and self-directed learning were posted for viewing and downloading on the CRGC website.

Endorsement

Associations were invited to consider endorsing the approved guideline for listing in the final publication. These organizations were requested to help to promote the publication to their memberships through newsletters, websites, and other means.

Updating

CHEST guidelines and consensus statements are living documents subject to updating as necessary. Annual reviews begin 1 year after publication. The CHEST GOC and CTS CRGC have established criteria to select and prioritize projects for updating, including the publication of new studies where the results might affect either the direction or the strength of the existing recommendations. Other criteria focus on new interventions or changes in practice that might require updating existing recommendations. The long-term goal is to maintain the currency of the guidance documents.

Recommendations for the Prevention of Acute Exacerbations of COPD

PICO 1: Do Nonpharmacologic Treatments and Vaccinations Prevent/Decrease Acute Exacerbations of COPD?

Effective support and management of individuals at risk for an AECOPD demands a comprehensive and patient-centered approach. The widely adopted Chronic Care Model[34,35] recognizes that improvements in care require approaches incorporating patient-, provider-, and system-level interventions. Key elements of the Chronic Care Model are the health system, delivery system design (including case management), decision support, clinical information systems, self-management support (including assessment, goal setting, action planning, problem solving, and follow-up), and community. The importance of incorporating nonpharmacologic approaches into the care of this population is reflected in international guidelines for COPD management.[20,36,37]

PICO question 1 addresses the following categories: (1) pneumococcal vaccinations; (2) influenza vaccinations; (3) smoking cessation programs; (4) pulmonary rehabilitation; (5) education, action plans, and case management; and (6) telemonitoring (Table 1). A definition of each intervention is specified in the text

that accompanies each recommendation. The present taxonomy and definitions of interventions differ from that of several other publications[38-40] related to nonpharmacologic management. We chose to create exclusive, clearly defined, and comparable categories and to characterize evolving technologies, such as telemonitoring.

These topics may be considered complex interventions[41] in that they contain multiple interacting components and possess nonlinear causal pathways subject to a host of variables.[42] Rigorous evaluation of complex interventions can be complicated by numerous factors, including the need to adapt interventions to local contexts and issues of feasibility and acceptability.[43] Many of the nonpharmacologic trials have limitations with respect to such methodological aspects as how the intervention was standardized and the details of the experimental treatment and comparator as they were implemented. Prevention of exacerbations often was not the primary outcome for many studies examining the efficacy and effectiveness of nonpharmacologic interventions, thus limiting our ability to make definitive recommendations. We recognize that some interventions may have beneficial outcomes relevant to overall health and quality of life but are insufficient to recommend their use to prevent exacerbations.

Pneumococcal Vaccine: The presence of underlying medical conditions such as COPD increases the risk for pneumococcal disease and its complications. Hospitalization rates for pneumococcal pneumonia are higher in patients with COPD than in the general population.[44,45] Pneumococcal vaccinations are effective for reducing the risk of infectious disease and may be beneficial in reducing infectious-related exacerbations in COPD.[46] Patients with COPD with persistent lower-airway bacterial colonization, those with *Streptococcus pneumoniae* in sputum, and those with newly acquired *Streptococcus* pneumonia have a significantly increased risk of COPD exacerbation.[47-49] COPD exacerbations associated with pneumococcal infection result in longer hospitalizations and greater impairment of lung function compared with noninfectious exacerbations.[50] Multiple guidelines, including those of the US Centers for Disease Control and Prevention (CDC) and Health Canada, recommend the use of pneumococcal vaccine for all adults aged ≥ 65 years and those aged 19 to 64 years with underlying medical conditions that put them at greater risk for serious pneumococcal infection, including those with COPD.[20,37,44,46,51]

Although existing recommendations support vaccination in patients with COPD in general, no clear evidence supports its use to prevent acute exacerbations of COPD as summarized in a Cochrane review.[52] Seven studies met inclusion criteria; two older trials used a 14-valent vaccine, and five more-recent trials used a 23-valent vaccine. Improvement in pneumonia rates in patients with COPD (six studies involving 1,372 individuals) did not achieve statistical significance for vaccination vs control (OR, 0.72; 95% CI, 0.51-1.01). The likelihood of acute exacerbations of COPD (two studies involving 216 individuals) was not different between the vaccination vs no vaccination groups (OR, 0.58; 95% CI, 0.30-1.13). Analysis of secondary outcomes found no statistically significant reduction in hospital admissions or ED visits. In pooled results from three studies (n = 888), there was no significant reduction in all-cause mortality for periods up to 48 months postvaccination (OR, 0.94; 95% CI, 0.67-1.33).

The COPD Clinical Research Network evaluated the safety and immunogenicity of a 7-valent protein-conjugated vs 23-valent polysaccharide pneumococcal vaccine in a randomized open-label trial in patients with COPD.[53] Both vaccines resulted in significant increases in postvaccination IgG levels for all serotypes compared with baseline; however, there were greater antibody responses in five of seven serotypes using the 7-valent protein-conjugated vs the 23-valent polysaccharide vaccine. No differences (hazard ratio [HR], 0.91; $P = .66$) were noted in the time to first exacerbation of COPD or in the number of exacerbations, cases of pneumonia, or hospitalizations, but the study was not powered to address these issues.

We also found one study that examined the additive effect of pneumococcal vaccine and influenza vaccine on acute exacerbations in patients with chronic lung diseases.[54] In this open-label RCT in 167 subjects randomly assigned to both vaccines compared with influenza vaccine alone, fewer episodes of infectious-related acute exacerbations were experienced over a 2-year period ($P = .022$).

1. In patients with COPD, we suggest administering the 23-valent pneumococcal vaccine as part of overall medical management but did not find sufficient evidence that pneumococcal vaccination prevents acute exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places high value on the benefits of pneumococcal vaccination for general health, and we endorse existing guidelines that recommend it for patients with COPD. Although evidence does not specifically support using the vaccine for the prevention of acute exacerbations, multiple bodies, including the CDC and World Health

Organization (WHO), recommend the use of pneumococcal vaccine for all adults aged ≥ 65 years and in those aged 19 to 64 years with underlying medical conditions such as COPD that put them at greater risk of serious pneumococcal infection.

Influenza Vaccine: Annual influenza vaccination is the primary means of influenza prevention and has been recommended since 2010 for all persons aged ≥ 6 months who do not have contraindications.[55] Influenza infection is associated with excessive mortality and morbidity in COPD that include detrimental effects on disease progression and increased risk of hospitalization.[1,20,36,37,56,57]

The evidence supporting the recommendation for influenza vaccine use in COPD was primarily derived from a Cochrane review last updated in May 2009.[58] This systematic review evaluated the evidence from RCTs regarding treatment effects of influenza vaccination in subjects with COPD, including exacerbation rates, hospitalizations, mortality, lung function, and adverse effects.[58] Eleven studies were included in this systematic, evidence-based review, with six specifically performed in patients with COPD and two evaluating exacerbation rates using inactivated virus vaccination.[59,60] These studies defined COPD minimally by specified COPD clinical diagnosis and measured exacerbations determined clinically without rigorous or adjudicated definitions. In a pooled analysis across 180 subjects, inactivated influenza vaccine in patients with COPD resulted in a significant reduction in the total number of exacerbations per vaccinated subject compared with those who received placebo (weighted mean difference [WMD], −0.37; 95% CI, −0.64 to −0.11; $P = .006$). The effect was further to occur only after 3 to 4 weeks, defined as late exacerbations (WMD, −0.39; 95% CI, −0.61 to −0.18; $P = .0004$). Both studies found a reduction in influenza-related respiratory infections (WMD, 0.19; 95% CI, 0.07-0.48; $P = .0005$).

Additional analyses in the Cochrane review[58] of other secondary outcomes found no effect on reduced hospitalization (OR, 0.33; 95% CI, 0.09-1.24; $P = .52$). Analyses of a broader pool of patients with COPD and in elderly patients in general (only a minority of whom had COPD) found a significant increase in the occurrence of local adverse reactions with vaccines, but the effects were generally mild and transient. There was no evidence of an effect of intranasal live attenuated virus when added to an inactivated intramuscular vaccination. The studies were reported to be too small to have detected any effect on mortality.

2. In patients with COPD, we recommend administering the influenza vaccine annually to prevent acute exacerbations of COPD (Grade 1B).

Underlying Values and Preferences: This recommendation places high value on the benefits of influenza vaccination for general health, the low risk of side effects, and the existing guidelines that recommend it for patients with COPD. Although the effect and evidence are moderate for the prevention of acute exacerbations of COPD, multiple bodies, including the CDC and WHO, recommend the use of a yearly influenza vaccine for all adults, including those with COPD.

Smoking Cessation: International organizations, including the CTS, WHO, National Institute for Health and Clinical Excellence, Burden of Chronic Obstructive Lung Disease, and US Preventive Services Task Force, recommend tobacco cessation for all adults with COPD, citing it as the most effective intervention in reducing COPD progression and morbidity. Smoking cessation is the only evidence-based intervention that improves COPD prognosis[61,62] by ameliorating the annual decline in lung function,[63] reducing cough and sputum production,[64] improving health-related quality of life, and reducing COPD exacerbations. Exacerbation frequency and active smoking may independently result in lung function decline.[65] Smoking cessation attempts may be difficult and frequently unsuccessful for patients with COPD who have prolonged exposure to tobacco smoke.[66,67] An effective smoking cessation program should address the behavioral, physiologic, and psychologic consequences of smoking; be cognizant of prior unsuccessful quit attempts; and target high-risk smokers. Smoking cessation programs that range from simple strategies to intensive, multicomponent programs have been tested in patients with COPD. These programs may comprise acknowledging current smoking followed by advice to quit, pharmacologic therapies (nicotine replacement therapy, antidepressants, nicotine receptor modifier therapy), or counseling (in-person or telephone counseling). These strategies have been used alone or in combination with varying success. Smoking cessation rates ranging from 8.8% to 34.5% have been reported and vary according to the strategy implemented, such as low-intensity counseling vs combination strategies that include psychosocial and pharmacologic interventions.[68] Most authors recommend a combination of pharmacologic and behavioral strategies for smokers with COPD.[68-70]

We identified two observational evaluations of tobacco cessation effects on COPD exacerbations and two RCTs

that were limited by quality and bias. Au et al[71] evaluated whether smoking status and duration of abstinence affected the risk for COPD exacerbations in a cohort of 23,971 current and former smokers from the Department of Veterans Affairs. Using Cox proportional hazards regression adjusting for age, comorbidity, markers of COPD severity, and socioeconomic status, smoking cessation was associated with a reduced risk for COPD exacerbations (adjusted HR, 0.78; 95% CI, 0.75-0.87). The magnitude of the reduced risk depended on the duration of smoking abstinence (adjusted HR: quit < 1 year, 1.04 [95% CI, 0.87-1.26]; quit 1-5 years, 0.93 [95% CI, 0.79-1.08]; quit 5-10 years, 0.84 [95% CI, 0.70-1.00]; quit ≥ 10 years, 0.65 [95% CI, 0.58-0.74]; linear trend $P < .001$). A cost-effectiveness analysis was performed on a randomized clinical trial comparing the effectiveness of a high-intensity smoking cessation intervention vs a medium-intensity strategy.[72] After 1 year, the high-intensity strategy (individual counseling sessions, telephone contacts, small-group counseling sessions, and pharmacologic support) was associated with a higher continuous abstinence rate (salivary cotinine-validated abstinence at 6 and 12 months, 19% vs 9%, respectively; relative risk, 2.22; 95% CI, 1.06-4.65; $P = .03$). Additionally, the high-intensity strategy was associated with lower cost (€581 vs €595), a lower average number of exacerbations (0.38 vs 0.60), and a reduced number of hospital days (0.39 vs 1.00) per patient.

In a single-center study, Borglykke et al[73] randomized 223 smokers hospitalized with symptoms consistent with a COPD exacerbation to a smoking cessation program vs usual care. After 1 year, the 48 subjects enrolled in the intervention group were more likely to be abstinent (30% vs 13%; OR, 2.83; 95% CI, 1.40-5.74). After 3 years, the intervention group had fewer hospital admissions and number of days admitted, although these differences were not statistically significant.

Hospital admission following a smoking cessation intervention was evaluated in 19,709 participants from three prospective population studies in Copenhagen, Denmark.[74] Compared with current smokers, former smokers had a significant reduction in the risk of hospital admission (HR, 0.57; 95% CI, 0.33-0.99). Smoking cessation was demonstrated to be effective in reducing hospital admissions, but reduction in smoking was not associated with a significantly lower risk of hospitalization (HR, 0.93; 95% CI, 0.73-1.18).

The strength of the data is low; therefore, the benefits compared with risk for this outcome are uncertain. However, the additional benefits achieved from smoking cessation, such as reduction in precancerous lesions and reduction in lung cancer risk,[75] and other outcomes associated with improved COPD symptoms support this recommendation. Additionally, a consortium of specialty and primary care organizations comprising the American College of Physicians, CHEST, American Thoracic Society, and European Respiratory Society recommended smoking cessation for patients with COPD in a clinical practice guideline update published in 2011.[20]

3. In patients with COPD, we suggest including smoking cessation counseling and treatment using best practices as a component of a comprehensive clinical strategy to prevent acute exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places high value on the benefits of smoking cessation for all individuals. In particular, it is the only evidence-based intervention that improves COPD prognosis by mitigating lung function decline and reduces symptoms. Although the effect and evidence for smoking cessation in the prevention of acute exacerbations of COPD are low, evidence supports smoking cessation for many reasons. Among general health benefits, smoking cessation in patients with mild COPD who produce cough and phlegm leads to substantial symptom reduction in the first year, with less lung function decline and fewer symptoms upon sustained cessation as well as leads to a decreased risk for infections such as pneumonia, which has been associated with cigarette smoking. The benefit from smoking cessation outweighs the risks, and a myriad of strategies have been summarized by other guidelines and reviews. In general, effective smoking cessation programs include behavioral, physiologic, and psychologic components comprising an acknowledgment of current smoking followed by advice to quit, pharmacologic therapies (nicotine replacement therapy, antidepressants, nicotine receptor modifier therapy), and counseling (in-person or telephone counseling) with cessation rates ranging from 8.8% to 34.5%. Smoking cessation that includes counseling and pharmacologic interventions are cost-effective.

Pulmonary Rehabilitation: Pulmonary rehabilitation has been recently defined as "a comprehensive intervention based on exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviors."[76] The benefits of pulmonary rehabilitation in patients with COPD are considerable,[76-78] and rehabilitation has been shown to be the most effective therapeutic

strategy to improve shortness of breath, health-related quality of life, and exercise tolerance.[79,80] Pulmonary rehabilitation is a prominent component of integrated COPD care[81] and is considered a standard-of-care intervention for individuals with COPD who remain symptomatic despite optimal bronchodilator therapy.[37,77,78]

For this analysis, we assumed that an all-cause hospitalization reflected a COPD-specific hospitalization. In a pooled analysis across 623 patients with COPD from all nine studies,[82-90] pulmonary rehabilitation resulted in a significant reduction in hospitalizations compared with conventional care (OR, 0.45; 95% CI, 0.22-0.91; $P = .03$). Overall, the quality of evidence was rated low to very low due to risk of bias, inconsistency, and imprecision. Minimal harms were noted with participation in rehabilitation, with no serious adverse events reported. Considerable heterogeneity was observed between studies, with three of the nine showing a significant reduction in hospitalizations following rehabilitation ($P = .03$, $I^2 = 52\%$). In an attempt to examine study heterogeneity, the studies were further categorized based on whether pulmonary rehabilitation was given immediately (ie, <1 month) following a recent COPD hospitalization (unstable state or recovery phase) or in patients with stable disease. In the studies that examined the effect of pulmonary rehabilitation given immediately after a COPD hospitalization, the data show a reduction in COPD rehospitalizations following rehabilitation[82-84,87,88] (OR, 0.24; 95% CI, 0.07-0.88; $P = .03$). These findings are consistent with an earlier Cochrane review by Puhan et al.[91] Of note, grade 1C was given because the studies examining pulmonary rehabilitation immediately after an acute exacerbation were judged to be of low or very-low quality, and significant heterogeneity was observed between studies ($P = .008$, $I^2 = 71\%$).

In the four studies examining patients without a recent history of exacerbation (stable state), pulmonary rehabilitation consistently did not reduce COPD hospitalizations (OR, 0.79; 95% CI, 0.42-1.5; $P = .47$).[85,86,89,90] However, as previously mentioned, among patients with a recent exacerbation (≤ 4 weeks from prior hospitalization), pulmonary rehabilitation has shown benefit in reducing COPD hospitalizations, adding to the growing literature detailing the considerable patient benefits from pulmonary rehabilitation and supporting earlier statements advocating for greater access to pulmonary rehabilitation for patients with COPD.[76,77] The recommendation would be strengthened by consistent, high-quality, large RCTs that specifically track both acute exacerbations and exacerbation-related hospitalizations.

4. In patients with moderate, severe, or very severe COPD who have had a recent exacerbation (ie, ≤ 4 weeks), we recommend pulmonary rehabilitation to prevent acute exacerbations of COPD (Grade 1C).

Underlying Values and Preferences: The pulmonary rehabilitation recommendations place high value on pulmonary rehabilitation reducing the risk of hospitalizations in patients with COPD who have had a recent COPD exacerbation (ie, ≤ 4 weeks posthospitalization). Although it has been well established that pulmonary rehabilitation improves quality of life, exercise tolerance, and dyspnea, these recommendations do not support pulmonary rehabilitation for the prevention of rehospitalizations in patients with COPD greater than 4 weeks after a recent hospitalization.

5. In patients with moderate, severe, or very severe COPD who have had an exacerbation greater than the past 4 weeks, we do not suggest pulmonary rehabilitation to prevent acute exacerbations of COPD (Grade 2B).

Underlying Values and Preferences: The pulmonary rehabilitation recommendations place high value on pulmonary rehabilitation reducing the risk of hospitalizations in patients with COPD who have had a recent COPD exacerbation (ie, ≤ 4 weeks posthospitalization). Although it has been well established that pulmonary rehabilitation improves quality of life, exercise tolerance, and dyspnea, these recommendations do not support pulmonary rehabilitation for the prevention of rehospitalizations in patients with COPD greater than 4 weeks after a recent hospitalization.

Education, Action Plans, and Case Management: Education, action plans, and case management are interventions that directly relate to the tenets of the Chronic Care Model.[92] They focus on enabling patients to be knowledgeable about COPD, to have the necessary skills to manage their chronic disease, and to be motivated to take an active part in their health care in partnership with an experienced and engaged health-care team. There is no consensus on the definition of education, action plans, and case management in COPD care. We defined education as formal delivery of information on topics related to COPD with the aim of improving the knowledge and understanding of COPD. Patient education was categorized as self-management education (eg, education aiming at patient self-management). An

action plan was defined as a written plan produced for the purpose of patient self-management of COPD exacerbations. Case management was defined as "a collaborative process of assessment, planning, facilitation, care coordination, evaluation, and advocacy for options and services to meet an individual's and family's comprehensive health needs through communication and available resources to promote quality, cost-effective outcomes."[93] In this review, case management was identified as structured follow-up, communication, or both with a health-care professional with a particular focus on changes in the patient's signs and symptoms; advice on appropriate interventions; referral to physicians; and recommendations for the initiation of therapy to prevent or reduce the risk of a serious AECOPD. The communication could be in person or through telephone or other teletechnology but did not include biomonitoring with data transferred over teletechnology.

This systematic review was completed before the 2014 Cochrane review on self-management for patients with COPD by Zwerink et al[94] and differs from that review in several important ways. Zwerink et al[94] searched the literature from 1994 to 2011, whereas the current literature review was not limited by publication date. The Cochrane review did not focus specifically on prevention of acute exacerbations of COPD and used a broad definition of self-management that included smoking cessation, self-recognition, and self-treatment of acute exacerbations of COPD; exercise and physical activity; action plans; and advice on diet, medication, and coping with dyspnea. In the present review, we chose to examine the effects of many of these interventions separately because these interventions often are delivered separately in current clinical practice.

Education Alone: One RCT[95] investigated the benefits of pharmacist-delivered patient education on health-related quality of life. Using the motivational interviewing technique, pharmacists in an outpatient clinic delivered one-on-one education with study participants on disease management topics, including medications, the importance of exercise, and airway clearance. Neither the duration of the intervention nor the number of sessions was reported. The primary outcome measure was improvement in quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ). Prevention of COPD-related ED visits and hospitalizations were secondary outcome measures. The method of measuring ED visits and hospitalizations was done through patient interview, medical records, and hospital databases. In this study of 133 patients (61% women; FEV_1, 54% predicted; 66 in intervention arm; 67 in control arm), patient education delivered by a pharmacist resulted in a statistically significant reduction in COPD-related hospitalizations over a 6-month follow-up period. Based on the published data, we calculated an OR of 0.24 (95% CI, 0.06-0.91).

There is lack of data to recommend education alone to prevent COPD exacerbations. Only one study was conducted in a single hospital with a small sample size. Furthermore, the lack of information on the implementation of the patient education limits the ability of other investigators to replicate this intervention.

6. In patients with COPD, we suggest that education alone should not be used for prevention of acute exacerbations of COPD (Ungraded Consensus-Based Statement).

Underlying Values and Preferences: This recommendation places high value on reducing hospitalizations for COPD exacerbations, as these are associated with increased morbidity and mortality. A lower value was placed on the motivational educational intervention because it is labor intensive compared with traditional education techniques.

Case Management Alone: One RCT[96] investigated the benefits of a 1-year period of case management alone on health-care use, which was a prespecified secondary outcome of the study. The method of measuring ED visits, hospital admissions, and number of hospital days was not specified. In this study, 122 patients who had been receiving long-term oxygen therapy for at least 6 months and who had a mean FEV_1 of 28% predicted were randomly assigned to an intervention or a usual-care group. The intervention combined home care management and easy access to hospital resources. It included a monthly telephone call and a home visit every 3 months as well as a rapid response to patient requests for assistance with respiratory issues over the 1-year study period. The intervention was associated with a highly significant reduction in the number of hospitalizations (intervention group, 0.5 ± 0.86; control group, 1.29 ± 1.7; Mann-Whitney U test $P = .001$), ED visits (intervention group, 0.45 ± 0.83; control group, 1.58 ± 1.96; Mann-Whitney U test $P = .0001$), and hospitalization days (intervention group, 7.43 ± 15.6; control group, 18.20 ± 24.55; t test $P = .01$). The study had a high risk of bias related to unclear randomization techniques, incomplete outcome data, lack of blinded assessments, and low number of participants. Furthermore, it is not clear how the intervention affected acute exacerbations of COPD.

Although the intervention resulted in a statistically significant reduction in ED visits, hospitalizations, and hospitalization days, this evidence was from one study with a high risk of bias. Therefore, because of the lack of sufficient evidence for a graded recommendation, there is uncertainty about the effect of case management alone to prevent acute exacerbations of COPD.

7. In patients with COPD, we suggest that case management alone should not be used for prevention of acute exacerbations of COPD (Ungraded Consensus-Based Statement).

Underlying Values and Preferences: This recommendation places high value on reducing hospitalizations for COPD exacerbations, as these are associated with increased morbidity and mortality. A lower value was placed on the lack of change in quality of life in either group because this information was present for only a small proportion of the entire sample.

Education and Case Management (Without Action Plan): Three studies[97-99] met our inclusion criteria and assessed changes in hospitalizations, although not always as the primary outcome measure. None of these studies included an action plan in the intervention. Other outcome measures included visits to the physician's office, clinic, or ED. Two studies[97,99] reported a decrease in hospitalizations in the intervention group, whereas the other found no difference between groups.[98] The data from two studies[97,98] were combined in a meta-analysis to assess the effect on hospitalizations. The results demonstrated no statistically significant differences between groups. After a 6-month follow-up period, Lainscak et al[97] reported a 14% hospitalization rate for the intervention group vs 31% for the control group, whereas Smith et al[98] reported that 70% of participants in the intervention group and 55% in the control group had one or more respiratory-related hospitalization. The pooled OR was 0.82 (95% CI, 0.17-3.99), with significant heterogeneity between studies ($P = .003$, $I^2 = 89\%$). The study by Soler et al[99] reported a significant decrease in hospitalizations. Smith et al reported no impact of education and case management on hospitalizations, hospital length of stay, or ED visits; however, these results must be viewed with caution because the sample size was small and the dropout rate high and the data were missing in one-third of the study participants.

Heterogeneity in participant characteristics and study methodology affected our conclusion about the effect of education and case management on exacerbations. Although patients in all three studies had moderate to severe disease, their exacerbation histories differed. The studies by Lainscak et al[97] and Soler et al[99] recruited participants with a history of exacerbations and reported decreases in hospitalizations, whereas Smith et al[98] did not specify an exacerbation history as an inclusion criterion and found that the intervention did not affect hospitalizations. The intensity, content, and duration of the intervention also varied among the three studies. Smith et al[98] reported on respiratory-specific hospitalizations, whereas Lainscak et al[97] and Soler et al[99] used all-cause hospitalization data. All studies had small participant numbers. Only Lainscak et al[97] had $>$ 100 participants per group. The other studies had $<$ 50 participants per group.

8. In patients with COPD with a previous or recent history of exacerbations, we recommend education and case management that includes direct access to a health-care specialist at least monthly to prevent severe acute exacerbations of COPD, as assessed by decreases in hospitalizations (Grade 1C).

Underlying Values and Preferences: This recommendation places high value on reducing hospitalizations for COPD exacerbations, as these are associated with increased morbidity and mortality.

Education and Action Plan: Four studies[100-103] met our inclusion criteria and assessed the effect of structured education and action plans on the prevention of acute exacerbations of COPD. Two studies[102,103] assessed changes in mean ED visits and mean hospitalizations, whereas the other two[100,101] assessed hospitalization rates. None of the studies assessed ED visits or hospitalizations as the primary outcome measure.

The inclusion criteria varied among the studies. McGeoch et al[101] required a previous history of an AECOPD within the past year, whereas the other three studies did not have this criterion. Gallefoss[100] required an FEV_1 between 40% and 80% predicted; Wood-Baker et al[103] required an $FEV_1 < 65\%$ predicted; and Wakabayashi et al[102] and McGeoch et al[101] had no FEV_1 percent predicted requirement. The number of participants in the study ranged from 52 in Gallefoss[100] to 154 in the intervention reported by McGeoch et al.[101] The number of events or the event rates were low in the four studies. The data from all studies were combined in separate meta-analyses to assess the effect of education combined with an action plan on ED visits and hospitalizations. These studies demonstrated no effect on mean ED visits, mean hospitalizations, or hospitalization rates. Gallefoss[100] and Wood-Baker et al[103] also assessed the impact of the intervention on general practitioner visits. Gallefoss[100] reported that the intervention reduced the

number of nonacute general practitioner visits, but there was no difference in the number of acute care visits. Wood-Baker et al[103] reported no differences between the groups in general practitioner visits. None of the studies reported any adverse events related to the intervention. The risk of bias was rated serious to very serious in all the studies.

9. In patients with moderate to severe COPD, we suggest education together with an action plan but without case management does not prevent severe acute exacerbations of COPD, as assessed by a decrease in ED visits or hospitalizations over a 12-month period (Grade 2C).

Underlying Values and Preferences: This recommendation places high value on reducing hospitalizations for COPD exacerbations, as these are associated with increased morbidity and mortality.

Education and Action Plan and Case Management: We identified 16 studies that met our inclusion criteria. Twelve presented original data that assessed the effect of education combined with a written action plan and individualized case management on hospital admissions and ED visits. The results of eight studies[104-111] were combined in a meta-analysis to assess the effect of the intervention on hospitalizations. Four of these studies[104,107-109] provided data for a meta-analysis of the effect of the intervention on ED visits. An additional four studies[112-115] addressed outcomes of interest but could not be included in the meta-analyses.

Six studies[104-106,109,114,115] specifically recruited participants with a history of exacerbations. Two studies[114,115] measured differences in all-cause hospitalizations and ED visits, whereas the other studies focused on acute exacerbations of COPD. Seven studies included in the meta-analysis reported the effect of a 12-month intervention on hospitalizations,[104-109,111] and one study assessed a 6-month intervention.[110]

In the meta-analysis assessing hospitalizations, 1,094 individuals received the intervention and 1,107 received usual care. Eight studies[104-111] favored the intervention (pooled OR, 0.64; 95% CI, 0.46-0.90). There was heterogeneity in the study results ($P = .05$, $I^2 = 51\%$), with three studies[106,110,111] showing nonsignificant effects. The study by Fan et al[106] was stopped early due to excess mortality in the intervention group. Three studies[113-115] could not be included in the meta-analysis. These studies assessed hospitalizations at 3,[115] 6,[113] and 12[114] months. None of the studies demonstrated a difference in hospitalizations between groups. Eight studies[104,106-108,110-112,114] had a low risk of bias, and the risk of bias was unclear in the rest.

Seven studies[104,107-109,113-115] examined the effect of interventions on ED visits. Four of these[104,107-109] were combined in a meta-analysis, and the others[113-115] were considered separately. One-half of the studies[104,109] in the meta-analysis recruited participants who had a history of exacerbations, and three[104,108,109] reported COPD-specific results. The results of the meta-analysis clearly favored the 12-month intervention (pooled OR, 0.48; 95% CI, 0.36-0.63). The study by Rice et al[109] showed a positive effect and contributed 54% of the total weight. Of the three studies not included in the meta-analysis, only Gadoury et al[114] reported a reduction in all-cause visits. Participants had a history of exacerbations on entry into the study, and the study itself had a low risk of bias.

One study[112] assessed the effects of an intervention on the frequency of exacerbations over a 24-month intervention period. Participants were randomized into a usual-care, routine monitoring, or self-management group. Randomization included stratification for disease severity and the frequency of exacerbation in the 24 months prior to entering the study. Most of the study participants had mild to moderately severe disease. There was no difference in unscheduled medical contact between the groups during the first month (OR, 1.09; 95% CI, 0.42-2.81) or the subsequent 12 months (OR, 2.07; 95% CI, 0.60-7.15). There were no differences in the frequency of exacerbations at 12 (RR, 1.10; 95% CI, 0.86-1.40) or 24 (OR, 1.16; 95% CI, 0.81-1.67) months.

The study by Fan et al,[106] a large, multisite study conducted in the Veterans Administration system, was stopped early due to excess mortality in the intervention group. At study termination, 426 individuals had been randomized to the usual-care or intervention group. There was no difference in COPD-related exacerbations over the mean follow-up period of 250 days, but there were 28 deaths in the intervention group compared with 10 in the usual-care group. Deaths due to COPD accounted for the largest difference between the groups. Despite careful analysis, the authors were not able to explain the difference in mortality between the groups. Comparison with large studies with similar interventions[104,109] did not help to explain the higher mortality in the case management group. These unexpected results demonstrate that we do not yet fully understand the effects of this type of intervention.

10. For patients with COPD, we suggest education with a written action plan and case management for the prevention of severe acute exacerbations of COPD as assessed by a decrease in hospitalizations and ED visits (Grade 2B).

Underlying Values and Preferences: This recommendation places high value on reducing COPD-related hospitalizations, as these are associated with increased morbidity and mortality. Hospitalizations were believed to best reflect exacerbations because increased physician visits or increased medication use could be a result of the intervention to prevent an exacerbation. High value was also placed on changes in individuals with a history of exacerbations and on outcomes that specifically identified COPD-related hospitalizations. The recommendation reflects the fact that one study reported increased mortality in the intervention group. Although we do not know the reason for increased mortality in this one study, patients with underlying severe disease and clinical instability need close attention and careful follow-up. This point emphasizes that a specially trained staff is required to supervise this intervention and that patient selection must be individualized.

Telemonitoring: Information and communications technologies have rapidly developed the potential to contribute to the delivery of accessible, cost-effective, high-quality health-care services, although evaluation of these services is still at an early stage.[116] Although there is no single definitive definition of telemedicine, the American Telemedicine Association defines it as "the use of medical information exchanged from one site to another via electronic communications to improve a patient's clinical health status."[117] "Telemedicine" is a broad term that encompasses a wide range of services, including video conferencing; e-health, such as patient portals; transmission of still images; continuing medical education; consumer-focused wireless applications; and remote monitoring of vital signs.[117]

Given the range of telemedicine options, we have restricted our review to studies dealing with telemonitoring to provide care for patients at risk for acute exacerbations of COPD. We defined telemonitoring as comprising the following elements: (1) electronic transfer of self-report or biometric data (eg, oxygen saturation, pulse rate, BP) over a distance; (2) use of a device located in the patient's home or on his or her person (mobile device); and (3) personalized feedback from a health-care professional who exercises his or her skills and judgment in the provision of tailored advice to the patient or automated feedback based on a predetermined algorithm.

Our recommendation is based on three RCTs[118-120] from one systematic review[121] that met our definition and 18 additional RCTs.[122-139] Of these, only six studies[127,130-134] in 707 subjects were poolable, although we did take into account the findings of studies not included in the meta-analysis in making our recommendation. In the excluded studies, telemonitoring was demonstrated to be feasible and acceptable to patients[122,123,136,139] and providers.[136] Evidence on the association between telemonitoring and hospital admissions was mixed,[122,124,135,137,138] as was evidence on cost-effectiveness,[126,128] likely reflecting the variability in program implementation. We examined the outcomes of telemonitoring on the number of ED visits, exacerbations, and hospitalizations. No statistically significant results were found for any of these outcomes. For ED visits within 3 to 6 months,[120,130,131,133] the pooled OR was 0.45 (95% CI, 0.18-1.12), with nonsignificant heterogeneity between studies ($P = .14$, $I^2 = 46\%$). For ED visits within 12 months,[118,119] the pooled OR was 0.19 (95% CI, 0.03-1.27), with significant heterogeneity between studies ($P = .004$, $I^2 = 88\%$). For exacerbations within 4 to 9 months of implementing the telemonitoring intervention,[127,134] the OR was 0.58 (95% CI, 0.30-1.12), with nonsignificant heterogeneity between studies ($P = .67$, $I^2 = 0\%$). In terms of hospitalizations within a 3-month time frame,[130,131] the OR was 0.87 (95% CI, 0.18-4.20), with nonsignificant heterogeneity between studies ($P = .25$, $I^2 = 26\%$), whereas the OR was 0.63 (95% CI, 0.40-1.01) for hospitalizations within a 6- to 12-month time frame,[118,119,132,133] with nonsignificant heterogeneity between studies ($P = .32$, $I^2 = 15\%$).

Importantly, there was substantial variability in the telemonitoring interventions and equipment used, which included recording and electronic transmission of vital signs (spirometry, pulse oximetry, heart rate, and BP)[130,131]; a technology platform for delivery of education and transmission of pedometer results[131]; a hand-held monitor, self-reported symptoms, and manually entered temperature and oximetry[132]; sensor-containing wristbands for heart rate, physical activity, near body temperature, and galvanic skin response; a commercial oximeter and cell phone coupled with a wristband[134]; self-report data (EXACT-PRO [Exacerbations of Chronic Pulmonary Disease Tool Patient-Oriented Outcome] questionnaire) transmitted through cell phones; and automated alert calls based on winter weather conditions.[127] The variability among the telemonitoring applications precludes accurate comparison between studies.

A review by Wootton[140] noted that the majority of RCTs on telemedicine for chronic disease management reported positive effects, raising the possibility that a publication bias exists favoring only positive results. Wootton further suggested that understanding the true effects of any intervention to improve chronic illness care will require interventions lasting years rather than

weeks or months. Although telemonitoring holds promise for COPD management, there is no evidence at this time that telemonitoring significantly reduces acute exacerbations of COPD, and in many countries, it is too expensive.

11. For patients with COPD, we suggest that telemonitoring compared with usual care does not prevent acute exacerbations of COPD, as assessed by decreases in emergency room visits, exacerbations, or hospitalizations over a 12-month period (Grade 2C).

Underlying Values and Preferences: There is insufficient evidence at this time to support the contention that telemonitoring prevents COPD exacerbations.

PICO 2: Does Maintenance Inhaled Therapy Prevent/Decrease Acute Exacerbations of COPD?

An extensive amount of data is available regarding the effects of inhaled therapy on the treatment and prevention of acute exacerbations of COPD. To examine this area in a systematic fashion, we organized the analysis of the efficacy of inhaled therapy to prevent COPD exacerbations into separate analyses of short-acting β_2-agonists and short-acting muscarinic antagonists vs placebo and long-acting β_2-agonists and long-acting muscarinic antagonists vs placebo with each other and in combination. Similarly, we compared inhaled corticosteroids with placebo and the combination of long-acting β_2-agonists plus inhaled corticosteroids with placebo and vs long-acting muscarinic antagonists and the combination of all three inhaled agents with placebo to prevent COPD exacerbations (Table 1).

Long-Acting Bronchodilators Compared With Placebo or Monotherapy: Inhaled long-acting β_2-agonists are an important therapeutic option for patients with COPD. They lead to the activation of the β_2-receptors lining the airway smooth muscle, resulting in bronchodilation. The majority of long-acting β_2-agonists are 12-h medications, thus requiring a twice-daily dosing regimen. This distinguishes them from ultralong-acting β_2-agonists that are once-daily medications. A recent systematic review of long-acting β_2-agonist in COPD[141] evaluating salmeterol (50 μg bid) and two doses of formoterol (12 and 24 μg bid) demonstrated a benefit of long-acting β_2-agonist vs placebo in reducing exacerbation rates. Data from seven studies enrolling 2,859 patients were combined to assess the rate of severe exacerbations requiring hospitalizations. For severe exacerbations, the OR was 0.73 (95% CI, 0.56-0.95). The overall quality of evidence was moderate due to risk of publication bias. Several studies did not report exacerbations in a form that could be included in any of the outcomes. The authors found no difference in the long-acting β_2-agonist or dose used for the effect. For assessing the impact of long-acting β_2-agonists on moderate exacerbations (requiring a course of antibiotics, oral steroids, or both), seven studies enrolling 3,375 patients were reviewed. For moderate exacerbations, the OR was 0.73 (95% CI, 0.61-0.87). The quality of evidence was deemed moderate due to risk of publication bias. However, for the lower dose of formoterol (12 μg bid), no benefit was seen (OR, 0.78; 95% CI, 0.56-1.07).

The review highlights other benefits of treatment with a long-acting β_2-agonist. There were significant improvements in quality of life as measured by the SGRQ. The SGRQ score improved by −2.32 (95% CI, −3.09 to −1.54) in the patients treated with long-acting β_2-agonists. Furthermore, more patients reached the minimally clinically important difference of −4 units on the SGRQ in the long-acting β_2-agonist vs placebo group (OR, 1.58; 95% CI, 1.32-1.90). Again, there was no difference between the drug and dose used in the studies.

The safety of this class of medications was evident. When all studies were pooled and analyzed, the rate of adverse events was similar between the long-acting β_2-agonist and placebo arms (OR, 0.97; 95% CI, 0.83-1.14). The long-acting β_2-agonist arm did not affect mortality (OR, 0.90; 95% CI, 0.75-1.08). In summary, patients with moderate to severe COPD had reduced rates of exacerbations (both moderate and severe) with a long-acting β_2-agonist vs placebo. Benefits in other aspects of COPD management were demonstrated, with strong safety data.

12. In patients with moderate to severe COPD, we recommend the use of long-acting β_2-agonist compared with placebo to prevent moderate to severe acute exacerbations of COPD (Grade 1B).

Underlying Values and Preferences: This recommendation places high value on long-acting β_2-agonist therapy reducing the risk of acute exacerbations of COPD, both moderate (required course of oral steroids, antibiotics, or both) and severe (required hospitalization), together with the comparative benefit of long-acting β_2-agonist therapy improving quality of life and lung function compared with placebo. This recommendation also acknowledges that there are no significant differences in serious adverse events or incidence of mortality between long-acting β_2-agonist therapy and placebo in this patient group.

Long-Acting Muscarinic Antagonists Compared With Placebo: Tiotropium is an inhaled long-acting muscarinic antagonist used in the treatment of COPD.

Tiotropium inhibits the release of acetylcholine at the receptor level by binding to the M2- and M3-muscarinic receptors that line the airway. The resulting bronchodilation has improved outcomes, including quality of life, increased exercise capacity, and a reduction in exacerbations.[23,142,143] Furthermore, its safety has been reviewed in several analyses, all of which demonstrate an acceptable safety profile. Until recently, tiotropium had only been delivered as a dry powder through the HandiHaler (Boehringer Ingelheim GmbH). The large majority of studies assessing the efficacy of tiotropium involved the use of the dry powder inhaler in the treatment arm. Respimat (Boehringer Ingelheim GmbH) is a novel delivery system using a soft mist rather than a dry powder as the means of delivering tiotropium.

There has been some concern regarding the safety of tiotropium delivered through Respimat[144] because studies have demonstrated an increase in associated mortality. To address this question, a large RCT assessing the safety of tiotropium delivered through the Respimat system has recently been published,[145] and this will be further in this guideline.

A systematic review[146] assessing the effectiveness of tiotropium vs placebo included 22 studies enrolling 22,309 patients. Nineteen studies assessed tiotropium 18 μg daily delivered by the HandiHaler. Three studies assessed tiotropium delivered by the Respimat system. One study examined a dose of 5 μg, and the other two examined doses of 5 and 10 μg. There was a reduction in the rate of acute exacerbations in the tiotropium arm compared with the placebo arm (OR, 0.78; 95% CI, 0.70-0.87; number needed to treat, 16). This was deemed high-quality evidence with no risk of bias. Furthermore, 21 studies enrolling 22,852 patients examined the rate of exacerbations requiring hospitalizations. Tiotropium treatment was associated with fewer hospitalizations due to exacerbations (OR, 0.85; 95% CI, 0.72-1.00), but there was no statistically significant difference in all-cause hospitalizations (OR, 1.00; 95% CI, 0.88-1.13) or nonfatal serious adverse events (OR, 1.03; 95% CI, 0.97-1.10).[146] The quality of evidence was deemed moderate due to imprecision because the CIs around the effect estimates were very wide. Regarding mortality, tiotropium delivered through the HandiHaler was associated with fewer deaths than placebo, but this was not statistically significant (OR, 0.92; 95% CI, 0.8-1.05). However, tiotropium delivered by the Respimat system had more associated deaths than placebo (OR, 1.47; 95% CI, 1.04-2.08). The authors recognized that the event rates were low and that this may have been affected by withdrawal rates, which were higher than mortality rates.

Since the publication of this systematic review, a large RCT (TIOSPIR [Tiotropium Safety and Performance in Respimat]) examining Respimat vs HandiHaler has been published. The study randomized 17,183 patients to Respimat 2.5 μg, Respimat 5.0 μg, or HandiHaler 18 μg. The primary safety outcome was time to death from any cause. The primary efficacy outcome was time to first COPD exacerbation. The HR for time to death with Respimat 5 μg vs HandiHaler was 0.96 (95% CI, 0.84-1.09) and for the Respimat 2.5 μg vs HandiHaler, 1.00 (95% CI, 0.87-1.14). Both were not statistically significant. Although this is reassuring, safety issues remain a concern with the Respimat system in secondary analysis of TIOSPIR data, especially in patients with renal disease (who were excluded from this study).

13. In patients with moderate to severe COPD, we recommend the use of a long-acting muscarinic antagonist compared with placebo to prevent moderate to severe acute exacerbations of COPD (Grade 1A).

Underlying Values and Preferences: This recommendation places high value on long-acting muscarinic antagonists reducing the risk of acute exacerbations of COPD, both moderate (required course of oral steroids, antibiotics, or both) and severe (required hospitalization), together with the comparative benefit of a long-acting muscarinic antagonist improving quality of life and lung function compared with placebo. Although pooled analyses show a reduction in COPD hospitalization with the use of a long-acting muscarinic antagonist compared with placebo, it does not reach statistical significance for all-cause hospitalization. This recommendation also acknowledges that there are no significant differences in serious adverse events or incidence of mortality between long-acting muscarinic antagonists and placebo in this patient group.

Long-Acting Muscarinic Antagonists Compared With Long-Acting β_2-Agonists: Pharmacologic therapy for COPD is implemented in a stepwise fashion.[142,147] Patients should be started initially on short-acting bronchodilators, and if symptoms persist, introduction of long-acting bronchodilators is recommended. The two classes of long-acting agents used in the treatment of COPD are long-acting muscarinic antagonists and long-acting β_2-agonists. Both classes have independent mechanisms of action, producing a bronchodilator effect resulting in improved symptoms, quality of life, and exercise tolerance.[148-150] In addition, each

class has been shown to reduce the rate of acute exacerbations.[23,151] However, the question remains about whether a difference exists between these classes of medications in their ability to reduce the risk of an exacerbation.

A systematic review by Chong et al[152] specifically addressed this question. This systematic review compared tiotropium (the most commonly used long-acting muscarinic antagonist in COPD) vs long-acting β_2-agonists in the treatment of stable COPD. The long-acting β_2-agonists reviewed were salmeterol, formoterol, and indacaterol. The authors included six studies enrolling 12,123 patients. The length of the studies varied from 3 to 12 months. In all the studies, patients in the tiotropium arm received the 18-μg dose administered through the HandiHaler. Three studies compared tiotropium to salmeterol 50 μg bid, and one study used formoterol 10 μg bid. For indacaterol, one dose-finding study used open-label tiotropium 150 and 300 μg; where possible, the results of the two doses were pooled. The other study was a double-dummy RCT using 150 μg indacaterol. It is important to note that in all the studies, patients were allowed to use inhaled corticosteroids at a stable dose.

Most studies used similar definitions of acute exacerbation, which was an increase in symptoms for at least 3 consecutive days resulting in additional treatment. Tiotropium was associated with a lower rate of exacerbations compared with long-acting β_2-agonists. Tiotropium had an OR of 0.86 (95% CI, 0.79-0.93). The strength of this evidence was deemed moderate because of a serious risk of bias. In the four studies that reported COPD hospitalization as an outcome, the number of participants requiring hospitalization for a COPD exacerbation was significantly lower in those who received tiotropium compared with those who received a long-acting β_2-agonist (OR, 0.87; 95% CI, 0.77-0.99; analysis, 1.15[152]). In three studies that allowed comparison of all-cause hospitalization, there was no statistical difference in hospitalizations between tiotropium and long-acting β_2-agonists (OR, 0.93; 95% CI, 0.57-1.54).[140]

The authors recognized that the largest and longest study comparing tiotropium to salmeterol had a statistically significant difference in the rate of exacerbation.[153] All the other studies reviewed did not demonstrate that tiotropium was significantly better at preventing exacerbations than long-acting β_2-agonists, which one must keep in mind while interpreting the recommendation. Furthermore, a large majority of patients were using inhaled corticosteroids during the study. The impact that this may have on the exacerbation rate is difficult to determine.

14. In patients with moderate to severe COPD, we recommend the use of long-acting muscarinic antagonists compared with long-acting β_2-agonist to prevent moderate to severe acute exacerbations of COPD (Grade 1C).

Underlying Values and Preferences: This recommendation places high value on long-acting muscarinic antagonists reducing the risk of acute exacerbations of COPD, both moderate (required course of oral steroids, antibiotics, or both) and severe (required hospitalization), together with the comparative benefit of long-acting muscarinic antagonists having a lower rate of nonfatal serious adverse events compared with long-acting β_2-agonists. This comparative benefit may not apply with the new ultralong-acting β_2-agonists that are a once-daily medication. Although pooled analyses show a reduction in COPD hospitalization with the use of a long-acting muscarinic antagonist compared with placebo, it does not reach statistical significance for all-cause hospitalization. A lower value was placed on the lack of statistically significant differences in changes in lung function, quality of life, and patient symptoms between the two drug groups.

Short-Acting Muscarinic Antagonist Compared With Short-Acting β_2-Agonist Monotherapy: Based on the available data, comparing treatment with short-acting β_2-agonist monotherapy with ipratropium alone (short-acting muscarinic antagonist) for 1 to 3 months resulted in no significant improvement in postbronchodilator FEV_1 measurement, but there was a small benefit in prebronchodilator FEV_1 of borderline statistical significance. There was a small increase in prebronchodilator FVC and a postbronchodilator increase in the FVC area under the curve over 8 h, and this approached statistical significance. These data suggest that the beneficial effects of a short-acting muscarinic antagonist over short-acting β_2-agonist are small in terms of lung function.[154-160]

There was no study evaluating exacerbation as a primary end point. However, four studies enrolling 1,218 patients with a serious risk of bias and overall moderate quality of evidence examined the number of subjects who had to add or increase systemic oral corticosteroids, which could be interpreted as a surrogate marker for exacerbations.[157,161-163] Meta-analysis of the four studies indicated that significantly fewer subjects receiving short-acting muscarinic antagonist therapy added or increased use of oral steroids compared with

those receiving short-acting β_2-agonist therapy (OR, 0.52; 95% CI, 0.37-0.74). This would give a number needed to treat of 15 patients treated with short-acting muscarinic antagonist therapy compared with 28 patients treated with short-acting β_2-agonist therapy to prevent the need for oral steroids.

Therefore, this treatment comparison receives a grade 2C recommendation based on the body of reported evidence. The grade 2C categorization is weak, with low- or very-low-quality evidence and uncertainty in the estimates of the benefits, risks, and burdens, all of which are closely balanced. However, there is evidence of benefit for at least one critical outcome (addition or increase in the use of oral steroids) that may be considered a surrogate marker of a moderate exacerbation. Higher-quality research may have an important impact on the confidence of estimated effect in the future. Patient preference and cost should be taken into consideration. Future studies could incorporate measures of health-care use and be of longer duration to capture the effects on exacerbation rates.

15. In patients with moderate to severe COPD, we suggest the use of a short-acting muscarinic antagonist compared with short-acting β_2-agonist monotherapy to prevent acute mild-moderate exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places value on a short-acting muscarinic antagonist reducing the risk of acute exacerbations of COPD together with the comparative benefit of a short-acting muscarinic antagonist improving quality of life and lung function compared with short-acting β_2-agonist monotherapy. No data favor one therapy over the other in terms of COPD hospitalizations. This recommendation also acknowledges that medication-related adverse events were fewer in the short-acting muscarinic antagonist than in the short-acting β_2-agonist group.

Short-Acting Muscarinic Antagonist Plus Short-Acting β_2-Agonist Compared With Short-Acting β_2-Agonist: Stepwise pharmacologic therapy, particularly when two different agents with different mechanisms of action are used, is the standard therapy for asthma and COPD care in all guidelines. Long-term combination therapy of a short-acting muscarinic antagonist and a short-acting β_2-agonist over 12 weeks with ipratropium plus a short-acting β_2-agonist is associated with some clinically meaningful postbronchodilator outcomes compared with β_2-agonist treatment alone, but these outcomes were not reflected in subjective improvements in quality of life or symptom scores.[154] The evidence for this combined therapy vs monotherapy using short-acting bronchodilators to reduce exacerbations is either weak or lacking.

There has been only one study with exacerbation as an end point, and that favored the combination (ipratropium plus short-acting β_2-agonist).[164] The study had serious bias and inconsistency. The evidence, therefore, was rated as overall low quality. Five additional studies enrolling 1,591 patients from 42 to 85 days recorded the addition of or increase in oral steroids as an end point.[157,160-167] These studies in aggregate had no serious inconsistencies in quality assessment and an overall moderate quality of evidence. We have given this recommendation a grade 2B, which is weak with moderate-quality evidence because of the long history of safety and clinical guideline data formulated throughout the years.

The patient's preference is an important factor that requires consideration in using these agents, and generally, these agents are first line because of their safety profile and ease of use. Future studies should be of longer duration to more robustly capture the effects of these agents on exacerbation rates and incorporate outcomes that measure health-care use.

16. In patients with moderate to severe COPD, we suggest the use of short-acting muscarinic antagonist plus short-acting β_2-agonist compared with short-acting β_2-agonist alone to prevent acute moderate exacerbations of COPD (Grade 2B).

Underlying Values and Preferences: This recommendation places value on a short-acting muscarinic antagonist plus a short-acting β_2-agonist reducing the risk of acute exacerbations of COPD together with the comparative small benefits of a short-acting muscarinic antagonist plus a short-acting β_2-agonist improving quality of life, exercise tolerance, and lung function compared with a short-acting β_2-agonist alone. This recommendation also acknowledges that there are no significant differences in serious adverse events with the use of a short-acting muscarinic antagonist plus a short-acting β_2-agonist vs a short-acting β_2-agonist alone.

Short-Acting Muscarinic Antagonists Compared With Long-Acting β_2-Agonist Monotherapy: The primary classes of bronchodilators used in the treatment of COPD have both short-acting and long-acting formulations. Current guidelines suggest that patients with moderate to severe COPD use the short-acting formulations for rescue and the long-acting bronchodilators as maintenance therapy.[142,147] This recommendation is based on several advantages the long-acting formulations have over the short-acting agents, including

sustained bronchodilation, improved quality of life, and improved compliance.[168-170]

A systematic review comparing short-acting muscarinic antagonist (ipratropium) monotherapy vs long-acting β_2-agonist therapy assessed change in lung function, quality of life, symptom scores, and exacerbation rates.[154] This analysis included four studies comparing ipratropium 42 μg with salmeterol 50 μg and placebo. As well, one study comparing ipratropium 80 μg tid with formoterol 18 μg bid and placebo and another comparing ipratropium 40 μg qid with formoterol 12 or 24 μg and placebo were included for analysis.

For the ipratropium vs salmeterol studies, there was no significant difference in the patients experiencing one or more exacerbations (OR, 1.23; 95% CI, 0.84-1.80). The quality of evidence was low given inconsistency and imprecision. For the formoterol studies, there was no significant difference in exacerbation rates, but values were not provided. The studies used in the systematic review had varying inclusion criteria, used unconventional dosing for both ipratropium and the long-acting β_2-agonists, and did not provide clear definitions for exacerbations. Given the poor evidence addressing the question of ipratropium vs long-acting β_2-agonists for the prevention of acute exacerbations, the current recommendation is made based on the known benefits of long-acting β_2-agonists in patients with COPD.[141]

17. In patients with moderate to severe COPD, we suggest the use of long-acting β_2-agonist monotherapy compared with short-acting muscarinic antagonist monotherapy to prevent acute exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places value on long-acting β_2-agonist therapy reducing the risk of acute exacerbations of COPD in patients treated with long-acting β_2-agonist monotherapy over short-acting muscarinic antagonist monotherapy and the comparative value of long-acting β_2-agonist monotherapy improving lung function, quality of life, and dyspnea scores compared with short-acting muscarinic antagonist monotherapy. No data favor one therapy over the other in terms of COPD hospitalizations. This recommendation also acknowledges that there are no significant differences in serious adverse events with the use of long-acting β_2-agonist monotherapy over short-acting muscarinic antagonist monotherapy.

Long-Acting Muscarinic Antagonist Compared With Short-Acting Muscarinic Antagonist: The airflow obstruction associated with moderate to severe COPD results in exercise limitation, poor quality of life, and a predisposition to exacerbations. Bronchodilators, both short-acting and long-acting, play an important role in helping patients with COPD to cope with the disease by improving many of the physiologic limitations that develop with activity in these patients.[148,150,171] Inhaled muscarinic antagonists (or anticholinergics) have long been recognized as an important pharmacologic class of bronchodilators that result in improved quality of life, symptom limitation, and reduced rate of exacerbations.[146,172]

Ipratropium is a short-acting muscarinic antagonist that nonspecifically binds to airway muscarinic receptors. Tiotropium is a long-acting muscarinic antagonist that selectively binds to M1- and M3-muscarinic receptors in the airway. Until recently, it has been the only inhaled muscarinic antagonist available for treating COPD.[142,147] Newer muscarinic antagonists are now available, including aclidinium bromide, glycopyrronium bromide, and umeclidinium bromide. The majority of studies involving these newer compounds compared efficacy to either placebo or tiotropium and not to ipratropium. Furthermore, there is no meta-analysis comparing these compounds with ipratropium. Thus, for the question of the benefit of a long-acting muscarinic antagonist vs short-acting muscarinic antagonist for the prevention of an exacerbation, the evidence for tiotropium vs ipratropium was assessed.

A recent systematic review compared tiotropium and ipratropium in the treatment of stable COPD.[173] The review included two studies enrolling 1,073 patients. One study randomized patients to tiotropium 18 μg delivered by HandiHaler, and the other used tiotropium 5 and 10 μg delivered by the Respimat system. Both studies used an ipratropium metered-dose inhaler as the comparator arm. In both studies, the rates of acute exacerbations and COPD hospitalizations were secondary outcomes. Tiotropium was superior to ipratropium in exacerbation prevention (OR, 0.71; 95% CI, 0.52-0.95). The quality of the evidence was high, and there was no risk of bias. Furthermore, use of tiotropium resulted in a lower rate of hospitalization due to exacerbation compared with ipratropium (OR, 0.56; 95% CI, 0.31-0.99). The quality of evidence for this outcome was also deemed to be high with no risk of bias. The superiority of tiotropium over ipratropium was also seen in trough FEV_1 values and quality of life. There were insufficient data available to recommend one delivery device for tiotropium over another; however, no harm was demonstrated in the study using the Respimat delivery system.

The authors supported the use of tiotropium over ipratropium in the treatment of stable COPD because physiologic and clinical benefits, including reduced rates of exacerbation, were seen in the patients randomized to tiotropium. Their conclusion supports current clinical thinking and guideline recommendations.[142,147] In addition to a clinical benefit, the once-daily dosing of tiotropium is associated with improved compliance compared with ipratropium.[170] The safety of the Respimat system used to deliver tiotropium remains controversial.[144] In this review, no conclusions could be made regarding the superiority of one delivery device over the other, and no safety concerns were noted. Concern regarding safety of tiotropium delivered through the Respimat system has been well documented. A recent multicenter international RCT demonstrated the safety of the Respimat delivery system for tiotropium vs HandiHaler.[145] However, controversy still remains because a secondary analysis of the RCT data suggests that specific patient populations may be at risk for adverse events or higher mortality.[174-176]

18. In patients with moderate to severe COPD, we recommend the use of a long-acting muscarinic antagonist compared with a short-acting muscarinic antagonist to prevent acute moderate to severe exacerbations of COPD (Grade 1A).

Underlying Values and Preferences: This recommendation places high value on a long-acting muscarinic antagonist reducing the risk of acute exacerbations of COPD, both moderate (required course of oral steroids, antibiotics, or both) and severe (required hospitalization), together with the comparative benefit of a long-acting muscarinic antagonist improving quality of life and lung function compared with a short-acting muscarinic antagonist. This recommendation also acknowledges that there were fewer nonfatal serious adverse events in subjects treated with a long-acting muscarinic antagonist than in those treated with a short-acting muscarinic antagonist.

Short-Acting Muscarinic Antagonist Plus Long-Acting β_2-Agonist Compared With Long-Acting β_2-Agonist Monotherapy: The natural progression of COPD results in increased symptoms, a decline in quality of life, and an increased risk of exacerbations. As the disease progresses and the patient's needs change, current guidelines recommend add-on pharmacotherapy to address the symptoms. One option is the addition of regular ipratropium, a short-acting muscarinic antagonist, to a long-acting β_2-agonist. Using bronchodilators that target different receptors may improve clinical symptoms and, therefore, may prevent exacerbations. Although this combination may be viewed as unique, some studies assessed its effectiveness in patients with COPD. A meta-analysis reviewed the available data comparing ipratropium plus long-acting β_2-agonist vs long-acting β_2-agonist alone in the treatment of stable COPD.[154] This analysis highlighted that few studies (two unpublished and one published) exist on this therapeutic strategy for COPD. The one published study examined the impact that the ipratropium and long-acting β_2-agonist combination has on the prevention of exacerbations. The 12-week study enrolled 94 patients who were randomized to ipratropium plus salmeterol vs salmeterol alone. Patients were allowed to use a short-acting β_2-agonist for rescue. The combination therapy demonstrated a lower rate of exacerbations but was not statistically significant (OR, 0.49; 95% CI, 0.17-1.40). However, there was a low rate of exacerbation in both groups and improvements in lung function and quality of life with the combination vs lone long-acting β_2-agonist therapy. The long-acting β_2-agonist used in this study was salmeterol, and currently, no other published studies used other long-acting β_2-agonists in combination with ipratropium. The authors concluded that more studies are needed to examine this combination because of some suggestion of benefit.

We recognize that with the development of new long-acting β_2-agonists and long-acting muscarinic antagonists to treat COPD, including the combination of long-acting β_2-agonist and long-acting muscarinic antagonist in a single inhaler, the utility of ipratropium plus long-acting β_2-agonist is limited, which may explain the limited number of studies examining this combination. However, availability of these novel therapies, especially in resource-limited settings, can affect one's approach to therapy. Therefore, having multiple therapeutic options that may provide similar outcomes for a global population would be ideal. For the combination of ipratropium plus long-acting β_2-agonist vs long-acting β_2-agonist alone for the prevention of acute exacerbations of COPD, a grade 2C recommendation favoring the combination is given. This is based on the demonstrated safety of this combination, the improvements in functional and quality-of-life measures, and an indication of benefit in reducing the frequency of exacerbations.

19. In patients with moderate to severe COPD, we suggest the combination use of a short-acting muscarinic antagonist plus long-acting β_2-agonist compared with long-acting β_2-agonist monotherapy to

prevent acute mild to moderate exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places value on the combination of short-acting muscarinic antagonist plus long-acting β_2-agonist therapy reducing the risk of acute exacerbations of COPD compared with the use of long-acting β_2-agonist therapy alone and the comparative value of short-acting muscarinic antagonist plus long-acting β_2-agonist therapy improving lung function, quality of life, and dyspnea scores compared with long-acting β_2-agonist monotherapy. No data favor one therapy over the other in terms of COPD hospitalizations. This recommendation also acknowledges that there are no significant differences in serious adverse events with the combined use of short-acting muscarinic antagonist plus long-acting β_2-agonist therapy vs long-acting β_2-agonist therapy alone.

Inhaled Corticosteroids Compared With Placebo or Other Monotherapy: Airway inflammation plays an important role in the pathophysiology of COPD,[177] which has suggested a potential role for inhaled corticosteroids in the treatment of this disease and has led to their excessive use in clinical practice.[178,179] However, although inhaled corticosteroids have significant effects in suppressing airway inflammation in asthma, their antiinflammatory effects in COPD are debatable.[180-182] The reported relative resistance to the antiinflammatory effects of corticosteroids observed in COPD may be attributed to oxidative stress from smoke exposure or from neutrophilic inflammation. In vitro and in vivo evidence suggest that histone deacetylase 2 enzyme activity and expression are suppressed in patients with COPD, thus blunting the antiinflammatory effects of corticosteroids.[180-185] Nevertheless, a meta-analysis of eight RCTs that used bronchial biopsy specimens and BAL fluid to evaluate the effects of inhaled corticosteroids in stable COPD showed that inhaled corticosteroids reduce lymphocytic inflammation in COPD.[186] These findings suggest that antiinflammatory effects of inhaled corticosteroids may be more pronounced in patients with predominant lymphocytic airway inflammation.

Several short- and long-term studies (up to 3 years) evaluated the efficacy and safety of inhaled corticosteroids when used in combination with inhaled long-acting β_2-agonists.[22,151,187-199] In addition, several systematic reviews and meta-analyses have been published on the topic.[200-204] These studies evaluated several important outcomes, including lung function, mortality, exacerbations, health-related quality of life, and symptoms. Despite the plethora of studies, the precise role of role of inhaled corticosteroids in improving lung function and other patient outcomes in COPD is still controversial. Furthermore, predictors of response to inhaled corticosteroids in COPD have not been fully evaluated, and existing evidence is based on few studies in the general COPD population. Because the use of inhaled corticosteroids may be associated with potential local and systemic adverse effects, careful evaluation of the benefit and risk ratio is essential.

Long-Term Effects of Inhaled Corticosteroids Compared With Placebo: A systematic review evaluated the role of inhaled corticosteroids vs placebo in COPD by examining data from 55 primary studies enrolling 16,154 participants.[204] Long-term use of inhaled corticosteroids reduced the mean rate of exacerbations in those studies where pooling of data was possible (generic inverse variance analysis using the total exacerbations per patient per year and SE from each study: relative effect, −0.26 exacerbations/patient/year [95% CI, −0.37 to −0.14; 2,586 participants]; moderate overall quality of evidence due to risk of bias by pooled means analysis: relative effect, −0.19 exacerbations/patient/year [95% CI, −0.30 to −0.08; 2,253 participants]; overall quality of evidence low due to risk of bias and inconsistency). Response to inhaled corticosteroids was not predicted by oral steroid response, bronchodilator reversibility, or bronchial hyperresponsiveness in patients with COPD. Studies of < 1,000 μg beclomethasone dipropionate equivalents per day did not show a statistically significant difference compared with placebo.

There was an increased risk of oropharyngeal candidiasis (OR, 2.65; 95% CI, 2.03-3.46; 5,586 participants) and hoarseness. In the long-term studies, the rate of pneumonia was increased in the inhaled corticosteroid group compared with the placebo group in studies that reported pneumonia as an adverse event (OR, 1.56; 95% CI, 1.30-1.86; 6,235 participants). The long-term studies that measured bone effects generally showed no major effect on fractures and bone mineral density over 3 years.

Inhaled Corticosteroids Compared With Long-Acting β_2-Agonists: Both long-acting β_2-agonists and inhaled corticosteroids are used in the treatment of COPD. Although these treatments can sometimes be taken together, the value of the two individual components is unclear. To evaluate the efficacy and safety of inhaled corticosteroids vs long-acting β_2-agonists in COPD, a review examined data from seven randomized trials (5,997 participants) of good quality with a duration of 6 months to 3 years.[202] All the trials compared inhaled

corticosteroid/long-acting β_2-agonist combination inhalers with long-acting β_2-agonist and inhaled corticosteroid as individual components.

Four studies (4,750 participants) reported exacerbation RRs between inhaled corticosteroid or long-acting β_2-agonist and placebo or an inhaled corticosteroid/long-acting β_2-agonist combination.[22,151,190,199] The RR between inhaled corticosteroid and long-acting β_2-agonist was not statistically significant (0.96; 95% CI, 0.89-1.02), which suggests moderate overall quality of evidence due to risk of bias. There was no statistically significant difference in exacerbation RR between studies of 1 year and > 1 year of treatment ($\chi^2 = 0.11$, degrees of freedom = 1, $P = .75$). Two studies comparing fluticasone with salmeterol reported the number of patients experiencing exacerbations requiring treatment with antibiotics, corticosteroids, or both or hospitalization during the treatment period (688 participants).[193,196] In these studies, although more patients on inhaled corticosteroids (136 of 351) experienced exacerbations than those on long-acting β_2-agonists (115 of 337), there was no statistically significant difference between the groups (OR, 1.22; 95% CI, 0.89-1.67).

Exacerbations leading to hospitalizations were only reported in a single trial with 3,093 participants.[151] A comparison of RRs showed no significant difference in the risk of hospitalization due to exacerbation between fluticasone and salmeterol (RR, 1.07; 95% CI, 0.91-1.26). The incidence of pneumonia was significantly higher among patients on inhaled corticosteroids than on long-acting β_2-agonists whether classified as an adverse event (OR, 1.38; 95% CI, 1.10-1.73) or serious adverse event (OR, 1.48; 95% CI, 1.13-1.93).

Budesonide Compared With Formoterol or Fluticasone Compared With Salmeterol: Four of the trials included in the aforementioned review evaluated fluticasone and salmeterol monotherapy components, and the remaining three included budesonide and formoterol monotherapy components.[202] There was no evidence of a class effect between the fluticasone/salmeterol and budesonide/formoterol trials in a subgroup analysis ($\chi^2 = 1.57$, degrees of freedom = 1, $P = .21$).

In summary, there was no statistically significant differences in the number of patients experiencing exacerbations (OR, 1.22; 95% CI, 0.89-1.67) or the rate of exacerbations per patient year (RR, 0.96; 95% CI, 0.89-1.02) between inhaled corticosteroids and long-acting β_2-agonists. Both inhaled corticosteroids and long-acting β_2-agonists contribute to a decrease in exacerbation rates, but there is insufficient evidence to recommend maintenance inhaled corticosteroid therapy over maintenance long-acting β_2-agonist therapy in preventing acute exacerbations of COPD. Although inhaled corticosteroid therapy may benefit some patients with COPD, it also increases the risk of systemic adverse effects, including pneumonia.

Combination Inhaled Therapies: Long-Acting Muscarinic Antagonists, Inhaled Corticosteroids, and Long-Acting β_2-Agonists: *Long-Acting Bronchodilator and Corticosteroid Therapy:* The past decades have seen a significant increase in the number of pharmacologic agents available to treat patients with COPD. However, they are basically longer-acting variations of the primary agents long-acting muscarinic antagonists[18,23,205-208]; long-acting β_2-agonists[209-211] and ultralong-acting β_2-agonists[212-214] that have a 12- or 24-h administration regimen, respectively; and 12- and 24-h inhaled corticosteroids.[215-218] Each agent, singularly or in combination, has been shown to improve lung function (degree of obstruction and decrease static and dynamic hyperinflation), relieve symptoms, and improve health-related quality of life and exercise endurance.

Double or Triple Therapy: Existing national and international COPD guidelines have recommended that if COPD symptoms are not well controlled with single agents, the combination of two or more agents in a stepwise manner is reasonable.[17,142,147] The effect of combination therapy has proven beneficial for lung function and health-related quality of life, but the effectiveness on exacerbations remains less clear.[219,220] In its most recent iteration,[142] the GOLD (Global Initiative for Chronic Obstructive Lung Disease) grades disease severity using the number of exacerbations as a risk categorization and recommends combination therapy for patients with two or more exacerbations (categories C and D). Exacerbations were also highlighted and specifically targeted for combination therapy in prior CTS practice guidelines.[147] The combination includes primarily an inhaled corticosteroid and a long-acting β_2-agonist, although potential use of a long-acting muscarinic antagonist plus a long-acting β_2-agonist is also recommended based primarily on consensus. In patients with more severe COPD (GOLD category D), triple therapy is considered appropriate.

Evidence for Combination Inhaled Corticosteroid/Long-Acting β_2-Agonist Compared With Single Bronchodilator: Relatively few long-term studies have compared combination inhaled corticosteroid and

long-acting β_2-agonist with single drugs, with exacerbations as the main outcome. A Cochrane meta-analysis[220] found 14 studies that met these inclusion criteria, randomizing 11,794 patients with severe COPD. The review evaluated 10 studies assessing fluticasone plus salmeterol and four studies assessing budesonide plus formoterol separately. The studies were well designed with a low risk of bias for randomization and blinding, but they had high rates of attrition, which reduced confidence in the results for outcomes. The reviewers concluded that the combination inhaled corticosteroid/long-acting β_2-agonist therapy reduced the number of exacerbations but did not affect the rate of hospitalizations compared with long-acting β_2-agonist therapy alone. The combination did result in better lung function, health-related quality of life, dyspnea, and reduced use of rescue medication, but the differences did not reach clinical significance. There was a 4% increased risk of pneumonia in the combination therapy group compared with the long-acting β_2-agonist alone group. There are no head-to-head comparisons of the newer combinations (once-a-day formulations) that provide firm recommendations regarding their use and indications. However, the studies of the once-a-day single delivery combination of inhaled corticosteroid and long-acting β_2-agonist again show better lung function and less dyspnea and rescue medication use with a small effect on exacerbations and no effect on hospitalizations over bronchodilators alone.[191,221]

There are few data comparing triple therapy with double or single therapy. A systematic review compared the efficacy of three therapeutic approaches: tiotropium plus long-acting β_2-agonist (dual therapy), long-acting β_2-agonist plus inhaled corticosteroid (combined therapy), and tiotropium plus inhaled corticosteroid plus long-acting β_2-agonist (triple therapy), each compared with tiotropium single therapy.[214] Twenty trials enrolling 6,803 patients were included in the review. The authors concluded that dual therapy improved lung function and health-related quality of life but failed to decrease exacerbation frequency compared with tiotropium monotherapy. Combined therapy also improved lung function, health-related quality of life, and dyspnea without a significant impact on risk of exacerbations. Again, the authors observed an increased risk of adverse events in patients receiving this therapy. Triple therapy increased lung function and improved health-related quality of life (reaching minimally important clinical thresholds in both outcomes) and marginally improved risk for exacerbations. However, the authors still concluded that the data were insufficient to make strong recommendations.

In some of these studies, the responses or benefits in end points, such as lung function, health-related quality of life, and dyspnea, do not always parallel the observed responses in reducing acute exacerbations. Although the reasons for these occasional dissimilar responses are not clearly obvious, it appears reasonable to independently assess the specific impact of these interventions on reducing exacerbations.

20. For patients with stable moderate, severe, and very severe COPD, we recommend maintenance, combination inhaled corticosteroid/long-acting β_2-agonist therapy (and not inhaled corticosteroid monotherapy) compared with placebo to prevent acute exacerbations of COPD (Grade 1B).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD together with slowing the rate of decline in health-related quality of life and a relatively lower value on the risks and consequences of oral candidiasis, hoarseness and dysphonia, bruising, and pneumonia.

21. For patients with stable moderate, severe, and very severe COPD, we recommend maintenance combination inhaled corticosteroid/long-acting β_2-agonist therapy compared with long-acting β_2-agonist monotherapy to prevent acute exacerbations of COPD (Grade 1C).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD together with improved health-related quality of life, reduced dyspnea, less rescue medication use, and improved lung function and a relatively lower value on the risks and consequences of oral candidiasis, upper respiratory tract infections, and pneumonia.

22. For patients with stable moderate to very severe COPD, we recommend maintenance combination inhaled corticosteroid/long-acting β_2-agonist therapy compared with inhaled corticosteroid monotherapy to prevent acute exacerbations of COPD (Grade 1B).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD together with the comparative mortality benefit of combination inhaled corticosteroid/long-acting β_2-agonist therapy, acknowledging that there were no significant differences in serious adverse events or incidence of pneumonia between the groups.

This recommendation does not support the use of inhaled corticosteroid monotherapy in COPD.

23. For patients with stable COPD, we recommend inhaled long-acting anticholinergic/long-acting β_2-agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 1C).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD.

24. For patients with stable COPD, we recommend maintenance combination of inhaled corticosteroid/long-acting β_2-agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 1C).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD and a relatively lower value on the risks and consequences of pneumonia.

25. For patients with stable COPD, we suggest maintenance combination of inhaled long-acting anticholinergic/corticosteroid/long-acting β_2-agonist therapy or inhaled long-acting anticholinergic monotherapy, since both are effective to prevent acute exacerbations of COPD (Grade 2C).

Underlying Values and Preferences: This recommendation places high value on reducing the risk of acute exacerbations of COPD.

PICO 3: In Patients Aged > 40 Years Who Are Previous or Current Smokers With COPD, Does Oral Therapy Prevent/Decrease Acute Exacerbations of COPD?

In the administration of treatment medication for COPD, the inhalation route has been favored for the past 30 years. This technique enables the drugs to act directly on the airways, provided that the inhalation device is used correctly. Although inhaled medications are not without adverse effects, they often are seen as having a better tolerability and safety profile than oral medications. Some medications can only be administered orally. Selecting drugs that are orally administered depends on the type of drug and the patient. Furthermore, poor access to inhaled medications can be a problem in some countries. We chose to organize the review of oral therapy by the following categories: antibiotics, oral corticosteroids, phosphodiesterase inhibitors (roflumilast, theophylline), mucolytic agents (N-acetylcysteine [NAC], erdosteine, and carbocysteine), and statins (Table 1).

Some of the oral medications (eg, antibiotics, corticosteroids) are primarily prescribed to treat acute exacerbations of COPD. In this review, we did not assess the interventions used to treat acute exacerbations; we evaluated the evidence around the use of the interventions to prevent or decrease acute exacerbations.

Antibiotics: Macrolide antibiotics have a number of antimicrobial, antiinflammatory, and immunomodulating effects and have been used for many years in the management of other chronic airway diseases, including diffuse panbronchiolitis and cystic fibrosis. Given this successful use and the significant role airway inflammation and bacterial infection play in the pathogenesis of COPD exacerbations, there has been increasing interest in the use of macrolides to prevent these events.

Five RCTs comparing the administration of a macrolide vs placebo or another agent were identified for final inclusion of which three were ultimately included in the analysis on the basis of matched outcomes.[21,222,223] Seemungal et al[223] conducted a double-blind, randomized, placebo-controlled study of erythromycin 250 mg bid in 109 patients with moderate to severe COPD and found that the frequency of acute exacerbations of COPD was significantly reduced in the erythromycin group (RR, 0.648; 95% CI, 0.489-0.859; $P = .003$). A similar randomized, placebo-controlled study by He et al[222] using erythromycin 125 mg tid found a comparable protective effect on exacerbation risk (RR, 0.554; 95% CI, 0.314-0.979; $P = .042$). Albert et al[21] conducted the largest RCT of macrolides to date (n = 1,142) and compared azithromycin 250 mg daily with placebo for 1 year in patients with moderate to severe COPD who had either suffered a similar event in the year prior to enrollment or who were on long-term oxygen therapy. The number of patients who were enrolled based solely on meeting the oxygen requirement was only 12%. The exacerbation rate was significantly reduced from 1.83 to 1.48 acute exacerbations of COPD per patient-year (RR, 0.83; 95% CI, 0.72-0.95; $P = .01$), and this remained significant after adjustment for sex, FEV_1, age, and smoking status. Given the similar patient populations and comparable effect sizes, the pooled effects (RR, 0.73; 95% CI, 0.58-0.91) provide high-quality evidence to support the use of macrolides for the prevention of acute exacerbations. In the study by Albert et al,[21] fewer patients in the azithromycin group developed nasopharyngeal colonization during the study with common respiratory pathogens, but those who did were more likely to become

colonized with organisms that were resistant to azithromycin. The significance of these findings is uncertain because colonization was not associated with an increase in COPD exacerbations or pneumonia. There was also a modest increase in the risk of hearing loss in those assigned to azithromycin, although this often was reversible. Although there was no increase in the risk of adverse cardiovascular events in patients taking azithromycin in the study by Albert et al,[21] other large population-based studies suggested that the drug may increase the risk of cardiac death, and thus, patients should be carefully evaluated for predisposing conditions or medications before initiating therapy. The cardiac safety of azithromycin in the study by Albert et al[21] may be partly due to excluding patients with QT prolongation or who were taking other drugs that could prolong the QT interval. The data from the available clinical trials demonstrate that regular macrolide therapy definitively reduces the risk of acute exacerbations. Although these results are robust and would support a level 1 recommendation, safety data from the largest of these studies (Albert et al[21]) raise concerns about the development of antibiotic resistance as well as hearing loss. In addition, data from large observational studies in other populations suggest the potential for cardiovascular side effects, including prolongation of the QT interval, although these were not observed in the randomized trials reviewed for these guidelines. Based on these potential safety concerns, macrolide therapy is suggested (grade 2A) as a therapeutic option in patients with a history of exacerbations, and clinicians should be aware of the potential for adverse effects. The duration and exact dosage of macrolide therapy is unknown, but given the efficacy of the macrolides, strategies to mitigate these potential adverse effects are recommended.

26. For patients with moderate to severe COPD, who have a history of one or more moderate or severe COPD exacerbations in the previous year despite optimal maintenance inhaler therapy, we suggest the use of a long-term macrolide to prevent acute exacerbations of COPD (Grade 2A).

Underlying Values and Preferences: This recommendation places high value on the prevention of COPD exacerbations. However, clinicians prescribing macrolides need to consider in their individual patients the potential for prolongation of the QT interval and hearing loss as well as bacterial resistance. The duration and exact dosage of macrolide therapy are unknown.

Corticosteroids: Systemic oral corticosteroids for the long-term treatment of COPD are not recommended (GOLD guidelines), but their use is recommended for treating acute exacerbations of COPD (GOLD guidelines).[1] Systemic corticosteroids have been shown to improve symptoms and lung function, reduce treatment failure, and shorten length of hospital stay.[224-227] The effect of preventing a subsequent exacerbation is more controversial and was the focus of our review.

Four studies addressed hospitalization within 30 days following an exacerbation,[224,226,228,229] whereas two studies addressed hospitalization for acute exacerbations of COPD at 6 months.[226,230] Aggarwal et al[228] compared 2 weeks of either hydrocortisone or methylprednisolone along with standard therapy in patients treated for acute exacerbations of COPD in the ED. They found no difference in the readmission rate between the two groups during the 2-week follow-up period (OR, 0.18; 95% CI, 0.01-3.85). Niewoehner et al[226] randomized patients hospitalized for acute exacerbations of COPD to 8 weeks of corticosteroids, 2 weeks of corticosteroids with 6 weeks of placebo, or 8 weeks of placebo. Compared with placebo, there was a reduction in treatment failure for the combined corticosteroid group at 30 days (23% vs 33%, $P = .04$), but there was no difference in the 30-day readmission rates between the corticosteroid and placebo groups (4% vs 5%), leading to a nonsignificant OR of 0.54 (95% CI, 0.10-2.88). Ställberg et al[229] treated outpatients with COPD for an acute exacerbation with either high-dose inhaled budesonide/formoterol or 30 mg prednisolone daily and inhaled formoterol bid for 2 weeks. Three patients (5.6%) in the prednisolone group and one (1.8%) in the inhaled therapy group required hospitalization during the 12-week follow-up period, providing a nonsignificant OR for hospitalization of 1.02 (95% CI, 0.06-16.71). Aaron et al[224] treated patients presenting to the ED with an AECOPD not requiring admission with either prednisone 40 mg daily or placebo once daily for 10 days. Prednisone reduced the 30-day risk of the combined end point of unscheduled physician visit or return to the ED compared with placebo (27% vs 43%, $P = .05$), and there was a trend toward lower hospitalization in the prednisone group (11% vs 21%, $P = .11$). The calculated OR for hospitalization favored the prednisone group in this study (0.40; 95% CI, 0.16-0.99). The pooled data from these studies suggest that systemic corticosteroids used to treat an AECOPD can reduce 30-day readmission rates due to recurrent AECOPD (OR, 0.43; 95% CI, 0.20-0.91).

Rice et al[230] randomly assigned patients with COPD on long-term corticosteroid therapy to either their usual dose of corticosteroids for 6 months or gradual tapering

of corticosteroid therapy at a rate of 5 mg/wk. The primary outcome of the study was the average number of AECOPD during the 6-month treatment period. There was no difference in the number of exacerbations between the two groups. Additionally, there were three admissions (15%) in the usual dose group and none in the tapering group (OR, 7.40; 95% CI, 0.36-153.8). The previously discussed Niewoehner et al[226] trial also failed to show a reduction in 6-month hospitalizations between placebo group and group treated with 8 weeks of systemic corticosteroids (OR, 1.07; 95% CI, 0.49-2.36). Pooling the data from these studies shows no support for treating an AECOPD with systemic corticosteroids to reduce future exacerbations during the following 6 months (OR, 1.6; 95% CI, 0.34-7.51). This would not preclude the short-term use of systemic corticosteroids for treating an AECOPD in either the outpatient or the inpatient setting.

27. For patients with an acute exacerbation of COPD in the outpatient or inpatient setting, we suggest that systemic corticosteroids be given orally or intravenously to prevent hospitalization for subsequent acute exacerbations of COPD in the first 30 days following the initial exacerbation (Grade 2B).

Underlying Values and Preferences: We place high value on reducing recurrent exacerbations in the first 30 days following an initial acute exacerbation of COPD by treating the exacerbation with systemic corticosteroids. This recommendation takes into consideration the risks associated with the short-term use of systemic corticosteroids, which include hyperglycemia, weight gain, and insomnia, but the benefits of this intervention are believed to outweigh the risks. The use of systemic corticosteroids to treat an acute exacerbation has not been shown to reduce acute exacerbations beyond the 30-day window. Furthermore, no evidence supports the use of long-term corticosteroids to reduce acute exacerbations of COPD, and the risks of hyperglycemia, weight gain, infection, osteoporosis, and adrenal suppression far outweigh any benefits.

28. For patients with an acute exacerbation of COPD in the outpatient or inpatient setting, we recommend that systemic corticosteroids not be given orally or intravenously for the sole purpose of preventing hospitalization due to subsequent acute exacerbations of COPD beyond the first 30 days following the initial acute exacerbation of COPD (Grade 1A).

Remark: This does not preclude the use of systemic corticosteroids for the treatment of acute exacerbations of COPD.

Underlying Values and Preferences: We place high value on reducing recurrent exacerbations in the first 30 days following an initial acute exacerbation of COPD by treating the exacerbation with systemic corticosteroids. This recommendation takes into consideration the risks associated with the short-term use of systemic corticosteroids, which include hyperglycemia, weight gain, and insomnia, but the benefits of this intervention are believed to outweigh the risks. The use of systemic corticosteroids to treat an acute exacerbation has not been shown to reduce acute exacerbations beyond the 30-day window. Furthermore, no evidence supports the use of long-term corticosteroids to reduce AECOPD, and the risks of hyperglycemia, weight gain, infection, osteoporosis, and adrenal suppression far outweigh any benefits.

Phosphodiesterase 4 Inhibitor: The phosphodiesterase 4 inhibitor roflumilast has been evaluated for its ability to prevent future exacerbations in patients with moderate to severe COPD with a history of chronic cough and sputum production and exacerbations. Two of the included studies[231,232] were large, placebo-controlled, multicenter trials. The results from the centers participating in the Calverley et al[231] trial were pooled because the protocols were identical for the participating centers. Fabbri et al[232] conducted four studies comparing roflumilast with placebo; one compared roflumilast and either salmeterol or tiotropium with bronchodilator alone and, therefore, was analyzed as two separate studies. One study[221] was actually a post hoc analysis of the two studies reported in Calverley et al[231] and looked at the value of roflumilast in reducing the frequency of COPD exacerbations in the frequent exacerbator phenotype (two or more exacerbations in the previous year) compared with the infrequent exacerbator phenotype. One study[233] had FEV_1 as a primary outcome and COPD exacerbations as a secondary outcome. Because the study was only 12 weeks long and the number of exacerbations was low in both the placebo and the roflumilast groups, this study was excluded from the pooled data.

We were able to match three studies, one from Calverley et al[231] and two from Fabbri et al[232] reporting the median time to first COPD exacerbation. The mean HR was 0.87 (95% CI, 0.80-0.95) for roflumilast. Two studies[151,221] reported the number of subjects experiencing two or more exacerbations per year. The HR for roflumilast was 0.95 (95% CI, 0.83-1.08). Two studies from Calverley et al and two from Fabbri et al were matched to report the mean rate of exacerbations per year, although the two Fabbri et al studies included mild exacerbations in addition to the moderate and severe exacerbations counted in the Calverley et al studies.[151,231] The HR for roflumilast was 0.85 (95% CI, 0.79-0.92).

Each included trial for the pooled exacerbation data was large and well designed. However, they only included a subset of patients with COPD with grade III or IV obstruction ($FEV_1 < 50\%$ predicted), a history of chronic bronchitis, and at least one reported exacerbation requiring treatment or hospitalization in the previous year. There were a number of medication exclusions for the trials. Most excluded the use of theophylline and inhaled corticosteroids.[221,231,232] More than 40% of patients in the roflumilast and placebo groups had been treated with long-term inhaled corticosteroids prior to the studies, and previous studies suggested that inhaled corticosteroid withdrawal may be associated with an increased subsequent risk of exacerbations. Long-term use of inhaled corticosteroids up to 2,000 μg beclomethasone equivalents was allowed in the study by Calverley et al.[151] This may explain the somewhat lower mean exacerbation rate in both the placebo and the roflumilast groups in this study compared with the other studies that excluded inhaled corticosteroids. However, the benefit of roflumilast in reducing exacerbations was similar between subjects previously on inhaled corticosteroids and those who were not in the latter studies.

The use of long-acting muscarinic agents was excluded in each study aside from Fabbri et al,[232] which specifically looked at the benefit of roflumilast vs placebo added to tiotropium. The use of long-acting β-agonists was excluded from the study by Calverley et al.[151] Each study had a number of secondary end points, including prebronchodilator and postbronchodilator FEV_1, both values of which increased by a statistically significant amount. The improvements in prebronchodilator FEV_1 between the roflumilast and placebo groups ranged from 39[151] to 80 mL when added to tiotropium.[232] The postbronchodilator improvement ranged from 36[151] to 81 mL when added to tiotropium.[232] In a smaller study by Lee et al[233] looking at the benefit of roflumilast vs placebo in Asian patients with COPD with slightly less severe airflow obstruction compared with those enrolled in the exacerbation studies, improvements in prebronchodilator FEV_1 averaged 95 mL and postbronchodilator FEV_1 79 mL (both $P < .0001$).

Side effects of nausea, diarrhea, headache, and weight loss averaging about 2.1 kg were more common in the roflumilast-treated patients and led to increased patient withdrawals from the study, particularly in the first 3 to 4 weeks. The side effects may limit the use of this medication in the clinical setting.

29. For patients with moderate to severe COPD with chronic bronchitis and a history of at least one exacerbation in the previous year, we suggest the use of roflumilast to prevent acute exacerbations of COPD (Grade 2A).

Underlying Values and Preferences: Clinicians prescribing roflumilast need to advise their patients of the potential side effects of weight loss and diarrhea. Patients may have to discontinue the therapy because of side effects. The decision to prescribe this medication should also be informed by the fact that there are limited data for supplemental effectiveness in patients concurrently using inhaled therapies.

Theophylline: Theophylline has been used to treat airway diseases for decades. Its bronchodilator effects are mediated through inhibition of phosphodiesterase 3,[234] although this requires fairly high serum levels, which are associated with frequent side effects of nausea, vomiting, and gastroesophageal reflux as well as headache. At lower doses, theophylline also likely has antiinflammatory effects, although these may be mediated through phosphodiesterase 4 inhibition and activation of histone deacetylase 2, which downregulates a number of inflammatory genes. The drug is metabolized by the hepatic cytochrome p450 system and, thus, has a number of important drug interactions. As a bronchodilator in patients with COPD, theophylline improves lung function when added to long-acting β-agonists, and there is some evidence that it may reverse corticosteroid resistance in this group.

Of the 18 studies of oral theophylline compared with placebo, an active comparator, or both, two met criteria for further review.[235,236] Rossi et al[235] randomized 854 patients with COPD ($FEV_1 < 70\%$ predicted) to one of two doses of formoterol (12 or 24 μg bid), oral slow-release theophylline twice daily and titrated to 8 to 20 mg/L 3 to 4 h after dosing, or placebo for 1 year. The primary end point was FEV_1, but the number of patients experiencing moderate to severe exacerbations was also assessed and shown to be reduced in both the formoterol dosage arms compared with placebo. There was no difference in the number of patients with exacerbations in the theophylline vs placebo arms. GI side effects were threefold higher in those receiving theophylline than either formoterol arm, and this led to a 27% withdrawal rate in the first 3 months of the study. Zhou et al[236] performed a 1-year randomized, double-blind, parallel group and placebo-controlled trial of slow-release theophylline 100 mg bid in 110 patients with COPD ($FEV_1 > 30\%$ predicted but poor response to short-term bronchodilators). The odds of exacerbation in the theophylline group were reduced (0.73) vs placebo,

although the risk of GI side effects was also higher in those receiving theophylline. The pooled analysis of these two studies revealed an effect estimate of 0.83 (95% CI, 0.47-1.47), suggesting moderate-quality evidence supporting theophylline in the prevention of acute exacerbations. From a clinical standpoint, there are no studies examining the role of theophylline as add-on therapy in patients with ongoing exacerbations despite inhaled therapies, although this is a common manner in which the drug is used. The unfavorable side effect profile of theophylline compared with inhaled agents that more clearly reduce exacerbations also makes treatment with the drug less useful.

30. For stable patients with COPD, we suggest treatment with oral slow-release theophylline twice daily to prevent acute exacerbations of COPD (Grade 2B).

Underlying Values and Preferences: Physicians should inform their patients with COPD who are being treated with maintenance bronchodilator therapy and inhaled corticosteroids and who continue to have periodic exacerbations that theophylline may reduce the number of exacerbations. Patient decisions may also be informed by the relatively narrow therapeutic window with respect to adverse effects of treatment with theophylline. Physicians should use the lowest effective dose in prescribing theophylline in order to avoid adverse effects. Theophylline use requires vigilance on the part of the physician in order to avoid serious drug interactions, which lead to changes in serum theophylline levels. Patients should be advised that changes in tobacco use habits will affect serum theophylline levels and that they should inform their physicians if they stop smoking while taking theophylline.

N-acetylcysteine: Patients with COPD and chronic bronchitis may experience exacerbations of their condition because of thick secretions that are difficult to eliminate from the tracheobronchial tree. NAC has been proposed as an agent that may act as a mucolytic in the respiratory tract and aid in the elimination of secretions. NAC reduces the viscosity of respiratory secretions as a result of the cleavage of disulfide bonds.[237] In patients with COPD and chronic bronchitis, oral NAC has been proposed as a mucolytic agent because it is rapidly absorbed from the GI tract, has been reported to be rapidly present after ingestion in an active form in lung tissue and respiratory secretions, and is well tolerated except for in rare patients with adverse GI effects.[238] Investigators first suggested that NAC might be effective in reducing exacerbations of COPD more than 3 decades ago.[238,239]

We identified 11 RCTs comparing the administration of NAC with placebo or another agent, of which three were ultimately included in the meta-analysis based on matched outcomes.[240-242] The other studies[243-248] were either not conducted at the patient level but, instead, at the exacerbation count level or had exacerbations as a secondary outcome measure.

Hansen et al[240] randomized 129 patients to a prospective, placebo-controlled, double-blind study with oral NAC administered twice daily as the study intervention. The authors found an improvement in subjective complaints using the General Health Score, an established psychiatric instrument measuring symptomatic well-being. This finding was mitigated by scores being different between the two groups at baseline. The number of exacerbations in the NAC group was not significantly different from that in the placebo group.

Pela et al[241] studied 169 patients randomized to receive oral NAC 600 mg once daily vs placebo. The primary outcome measurement was the rate of COPD exacerbations, which was reduced by 41% in the intervention group compared with the control group. The study drug reduced the number of patients having multiple exacerbations, and pulmonary function measurements were slightly, but significantly improved. NAC was well tolerated, with no difference in adverse events between groups.

In the largest study to date by Zheng et al[242] randomized 1,006 patients to receive oral NAC 600 mg bid vs placebo. This study was a large, multicenter, prospective, placebo-controlled, parallel group trial performed in China. Patients were selected if they had moderate to severe COPD based on spirometric measurements, were aged 40 to 80 years, and had at least two COPD exacerbations within the 2 years prior to enrollment. Patients were also stratified according to their use of inhaled corticosteroids. The exacerbation rate was 1.16 in the NAC group vs 1.49 in the placebo group (RR, 0.78 for the NAC group). Time to first exacerbation was not different between the study and placebo groups, but time to second and third exacerbations was shorter in the placebo arm. NAC appeared to be more effective in patients with GOLD II COPD compared with those with GOLD III, with time to first exacerbation being longer in the GOLD II group than in the GOLD III group. The incidence of adverse effects attributed to the study drug did not differ between the NAC and placebo groups.

When examined together, the combined data from these studies[240-242] demonstrate a reduction in the rate of exacerbations in COPD associated with the use of NAC

compared with placebo (OR, 0.61; 95% CI, 0.37-0.99). Although conclusions are limited by the sample size of the studies assessed, oral NAC is well tolerated and appears to represent a low risk to patients.

31. For patients with moderate to severe COPD and a history of two or more exacerbations in the previous 2 years, we suggest treatment with oral N-acetylcysteine to prevent acute exacerbations of COPD (Grade 2B).

Underlying Values and Preferences: Physicians should inform their patients with COPD who are being treated with maintenance bronchodilator therapy and inhaled corticosteroids and who continue to have periodic exacerbations that N-acetylcysteine may reduce the number of exacerbations. Patient decisions may also be informed by the low risk of adverse effects from treatment with N-acetylcysteine.

Erdosteine: Erdosteine, a mucolytic, has potential to reduce exacerbations in patients with COPD. The only study identified in the systematic review was a small RCT in 124 patients over 8 months.[249] Therefore, we determined that insufficient evidence supports a recommendation about the use of erdosteine for the prevention of COPD exacerbations.

Carbocysteine: S-carboxymethylcysteine (carbocysteine or S-CMC) is a thiol derivative of L-cysteine and is available as carbocysteine or its lysine salt (S-CMC-lys), which is cleaved in the GI tract to the active drug carbocysteine. This drug is a mucolytic agent available in Europe and Asia that has been demonstrated to reduce sputum viscosity and increase mucociliary transport.[250]

Only three studies[251-253] were deemed to be of sufficient quality to be included, but a pooled analysis could not be performed because of the heterogeneous nature of the studies. S-CMC-lys was given to patients in a multicenter randomized placebo-controlled trial performed in 662 outpatients with chronic obstructive bronchitis.[252] Patients were randomized to S-CMC-Lys daily, placebo, or intermittent treatment with alternating 1-week courses of S-CMC-Lys and placebo for 6 months. The percentage of patients who were exacerbation free during the 6-month trial was significantly greater in the group randomized to once daily S-CMC-Lys compared with placebo (70.4% vs 54.1%, $P = .001$), and the time to a first AECOPD was prolonged compared with placebo. Another trial enrolled 109 patients with obstructive chronic bronchitis to either carbocysteine or placebo for a 6-month winter period, but the investigators found no difference in the number of acute exacerbations of chronic bronchitis between the two groups.[252] The largest study to date has been the PEACE Study (Effect of Carbocysteine on Acute Exacerbation of COPD), which randomized 709 outpatients with COPD with a history of at least two acute exacerbations of COPD in the previous 2 years to either placebo or carbocysteine for 1 year. There was a significant reduction in the number of exacerbations in the carbocysteine group compared with the placebo group (RR, 0.75; 95% CI, 0.62-0.92) with the difference becoming significant after 6 months of therapy.[253] These studies did not permit a pooled analysis; therefore, we can only suggest that carbocysteine may be beneficial in reducing acute exacerbations of COPD, but more data from randomized placebo-controlled clinical trials are needed before an evidence-based recommendation can be made.

32. For stable outpatients with COPD who continue to experience acute exacerbations of COPD despite maximal therapy designed to reduce acute exacerbations of COPD, we suggest that oral carbocysteine could be used to prevent acute exacerbations where this therapy is available (Ungraded Consensus-Based Statement).

Underlying Values and Preferences: This suggestion places high value on preventing acute exacerbations of COPD, with minimal risks associated with carbocysteine. The main adverse events reported in studies were mild GI symptoms.

Statins: Statins are well-known and widely prescribed for their lipid-lowering effects and improved outcomes related to cardiovascular disease. Statins are also known for their pleotropic effects, which include an antiinflammatory effect. In view of this attribute, statins have been evaluated for their role in preventing COPD exacerbations.

We found five observational studies[254-258] that explored the impact of statins on COPD exacerbations as reflected in large patient databases. Hospitalizations decreased for the patients receiving statins in three studies (RR, 0.66 [95% CI, 0.51-0.85]; OR, 0.68 [95% CI, 0.44-1.04]; HR, 0.66 [95% CI, 0.60-0.74]).[256-258] Two studies were pooled on COPD exacerbations, resulting in a pooled effect estimate OR of 0.58 (95% CI, 0.45-0.74)[255,258] in favor of statins. These observational studies all significantly supported an effect of statins on reducing COPD exacerbations. However, the authors of these studies concluded that an RCT would be needed to support the results.

A prospective RCT by Criner et al[259] included 885 patients with moderate to severe COPD who met at least one of the following criteria within the previous year: use of

supplemental oxygen, receipt of systemic glucocorticoids or antibiotics, ED visits, or hospital admissions for COPD exacerbations. Patients who had known cardiovascular risk factors and met criteria for statin use based on current guidelines were excluded. After recruitment of 885 of the anticipated 1,200 patients who were to be treated for 12 to 36 months, the trial was stopped due to futility by the data safety and monitoring board, which concluded that there was no signal for an immediate or delayed effect in an intention-to-treat analysis of the entire cohort or in any subgroup analyses. The COPD exacerbation rate was 1.36 ± 1.61 and 1.39 ± 1.73 per person-year ($P = .54$) in the statin and placebo groups, respectively. There was no effect on ED visits, unscheduled physician visits, or severity of exacerbations. Furthermore, no effect was seen in reducing severe exacerbations or hospitalizations. This RCT was determined to have a low risk of bias from the Cochrane Risk of Bias Tool. Accordingly, the highest level of evidence did not support the use of statins in COPD in preventing exacerbations.

33. For patients with moderate to severe COPD who are at risk for COPD exacerbations, we do not recommend using statins to prevent acute exacerbations of COPD (Grade 1B).

Underlying Values and Preferences: We place high value on reducing exacerbations in patients with COPD and, thus, do not recommend statins for preventing acute exacerbations. However, patients with COPD may meet accepted criteria for initiating statins because of the presence of cardiovascular risk factors.

Novel Therapies Not Included in the Guidelines

Several novel therapies are now in various stages of development for use alone or in combination with other agents in the management of COPD. Studies examining the effect of these agents on COPD exacerbations are either nonexistent or too small to include in the current guidelines. A short description of such agents is included here.

Most of the novel agents that have been recently approved or are in late stages of development include once-daily long-acting β_2-agonists olodaterol and vilanterol and long-acting muscarinic antagonists umeclidinium and glycopyrronium delivered through novel delivery devices. Olodaterol, recently approved by the US Food and Drug Administration for COPD is a new inhaled ultralong-acting β-agonist that offers the potential adherence and therapeutic advantage of once-daily therapy.[260,261] Additionally, multiple formulations of once-daily agents that use combinations of long-acting β_2-agonists and long-acting muscarinic antagonists (vilanterol/umeclidinium, tiotropium/olodaterol, aclidinium/formoterol, glycopyrronium/indacaterol, glycopyrronium/formoterol) are under development.[221,262-274] One such combination is vilanterol/umeclidinium that was recently approved by the Food and Drug Administration for COPD as once-daily combination bronchodilator therapy.[275-278] Similarly, once-daily long-acting β_2-agonist/inhaled corticosteroid formulations are being investigated. One such agent recently approved is fluticasone furoate/vilanterol, and several studies reported that this combination improves lung function and reduces exacerbations more effectively than either of its monocomponents.[188,191,194,197,279,280]

A large long-term study investigating fluticasone furoate/vilanterol in patients with cardiovascular risk factors (SUMMIT [Study to Understand Mortality and Morbidity in COPD]) is currently under way.[281] Other novel agents in early development are those that target airway inflammation in COPD, such as adenosine A2A-receptor agonists, inhibitors of proinflammatory pathways, and activators of antiinflammatory pathways. Among these are mimics of IL-10 and inhibitors of (1) tumor necrosis factor-α, (2) chemokines, (3) nuclear factor-κB; (4) p38 mitogen-activated protein kinase, (5) phosphoinositide 3-kinase, and (6) leukotriene B4. Other drugs under investigation include those with antioxidant effects and that may have effects on lung regeneration (retinoids) as well as mucoactive drugs.[184,185,270,282-285]

Conclusions

These guidelines provide the clinician with evidence-based information on therapies to prevent COPD exacerbations using an objective, rigorous, evidence-based approach to the assessment of the existing literature regarding nonpharmacologic inhaled and oral therapies (Fig 1). We have avoided providing opinions, instead using objective assessment of each recommendation where the data are robust enough to provide a meaningful conclusion based on the available data. This assessment also highlights areas where more research is needed as demonstrated by CB recommendations as well as recommendations given a grade of C. It is clear that large gaps in knowledge currently exist about exacerbation prevention that limit our ability to prioritize one type of therapy over another or make recommendations about combinations of therapy to prevent exacerbations. Hopefully, future research will evaluate combinations of

therapies across PICO groups and their impact on exacerbation prevention. Newer therapies that are soon to be released for clinical use or that are currently under investigation that focus on the prevention of COPD exacerbations also promise to rapidly improve the future armamentarium for the treatment of the patient with COPD.

Acknowledgments

Author contributions: G. J. C. is the guarantor of the manuscript. G. J. C. drafted recommendations and supporting text for the Inhaled Therapies section and Introduction, oversaw the drafting of the Inhaled Therapies section and the entire manuscript, and synthesized all of the sections in the final manuscript and executive summary; J. B. oversaw the drafting of the Oral Therapies section and drafted supporting text for the section, advised the nonpharmacologic therapies writing committee, and reviewed and provided feedback on the entire manuscript; R. L. D. conducted systematic reviews for the Nonpharmacologic Therapies section, oversaw the systematic reviews for inhaled and oral therapies as well as advising all of the writing committees on drafting recommendations and supporting text, drafted the Methodology section, and reviewed and provided feedback on the entire manuscript; D. R. O. served as the liaison to the Guidelines Oversight Committee, drafted recommendations and supporting text for the Oral Therapies section, and reviewed and provided feedback on the entire manuscript; D. G. and P. H. led the nonpharmacologic therapies writing committee, drafted recommendations and supporting text for the section, and reviewed and provided feedback on the entire manuscript; K. C. coordinated all of the writing committee and executive committee meetings, facilitated the review of the entire manuscript, drafted the Knowledge Translation section, and reviewed and provided feedback on the entire manuscript; M. S. B. drafted supporting text for the Oral Therapies section and reviewed the entire manuscript; M. B., B. R. C., S. B. F., and N. A. H. drafted supporting text for the Inhaled Therapies section and reviewed the entire manuscript; P. G. C., G. D., M. G. F., R. A. M., and M. K. S. drafted recommendations and supporting text for the Nonpharmacologic Therapies section and reviewed the entire manuscript; M. T. D., N. M., and J. D. R. drafted recommendations and supporting text for the Oral Therapies section and reviewed the entire manuscript; B. K. I. conducted systematic reviews for the Inhaled Therapies section and reviewed the recommendations and supporting text for the Inhaled Therapies and Methodology sections; D. D. M. drafted recommendations and supporting text for the Inhaled Therapies section and reviewed the entire manuscript; and J. O. conducted systematic reviews for the Oral Therapies section and reviewed the recommendations and supporting text for the Oral Therapies and Methodology sections.

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following conflicts of interest: Dr Bourbeau received government grants for conducting the longitudinal population-based Canadian Cohort Obstructive Lung Disease (CanCOLD) study from the Canadian Institute of Health Research (CIHR) Rx&D collaborative program (AstraZeneca, Boehringer Ingelheim GmbH, GlaxoSmithKline plc, Merck Sharp & Dohme Corp, Nycomed, Novartis AG), Canadian Respiratory Research Network, Respiratory Health Network of the Fonds de recherche du Québec-Santé, and Research Institute of the McGill University Health Centre. Ms Diekemper is a codeveloper of the DART (Document and Appraisal Review Tool), which was used in the AECOPD Guideline to assess the quality of the systematic reviews that informed some of the recommendations. Dr Hernandez reports that his institution has received pharmaceutical company grant monies for research studies on which he has been an investigator, including CSL Behring, Boehringer Ingelheim GmbH, and Grifols International SA. His institution also has received grant monies for research studies for which he has been an investigator, including CIHR and Lung Association of Nova Scotia. He has participated in speaking activities, industry advisory committees, and other activities related to industry sources with the following pharmaceutical companies: Actelion Pharmaceuticals US, Inc; Almirall, SA; AstraZeneca; Boehringer Ingelheim GmbH; GlaxoSmithKline plc; Grifols; Intermune; Merck Sharp & Dohme Corp; and Novartis AG. Dr Balter has served over the past 3 years on advisory boards for and has presented at continuing education meetings for Almirall, SA; AstraZeneca; Boehringer Ingelheim GmbH; GlaxoSmithKline plc; Merck Frosst Canada Inc; Novartis AG; and Takeda Pharmaceutical Company Limited. Dr Bhutani receives university grant money, pharmaceutical grant money, grant money from government organizations in Canada and participates in speakers bureaus and speaks publicly on the topic of acute exacerbations of COPD. Dr Camp has received operating grant funding from CIHR, Canadian Lung Association, and Physiotherapy Foundation of Canada. She has received research infrastructure funding from the Canadian Foundation of Innovation and the British Columbia Lung Association and a scholar award from the Michael Smith Foundation of Health Research. She has received honoraria for speaking engagements from the Canadian Lung Association and the University of British Columbia Respiratory Division. Dr Celli's division has received grants from AstraZeneca to complete research studies. He has served on an advisory board or as a consultant to GlaxoSmithKline plc; Boehringer Ingelheim GmbH; Almirall, SA; AstraZeneca; Takeda Pharmaceutical Company Limited; and Novartis AG. Neither he nor any member of his family has shares or interest in any company. Dr Celli has not received or had any relationship with tobacco money. Dr Dechman speaks to health professionals about the management of COPD, including acute exacerbations of COPD, but does not gain financially from doing so. Dr Dransfield has served as a consultant for GlaxoSmithKline plc; Boehringer Ingelheim GmbH; and Ikaria, Inc. His institution has received research grant support from the American Heart Association; National Heart, Lung, and Blood Institute; GlaxoSmithKline plc; and Forest Laboratories, Inc, and has received contracted support for enrollment in clinical trials from Aeris; Boehringer Ingelheim GmbH; Boston Scientific Corporation; Janssen Biotech, Inc (formerly Centocor Biotech, Inc); GlaxoSmithKline plc; Forest Laboratories, Inc; Otsuka America Pharmaceutical, Inc; Pearl Therapeutics Inc; Pfizer, Inc; PneumRx, Inc; and Pulmonx. Dr Fiel has received grant support from the Cystic Fibrosis Foundation and grants for clinical trials from Vertex Pharmaceuticals Incorporated, Gilead, Novartis AG, and PTC Therapeutics. Dr Foreman is PI for the Forest ASCENT COPD study (LAS-MD-45). Dr Hanania serves as a consultant to Boehringer Ingelheim GmbH; Sunovion Pharmaceuticals Inc; Novartis AG; Mylan Inc; Pearl Therapeutics Inc; and Pfizer, Inc. Her institution receives grant support on her behalf from GlaxoSmithKline plc; Boehringer Ingelheim GmbH; Pfizer, Inc; Pearl Therapeutics Inc; and Sunovion Pharmaceuticals Inc. Dr Marchetti has served as principal investigator for a pharmaceutical-funded clinical trial with GlaxoSmithKline plc. Dr Marciniuk has provided consultation for Health Canada, the Public Health Agency of Canada, and the Saskatoon Health Region. He has received research funding (all held and managed by the University of Saskatchewan) from AstraZeneca; Boehringer Ingelheim GmbH; CIHR; Forest Laboratories Inc; the Lung Association of Saskatchewan; Novartis AG; Pfizer, Inc; Saskatchewan Health Research Foundation; and Schering-Plough Corporation. He holds fiduciary positions with the American College of Chest Physicians, the Chest Foundation, and the Lung Health Institute of Canada. Drs Criner, Ouellette, Goodridge, Ireland, Mularski, Road, and Stickland; Ms Curren; and Mr Ornelas have reported that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Endorsements: This guideline is endorsed by the US COPD Coalition, the International Primary Care Respiratory Group, and the Canadian Respiratory Health Professionals.

Role of sponsors: The American College of Chest Physicians provided methodology support, and the American Thoracic Society provided project management support to the Guideline.

Other contributions: This process spanned > 18 months and required the dedicated efforts of many from both the American College of Chest Physicians and the Canadian Thoracic Society in selecting panelists, organizing the systematic reviews and the regular executive and panelist conference calls and in-person meetings, and extracting information from the systematic reviews. We are indebted to Rebecca Diekemper, MPH; Kristen Curren, MA; Belinda Ireland, MD; Joe Ornelas, MS; Joyce Bruno, MBA, MIPH; Nanette Umphrey, BS;

Sandra Zelman Lewis, PhD; and Marianne Wright, BS (Dr Lewis and Ms Wright helped in the early stages of the guideline) for their tireless efforts to make this guideline a current and valuable addition to the management of the patient with COPD.

Additional information: The e-Appendix and e-Tables can be found in the Supplemental Materials section of the online article.

References

1. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. Updated 2103. Global Initiative for Chronic Obstructive Lung Disease website. http://www.goldcopd.org/uploads/users/files/GOLD_Report_2013_Feb20.pdf. Accessed May 15, 2014.
2. Brusasco V. Reducing cholinergic constriction: the major reversible mechanism in COPD. *Eur Respir Rev*. 2006;15(99):32-36.
3. Cooper CB. Airflow obstruction and exercise. *Respir Med*. 2009; 103(3):325-334.
4. Public Health Agency of Canada. Chronic obstructive pulmonary disease (COPD). Public Health Agency of Canada website. http://www.phac-aspc.gc.ca/cd-mc/crd-mrc/copd-mpoc-eng.php. Accessed June 28, 2012.
5. Centers for Disease Control and Prevention; National Center for Health Statistics. Deaths: final data for 2009. *Natl Vital Stat Rep*. 2012;60(3):1-117.
6. Centers for Disease Control and Prevention; National Center for Health Statistics. *National Health Interview Survey Raw Data, 1999-2011. Analysis performed by the American Lung Association Research and Health Education Division using SPSS and SUDAAN software*. Atlanta, GA: Centers for Disease Control and Prevention; 2011.
7. Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC; Centers for Disease Control and Prevention. Chronic obstructive pulmonary disease surveillance—United States, 1971-2000. *MMWR Surveill Summ*. 2002;51(6):1-16.
8. Centers for Disease Control and Prevention; National Center for Health Statistics. *National Hospital Discharge Survey Raw Data, 1999-2010. Analysis Performed by the American Lung Association Research and Health Education Division Using SPSS Software*. Atlanta, GA: Centers for Disease Control and Prevention; 2010.
9. *Confronting COPD in America, 2000*. Silver Spring, MD: Schulman, Ronca and Bucuvalas, Inc (SRBI); 2000. Funded by GlaxoSmithKline plc.
10. Mittmann N, Kuramoto L, Seung SJ, Haddon JM, Bradley-Kennedy C, Fitzgerald JM. The cost of moderate and severe COPD exacerbations to the Canadian healthcare system. *Respir Med*. 2008;102(3):413-421.
11. Chapman KR, Bourbeau J, Rance L. The burden of COPD in Canada: results from the Confronting COPD survey. *Respir Med*. 2003;97(suppl C):S23-S31.
12. Connors AF Jr, Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). *Am J Respir Crit Care Med*. 1996;154(4):959-967.
13. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1998;157(5):1418-1422.
14. Miravitlles M, Murio C, Guerrero T, Gisbert R; DAFNE Study Group. Pharmacoeconomic evaluation of acute exacerbations of chronic bronchitis and COPD. *Chest*. 2002;121(5):1449-1455.
15. Miravitlles M, García-Polo C, Domenech A, Villegas G, Conget F, de la Roza C. Clinical outcomes and cost analysis of exacerbations in chronic obstructive pulmonary disease. *Lung*. 2013;191(5):523-530.
16. Wouters EF. Economic analysis of the Confronting COPD survey: an overview of results. *Respir Med*. 2003;97(suppl C):S3-S14.
17. Celli BR, MacNee W; ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J*. 2004;23(6):932-946.
18. Maltais F, Celli B, Casaburi R, et al. Aclidinium bromide improves exercise endurance and lung hyperinflation in patients with moderate to severe COPD. *Respir Med*. 2011;105(4):580-587.
19. Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. *Chest*. 2000;117(5_suppl_2):398S-401S.
20. Qaseem A, Wilt TJ, Weinberger SE, et al; American College of Physicians; American College of Chest Physicians; American Thoracic Society; European Respiratory Society. 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. *Ann Intern Med*. 2011;155(3):179-191.
21. Albert RK, Connett J, Bailey WC, et al; COPD Clinical Research Network. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med*. 2011;365(8):689-698.
22. Calverley P, Pauwels R, Vestbo J, et al; TRial of Inhaled STeroids ANd long-acting beta2 agonists study group. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet*. 2003;361(9356): 449-456.
23. Tashkin DP, Celli B, Senn S, et al; UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359(15):1543-1554.
24. Lewis SZ, Diekemper R, Ornelas J, Casey KR. Methodologies for the development of CHEST guidelines and expert panel reports. *Chest*. 2014;146(1):182-192.
25. Brouwers MC, Kho ME, Browman GP, et al; AGREE Next Steps Consortium. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ*. 2010;182(18): E839-E842.
26. Diekemper R, Ireland B, Merz L. P154 development of the Documentation And Appraisal Review Tool (DART) for systematic reviews [poster]. *BMJ Qual Saf*. 2013;22:61-62.
27. Higgins JPT, Altman DG, Sterne JAC; Cochrane Statistical Methods Group; Cochrane Bias Methods Group. Chapter 8: assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 5.1.0 [updated March 2011]. London, England: The Cochrane Collaboration; 2011.
28. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*. 1998;52(6):377-384.
29. Langer-Gould A, Popat RA, Huang SM, et al. Clinical and demographic predictors of long-term disability in patients with relapsing-remitting multiple sclerosis: a systematic review. *Arch Neurol*. 2006;63(12):1686-1691.
30. Aaron SD, Fergusson D, Marks GB, et al; Canadian Thoracic Society/Canadian Respiratory Clinical Research Consortium. Counting, analysing and reporting exacerbations of COPD in randomised controlled trials. *Thorax*. 2008;63(2):122-128.
31. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64(4): 401-406.
32. Guyatt G, Gutterman D, Baumann MH, et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an American College of Chest Physicians task force. *Chest*. 2006;129(1):174-181.
33. Graham ID, Logan J, Harrison MB, et al. Lost in knowledge translation: time for a map? *J Contin Educ Health Prof*. 2006;26(1):13-24.
34. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness. *JAMA*. 2002;288(14):1775-1779.
35. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness: the chronic care model, part 2. *JAMA*. 2002;288(15):1909-1914.
36. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care (partial update). National Institute for Health and Care Excellence website. http://guidance.nice.org.uk/CG101/Guidance/pdf/English. Accessed May 15, 2014.

37. O'Donnell DE, Aaron S, Bourbeau J, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2007 update. *Can Respir J*. 2007;14(suppl B): 5B-32B.
38. Disler RT, Inglis SC, Davidson PM. Non-pharmacological management interventions for COPD: an overview of Cochrane systematic reviews (protocol). *Cochrane Database Syst Rev*. 2013;(2):CD010384.
39. Kruis AL, Smidt N, Assendelft WJJ, et al. Integrated disease management interventions for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2011;(10): CD009437.
40. Krumholz HM, Currie PM, Riegel B, et al; American Heart Association Disease Management Taxonomy Writing Group. A taxonomy for disease management: a scientific statement from the American Heart Association Disease Management Taxonomy Writing Group. *Circulation*. 2006;114(13):1432-1445.
41. Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M; Medical Research Council Guidance. Developing and evaluating complex interventions: the new Medical Research Council guidance. *BMJ*. 2008;337:a1655.
42. Petticrew M. When are complex interventions 'complex'? When are simple interventions 'simple'? *Eur J Public Health*. 2011; 21(4):397-398.
43. Weightman A, Ellis S, Cullum A, Sander L, Turley R. *Grading Evidence and Recommendations for Public Health Interventions: Developing and Piloting a Framework*. London, England: Health Development Agency; 2005.
44. Vaccines and immunizations. Centers for Disease Control and Prevention website. http://www.cdc.gov/vaccines/vpd-vac/pneumo. Accessed March 3, 2014.
45. Lee TA, Weaver FM, Weiss KB. Impact of pneumococcal vaccination on pneumonia rates in patients with COPD and asthma. *J Gen Intern Med*. 2007;22(1):62-67.
46. Centers for Disease Control and Prevention; Advisory Committee on Immunization Practices. Updated recommendations for prevention of invasive pneumococcal disease among adults using 23-valent pneumococcal polysaccharide vaccine (PPSV23). *MMWR Morb Mortal Wkly Rep*. 2010;59(34):1102-1106.
47. Bogaert D, van der Valk P, Ramdin R, et al. Host-pathogen interaction during pneumococcal infection in patients with chronic obstructive pulmonary disease. *Infect Immun*. 2004;72(2):818-823.
48. Patel IS, Seemungal TAR, Wilks M, Lloyd-Owen SJ, Donaldson GC, Wedzicha JA. Relationship between bacterial colonisation and the frequency, character, and severity of COPD exacerbations. *Thorax*. 2002;57(9):759-764.
49. Sethi S, Evans N, Grant BJB, Murphy TF. New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. *N Engl J Med*. 2002;347(7):465-471.
50. Papi A, Bellettato CM, Braccioni F, et al. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med*. 2006;173(10):1114-1121.
51. WHO recommendations for routine immunization summary tables. World Health Organization website. http://www.who.int/immunization/policy/immunization_tables/en. Accessed March 3, 2014.
52. Walters JA, Smith S, Poole P, Granger RH, Wood-Baker R. Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2010;(11):CD001390.
53. Dransfield MT, Harnden S, Burton RL, et al; NIH COPD Clinical Research Network. Long-term comparative immunogenicity of protein conjugate and free polysaccharide pneumococcal vaccines in chronic obstructive pulmonary disease. *Clin Infect Dis*. 2012; 55(5):e35-e44.
54. Furumoto A, Ohkusa Y, Chen M, et al. Additive effect of pneumococcal vaccine and influenza vaccine on acute exacerbation in patients with chronic lung disease. *Vaccine*. 2008;26(33):4284-4289.
55. Fiore AE, Uyeki TM, Broder K, et al; Centers for Disease Control and Prevention. Prevention and control of influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Recomm Rep*. 2010;59(RR-8):1-62.
56. Centanni S, Pregliasco F, Bonfatti C, et al. Clinical efficacy of a vaccine-immunostimulant combination in the prevention of influenza in patients with chronic obstructive pulmonary disease and chronic asthma. *J Chemother*. 1997;9(4):273-278.
57. Monto AS. Influenza: quantifying morbidity and mortality. *Am J Med*. 1987;82(6A):20-25.
58. Poole P, Chacko EE, Wood-Baker R, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2006;(1):CD002733.
59. Howells CH, Tyler LE. Prophylactic use of influenza vaccine in patients with chronic bronchitis. A pilot trial. *Lancet*. 1961;278(7218): 1428-1432.
60. Wongsurakiat P, Maranetra KN, Wasi C, Kositanont U, Dejsomritrutai W, Charoenratanakul S. Acute respiratory illness in patients with COPD and the effectiveness of influenza vaccination: a randomized controlled study. *Chest*. 2004;125(6):2011-2020.
61. Fletcher C, Peto R. The natural history of chronic airflow obstruction. *BMJ*. 1977;1(6077):1645-1648.
62. Hersh CP, DeMeo DL, Al-Ansari E, et al. Predictors of survival in severe, early onset COPD. *Chest*. 2004;126(5):1443-1451.
63. Scanlon PD, Connett JE, Waller LA, et al; Lung Health Study Research Group. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. The Lung Health Study. *Am J Respir Crit Care Med*. 2000;161(2):381-390.
64. Kanner RE, Connett JE, Williams DE, Buist AS. Effects of randomized assignment to a smoking cessation intervention and changes in smoking habits on respiratory symptoms in smokers with early chronic obstructive pulmonary disease: the Lung Health Study. *Am J Med*. 1999;106(4):410-416.
65. Makris D, Moschandreas J, Damianaki A, et al. Exacerbations and lung function decline in COPD: new insights in current and ex-smokers. *Respir Med*. 2007;101(6):1305-1312.
66. Tashkin D, Kanner R, Bailey W, et al. Smoking cessation in patients with chronic obstructive pulmonary disease: a double-blind, placebo-controlled, randomised trial. *Lancet*. 2001;357(9268): 1571-1575.
67. Jiménez-Ruiz CA, Masa F, Miravitlles M, et al. Smoking characteristics: differences in attitudes and dependence between healthy smokers and smokers with COPD. *Chest*. 2001;119(5):1365-1370.
68. Strassmann R, Bausch B, Spaar A, Kleijnen J, Braendli O, Puhan MA. Smoking cessation interventions in COPD: a network meta-analysis of randomised trials. *Eur Respir J*. 2009;34(3):634-640.
69. van der Meer RM, Wagena EJ, Ostelo RW, Jacobs JE, van Schayck CP. Smoking cessation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2003;(2):CD002999.
70. Tønnesen P, Carrozzi L, Fagerström KO, et al. Smoking cessation in patients with respiratory diseases: a high priority, integral component of therapy. *Eur Respir J*. 2007;29(2):390-417.
71. Au DH, Bryson CL, Chien JW, et al. The effects of smoking cessation on the risk of chronic obstructive pulmonary disease exacerbations. *J Gen Intern Med*. 2009;24(4):457-463.
72. Christenhusz LC, Prenger R, Pieterse ME, Seydel ER, van der Palen J. Cost-effectiveness of an intensive smoking cessation intervention for COPD outpatients. *Nicotine Tob Res*. 2012;14(6):657-663.
73. Borglykke A, Pisinger C, Jørgensen T, Ibsen H. The effectiveness of smoking cessation groups offered to hospitalised patients with symptoms of exacerbations of chronic obstructive pulmonary disease (COPD). *Clin Respir J*. 2008;2(3):158-165.
74. Godtfredsen NS, Vestbo J, Osler M, Prescott E. Risk of hospital admission for COPD following smoking cessation and reduction: a Danish population study. *Thorax*. 2002;57(11):967-972.
75. Szabo E, Mao JT, Lam S, Reid ME, Keith RL. Chemoprevention of lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5_suppl):e40S-e60S.
76. Spruit MA, Singh SJ, Garvey C, et al; ATS/ERS Task Force on Pulmonary Rehabilitation. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2013;188(8):e13-e64.

77. Marciniuk DD, Brooks D, Butcher S, et al; Canadian Thoracic Society COPD Committee Expert Working Group. Optimizing pulmonary rehabilitation in chronic obstructive pulmonary disease—practical issues: a Canadian Thoracic Society Clinical Practice Guideline. *Can Respir J*. 2010;17(4):159-168.
78. Ries AL, Bauldoff GS, Carlin BW, et al. Pulmonary rehabilitation: joint ACCP/AACVPR evidence-based clinical practice guidelines. *Chest*. 2007;131(5_suppl):4S-42S.
79. Lacasse Y, Goldstein R, Lasserson TJ, Martin S. Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2006;(4):CD003793.
80. Lacasse Y, Wong E, Guyatt GH, King D, Cook DJ, Goldstein RS. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. *Lancet*. 1996;348(9035):1115-1119.
81. Nici L, ZuWallack R; American Thoracic Society Subcommittee on Integrated Care of the COPD Patient. An official American Thoracic Society workshop report: the integrated care of the COPD patient. *Proc Am Thorac Soc*. 2012;9(1):9-18.
82. Ko FW, Dai DL, Ngai J, et al. Effect of early pulmonary rehabilitation on health care utilization and health status in patients hospitalized with acute exacerbations of COPD. *Respirology*. 2011;16(4):617-624.
83. Behnke M, Taube C, Kirsten D, Lehnigk B, Jörres RA, Magnussen H. Home-based exercise is capable of preserving hospital-based improvements in severe chronic obstructive pulmonary disease. *Respir Med*. 2000;94(12):1184-1191.
84. Murphy N, Bell C, Costello RW. Extending a home from hospital care programme for COPD exacerbations to include pulmonary rehabilitation. *Respir Med*. 2005;99(10):1297-1302.
85. Ringbaek T, Brondum E, Martinez G, Thogersen J, Lange P. Long-term effects of 1-year maintenance training on physical functioning and health status in patients with COPD: a randomized controlled study. *J Cardiopulm Rehabil Prev*. 2010;30(1):47-52.
86. Román M, Larraz C, Gómez A, et al. Efficacy of pulmonary rehabilitation in patients with moderate chronic obstructive pulmonary disease: a randomized controlled trial. *BMC Fam Pract*. 2013;14:21.
87. Man WD, Polkey MI, Donaldson N, Gray BJ, Moxham J. Community pulmonary rehabilitation after hospitalisation for acute exacerbations of chronic obstructive pulmonary disease: randomised controlled study. *BMJ*. 2004;329(7476):1209.
88. Seymour JM, Moore L, Jolley CJ, et al. Outpatient pulmonary rehabilitation following acute exacerbations of COPD. *Thorax*. 2010;65(5):423-428.
89. Boxall AM, Barclay L, Sayers A, Caplan GA. Managing chronic obstructive pulmonary disease in the community. A randomized controlled trial of home-based pulmonary rehabilitation for elderly housebound patients. *J Cardiopulm Rehabil*. 2005;25(6):378-385.
90. Eaton T, Young P, Fergusson W, et al. Does early pulmonary rehabilitation reduce acute health-care utilization in COPD patients admitted with an exacerbation? A randomized controlled study. *Respirology*. 2009;14(2):230-238.
91. Puhan MA, Gimeno-Santos E, Scharplatz M, Troosters T, Walters EH, Steurer J. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2011;(10):CD005305.
92. Wagner EH. Chronic disease management: what will it take to improve care for chronic illness? *Eff Clin Pract*. 1998;1(1):2-4.
93. Case Management Society of America. What is a case manager? Case Management Society of America website. http://www.cmsa.org/Home/CMSA/WhatisaCaseManager/tabid/224/Default.aspx. Accessed March 18, 2014.
94. Zwerink M, Brusse-Keizer M, van der Valk PD, et al. Self management for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2014;(3):CD002990.
95. Jarab AS, Alqudah SG, Khdour M, Shamssain M, Mukattash TL. Impact of pharmaceutical care on health outcomes in patients with COPD. *Int J Clin Pharmacol*. 2012;34(1):53-62.
96. Farrero E, Escarrabill J, Prats E, Maderal M, Manresa F. Impact of a hospital-based home-care program on the management of COPD patients receiving long-term oxygen therapy. *Chest*. 2001;119(2):364-369.
97. Lainscak M, Kadivec S, Kosnik M, et al. Discharge coordinator intervention prevents hospitalizations in patients with COPD: a randomized controlled trial. *J Am Med Dir Assoc*. 2013;14(6):450.e1-450.e6.
98. Smith BJ, Appleton SL, Bennett PW, et al. The effect of a respiratory home nurse intervention in patients with chronic obstructive pulmonary disease (COPD). *Aust N Z J Med*. 1999;29(5):718-725.
99. Soler JJ, Martínez-García MA, Román P, Orero R, Terrazas S, Martínez-Pechuán A. Effectiveness of a specific program for patients with chronic obstructive pulmonary disease and frequent exacerbations [in Spanish]. *Arch Bronconeumol*. 2006;42(10):501-508.
100. Gallefoss F. The effects of patient education in COPD in a 1-year follow-up randomised, controlled trial. *Patient Educ Couns*. 2004;52(3):259-266.
101. McGeoch GR, Willsman KJ, Dowson CA, et al. Self-management plans in the primary care of patients with chronic obstructive pulmonary disease. *Respirology*. 2006;11(5):611-618.
102. Wakabayashi R, Motegi T, Yamada K, et al. Efficient integrated education for older patients with chronic obstructive pulmonary disease using the Lung Information Needs Questionnaire. *Geriatr Gerontol Int*. 2011;11(4):422-430.
103. Wood-Baker R, McGlone S, Venn A, Walters EH. Written action plans in chronic obstructive pulmonary disease increase appropriate treatment for acute exacerbations. *Respirology*. 2006;11(5):619-626.
104. Bourbeau J, Julien M, Maltais F, et al; Chronic Obstructive Pulmonary Disease axis of the Respiratory Network Fonds de la Recherche en Santé du Québec. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease: a disease-specific self-management intervention. *Arch Intern Med*. 2003;163(5):585-591.
105. Casas A, Troosters T, Garcia-Aymerich J, et al; Members of the CHRONIC Project. Integrated care prevents hospitalisations for exacerbations in COPD patients. *Eur Respir J*. 2006;28(1):123-130.
106. Fan VS, Gaziano JM, Lew R, et al. A comprehensive care management program to prevent chronic obstructive pulmonary disease hospitalizations: a randomized, controlled trial. *Ann Intern Med*. 2012;156(10):673-683.
107. Khdour MR, Kidney JC, Smyth BM, McElnay JC. Clinical pharmacy-led disease and medicine management programme for patients with COPD. *Br J Clin Pharmacol*. 2009;68(4):588-598.
108. Rea H, McAuley S, Stewart A, Lamont C, Roseman P, Didsbury P. A chronic disease management programme can reduce days in hospital for patients with chronic obstructive pulmonary disease. *Intern Med J*. 2004;34(11):608-614.
109. Rice KL, Dewan N, Bloomfield HE, et al. Disease management program for chronic obstructive pulmonary disease: a randomized controlled trial. *Am J Respir Crit Care Med*. 2010;182(7):890-896.
110. Trappenburg JC, Monninkhof EM, Bourbeau J, et al. Effect of an action plan with ongoing support by a case manager on exacerbation-related outcome in patients with COPD: a multicentre randomised controlled trial. *Thorax*. 2011;66(11):977-984.
111. Walters J, Cameron-Tucker H, Wills K, et al. Effects of telephone health mentoring in community-recruited chronic obstructive pulmonary disease on self-management capacity, quality of life and psychological morbidity: a randomised controlled trial. *BMJ Open*. 2013;3(9):e003097.
112. Bischoff EW, Akkermans R, Bourbeau J, van Weel C, Vercoulen JH, Schermer TR. Comprehensive self management and routine monitoring in chronic obstructive pulmonary disease patients in general practice: randomised controlled trial. *BMJ*. 2012;345:e7642.
113. Coultas D, Frederick J, Barnett B, Singh G, Wludyka P. A randomized trial of two types of nurse-assisted home care for patients with COPD. *Chest*. 2005;128(4):2017-2024.
114. Gadoury MA, Schwartzman K, Rouleau M, et al; Chronic Obstructive Pulmonary Disease axis of the Respiratory Health Network, Fonds de la recherche en santé du Québec (FRSQ). Self-management reduces both short- and long-term hospitalisation in COPD. *Eur Respir J*. 2005;26(5):853-857.
115. Hermiz O, Comino E, Marks G, Daffurn K, Wilson S, Harris M. Randomised controlled trial of home based care of patients with chronic obstructive pulmonary disease. *BMJ*. 2002;325(7370):938.

116. Telemedicine: opportunities and developments in member states. Report on the second global survey on eHealth. World Health Organization website. http://www.who.int/goe/publications/goe_telemedicine_2010.pdf. Accessed March 13, 2014.
117. What is telemedicine? American Telemedicine Association website. http://www.americantelemed.org/about-telemedicine/what-is-telemedicine. Accessed March 13, 2014.
118. de Toledo P, Jiménez S, del Pozo F, Roca J, Alonso A, Hernandez C. Telemedicine experience for chronic care in COPD. *IEEE Trans Inf Technol Biomed*. 2006;10(3):567-573.
119. Vitacca M, Bianchi L, Guerra A, et al. Tele-assistance in chronic respiratory failure patients: a randomised clinical trial. *Eur Respir J*. 2009;33(2):411-418.
120. Wong KW, Wong FK, Chan MF. Effects of nurse-initiated telephone follow-up on self-efficacy among patients with chronic obstructive pulmonary disease. *J Adv Nurs*. 2005;49(2):210-222.
121. McLean S, Nurmatov U, Liu JL, Pagliari C, Car J, Sheikh A. Telehealthcare for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2011;(7):CD007718.
122. Antoniades NC, Rochford PD, Pretto JJ, et al. Pilot study of remote telemonitoring in COPD. *Telemed J E Health*. 2012;18(8):634-640.
123. Chau JP, Lee DT, Yu DS, et al. A feasibility study to investigate the acceptability and potential effectiveness of a telecare service for older people with chronic obstructive pulmonary disease. *Int J Med Inform*. 2012;81(10):674-682.
124. Dinesen B, Haesum LK, Soerensen N, et al. Using preventive home monitoring to reduce hospital admission rates and reduce costs: a case study of telehealth among chronic obstructive pulmonary disease patients. *J Telemed Telecare*. 2012;18(4):221-225.
125. Gellis ZD, Kenaley B, McGinty J, Bardelli E, Davitt J, Ten Have T. Outcomes of a telehealth intervention for homebound older adults with heart or chronic respiratory failure: a randomized controlled trial. *Gerontologist*. 2012;52(4):541-552.
126. Haesum LK, Soerensen N, Dinesen B, et al. Cost-utility analysis of a telerehabilitation program: a case study of COPD patients. *Telemed J E Health*. 2012;18(9):688-692.
127. Halpin DM, Laing-Morton T, Spedding S, et al. A randomised controlled trial of the effect of automated interactive calling combined with a health risk forecast on frequency and severity of exacerbations of COPD assessed clinically and using EXACT PRO. *Prim Care Respir J*. 2011;20(3):324-331.
128. Henderson C, Knapp M, Fernández JL, et al; Whole System Demonstrator Evaluation Team. Cost effectiveness of telehealth for patients with long term conditions (Whole Systems Demonstrator telehealth questionnaire study): nested economic evaluation in a pragmatic, cluster randomised controlled trial. *BMJ*. 2013;346:f1035.
129. Holland A. Telehealth reduces hospital admission rates in patients with COPD. *J Physiother*. 2013;59(2):129.
130. Jódar-Sánchez F, Ortega F, Parra C, et al. Implementation of a telehealth programme for patients with severe chronic obstructive pulmonary disease treated with long-term oxygen therapy. *J Telemed Telecare*. 2013;19(1):11-17.
131. Koff PB, Jones RH, Cashman JM, Voelkel NF, Vandivier RW. Proactive integrated care improves quality of life in patients with COPD. *Eur Respir J*. 2009;33(5):1031-1038.
132. Lewis KE, Annandale JA, Warm DL, et al. Does home telemonitoring after pulmonary rehabilitation reduce healthcare use in optimized COPD? A pilot randomized trial. *COPD*. 2010;7(1):44-50.
133. Paré G, Poba-Nzaou P, Sicotte C, et al. Comparing the costs of home telemonitoring and usual care of chronic obstructive pulmonary disease patients: a randomized controlled trial. *Eur Res Telemed*. 2013;2(2):35-47.
134. Pedone C, Chiurco D, Scarlata S, Incalzi RA. Efficacy of multi-parametric telemonitoring on respiratory outcomes in elderly people with COPD: a randomized controlled trial. *BMC Health Serv Res*. 2013;13:82.
135. Pinnock H, Hanley J, Lewis S, et al; TELESCOT Programme Group. The impact of a telemetric chronic obstructive pulmonary disease monitoring service: randomised controlled trial with economic evaluation and nested qualitative study. *Prim Care Respir J*. 2009;18(3):233-235.
136. Shany T, Hession M, Pryce D, et al. Home telecare study for patients with chronic lung disease in the Sydney West Area Health Service. *Stud Health Technol Inform*. 2010;161:139-148.
137. Sorknaes AD, Madsen H, Hallas J, Jest P, Hansen-Nord M. Nurse tele-consultations with discharged COPD patients reduce early readmissions–an interventional study. *Clin Respir J*. 2011;5(1):26-34
138. Steventon A, Bardsley M, Billings J, et al; Whole System Demonstrator Evaluation Team. Effect of telehealth on use of secondary care and mortality: findings from the Whole System Demonstrator cluster randomised trial. *BMJ*. 2012;344:e3874.
139. Venter A, Burns R, Hefford M, Ehrenberg N. Results of a telehealth-enabled chronic care management service to support people with long-term conditions at home. *J Telemed Telecare*. 2012;18(3):172-175.
140. Wootton R. Twenty years of telemedicine in chronic disease management—an evidence synthesis. *J Telemed Telecare*. 2012;18(4):211-220.
141. Kew KM, Mavergames C, Walters JA. Long-acting beta2-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2013;(10):CD010177.
142. Vestbo J, Hurd SS, Agustí AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2013;187(4):347-365.
143. Barr RG, Bourbeau J, Camargo CA, Ram FS. Tiotropium for stable chronic obstructive pulmonary disease: A meta-analysis. *Thorax*. 2006;61(10):854-862.
144. Singh S, Loke YK, Enright PL, Furberg CD. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. *BMJ*. 2011;342:d3215.
145. Wise RA, Anzueto A, Cotton D, et al; TIOSPIR Investigators. Tiotropium Respimat inhaler and the risk of death in COPD. *N Engl J Med*. 2013;369(16):1491-1501.
146. Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2012;(7):CD009285.
147. O'Donnell DE, Hernandez P, Kaplan A, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2008 update - highlights for primary care. *Can Respir J*. 2008;15(suppl A):1A-8A.
148. O'Donnell DE, Flüge T, Gerken F, et al. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. *Eur Respir J*. 2004;23(6):832-840.
149. Celli B, ZuWallack R, Wang S, Kesten S. Improvement in resting inspiratory capacity and hyperinflation with tiotropium in COPD patients with increased static lung volumes. *Chest*. 2003;124(5):1743-1748.
150. O'Donnell DE, Voduc N, Fitzpatrick M, Webb KA. Effect of salmeterol on the ventilatory response to exercise in chronic obstructive pulmonary disease. *Eur Respir J*. 2004;24(1):86-94.
151. Calverley PM, Anderson JA, Celli B, et al; TORCH Investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med*. 2007;356(8):775-789.
152. Chong J, Karner C, Poole P. Tiotropium versus long-acting beta-agonists for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2012;(9):CD009157.
153. Vogelmeier C, Hederer B, Glaab T, et al; POET-COPD Investigators. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. *N Engl J Med*. 2011;364(12):1093-1103.
154. Appleton S, Jones T, Poole P, et al. Ipratropium bromide versus long-acting beta-2 agonists for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2006;(3):CD006101.
155. Brown D ea. A randomized, double blind, parallel, multi-centre comparison of inhalation solution with albuterol inhalation solution following single-dose and chronic administration (85 days) in patients with chronic obstructive pulmonary disease. Boehringer Ingelheim unpublished report USA U91-0865, 1991.
156. Brown D ea. A randomized, double blind, parallel, multicentre comparison of Atrovent (ipratropium bromide) inhalation solution with metaproterenol inhalation solution following single-dose and

chronic administration (85 days) in patient with chronic obstructive pulmonary disease. Boehringer Ingelheim unpublished report USA U91-0866, 1991.

157. Friedman M. A multicenter study of nebulized bronchodilator solutions in chronic obstructive pulmonary disease. *Am J Med*. 1996;100(suppl 1):S30-S39.

158. Rennard SI, Serby CW, Ghafouri M, Johnson PA, Friedman M. Extended therapy with ipratropium is associated with improved lung function in patients with COPD. A retrospective analysis of data from seven clinical trials. *Chest*. 1996;110(1):62-70.

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

160. Tashkin DP, Bleecker E, Braun S, et al. Results of a multicenter study of nebulized inhalant bronchodilator solutions. *Am J Med*. 1996;100(suppl 1):S62-S69.

161. COMBIVENT Inhalation Aerosol Study Group. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. *Chest*. 1994;105(5):1411-1419.

162. COMBIVENT Inhalation Solution Study Group. Routine nebulized ipratropium and albuterol together are better than either alone in COPD. *Chest*. 1997;112(6):1514-1521.

163. Colice GL. Nebulized bronchodilators for outpatient management of stable chronic obstructive pulmonary disease. *Am J Med*. 1996;100(suppl 1):S11-S18.

164. Campbell S. For COPD a combination of ipratropium bromide and albuterol sulfate is more effective than albuterol base. *Arch Intern Med*. 1999;159(2):156-160.

165. Alexander KM ea. A randomized, double blind, parallel, multi-center comparison of Combivent (ipratropium bromide and albuterol sulfate) inhalation solution with its components following single-dose and chronic administration (85 days) in patients with chronic pulmonary disease. Boehringer Ingelheim unpublished report: USA U92-0801, 1992.

166. Gross N, Tashkin D, Miller R, Oren J, Coleman W, Linberg S; Dey Combination Solution Study Group. Inhalation by nebulization of albuterol-ipratropium combination (Dey combination) is superior to either agent alone in the treatment of chronic obstructive pulmonary disease. *Respiration*. 1998;65(5):354-362.

167. Levin DC, Little KS, Laughlin KR, et al. Addition of anticholinergic solution prolongs bronchodilator effect of beta 2 agonists in patients with chronic obstructive pulmonary disease. *Am J Med*. 1996;100(suppl 1):S40-S48.

168. van Noord JA, Bantje TA, Eland ME, Korducki L, Cornelissen PJ; The Dutch Tiotropium Study Group. A randomised controlled comparison of tiotropium and ipratropium in the treatment of chronic obstructive pulmonary disease. *Thorax*. 2000;55(4):289-294.

169. Mahler DA, Donohue JF, Barbee RA, et al. Efficacy of salmeterol xinafoate in the treatment of COPD. *Chest*. 1999;115(4):957-965.

170. Cramer JA, Bradley-Kennedy C, Scalera A. Treatment persistence and compliance with medications for chronic obstructive pulmonary disease. *Can Respir J*. 2007;14(1):25-29.

171. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2001;164(5):770-777.

172. Anthonisen NR, Connett JE, Kiley JP, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *JAMA*. 1994;272(19):1497-1505.

173. Cheyne L, Irvin-Sellers MJ, White J. Tiotropium versus ipratropium bromide for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2013;(9):CD009552.

174. Loke YK, Singh S, Furberg CD. Tiotropium and the risk of death in COPD. *N Engl J Med*. 2014;370(5):480-481.

175. Verhamme KM, van Blijderveen N, Sturkenboom MC. Tiotropium and the risk of death in COPD. *N Engl J Med*. 2014;370(5):481-482.

176. Jenkins CR. Tiotropium and the risk of death in COPD. *N Engl J Med*. 2014;370(5):482-483.

177. Sethi S, Mahler DA, Marcus P, Owen CA, Yawn B, Rennard S. Inflammation in COPD: implications for management. *Am J Med*. 2012;125(12):1162-1170.

178. Izquierdo Alonso JL, Rodríguez Glez-Moro JM. The excessive use of inhaled corticosteroids in chronic obstructive pulmonary disease. *Arch Bronconeumol*. 2012;48(6):207-212.

179. de Miguel-Díez J, Carrasco-Garrido P, Rejas-Gutierrez J, et al. Inappropriate overuse of inhaled corticosteroids for COPD patients: impact on health costs and health status. *Lung*. 2011;189(3):199-206.

180. Barnes PJ. Inhaled corticosteroids in COPD: a controversy. *Respiration*. 2010;80(2):89-95.

181. Price D, Yawn B, Brusselle G, Rossi A. Risk-to-benefit ratio of inhaled corticosteroids in patients with COPD. *Prim Care Respir J*. 2013;22(1):92-100.

182. Zervas E, Samitas K, Gaga M, Beghe B, Fabbri LM. Inhaled corticosteroids in COPD: pros and cons. *Curr Drug Targets*. 2013;14(2):192-224.

183. Barnes PJ. Role of HDAC2 in the pathophysiology of COPD. *Annu Rev Physiol*. 2009;71:451-464.

184. Barnes PJ. Glucocorticosteroids: current and future directions. *Br J Pharmacol*. 2011;163(1):29-43.

185. Mercado N, Thimmulappa R, Thomas CMR, et al. Decreased histone deacetylase 2 impairs Nrf2 activation by oxidative stress. *Biochem Biophys Res Commun*. 2011;406(2):292-298.

186. Jen R, Rennard SI, Sin DD. Effects of inhaled corticosteroids on airway inflammation in chronic obstructive pulmonary disease: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis*. 2012;7:587-595.

187. Anzueto A, Ferguson GT, Feldman G, et al. Effect of fluticasone propionate/salmeterol (250/50) on COPD exacerbations and impact on patient outcomes. *COPD*. 2009;6(5):320-329.

188. Boscia JA, Pudi KK, Zvarich MT, Sanford L, Siederer SK, Crim C. Effect of once-daily fluticasone furoate/vilanterol on 24-hour pulmonary function in patients with chronic obstructive pulmonary disease: a randomized, three-way, incomplete block, crossover study. *Clin Ther*. 2012;34(8):1655-1666.

189. Burge PS, Calverley PMA, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ*. 2000; 320(7245):1297-1303.

190. Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *Eur Respir J*. 2003; 22(6):912-919.

191. Dransfield MT, Bourbeau J, Jones PW, et al. Once-daily inhaled fluticasone furoate and vilanterol versus vilanterol only for prevention of exacerbations of COPD: two replicate double-blind, parallel-group, randomised controlled trials. *Lancet Respir Med*. 2013;1(3):210-223.

192. Ferguson GT, Anzueto A, Fei R, Emmett A, Knobil K, Kalberg C. Effect of fluticasone propionate/salmeterol (250/50 μg) or salmeterol (50 μg) on COPD exacerbations. *Respir Med*. 2008;102(8):1099-1108.

193. Hanania NA, Darken P, Horstman D, et al. The efficacy and safety of fluticasone propionate (250 μg)/salmeterol (50 μg) combined in the Diskus inhaler for the treatment of COPD. *Chest*. 2003;124(3):834-843.

194. Kerwin EM, Scott-Wilson C, Sanford L, et al. A randomised trial of fluticasone furoate/vilanterol (50/25 μg; 100/25 μg) on lung function in COPD. *Respir Med*. 2013;107(4):560-569.

195. Lapperre TS, Snoeck-Stroband JB, Gosman MME, et al; Groningen Leiden Universities Corticosteroids in Obstructive Lung Disease Study Group. Effect of fluticasone with and without salmeterol on pulmonary outcomes in chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med*. 2009;151(8):517-527.

196. Mahler DA, Wire P, Horstman D, et al. Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2002;166(8):1084-1091.

197. Martinez FJ, Boscia J, Feldman G, et al. Fluticasone furoate/vilanterol (100/25; 200/25 μg) improves lung function in COPD: a randomised trial. *Respir Med*. 2013;107(4):550-559.

198. Sharafkhaneh A, Southard JG, Goldman M, Uryniak T, Martin UJ. Effect of budesonide/formoterol pMDI on COPD exacerbations: a double-blind, randomized study. *Respir Med*. 2012;106(2):257-268.

199. Szafranski W, Cukier A, Ramirez A, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *Eur Respir J*. 2003;21(1):74-81.

200. Agarwal R, Aggarwal AN, Gupta D, Jindal SK. Inhaled corticosteroids vs placebo for preventing COPD exacerbations: a systematic review and metaregression of randomized controlled trials. *Chest*. 2010;137(2):318-325.

201. Glaab T, Taube C. Effects of inhaled corticosteroids in stable chronic obstructive pulmonary disease. *Pulm Pharmacol Ther*. 2011;24(1):15-22.

202. Spencer S, Karner C, Cates CJ, Evans DJ. Inhaled corticosteroids versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2011;(12):CD007033.

203. van Grunsven PM, van Schayck CP, Derenne JP, et al. Long term effects of inhaled corticosteroids in chronic obstructive pulmonary disease: a meta-analysis. *Thorax*. 1999;54(1):7-14.

204. Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2012;(7):CD002991.

205. Jones PW, Singh D, Bateman ED, et al. Efficacy and safety of twice-daily aclidinium bromide in COPD patients: the ATTAIN study. *Eur Respir J*. 2012;40(4):830-836.

206. Niewoehner DE, Rice K, Cote C, et al. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. *Ann Intern Med*. 2005;143(5):317-326.

207. Cazzola M, Di Marco F, Santus P, et al. The pharmacodynamic effects of single inhaled doses of formoterol, tiotropium and their combination in patients with COPD. *Pulm Pharmacol Ther*. 2004;17(1):35-39.

208. Gross NJ, Nelson HS, Lapidus RJ, et al; Formoterol Study Group. Efficacy and safety of formoterol fumarate delivered by nebulization to COPD patients. *Respir Med*. 2008;102(2):189-197.

209. Tashkin DP, Cooper CB. The role of long-acting bronchodilators in the management of stable COPD. *Chest*. 2004;125(1):249-259.

210. Aaron SD, Vandemheen KL, Fergusson D, et al; Canadian Thoracic Society/Canadian Respiratory Clinical Research Consortium. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med*. 2007;146(8):545-555.

211. Brusasco V, Hodder R, Miravitlles M, Korducki L, Towse L, Kesten S. Health outcomes following treatment for 6 months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax*. 2006;61(1):91.

212. Barnes PJ, Pocock SJ, Magnussen H, et al. Integrating indacaterol dose selection in a clinical study in COPD using an adaptive seamless design. *Pulm Pharmacol Ther*. 2010;23(3):165-171.

213. Beier J, Chanez P, Martinot JB, et al. Safety, tolerability and efficacy of indacaterol, a novel once-daily beta(2)-agonist, in patients with COPD: a 28-day randomised, placebo controlled clinical trial. *Pulm Pharmacol Ther*. 2007;20(6):740-749.

214. Jones PW, Mahler DA, Gale R, Owen R, Kramer B. Profiling the effects of indacaterol on dyspnoea and health status in patients with COPD. *Respir Med*. 2011;105(6):892-899.

215. Cazzola M, Santus P, Di Marco F, et al. Bronchodilator effect of an inhaled combination therapy with salmeterol + fluticasone and formoterol + budesonide in patients with COPD. *Respir Med*. 2003;97(5):453-457.

216. Jones PW, Willits LR, Burge PS, Calverley PM; Inhaled Steroids in Obstructive Lung Disease in Europe study investigators. Disease severity and the effect of fluticasone propionate on chronic obstructive pulmonary disease exacerbations. *Eur Respir J*. 2003;21(1):68-73.

217. Vestbo J, Soriano JB, Anderson JA, Calverley P, Pauwels R, Jones P; TRISTAN Study Group. Gender does not influence the response to the combination of salmeterol and fluticasone propionate in COPD. *Respir Med*. 2004;98(11):1045-1050.

218. Calverley PM. Reducing the frequency and severity of exacerbations of chronic obstructive pulmonary disease. *Proc Am Thorac Soc*. 2004;1(2):121-124.

219. Rodrigo GJ, Plaza V, Castro-Rodríguez JA. Comparison of three combined pharmacological approaches with tiotropium monotherapy in stable moderate to severe COPD: a systematic review. *Pulm Pharmacol Ther*. 2012;25(1):40-47.

220. Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2012;(9):CD006829.

221. Wedzicha JA, Decramer M, Ficker JH, et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. *Lancet Respir Med*. 2013;1(3):199-209.

222. He ZY, Ou LM, Zhang JQ, et al. Effect of 6 months of erythromycin treatment on inflammatory cells in induced sputum and exacerbations in chronic obstructive pulmonary disease. *Respiration*. 2010; 80(6):445-452.

223. Seemungal TA, Wilkinson TM, Hurst JR, Perera WR, Sapsford RJ, Wedzicha JA. Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. *Am J Respir Crit Care Med*. 2008;178(11):1139-1147.

224. Aaron SD, Vandemheen KL, Hebert P, et al. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. *N Engl J Med*. 2003;348(26):2618-2625.

225. Davies L, Angus RM, Calverley PM. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. *Lancet*. 1999;354(9177):456-460.

226. Niewoehner DE, Erbland ML, Deupree RH, et al; Department of Veterans Affairs Cooperative Study Group. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. *N Engl J Med*. 1999;340(25): 1941-1947.

227. Thompson WH, Nielson CP, Carvalho P, Charan NB, Crowley JJ. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. *Am J Respir Crit Care Med*. 1996;154(2): 407-412.

228. Aggarwal P, Wig N, Bhoi S. Efficacy of two corticosteroid regimens in acute exacerbation of chronic obstructive pulmonary disease. *Int J Tuberc Lung Dis*. 2011;15(5):687-692.

229. Ställberg B, Selroos O, Vogelmeier C, Andersson E, Ekström T, Larsson K. Budesonide/formoterol as effective as prednisolone plus formoterol in acute exacerbations of COPD. A double-blind, randomised, non-inferiority, parallel-group, multicentre study. *Respir Res*. 2009;10:11.

230. Rice KL, Rubins JB, Lebahn F, et al. Withdrawal of chronic systemic corticosteroids in patients with COPD: a randomized trial. *Am J Respir Crit Care Med*. 2000;162(1):174-178.

231. Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ; M2-124 and M2-125 Study Groups. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet*. 2009;374(9691):685-694.

232. Fabbri LM, Calverley PM, Izquierdo-Alonso JL, et al; M2-127 and M2-128 Study Groups. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. *Lancet*. 2009;374(9691): 695-703.

233. Lee SD, Hui DS, Mahayiddin AA, et al. Roflumilast in Asian patients with COPD: a randomized placebo-controlled trial. *Respirology*. 2011;16(8):1249-1257.

234. Rabe KF, Magnussen H, Dent G. Theophylline and selective PDE inhibitors as bronchodilators and smooth muscle relaxants. *Eur Respir J*. 1995;8(4):637-642.

235. Rossi A, Kristufek P, Levine BE, et al; Formoterol in Chronic Obstructive Pulmonary Disease (FICOPD) II Study Group. Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD. *Chest*. 2002;121(4):1058-1069.

236. Zhou Y, Wang X, Zeng X, et al. Positive benefits of theophylline in a randomized, double-blind, parallel-group, placebo-controlled study of low-dose, slow-release theophylline in the treatment of COPD for 1 year. *Respirology*. 2006;11(5):603-610.

237. Sheffner AL, Medler EM, Jacobs LW, Sarett HP. The in vitro reduction in viscosity of human tracheobronchial secretions by acetylcysteine. *Am Rev Respir Dis*. 1964;90:721-729.

238. Boman G, Bäcker U, Larsson S, Melander B, Wåhlander L. Oral acetylcysteine reduces exacerbation rate in chronic bronchitis: report of a trial organized by the Swedish Society for Pulmonary Diseases. *Eur J Respir Dis*. 1983;64(6):405-415.

239. Grassi C, Morandini GC. A controlled trial of intermittent oral acetylcysteine in the long-term treatment of chronic bronchitis. *Eur J Clin Pharmacol*. 1976;9(5-6):393-396.

240. Hansen NC, Skriver A, Brorsen-Riis L, et al. Orally administered N-acetylcysteine may improve general well-being in patients with mild chronic bronchitis. *Respir Med*. 1994;88(7):531-535.

241. Pela R, Calcagni AM, Subiaco S, Isidori P, Tubaldi A, Sanguinetti CM. N-acetylcysteine reduces the exacerbation rate in patients with moderate to severe COPD. *Respiration*. 1999;66(6): 495-500.

242. Zheng JP, Wen FQ, Bai CX, et al; PANTHEON Study Group. Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): a randomised, double-blind placebo-controlled trial. *Lancet Respir Med*. 2014;2(3):187-194.

243. British Thoracic Society Research Committee. Oral N-acetylcysteine and exacerbation rates in patients with chronic bronchitis and severe airways obstruction. *Thorax*. 1985;40(11):832-835.

244. Decramer M, Rutten-van Mölken M, Dekhuijzen PN, et al. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. *Lancet*. 2005;365(9470):1552-1560.

245. Dueholm M, Nielsen C, Thorshauge H, et al. N-acetylcysteine by metered dose inhaler in the treatment of chronic bronchitis: a multi-centre study. *Respir Med*. 1992;86(2):89-92.

246. Parr GD, Huitson A. Oral Fabrol (oral N-acetyl-cysteine) in chronic bronchitis. *Br J Dis Chest*. 1987;81(4):341-348.

247. Rasmussen JB, Glennow C. Reduction in days of illness after long-term treatment with N-acetylcysteine controlled-release tablets in patients with chronic bronchitis. *Eur Respir J*. 1988;1(4):351-355.

248. Schermer T, Chavannes N, Dekhuijzen R, et al. Fluticasone and N-acetylcysteine in primary care patients with COPD or chronic bronchitis. *Respir Med*. 2009;103(4):542-551.

249. Moretti M, Bottrighi P, Dallari R, et al; EQUALIFE Study Group. The effect of long-term treatment with erdosteine on chronic obstructive pulmonary disease: the EQUALIFE Study. *Drugs Exp Clin Res*. 2004;30(4):143-152.

250. Braga PC, Allegra L, Rampoldi C, Ornaghi A, Beghi G. Long-lasting effects on rheology and clearance of bronchial mucus after short-term administration of high doses of carbocysteine-lysine to patients with chronic bronchitis. *Respiration*. 1990;57(6):353-358.

251. Allegra L, Cordaro CI, Grassi C. Prevention of acute exacerbations of chronic obstructive bronchitis with carbocysteine lysine salt monohydrate: a multicenter, double-blind, placebo-controlled trial. *Respiration*. 1996;63(3):174-180.

252. Grillage M, Barnard-Jones K. Long-term oral carbocisteine therapy in patients with chronic bronchitis. A double blind trial with placebo control. *Br J Clin Pract*. 1985;39(10):395-398.

253. Zheng JP, Kang J, Huang SG, et al. Effect of carbocisteine on acute exacerbation of chronic obstructive pulmonary disease (PEACE Study): a randomised placebo-controlled study. *Lancet*. 2008; 371(9629):2013-2018.

254. Bartziokas K, Papaioannou AI, Minas M, et al. Statins and outcome after hospitalization for COPD exacerbation: a prospective study. *Pulm Pharmacol Ther*. 2011;24(5):625-631.

255. Blamoun AI, Batty GN, DeBari VA, Rashid AO, Sheikh M, Khan MA. Statins may reduce episodes of exacerbation and the requirement for intubation in patients with COPD: evidence from a retrospective cohort study. *Int J Clin Pract*. 2008;62(9):1373-1378.

256. Huang CC, Chan WL, Chen YC, et al. Statin use and hospitalization in patients with chronic obstructive pulmonary disease: a nationwide population-based cohort study in Taiwan. *Clin Ther*. 2011;33(10): 1365-1370.

257. Mancini GB, Etminan M, Zhang B, Levesque LE, FitzGerald JM, Brophy JM. Reduction of morbidity and mortality by statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in patients with chronic obstructive pulmonary disease. *J Am Coll Cardiol*. 2006;47(12):2554-2560.

258. Wang MT, Lo YW, Tsai CL, et al. Statin use and risk of COPD exacerbation requiring hospitalization. *Am J Med*. 2013;126(7):598-606.

259. Criner GJ, Connett JE, Aaron SD, et al; COPD Clinical Research Network; Canadian Institutes of Health Research. Simvastatin for the prevention of exacerbations in moderate-to-severe COPD. *N Engl J Med*. 2014;370(23):2201-2210.

260. Casarosa P, Kollak I, Kiechle T, et al. Functional and biochemical rationales for the 24-hour-long duration of action of olodaterol. *J Pharmacol Exp Ther*. 2011;337(3):600-609.

261. van Noord JA, Smeets JJ, Drenth BM, et al. 24-hour bronchodilation following a single dose of the novel β(2)-agonist olodaterol in COPD. *Pulm Pharmacol Ther*. 2011;24(6):666-672.

262. Bateman ED, Ferguson GT, Barnes N, et al. Dual bronchodilation with QVA149 versus single bronchodilator therapy: the SHINE study. *Eur Respir J*. 2013;42(6):1484-1494.

263. Cazzola M, Calzetta L, Matera MG. β(2)-adrenoceptor agonists: current and future direction. *Br J Pharmacol*. 2011;163(1):4-17.

264. Cazzola M, Matera MG. Emerging inhaled bronchodilators: an update. *Eur Respir J*. 2009;34(3):757-769.

265. Cazzola M, Molimard M. The scientific rationale for combining long-acting beta2-agonists and muscarinic antagonists in COPD. *Pulm Pharmacol Ther*. 2010;23(4):257-267.

266. Cazzola M, Rogliani P, Matera MG. Aclidinium bromide/formoterol fumarate fixed-dose combination for the treatment of chronic obstructive pulmonary disease. *Expert Opin Pharmacother*. 2013; 14(6):775-781.

267. Cazzola M, Rogliani P, Segreti A, Matera MG. An update on bronchodilators in phase I and II clinical trials. *Expert Opin Investig Drugs*. 2012;21(10):1489-1501.

268. Dahl R, Chapman KR, Rudolf M, et al. Safety and efficacy of dual bronchodilation with QVA149 in COPD patients: the ENLIGHTEN study. *Respir Med*. 2013;107(10):1558-1567.

269. Mak G, Hanania NA. New bronchodilators. *Curr Opin Pharmacol*. 2012;12(3):238-245.

270. Matera MG, Calzetta L, Segreti A, Cazzola M. Emerging drugs for chronic obstructive pulmonary disease. *Expert Opin Emerg Drugs*. 2012;17(1):61-82.

271. Matera MG, Page CP, Cazzola M. Novel bronchodilators for the treatment of chronic obstructive pulmonary disease. *Trends Pharmacol Sci*. 2011;32(8):495-506.

272. Van de Maele B, Fabbri LM, Martin C, Horton R, Dolker M, Overend T. Cardiovascular safety of QVA149, a combination of Indacaterol and NVA237, in COPD patients. *COPD*. 2010;7(6):418-427.

273. van Noord JA, Buhl R, Laforce C, et al. QVA149 demonstrates superior bronchodilation compared with indacaterol or placebo in patients with chronic obstructive pulmonary disease. *Thorax*. 2010;65(12):1086-1091.

274. Vogelmeier CF, Bateman ED, Pallante J, et al. Efficacy and safety of once-daily QVA149 compared with twice-daily salmeterol-fluticasone in patients with chronic obstructive pulmonary disease (ILLUMINATE): a randomised, double-blind, parallel group study. *Lancet Respir Med*. 2013;1(1):51-60.

275. Donohue JF, Maleki-Yazdi MR, Kilbride S, Mehta R, Kalberg C, Church A. Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD. *Respir Med*. 2013;107(10):1538-1546.

276. Feldman G, Walker RR, Brooks J, Mehta R, Crater G. 28-day safety and tolerability of umeclidinium in combination with vilanterol in COPD: a randomized placebo-controlled trial. *Pulm Pharmacol Ther*. 2012;25(6):465-471.

277. Kelleher DL, Mehta RS, Jean-Francois BM, et al. Safety, tolerability, pharmacodynamics and pharmacokinetics of umeclidinium and vilanterol alone and in combination: a randomized crossover trial. *PLoS One*. 2012;7(12):e50716.

278. Mehta R, Kelleher D, Preece A, Hughes S, Crater G. Effect of verapamil on systemic exposure and safety of umeclidinium and

vilanterol: a randomized and open-label study. *Int J Chron Obstruct Pulmon Dis*. 2013;8:159-167.

279. Lötvall J, Bakke PS, Bjermer L, et al. Efficacy and safety of 4 weeks' treatment with combined fluticasone furoate/vilanterol in a single inhaler given once daily in COPD: a placebo-controlled randomised trial. *BMJ Open*. 2012;2(1):e000370.
280. Traynor K. Fluticasone-vilanterol combination approved for COPD. *Am J Health Syst Pharm*. 2013;70(12):1008.
281. Vestbo J, Anderson J, Brook RD, et al. The Study to Understand Mortality and Morbidity in COPD (SUMMIT) study protocol. *Eur Respir J*. 2013;41(5):1017-1022.
282. Barnes PJ. New therapies for chronic obstructive pulmonary disease. *Med Princ Pract*. 2010;19(5):330-338.
283. Barnes PJ. Development of new drugs for COPD. *Curr Med Chem*. 2013;20(12):1531-1540.
284. Cazzola M, Ciaprini C, Page CP, Matera MG. Targeting systemic inflammation: novel therapies for the treatment of chronic obstructive pulmonary disease. *Expert Opin Ther Targets*. 2007; 11(10):1273-1286.
285. Cazzola M, Page CP, Calzetta L, Matera MG. Emerging anti-inflammatory strategies for COPD. *Eur Respir J*. 2012;40(3): 724-741.