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PREVENTION OF COPD EXACERBATIONS: An European Respiratory Society/American Thoracic Society (ERS/ATS) guideline.

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Thoracic Society (ERS/ATS) guideline.

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ABSTRACT

Background: This document provides clinical recommendations for the prevention of chronic obstructive pulmonary disease (COPD) exacerbations. It represents a collaborative effort between the European Respiratory Society (ERS) and the American Thoracic Society (ATS).

Methods: Comprehensive evidence syntheses were performed to summarize all available evidence relevant to the guideline panel's questions. The evidence was appraised using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach and the results were summarized in evidence profiles. The evidence syntheses were discussed and recommendations formulated by a multi-disciplinary committee of COPD experts.

Results: After considering the balance of desirable (benefits) and undesirable consequences (burden, adverse effects, cost), quality of evidence, feasibility, and acceptability of various interventions, the guideline panel made recommendations for mucolytic, long-acting muscarinic antagonist, phosphodiesterase-4 inhibitor, and macrolide therapy, as well as a conditional recommendation against fluroquinolone therapy. All of the recommendations were conditional, indicating that there was uncertainty about the balance of desirable and undesirable consequences of the intervention, and that well-informed patients may make different choices regarding whether to have or not have the specific intervention.

Conclusion: The guideline summarises the evidence and provides conditional recommendations for pharmacologic therapy for the prevention of COPD exacerbations.

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INTRODUCTION

Prevention of exacerbations is a key objective in COPD management. There are patients with COPD that are prone to suffer from recurrent exacerbations (1) and they experience a more severe impairment in health status (2,3). Moreover, patients with recurrent hospitalizations for exacerbations have a reduced survival (4). Although no definitive evidence exists about the impact of prevention of exacerbations of COPD in reducing mortality, treatments that effectively reduce the frequency and/or the severity of exacerbations may have an impact on the progression and ultimately the prognosis of COPD.

This guideline was a collaborative effort between the European Respiratory Society (ERS) and the American Thoracic Society (ATS). It employed a systematic review of the literature, followed by use of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (5) approach to develop recommendations that answer the following five questions:

Question #1: Should mucolytics be prescribed to patients with stable COPD to prevent COPD exacerbations?

Question #2: Are long-acting beta-agonists or long-acting muscarinic antagonists preferable in patients with stable COPD to prevent COPD exacerbations?

Question #3: Should roflumilast be prescribed to patients with stable COPD, a history of COPD exacerbations, and chronic bronchitis to prevent COPD exacerbations?

Question #4: Should fluoroquinolones be prescribed to patients with stable COPD to prevent COPD exacerbations?

Question #5: Should macrolides be prescribed to patients with stable COPD to prevent COPD exacerbations?

This ERS/ATS guideline focuses on the prevention of COPD exacerbations. A separate ERS/ATS guideline was recently published that addresses the management of COPD exacerbations (6). We accepted other evidence-based evaluations of certain established therapies and did not seek to repeat the analyses already undertaken. Our role is to update and address gaps in the

existing evidence. Other therapies are effective and might be preferred to those we address here; e.g. smoking cessation or dual bronchodilator therapy, which were not considered within the time frame of this task force.

METHODS

The methodology followed for the development of this document regarding formulation of questions, rating the important outcomes, study selection, evidence synthesis and formulating and grading the evidence, has been described in detail in the previous publication of the guideline on treatment of COPD exacerbations (6) and can be found in the online supplement. Some important aspects of the methodology are summarised below:

Group composition

The guideline panel co-chairs (JAW, JAK) were selected by the European Respiratory Society (ERS) and American Thoracic Society (ATS). They led all aspects of project management and selected the panellists, which included 11 clinicians with experience in COPD management and research. In addition, there were two methodologists (TT, DR) and a clinician-methodologist (KCW). The lead methodologist (TT) identified and collected the evidence, performed the evidence syntheses, constructed the evidence profiles, and ensured that all the methodological requirements were met, with assistance from the other methodologists. The co-chairs and panellists discussed the evidence and formulated the recommendations; the methodologists did not participate in the development of recommendations. All panel members were required to disclose their conflicts of interest. Being an author of a publication reporting the effect of an intervention in prevention of exacerbations was considered as a COI. At least 50% of the co-chairs and 50% of the panel were required to be free from conflicts of interest. Individuals with potential conflicts of interest took part in the discussions about the evidence but did not participate in the formulation of recommendations.

Literature searches

Our literature searches used the National Institute of Health and Clinical Excellence (NICE) guidelines as a starting point (7). For questions that were addressed in the 2004 NICE guidelines, we conducted literature searches in Medline, Embase, and the Cochrane Database of Systematic Reviews beginning in 2003. For questions that were addressed in the 2010 NICE guidelines, we conducted literature searches in the same databases beginning in 2009. Initial searches were conducted in January 2012 and then updated in June 2012, February 2013, and

September 2015. We used the same or similar search strategies as those used by NICE. To search Embase and Medline, we searched only the English speaking literature using the search strategy shown in the online supplement, whereas to search the Cochrane Database of Systematic Reviews, we used the search term, "chronic obstructive pulmonary disease".

Manuscript preparation

The initial draft of the manuscript was prepared by the co-chairs, methodologists, and one panellist (MM). The lead methodologist wrote the content for the online supplement, which was edited by the co-chairs. Both the manuscript and the online supplement were reviewed, edited, and approved by all panel members prior to submission.

RESULTS

Question #1: Should mucolytics be prescribed to patients with stable COPD to prevent COPD exacerbations?

Summary of the evidence

We identified one relevant systematic review (8), which included four trials that met our inclusion criteria (9-12). Our own systematic review identified two additional trials (13,14). These six trials collectively informed the panel's judgments (9-14).

All six trials were randomized, placebo-controlled trials conducted in patients with COPD. Ninety-three percent of patients had moderate or severe airflow obstruction, defined as a post-bronchodilator forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) ratio (FEV1/FVC) <0.70 and an FEV1 30-79%. Three trials enrolled patients with COPD who had a history of at least two exacerbations per year during the previous two years (9,12,14), one trial enrolled patients with COPD who had a history of at least one exacerbation per year during the previous year (10), and two trials enrolled patients with COPD regardless of whether or not that had any exacerbations during the previous year (11,13). Mucolytic agents included N-acetylcysteine in four trials (9,11,13,14), ambroxol in one trial (10), and carbocisteine in one trial (12). Four trials administered mucolytic therapy for one year (10,12,14,15) and two trials administered mucolytic therapy for three years (11,13).

The guideline panel identified a priori four outcomes as "critical" to guide the formulation of treatment recommendations; three other outcomes were considered "important". The critical outcomes included the rate of COPD exacerbations, proportion of patients having at least one COPD exacerbation, hospitalizations, and quality of life, while the important outcomes included mortality, adverse events, and amount of sputum production.

When the data were pooled via meta-analysis (**see Evidence Profile #1**), mucolytic therapy decreased the likelihood of hospitalization (14.1% versus 18.1%; RR 0.76, 95% CI 0.59 to 0.97), indicating that 25 patients needed to be treated with mucolytics to prevent one hospitalization. When we segregated the analysis based upon dosage, the absolute and relative decreases in hospitalizations were similar among patients who received high-dose or low-dose mucolytic therapy compared with both doses pooled together, but due to smaller number of patients in each group, the confidence intervals widened to include no significant effect of the drug.

The effect of mucolytic therapy on COPD exacerbations varied according to the method of measurement. Mucolytic therapy reduced the relative rate of exacerbations when assessed as the number of exacerbations per patient-year (rate ratio 0.79, 95% CI 0.65-0.95), although the absolute rate reduction was small (rate difference of 0.38 fewer exacerbations per patient-year, 95% CI 0.23 fewer to 0.54 fewer). The reduced rate of COPD exacerbations was largely attributable to high-dose mucolytic therapy (rate ratio 0.69, 95% CI 0.50-0.94), as trials that used low-dose mucolytic therapy did not find a significant relative rate reduction (rate ratio 0.87, 95% CI 0.66-1.14). Mucolytic therapy had no effect on COPD exacerbations when assessed as the proportion of patients who remained exacerbation-free (34.1% versus 32.4%; RR 1.06, 95% CI 0.95 to 1.19).

Mucolytic therapy had no demonstrable effect on mortality (1.3% versus 1.1%; RR 1.15, 95% CI 0.55 to 2.43) or adverse events (26.9% versus 24.2%; RR 1.11, 95% CI 0.91 to 1.35). The effect on quality of life could not be estimated via meta-analysis and the individual studies provided inconsistent results. For all outcomes, the estimated effects did not change substantially when the trials were pooled according to whether or not a history of exacerbations was required for enrollment.

Of note, we were unable to review one potentially relevant trial (15); as this study included patients with chronic bronchitis, and we were not able to assess it ourselves, we decided not

to include it in the evidence tables. We conducted sensitivity analyses to determine if the trial would have significantly affected the results and determined that the measured outcomes did not differ substantially whether the trial was included or excluded.

Benefits: Mucolytic therapy reduced hospitalizations. Mucolytic therapy also reduced the number of COPD exacerbations per patient-year (an effect largely attributable to high-dose therapy), but not the proportion of patients who remained exacerbation-free.

Harms: None identified; there was no evidence that mucolytic therapy increased adverse events.

Other considerations: The overwhelming majority of patients had moderate or severe airflow obstruction; few patients had mild or very severe airflow obstruction. There was no information in any of the trials on the quantity of sputum production. In addition, the outcomes were limited by imprecise estimates, inconsistent results among the primary studies, or both; these limitations diminished the panel's confidence in the estimated effects. A systematic review was published following the completion of our evidence synthesis (16). The results support that mucolytic therapy may reduce the frequency of COPD exacerbations but raised the possibility that patients with more severe obstruction may require higher doses than those with less severe obstruction.

Conclusions and research needs

Mucolytic therapy (N-acetylcysteine, ambroxol, carbocisteine) reduces the likelihood of hospitalization and, when given in high doses, may also reduce COPD exacerbations. No effect on mortality was shown, although there was a very low number of deaths in the trials to definitively determine the effect on mortality. Similarly, there is no evidence that mucolytic therapy increases adverse effects or alters quality of life. The effects of mucolytic therapy in patients with mild or very severe COPD are important research needs, as the findings will help define the patient population most likely to benefit from mucolytic therapy. Since most of the trials used N-acetylcysteine, additional research is needed to determine if ambroxol and carbocisteine have similar effects. As some of the studies included patients who were not on optimal inhaled therapy, the efficacy of mucolytics on top of maximal inhaled treatment has yet to be clearly established.

What others are saying

The 2010 NICE Guidelines (7) recommended not to use mucolytic drugs routinely to prevent exacerbations in patients with stable COPD. The 2011 GOLD strategy document (17) stated that "although a few patients with viscous sputum may benefit from mucolytics, the overall benefits seem to be very small, and the widespread use of these agents cannot be recommended at present". The 2015 ACCP/CTS Guidelines recommended N-acetylcysteine treatment for patients with moderate to severe COPD and a history of two or more exacerbations during the previous two years (18).

ERS/ATS Recommendation

For patients who have COPD with moderate or severe airflow obstruction and exacerbations despite optimal inhaled therapy, we suggest treatment with an oral mucolytic agent to prevent future exacerbations (conditional recommendation, low quality of evidence).

Remarks

Moderate or severe airflow obstruction is defined as an FEV1/FVC <0.70 and an FEV1 of 30 to 79%. The beneficial effect of mucolytic therapy on the rate of COPD exacerbations was driven by trials that administered high-dose mucolytic therapy (e.g., N-acetylcysteine 600 mg twice daily).

Values and preferences

This recommendation places a high value on avoiding hospitalizations and a lower value on the cost and burden of taking daily medication.

Question #2: Are long-acting beta-agonists or long-acting muscarinic antagonists preferable in patients with stable COPD to prevent COPD exacerbations?

Summary of the evidence

Our systematic review identified two relevant trials (19,20). The first trial compared once daily tiotropium to once daily indacaterol (19). The second trial compared once daily tiotropium to twice daily treatment with salmeterol (20). Both trials were conducted over one year and required that patients had at least one COPD exacerbation during the past year. The overwhelming majority of patients had moderate or severe airflow obstruction, defined as a post-bronchodilator FEV1/FVC <0.70 and an FEV1 30 to 79%.

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The guideline panel identified a priori six outcomes as "critical" to guide the formulation of treatment recommendations; two other outcomes were considered "important". The critical outcomes included mortality, frequency of COPD exacerbations, hospitalizations, adverse events, quality of life, and FEV1, while the important outcomes included dyspnea and exercise tolerance.

When the trials were pooled via meta-analysis (**see Evidence Profile #2**), patients who received a long-acting muscarinic antagonist (LAMA) were less likely to have one or more moderate to severe COPD exacerbations (30.9% versus 34.6%, RR 0.89, 95% CI 0.85-0.94). In addition, there was a trend in patients who received a LAMA to have fewer severe adverse effects (14.7% versus 16.1%, RR 0.91, 95% CI 0.84 to 1.0). There was no difference in mortality.

One of the trials additionally reported that patients who received a LAMA were less likely to have a severe COPD exacerbation requiring hospitalization (7.1% versus 9.2%, RR 0.77, 95% CI 0.66-0.90) and had greater improvement in their FEV1 from baseline (mean difference +19 mL, 95% CI +11.34 mL to +28.66 mL) (20). The trial also found no difference in the quality of life, magnitude of improved dyspnea, or proportion of patients with less dyspnea.

Benefits: Patients who received a LAMA were less likely to have one or more moderate to severe COPD exacerbations, were less likely to have a severe exacerbation requiring hospitalization, and had greater improvement in the FEV1 than patients who received a LABA.

Harms: There was a trend toward more severe adverse events among patients who received a LABA than among those who received a LAMA.

Other considerations: The overwhelming majority of patients had moderate or severe airflow obstruction and there were no data from patients who had not had an exacerbation during the previous year. In addition, one outcome that the panel considered important (i.e., exercise tolerance) was not reported in either study. For several outcomes, the panel's confidence in estimating the relative effects of LABA versus LAMA treatment was diminished by imprecision (i.e., wide confidence intervals).

Conclusions and research needs

LAMA therapy reduces the likelihood of moderate to severe exacerbations compared to LABA therapy. It may be associated with fewer adverse events, however, additional data are needed to confirm or exclude this possibility. A differential effect of the agents on mortality has not been shown, although there were very few deaths in the trials to definitively confirm or exclude such an effect. The effects of LAMA vs LABA therapy in patients with mild or very severe COPD requires additional research. Additional data are also required to determine the difference in the effects of LAMA vs LABA therapy on mortality and adverse effects, as well as to determine the comparative effects of these two agents on other important clinical outcomes.

What others are saying

The 2010 NICE Guidelines (7) state, "In people with stable COPD who remain breathless or have exacerbations despite using short-acting bronchodilators as required, offer the following as maintenance therapy. If FEV1 ≥ 50% predicted: either long-acting beta2 agonist (LABA) or LAMA.   If FEV1 < 50% predicted: either LABA with an inhaled corticosteroid (ICS) in a combination inhaler, or a LAMA." The 2011 GOLD strategy document (17) recommend either a LAMA or a combined inhaled corticosteroid / LABA (but not LABA monotherapy) for patients with GOLD spirometry class 3 or 4 obstruction and either two or more exacerbations per year or one or more exacerbation requiring hospitalization. The 2015 ACCP/CTS Guidelines (18) stated, "in patients with moderate to severe COPD, we recommend the use of LAMAs compared with LABAs to prevent moderate to severe acute exacerbations of COPD."

ERS/ATS Recommendation

In patients who have COPD with moderate or severe airflow obstruction and a history of one or more COPD exacerbations during the previous year, we recommend that a LAMA be prescribed in preference to LABA monotherapy to prevent future exacerbations (strong recommendation, moderate quality of evidence).

Remarks

Moderate or severe airflow obstruction is defined as an FEV1/FVC <0.70 and an FEV1 of 30 to 79%.

Values and preferences

This recommendation places a high value on reducing the likelihood of a COPD exacerbation and a lower value on symptomatic relief, the burden of taking daily medication, and cost.

Question #3: Should roflumilast be prescribed to patients who have stable COPD with a history of COPD exacerbations and chronic bronchitis to prevent COPD exacerbations?

Summary of the evidence

The guideline panel made an a priori decision to look at the effects of roflumilast exclusively in patients who had chronic bronchitis. The rationale for focusing on this patient population was that initial trials conducted in patients with or without chronic bronchitis found only a small decrease in the exacerbation rate (21,22); however, a subsequent subgroup analysis found a much larger reduction in the exacerbation rate among patients with chronic bronchitis (22).

Our systematic review identified three trials that compared roflumilast to placebo in patients with stable COPD, a history of COPD exacerbations, and chronic bronchitis (23,24); two of the trials were reported together (23). Sixty-eight percent of patients had severe airflow obstruction, defined as a post-bronchodilator FEV1/FVC <0.70 and FEV1 30-49%, and 31% of patients had very severe airflow obstruction, defined as a post-bronchodilator FEV1/FVC <0.70 and FEV1 <30%. Two of the trials required participants to have had one or more COPD exacerbations during the previous year (23) and one trial required participants to have had two or more COPD exacerbations during the previous year (24). All three trials administered roflumilast for one year (23,24).

The guideline panel identified a priori six outcomes as "critical" to guide the formulation of treatment recommendations; three other outcomes were considered "important". The critical outcomes included rate of COPD exacerbations, proportion of patients having at least one COPD exacerbation, time to first COPD exacerbation, mortality, adverse events, and cardiovascular events; other important outcomes included changes in quality of life, FEV1, and FVC.

When the data were pooled via meta-analysis (**see Evidence Profile #3**), roflumilast therapy decreased the number of moderate or severe exacerbations per patient-year (rate ratio 0.85, 95% CI 0.78-0.91), as well as proportion of patients who had an exacerbation (21.4% versus 25.2%, RR 0.85, 95% CI 0.78 to 0.94). Roflumilast also increased time to next exacerbation (Hazard ratio 0.88, 95% CI 0.81 to 0.96). While these effects were relatively modest when the three trials were pooled together and analyzed, the largest and most recent trial found a larger

reduction in the number of severe exacerbations_(defined a severe exacerbation as one requiring hospitalization or resulting in death) per patient-year despite concomitant therapy with an ICS/LABA (rate ratio 0.76, 95% CI 0.60-0.95) (24); the trial.

The meta-analysis also demonstrated that patients who received roflumilast therapy had a larger increase in their post-bronchodilator FEV1 (mean difference 56.29 mL, 95% CI 45.45 mL to 67.14 mL) and FVC (mean difference 98.45 mL, 95% CI 79.35 mL to 117.55 mL). Roflumilast therapy had no effect on mortality (2.4% versus 2.4%, RR 0.99, 95% CI 0.70 to 1.42), adverse events (67.4% versus 60.9%, RR 1.11, 95% CI 1.06 to 1.15), or cardiovascular events (5.4% versus 4.9%, RR 1.11, 95% CI 0.88 to 1.40).

While the trials that we selected found no evidence of increased adverse events or cardiovascular events among patients who received roflumilast, the panel decided to broaden its selection criteria for these outcomes only. Specifically, we decided to include data from the trials that we had excluded from our systematic review because their duration was less than one year. The rationale was that whereas benefits may take a while to accrue, meaningful adverse effects often occur soon after the initiation of therapy and, therefore, would be detectable in the shorter trials. A Cochrane systematic review included all of the relevant trials (25). Premature treatment discontinuation due to adverse effects was more common with roflumilast than placebo (14.9% versus 9.0%; risk ratio 1.80, 95% CI 1.58 to 2.04). The most common adverse effects were diarrhea (9.7% versus 2.7%; risk ratio 3.96, 95% CI 3.20 to 4.89), nausea (4.8% versus 1.4%; risk ratio 3.54, 95% CI 2.63 to 4.78), weight loss (8.4% versus 2.3%; risk ratio 3.94, 95% CI 3.11 to 5.00), psychiatric disorders including anxiety and depressive symptoms (7.1% versus 3.5%; risk ratio 2.13, 95% CI 1.79 to 2.54), and sleep disturbance/insomnia (3.1% versus 1.1%; risk ratio 2.88, 95% CI 2.15 to 3.86). Mortality was rare, with no significant difference (<2% in both the roflumilast and placebo groups).

Benefits: Roflumilast therapy reduced the number of exacerbations per patient-year, an effect that was particularly strong for severe exacerbations. It also decreased the proportion of patients who developed an exacerbation, prolonged the time to next exacerbation, and modestly increased both FEV1 and FVC.

Harms: Adverse events were not increased in our systematic review; however, an independent systematic review that included trials with shorter durations demonstrated that patients

receiving roflumilast were more likely to prematurely discontinue treatment and develop diarrhea, nausea, weight loss, psychiatric disturbances, insomnia, or sleep disturbances.

Other considerations: The majority of patients had severe or very severe airflow obstruction, in contrast to the evidence reviewed for mucolytic therapy and LABA versus LAMA therapy that was predominately comprised of patients with moderate or severe airflow obstruction. Several outcomes were limited by imprecise estimates, which diminished the panel's confidence in those estimated effects. None of the trials measured quality of life as an outcome.

Conclusions and research needs

Roflumilast therapy reduces COPD exacerbations, particularly severe exacerbations, and modestly improves lung function. No effect on mortality was evident, although there were too few deaths in the trials to definitively confirm or exclude an effect on mortality. Roflumilast therapy increases the risk of gastro-intestinal, sleep, and psychiatric adverse effects in less than 10% of patients. The effect of roflumilast therapy in patients with mild or moderate airflow obstruction remains an important research need.

What others are saying

The 2010 NICE Guidelines (7) did not address roflumilast therapy and a previous version stated that there was not enough evidence to make recommendations. The 2011 GOLD strategy document (17) mentioned that "roflumilast may be useful to reduce exacerbations for patients with an FEV1 <50% predicted, a history of chronic bronchitis, and frequent exacerbations." The 2015 ACCP/CTS Guidelines suggests roflumilast for patients with moderate to severe COPD with chronic bronchitis and a history of at least one exacerbation during the previous year (18).

ERS/ATS Recommendation:

In patients who have COPD with severe or very severe airflow obstruction, symptoms of chronic bronchitis, and exacerbations despite optimal inhaled therapy, we suggest treatment with roflumilast to prevent future exacerbations (conditional recommendation, moderate quality of evidence).

Remarks:

Severe or very severe airflow obstruction is defined as an FEV1/FVC <0.70 and an FEV1 of <50%.

Values and preferences:

This recommendation places a high value on the prevention of exacerbations and a lower value on the burden, cost, and adverse effects of taking a daily medication.

Question #4: Should fluoroquinolones be prescribed to patients with stable COPD to prevent COPD exacerbations?

Summary of the evidence

We identified one trial that met our inclusion criteria (26). The trial was a randomized, placebo-controlled trial conducted in adults who had COPD (FEV1/FVC <0.70), chronic bronchitis, and at least two exacerbations per year during the previous year. Twenty-one percent of patients had moderate airflow obstruction (pre-bronchodilator FEV1 50-80%), 43.9% had severe airflow obstruction (pre-bronchodilator FEV1 30-49%), and 26.0% had very severe airflow obstruction (pre-bronchodilator FEV1 <30%). Participants received either moxifloxacin 400 mg or placebo once daily for five days, repeated every eight weeks for a total of six courses administered over 48 weeks. This trial informed the guideline panel's judgements.

The guideline panel identified a priori five outcomes as "critical" to guide the formulation of treatment recommendations; two other outcomes were considered "important". The critical outcomes included time to first COPD exacerbation, the proportion of patients who had one or more COPD exacerbation, hospitalization, mortality, and adverse events, while the important outcomes included changes in quality of life and the airway bacterial load.

The trial found no definitive effects among patients who received a fluoroquinolone. There were, however, trends toward all of the following: fewer patients developing COPD exacerbations (47.3% versus 50.9%, risk ratio 0.93, 95% CI 0.83 to 1.05), a longer duration to first exacerbation (p=0.062), and improved quality of life (mean difference -1.20, 95% CI -3.01 to 0.61) (**see Evidence Profile #4**). There were no differences in hospitalizations (23.0% versus 23.4%, risk ratio 0.98, 95% CI 0.80 to 1.21), mortality (2.6% versus 2.9%, risk ratio 0.91, 95% CI 0.45 to 1.78), or adverse events (82.1% versus 85%, risk ratio 0.97, 95% CI 0.92 to 1.02). When

the outcomes were re-analyzed using a per-protocol rather than an intention-to-treat approach, the results were similar.

Benefits: Fluoroquinolone therapy conferred no definitive benefits.

Harms: None identified; there was no evidence that fluoroquinolone therapy increased adverse events.

Other considerations: The study reported a statistically significant improvement in COPD exacerbation rate when it was measured using an odds ratio; however, the same outcome showed only a trend toward improvement when measured using a risk ratio. The panel decided to use risk ratios to inform its judgements. The study also reported a decreased COPD exacerbation rate in the subgroup of patients with mucopurulent sputum, but not in the subgroup without mucopurulent sputum; insufficient data was reported for us to re-analyze the subgroups using risk ratios. Several outcomes were limited by imprecise estimates, which diminished the panel's confidence in the estimated effects.

Conclusions and research needs

Fluoroquinolone therapy has not been proven to prevent COPD exacerbations or improve other clinical outcomes. The estimated 3.6% absolute risk reduction and 7% relative risk reduction in COPD exacerbations would be clinically important if real, but these effects can be neither confirmed nor excluded due to the wide confidence intervals. Additional trials are necessary to determine the impact of fluoroquinolone therapy to prevent exacerbations. The panel concluded that patients who produce mucopurulent sputum are a particularly important subgroup to evaluate in future trials.

What others are saying

The 2010 NICE Guidelines (7) did not address fluoroquinolone therapy and a previous version stated that there was not enough evidence to recommend prophylactic antibiotic therapy in general. The 2011 GOLD strategy document (17) said that ''the use of antibiotics, other than for treating infectious exacerbations of COPD and other bacterial infections, is currently not indicated.'' The 2015 ACCP/CTS Guidelines did not address fluoroquinolone therapy (18).

ERS/ATS Recommendation:

Fluoroquinolone therapy is not suggested as treatment for the sole purpose of preventing future COPD exacerbations (conditional recommendation, moderate quality of evidence).

Values and preferences:

This recommendation places a high value on avoiding unproven therapies (particularly when there is a risk of increasing bacterial resistance, which was of significant concern to the guideline panel) and a lower value on the potential to prevent COPD exacerbations.

Question #5: Should macrolides be prescribed to patients with stable COPD to prevent COPD exacerbations?

Summary of the evidence

We identified one relevant systematic review (27), which included three trials that met our inclusion criteria (28-30). Our own systematic review identified an additional trial (31). These four trials collectively informed the panel's judgments (28-31).

All four trials were randomized, placebo-controlled trials conducted in patients with COPD. Two trials reported the severity of airflow obstruction as the mean FEV1 in each treatment arm, which ranged from 1.27 L to 1.47 L (28,29). The remaining two trials reported that 0.4% of patients had mild airflow obstruction, 26.4% of patients had moderate airflow obstruction, 40.6% of patients had severe airflow obstruction, and 32.6% of patients had very severe airflow obstruction, when defined as a post-bronchodilator FEV1 of ≥80%, 50 to 79%, 30 to 49%, and <30%, respectively (30,31). One trial enrolled patients with COPD who had a history of at least three exacerbations during the previous year (31), one trial enrolled patients with COPD who had a history of at least one exacerbation during the previous year (30), and two trials enrolled patients with COPD regardless of whether or not that had any exacerbations during the previous year (28,29). Macrolide regimens included erythromycin 200mg to 400mg daily (28), erythromycin 250mg twice daily (29), azithromycin 250mg daily (30), and azithromycin 500mg three times per week (44). All of the trials administered the macrolide for one year (28-31).

The guideline panel identified a priori five outcomes as "critical" to guide the formulation of treatment recommendations; two other outcomes were considered "important". The critical outcomes included the rate of COPD exacerbations, time to first exacerbation, mortality,

hospitalizations, and serious adverse events. Important outcomes included quality of life and acquisition of macrolide resistance.

When the data were pooled via meta-analysis (**see Evidence Profile #5**), macrolide therapy decreased the rate of COPD exacerbations (rate ratio 0.76, 95% CI 0.68 to 0.86), although the absolute decrease was modest (rate difference 0.40 fewer exacerbations per patient-year, 95% CI 0.24 fewer to 0.55 fewer). Macrolide therapy also increased the time to first COPD exacerbation (mean difference 81.53 more days, 95% CI 53.29 more to 109.77 more). Of note, the largest trial performed subgroup analyses and found that the increase in the time to first COPD exacerbation varied in patients on the basis of smoking status and age. There was a significant reduction in the risk of COPD exacerbations among past smokers, but not current smokers (comparing azithromycin vs. placebo in past smokers: relative hazard 0.65, 95%CI 0.55 to 0.77; comparing azithromycin vs. placebo in current smokers, relative hazard 0.99, 95%CI 0.71 to 1.38; p=0.03 for interaction) and among patients older than 65 years, but not younger patients (older than 65 years: relative hazard 0.59, 95% 0.57 to 0.74; 65 years or younger, relative hazard 0.84, 95%CI 0.68 to 1.04; p=0.02 for interaction) (30). Although not a pre-specified outcome, macrolide therapy reduced the proportion of patients who developed an exacerbation (57% versus 68%, risk ratio 0.84, 95% CI 0.76 to 0.92) (30).

Macrolide therapy improved quality of life, measured using the St. George's Respiratory Questionnaire score. The improvement was seen across all domains: total (mean difference 2.18 lower, 95% CI 1.53 lower to 2.82 lower), symptoms (mean difference 3.36 lower, 95% CI 2.42 lower to 4.29 lower), activity (mean difference 1.82 lower, 95% CI 1.03 lower to 2.62 lower), and impacts (mean difference 2.04 lower, 95% CI 1.28 lower to 2.81 lower). There was no demonstrable effect on mortality (2.7% versus 3.0%, risk ratio 0.90, 95% CI 0.48 to 1.69). Data on hospitalizations could not be pooled because the trials reported the outcome differently; individual trials found a trend toward a decreased rate of hospitalization due to COPD exacerbations (30) and no difference in the time to first hospitalization (31). The effects of macrolide therapy on acquisition of macrolide resistance and the proportion of exacerbations requiring hospitalization were uncertain due to inconsistent results.

Our meta-analysis identified a trend toward fewer serious adverse events among patients who received macrolide therapy than among those who received placebo (28.3% versus 33%, risk ratio 0.86, 95% CI 0.74 to 1.01). While this suggests that macrolides are generally well tolerated, individual trials provide several reasons for caution. In the largest trial (the MACRO

trial), the most common adverse event that led to premature treatment discontinuation was a hearing decrement measured using audiometry performed by clinical research staff (25.4% versus 19.7%; risk ratio 1.29, 95% CI 1.04 to 1.61) (30). However, hearing as assessed by audiometry returned to baseline in about one-third of patients whether or not treatment was discontinued (21 out of 61 [34%] individuals after azithromycin was discontinued; 6 out of 19 [32%] individuals after azithromycin was not discontinued; 14 out of 37 [38%] individuals after placebo was discontinued; and, 2 out of 8 [25%] individuals after placebo was not discontinued). These improvements in both the azithromycin and placebo groups, together with a lack of hearing-related adverse events in the COLUMBUS trial (which did not use audiometry to monitor participants) (31), raise questions about the clinical significance of the hearing decrements as measured by audiometry noted in the MACRO trial. Macrolides are known to cause ventricular arrhythmias that could be fatal, but the incidence with long-term azithromycin in COPD is unknown. The MACRO study demonstrated no increased risk of cardiac arrhythmias over a study period of one year with use of daily azithromycin compared to placebo, however patients with baseline QTC prolongation were excluded from participation in the study and other drugs known to increase QTC interval were prohibited to be used during the conduct of the trial. Though not part of our systematic review, a well-known observational study that used a claims database suggests that the risk of a fatal ventricular arrhythmia due to a macrolide compared with amoxicillin is 1 in 4,100 among individuals at high cardiovascular risk and less than 1 in 100,000 among individuals at low cardiovascular risk (32); thus, the United States Food and Drug Administration (FDA) recommends careful review of patient-level risk factors for ventricular arrhythmias (e.g., a history of a prolonged QT interval, use of co-therapies that prolong the QT interval) when using azithromycin (33).

Benefits: Macrolide antibiotic therapy reduced the COPD exacerbation rate, reduced the proportion of patients who experience an exacerbation, increased the time to next exacerbation, and improved quality of life.

Harms: There was no evidence that macrolide therapy increased serious adverse events collectively, but there was an increased incidence of a hearing decrement measured by audiometry. The effect of macrolide therapy on the acquisition of macrolide-resistance was uncertain.

Other considerations: The overwhelming majority of patients had moderate, severe, or very severe airway obstruction; few patients with mild airway obstruction were studied. One trial (43) was much larger than the others and, therefore, drove the pooled results. Reduction in the risk of exacerbations may be limited to former smokers or older patients based on post-hoc analyses of one trial. The panel's confidence in the estimated effects for most outcomes was limited by inconsistency across trials or wide confidence intervals due to few events.

Conclusions and research needs

Macrolide therapy reduces the rate of COPD exacerbations and the proportion of patients who experience a COPD exacerbation. It also increases the time to next exacerbation and improves quality of life, although the magnitude of latter is smaller than what is typically considered clinically significant. No effect on mortality has been shown, but there were too few deaths in the trials to definitively confirm or exclude an effect on mortality. Similarly, there is uncertainty about the risk of serious adverse effects of chronic macrolide therapy in COPD (e.g., fatal arrhythmias) and its effect on the acquisition of macrolide resistance is uncertain. These effects of macrolide therapy need to be confirmed, since most of the outcomes were driven by a single large trial. In particular, a better understanding of the impact of macrolide therapy on the acquisition of macrolide resistance and cardiovascular adverse effects is needed. In addition, it needs to be determined whether the effects are shared by all antibiotics or specific to macrolides. Also, head-to-head studies comparing the benefits and adverse effects of oral medications that reduce the risk of COPD exacerbations (e.g., long-term azithromycin vs. roflumilast or N-acetylcysteine) are needed; previously published studies have been limited to comparisons with placebo. Finally, defining subgroups of patients who are more or less likely to benefit from macrolide therapy (e.g., by smoking status) is necessary to refine the appropriate target patient population for therapy. In any case, macrolide therapy should not be a first line treatment in COPD and should be considered in appropriately selected patients.

What others are saying

The 2010 NICE Guidelines (7) did not address macrolide therapy and a previous version stated that there was not enough evidence to recommend prophylactic antibiotic therapy in general. The 2011 GOLD strategy document (17) stated that "the use of antibiotics, other than for treating infectious exacerbations of COPD and other bacterial infections, is currently not indicated." The 2015 ACCP/CTS Guidelines say, "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" (18).

ERS/ATS Recommendation

For patients who have COPD with moderate to very severe airflow obstruction and exacerbations despite optimal inhaled therapy, we suggest treatment with a macrolide antibiotic to prevent future exacerbations (conditional recommendation, low quality of evidence).

Remarks

Moderate to very severe airflow obstruction is defined as an FEV1/FVC <0.70 and a post-bronchodilator FEV1 of ≤80%. Before prescribing macrolides, clinicians need to carefully consider patients' cardiovascular risk factors particularly for ventricular arrhythmias.

Values and preferences

This recommendation places a high value on reducing COPD exacerbations and a lower value on the suspected but unproven risk of inducing macrolide resistance and the cost and burden of taking daily medication.

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Evidence Profile # 1

Comparison: Mucolytics vs. placebo for patients with COPD to prevent COPD exacerbations
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Quality assessment						No. of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mucolytics	Placebo	Relative (95% Confidence Interval)	Absolute (95% Confidence Interval)		
Hospitalisations (proportion of patients hospitalized)												
All doses of mucolytics												
3 [1]	randomised trials	none	serious [2]	none	serious [3]	none	114/810 (14.1%)	150/827 (18.1%)	Risk Ratio 0.76 (0.59 to 0.97)	44 fewer per 1000 will be hospitalised (from 5 fewer to 74 fewer)	⊕⊕OO LOW	CRITICAL
High-dose mucolytics (N-acetylcysteine 600 mg PO BID)												
2 [4]	randomised trials	none	none	none	serious [3]	none	59/554 (10.6%)	81/560 (14.5%)	Risk Ratio 0.73 (0.0.49 to 1.11)	39 fewer per 1000 will be hospitalised (from 74 fewer to 16 more)	⊕⊕⊕O MODERATE	CRITICAL
Low-dose mucolytics (N-acetylcysteine 600 mg PO qD)												
1 [5]	randomised trials	none	none	none	serious [3]	none	55/256 (21.5%)	69/267 (25.8%)	Risk Ratio 0.83 (0.61 to 1.13)	44 fewer per 1000 will be hospitalised (from 101 fewer to 34 more)	⊕⊕⊕O MODERATE	CRITICAL
COPD exacerbation rate (exacerbations per patient-year)												
All doses of mucolytics												
4 [6]	randomised trials	none	serious [7]	none	serious [8]	none	1171	1185	Rate Ratio 0.79 (0.65 to 0.95)	--	⊕⊕OO LOW	CRITICAL
3 [9]	randomised trials	none	serious [10]	none	none	none	915	918	--	Rate difference = 0.38 fewer exacerbations per patient-year (from 0.23 fewer to 0.54 fewer)	⊕⊕⊕O MODERATE	CRITICAL

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№	design	risk of bias	inconsistency	indirectness	imprecision	other	n₁	n₂	Relative	Absolute	Quality	Importance
High-dose mucolytics (N-acetylcysteine 600 mg PO BID)												
2 [11]	randomised trials	none	serious [12]	none	serious [8]	none	562	564	Rate Ratio 0.69 (0.50 to 0.94)	--	⊕⊕OO LOW	CRITICAL
2 [11]	randomised trials	none	serious [12]	none	none	none	562	564		Rate difference = 0.49 fewer exacerbations per patient-year (from 0.09 fewer to 0.89 fewer)		CRITICAL
									--			
Low-dose mucolytics (N-acetylcysteine 600 mg PO qD, ambroxol 75 mg PO BID, and carbocisteine 500 mg PO TID)												
2 [13]	randomised trials	none	serious [14]	none	serious [8]	none			Rate Ratio 0.87 (0.66 to 1.14)	--	⊕⊕⊕O MODERATE	CRITICAL
1 [15]	randomised trials	none	none	none	none	none				Rate difference = 0.34 fewer exacerbations per patient-year (from 0.17 fewer to 0.51 fewer)		CRITICAL
									--			
COPD exacerbations (proportion of patients with no exacerbations)												
5 [16]	randomised trials	none	none	none	none	none	375/1098 (34.1%)	359/1107 (32.4%)	Risk Ratio 1.06 (0.95 to 1.19)	19 more per 1000 will be exacerbation-free (from 16 fewer to 62 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of Life (change in the St. George's Respiratory Questionnaire during treatment) (better quality of life indicated by lower values)												
4 [17]	randomised trials	none	very serious [18]	none	none	none	1165	1179	not estimable [19]	not estimable [19]	⊕⊕OO LOW	CRITICAL
Adverse events (proportion of patients experiencing an adverse event)												
4 [17]	randomised trials	none	none	none	none	none	149/553 (26.9%)	135/557 (24.2%)	Risk Ratio 1.11 (0.91 to 1.35) [20]	27 more per 1000 will have an adverse event (from 22 fewer to 85 more) [20]	⊕⊕⊕⊕ HIGH	IMPORTANT
Mortality (proportion of patients who died)												
5 [21]	randomised trials	none	none	none	serious [5]	none	16/1267 (1.3%)	14/1281 (1.1%)	Risk Ratio 1.15 (0.55 to 2.43)	2 more deaths per 1000 (from 5 fewer to 16 more)	⊕⊕⊕O MODERATE	IMPORTANT
Decrease in sputum production												
0												IMPORTANT

Notes :

[1] Decramer 2005, Tse 2013, and Zheng 2014.

[2] Large amount of heterogeneity across studies: for the mean difference, p- value (for heterogeneity) = 0.23 and I^2 = 33%.

[3] Wide confidence intervals: The ends of the confidence interval for the risk ratio will likely lead to different clinical decisions.

[4] Tse 2013 and Zheng 2014.

[5] Decramer 2005.

[6] Decramer 2005, Zheng 2008, Tse 2013, and Zheng 2014.

[7] Large amount of heterogeneity across studies: p- value (for heterogeneity) = 0.0004 and I^2 = 84%.

[8] Wide confidence intervals: The ends of the confidence interval for the rate ratio will likely lead to different clinical decisions.

[9] Zheng 2008, Tse 2013, and Zheng 2014.

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[10] Large amount of heterogeneity across studies: p- value (for heterogeneity) = 0.19 and I^2 = 39%.

[11] Tse 2013 and Zheng 2014.

[12] Large amount of heterogeneity across studies: p- value (for heterogeneity) = 0.07 and I^2 = 69%.

[13] Decramer 2005 and Zheng 2008.

[14] Large amount of heterogeneity across studies: p- value (for heterogeneity) = 0.002 and I^2 = 89%.

[15] Zheng 2008.

[16] Malerba 2004, Zheng 2008, Schermer 2009, Tse 2013, and Zheng 2014.

[17] Decramer 2005, Zheng 2008, Tse 2013, and Zheng 2014.

[18] Large amount of heterogeneity across studies: for the mean difference, p- value (for heterogeneity) <0.00001 and I^2 = 97%.

[19] Decramer 2005 and Zheng 2014 did not report sufficient crude data to be included in the meta-analysis. When Zheng 2008 and Tse 2013 were pooled, the heterogeneity was very serious, indicating that these studies should not be pooled because doing so provides misleading results.

[20] Tse 2013 and Zheng 2014. Decramer 2005 and Zheng 2008 reported the number of adverse events in each arm of the trial, not the number of patients experiencing an adverse event; therefore these trials were not included in the meta-analysis.

[21] Decramer 2005, Schermer 2009, Tse 2013, Zheng 2008, and Zheng 2014.

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Evidence Profile # 2

Comparison: Long-acting beta agonists versus long-acting muscarinic agents for patients with COPD to prevent COPD exacerbations
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Quality assessment						No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	LAMAs	LABAs	Relative (95% Confidence interval)	Absolute (95% Confidence interval)		
Mortality (proportion of patients on treatment +30 days who died)												
2 [1]	randomised trials	none	none	none	serious [2]	none	92/5425 (1.7%)	106/5390 (2%)	Risk Ratio 0.86 (0.65 to 1.14)	3 fewer per 1000 (from 7 fewer to 3 more)	⊕⊕⊕O MODERATE	CRITICAL
COPD exacerbations (proportion of patients with at least 1 moderate/severe exacerbation)												
2 [1]	randomised trials	none	none	none	none	none	1624/5250 (30.9%)	1795/5189 (34.6%)	Risk Ratio 0.89 (0.85 to 0.94)	38 fewer per 1000 (from 21 fewer to 52 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
COPD exacerbations (proportion of patients having a severe exacerbation requiring hospitalisation)												
1 [3]	randomised trials	none	none	none	serious [2]	none	262/3707 (7.1%)	336/3669 (9.2%)	Risk Ratio 0.77 (0.66 to 0.9)	21 fewer per 1000 (from 9 fewer to 31 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Severe adverse events (proportion of patients experiencing a severe adverse event)												
2 [1]	randomised trials	none	none	none	none	none	800/5425 (14.7%)	869/5390 (16.1%)	Risk Ratio 0.91 (0.84 to 1)	15 fewer per 1000 (from 26 fewer to 0 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Quality of Life (change in the St. George's Respiratory Questionnaire during treatment) (better quality of life indicated by lower values)												
1 [3]	randomised trials	none	none	none	none	none	1325	1281	-	Mean Difference 0.4 lower (1.56 lower to 0.76 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Forced expiratory volume in one second (mL)												
1 [3]	randomised trials	none	none	none	none	none	1362	1324	-	Mean Difference 19 greater (11.34 greater to 28.66 greater)	⊕⊕⊕⊕ HIGH	CRITICAL
Dyspnoea (change in the Transition Dyspnea Index [TDI] during treatment) (less dyspnea indicated by higher values)												
1 [3]	randomised	none	none	none	none	none	1332	1296	-	Mean Difference 0.3 lower (0.57	⊕⊕⊕⊕	IMPORTANT

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	trials										to 0.03 lower)	HIGH	
Exercise tolerance													
0													IMPORTANT

[1] Vogelmeier C 2011 and Decramer ML 2013.
[2] Wide confidence intervals: The ends of the confidence interval for the risk ratio will likely lead to different clinical decisions.
[3] Decramer ML 2013.

Evidence Profile # 3

Comparison: Roflumilast versus placebo for patients with COPD to prevent COPD exacerbations
Bibliography: 23) M2-124 and M2-125, both reported by Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. Lancet 2009;374(9691):685-94. **24)** Martinez FJ, Calverley PMA, Goehring UM. Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT):a multicentre randomised controlled trial. Lancet 2015; 385(9971):857-866.

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Roflumilast	Placebo	Relative (95% Confidence interval)	Absolute (95% Confidence interval)	Quality	Importance
			Quality assessment				No of patients		Effect			
COPD exacerbations (exacerbations per patient-year)												
3	randomised trials	none	none	none	serious[1]	none	2506	2520	Rate ratio 0.85 (0.78 to 0.92)	Rate difference = 0.14 fewer exacerbations per patient-year (from 0.25 fewer to 0.03 fewer)	⊕⊕⊕O MODERATE	CRITICAL
COPD exacerbations (proportion of patients with at least 1 moderate/severe exacerbation)												
3	randomised trials	none	none	none	serious[1]	none	537/2506 (21.4%)	636/2520 (25.2%)	Risk ratio 0.85 (0.78 to 0.94)	38 fewer per 1000 (from 15 fewer to 56 fewer)	⊕⊕⊕O MODERATE	CRITICAL
COPD exacerbations (time to first exacerbation, days)												
3	randomised trials	none	none	none	none	none	2506	2520	Hazard ratio 0.88 (0.81 to 0.96)	--	⊕⊕⊕⊕ HIGH	CRITICAL
Mortality (%)												
3	randomised trials	none	none	none	serious[1]	none	59/2506 (2.4%)	60/2520 (2.4%)	Risk ratio 0.99 (0.70 to 1.42)	0 fewer per 1000 (from 7 fewer to 10 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events (%)												
3	randomised trials	none	none	none	none	none	1688/2505 (67.4%)	1535/2521 (60.9%)	Risk ratio 1.11 (1.06 to 1.15)	67 more per 1000 (from 37 more to 91 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Cardiovascular events (%)												
3	randomised	none	none	none	none	none	136/2506	124/2520	Risk ratio 1.11	5 more per 1000 (from 6 fewer to	⊕⊕⊕⊕	CRITICAL

								(5.4%)	(4.9%)	(0.88 to 1.40)	20 more)	HIGH	
	trials												

Change in quality of life (assessed via the St. George's Respiratory Questionnaire) (Better indicated by lower values)

0													IMPORTANT
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Change in post-bronchodilator forced expiratory volume in one second, FEV1 (mL) (Better indicated by higher values)

3	randomised trials	none	none	none	none	none		2381	2441	--	Mean difference 56.29 mL higher (45.45 mL higher to 67.14 mL higher)	⊕⊕⊕⊕ HIGH	IMPORTANT

Change in post-bronchodilator forced vital capacity, FVC (mL) (Better indicated by higher values)

3	randomised trials	none	none	none	none	none		2381	2441	-	Mean difference 98.45 mL higher (79.35 mL higher to 117.55 mL higher)	⊕⊕⊕⊕ HIGH	IMPORTANT

[1] Wide confidence interval: the ends of the confidence interval would lead to different clinical decisions

Evidence Profile # 4

Comparison: Fluroquinolones vs. placebo for patients with COPD to prevent COPD exacerbations
Bibliography: 27) Sethi S, Jones PW, Schmitt Terron M, Miravitlles M, Rubinstein E, Wedzicha JA, Wilson R, the PULSE Study Group. Pulsed moxifloxacin for the prevention of exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. Respiratory Research 2010; 11:10.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluroquinolones	Placebo	Relative (95% Confidence interval)	Absolute (95% Confidence interval)		
COPD exacerbations (proportion of patients with at least 1 moderate/severe exacerbation)												
1	randomised trials	none	none	none	none	none	269/569[1] (47.3%)	295/580[1] (50.9%)	Risk ratio 0.93 (0.83 to 1.05)[1]		⊕⊕⊕⊕ HIGH	CRITICAL
Time to first COPD exacerbation (days)												
1	randomised trials	none	none	none	none	none	569[2]	580[2]	Not estimable[3]	Not estimable[3]	⊕⊕⊕⊕ HIGH	CRITICAL
Hospitalisation (%)												
1	randomised trials	none	none	none	serious[4]	none	131/569[5] (23%)	136/580[5] (23.4%)	Risk ratio 0.98 (0.8 to 1.21)[5]	5 fewer per 1000 (from 47 fewer to 49 more)[5]	⊕⊕⊕O MODERATE	CRITICAL
Mortality (%)												
1	randomised trials	none	none	none	serious[1]	none	15/569[6] (2.6%)	17/580[6] (2.9%)	Rate ratio 0.901 (0.45 to 1.78)[6]	3 fewer per 1000 (from 16 fewer to 23 more)[6]	⊕⊕⊕O MODERATE	CRITICAL
Adverse events (%)												
1	randomised trials	none	none	none	none	none	467/569 (82.1%)	493/580 (85.0%)	Rate ratio 0.97 (0.92 to 1.02)	25 fewer per 1000 (from 68 fewer to 17 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Change in quality of life (Assessed via the St. George's Respiratory Questionnaire) (Better indicated by lower values)												
1	randomised trials	none	none	none	none	none	503[7]	526[7]	-	Mean difference 1.2 lower (3.01 lower to 0.61 higher)[7]	⊕⊕⊕⊕ HIGH	IMPORTANT
Reduction in airway bacterial load												
0	-	-	-	-	-	-	-	-	-	-	-	IMPORTANT

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6   [1] Derived by intention-to-treat analysis. Per-protocol analysis found 153/351 (43.6%) versus 190/387 (49.1%), Risk ratio 0.89 (95% CI 0.76- to 1.04).
7   [2] For the intention-to-treat analysis: fluroquinolone (n=569), placebo (n=580). For the per-protocol analysis: fluroquinolone (n=351), placebo (n=387).
8   [3] The trial did not provide estimates of the time to exacerbation in each arm in days; however, it reported a trend toward a longer duration to first exacerbation among patients who received fluroquinolones than placebo according to both intention-to-treat and per-protocol analyses.
9   [4] Wide confidence intervals: The ends of the confidence intervals lead to different clinical decisions.
10 [5] Derived by intention-to-treat analysis. Per-protocol analysis found 56/351 (16.0%) versus 54/387 (14.0%), Risk ratio 1.14 (95% CI 0.81 to 1.61).
11 [6] Derived by intention-to-treat analysis. Per-protocol analysis found 1/351 (0.3%) versus 3/387 (0.8%), Risk ratio 0.36 (95% CI 0.04 to 3.43).
    [7] Derived by intention-to-treat analysis. Per-protocol analysis found fluroquinolone (n=569), placebo (n=580), mean difference -1.30 (95% CI -3.47 to 0.87).

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Evidence Profile # 5

Comparison: Macrolides vs. placebo for patients with COPD to prevent COPD exacerbations.
Bibliography: 28) Suzuki T, Yanai M, Yamaya M, Satoh-Nakawaga T, Sekizawa K, Ishida S, Sasaki H. Erythromycin and common cold in COPD. Chest 2001;120(3):730-3; the time to exacerbation; **29)** Seemungal TAR, Wilkinson TMA, 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; 178:1139-1147; **30)** Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JA, Jr., Criner GJ, Curtis JL, Dransfield MT, Han MK, Lazarus SC, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med 2011;365(8):689-98; and **31)** Uzun S, Djamin RS, Kluytmans JAJW et al. Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2014; 2: 361-368.

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	macrolide	placebo	Relative (95% Confidence interval)	Absolute (95% Confidence interval)	Quality	Importance
Quality assessment							**№ of patients**		**Effect**			
COPD exacerbation rate (exacerbations per patient-year)												
3 [1]	randomised trials	none	serious [2]	none	serious [3]	none	658	660	Rate ratio 0.76 (0.68 to 0.86)	--	⊕⊕○○ LOW	CRITICAL
2 [4]	randomised trials	none	serious [5]	none	none	none	605	604	--	Rate difference 0.40 fewer (0.24 fewer to 0.55 fewer)	⊕⊕⊕○ MODERATE	CRITICAL
Time to first exacerbation (days)												
3 [1]	randomised trials	none	none	none	none	none	658	660	--	Mean difference 81.53 fewer (53.29 fewer to 109.77 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Hospitalisation												
3 [1]	randomised trials	none	none	none	serious [3]	none	658	660	not estimable [6]	not estimable [6]	⊕⊕⊕○ MODERATE	CRITICAL

	Quality assessment						№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	macrolide	placebo	Relative (95% Confidence interval)	Absolute (95% Confidence interval)	Quality	Importance
Serious adverse events												
3 [7]	randomised trials	none	none	none	serious [5]	none	187/660 (28.3%)	217/658 (33.0%)	Risk ratio 0.86 (0.74 to 1.01)	46 fewer per 1000 (from 86 fewer to 3 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Mortality												
3 [7]	randomised trials	none	none	none	serious [5]	none	18/660 (2.7%)	20/657 (3.0%)	Risk ratio 0.90 (0.48 to 1.69)	3 fewer per 1000 (from 17 fewer to 23 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Acquisition of macrolide-resistant bacteria												
2 [3]	randomised trials	none	serious [8]	none	none	none	605	604	not estimable [9]	not estimable [9]	⊕⊕⊕◯ MODERATE	IMPORTANT
Quality of Life (St. George's Respiratory Questionnaire score) (Lower values indicate a better quality of life)												
Total												
2 [3]	randomised trials	serious [10]	none	none	none	none	491	498	-	Mean difference 2.18 lower (1.53 lower to 2.82 lower)	⊕⊕⊕◯ MODERATE	IMPORTANT
Symptoms												

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	№ of patients		Effect		Quality	Importance
							macrolide	placebo	Relative (95% Confidence interval)	Absolute (95% Confidence interval)		
2 [3]	randomised trials	serious [10]	none	none	none	none	491	498	-	Mean difference 3.36 lower (2.42 lower to 4.29 lower)	⊕⊕⊕◯ MODERATE	IMPORTANT
Activity												
2 [3]	randomised trials	serious [10]	not serious	none	none	none	491	498	-	Mean difference 1.82 lower (1.03 lower to 2.62 lower	⊕⊕⊕◯ MODERATE	IMPORTANT
Impacts												
2 [3]	randomised trials	serious [10]	serious [11]	none	none	none	491	498	-	Mean difference 2.04 lower (1.28 lower to 2.81 lower	⊕⊕◯◯ LOW	IMPORTANT

[1] Seemungal 2008, Albert 2011, and Uzun 2014.

[2] Inconsistency: I^2 = 57%, p_{het} = 0.10.

[3] Wide 95% confidence intervals: the ends of the confidence interval would lead to different clinical decisions.

[4] Albert 2011 and Uzun 2014.

[5] Inconsistency: I^2 = 85%, p_{het} = 0.010.

[6] The data could not be pooled because it was reported in different ways. Seemungal 2008 reported a non-significant decrease in the proportion of exacerbations that are severe enough to require hospitalization (7.4% versus 11.4%, risk ratio 0.66, 95% CI 0.27 to 1.65). Albert 2010 reported a non-significant reduction in the rate of hospitalization due to COPD (0.34 hospitalizations per patient-year versus 0.49 hospitalizations per patient-year, hazard ratio 0.82, 95% CI 0.64 to1.07). Uzun 2014 reported a non-significant increase in the time to first hospitalization (282 days versus 258 days, p=0.48) and a non-significant decrease in the proportion of exacerbations that are severe enough to require hospitalization (29.8% versus 24%, risk ratio 1.24, 95% CI 0.79 to 1.94).

[7] Suzuki 2001, Albert 2011, and Uzun 2014.

[8] One of the trials found an increase in the acquisition of macrolide-resistant organisms among patients who received macrolides, whereas the other trial found a decrease in the acquisition of macrolide-resistant organisms among patients who received macrolides.

[9] The data could not be pooled because one of the trials did not report the crude data. Albert 2011 reported the acquisition of macrolide-resistant organisms in 81% of patients who received macrolides and 41% of patients who received placebo; Uzun 2014 reported the acquisition of macrolide-resistant organisms in fewer patients who received macrolides than who received placebo (6% versus 24%, risk ratio 0.57, 95% CI 0.15 to 2.26).

[10] A large number of patients did not have quality of life assessed.

[11] Inconsistency: I^2 = 38%, p_{het} = 0.20.

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ONLINE SUPPLEMENT 1

PREVENTION OF COPD EXACERBATIONS: An European Respiratory Society/American

Thoracic Society (ERS/ATS) guideline.

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FULL METHODS SECTION

Group composition

The guideline panel co-chairs (JAW, JAK) were selected by the European Respiratory Society (ERS) and American Thoracic Society (ATS). They led all aspects of project management and selected the panellists, which included 11 clinicians with experience in COPD management and research. In addition, there were two methodologists (TT, DR) and a clinician-methodologist (KCW). The lead methodologist (TT) identified and collected the evidence, performed the evidence syntheses, constructed the evidence profiles, and ensured that all the methodological requirements were met, with assistance from the other methodologists. The co-chairs and panellists discussed the evidence and formulated the recommendations; the methodologists did not participate in the development of recommendations. All panel members were required to disclose their conflicts of interest. At least 50% of the co-chairs and 50% of the panel were required to be free from conflicts of interest. Individuals with potential conflicts of interest took part in the discussions about the evidence but did not participate in the formulation of recommendations.

Formulation of questions

Guideline panel members compiled a list of issues that they considered important and relevant to the treatment of COPD exacerbations. The questions were rephrased by the lead methodologist using the Population, Intervention, Comparator, and Outcomes (PICO) format (1). Discussion and consensus among the co-chairs and panellists was used to identify the six questions that would be addressed in the guideline.

Rating the importance of outcomes

After choosing the questions, the guideline panel identified outcomes that they considered relevant to each question prior to conducting the literature search. They rated the importance of each outcome using a scale from 1 to 9 (a rating of 1 to 3 was assigned to outcomes of low importance for decision-making, 4 to 6 to outcomes important for decision-making, and 7 to 9 to outcomes critically important for decision-making). A teleconference was convened during which the ratings were discussed and some additional outcomes were rated. At the conclusion of the teleconference, all outcomes were categorized as "critical", "important", or "not

important" for decision-making. The reason for the distinction is that only critical outcomes are used to determine the overall quality of evidence for a recommendation, even though the quality of evidence is assessed for every outcome.

Literature searches

Our literature searches used the National Institute of Health and Clinical Excellence (NICE) guidelines as a starting point (2,3). For questions that were addressed in the 2004 NICE guidelines, we conducted literature searches in Medline, Embase, and the Cochrane Database of Systematic Reviews beginning in 2003. For questions that were addressed in the 2010 NICE guidelines, we conducted literature searches in the same databases beginning in 2009. Initial searches were conducted in January 2012 and then updated in June 2012, February 2013, and September 2015. We used the same or similar search strategies as those used by NICE. To search Embase and Medline, we searched only the English speaking literature using the search strategy shown in the online supplement, whereas to search the Cochrane Database of Systematic Reviews, we used the search term, "chronic obstructive pulmonary disease".

Study selection

The lead methodologist screened the titles and abstracts of the retrieved studies and excluded studies on the basis of the pre-defined study selection criteria shown in the online supplement. For those studies that could not be excluded by the title and abstract, we obtained the full text of the studies and then included or excluded the studies on the basis of our full text review. In cases of uncertainty, the opinions of the co-chairs and panellists were obtained and decisions were reached by discussion and consensus. We also screened the reference lists from recent and well-conducted systematic reviews, in order to ensure that our literature review had not missed any relevant studies.

Evidence synthesis

Study characteristics, types of participants, interventions, the outcomes measured, and results were extracted from each study. If the data was amendable to pooling, effects were estimated via meta-analysis using Review Manager (4). For the meta-analyses, the random effects model was utilized unless otherwise specified. Dichotomous outcomes were reported as relative risks and continuous outcomes were reported as mean differences unless otherwise specified. The lead methodologist appraised the quality of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach (5-12).

The lead methodologist used GRADEpro to develop evidence profiles that summarized the findings for each outcome and the rationale for the quality of evidence appraisal (13-15). Thresholds for clinically important differences between treatment groups (used to judge imprecision) included the following relative risk reductions: mortality 15%, exacerbations 20%, hospitalizations 20%, and adverse events 15%. They also included the following absolute reduction: St. George's Respiratory Questionnaire score change of 4 points.

Formulating and grading recommendations

The evidence profiles were sent to the guideline panel members for review. Using an iterative consensus process conducted primarily by email, but also via teleconference and face-to-face meetings, recommendations were formulated on the basis of the following considerations: the balance of desirable (benefits) and undesirable consequences (burden, adverse effects, cost) of the intervention, the quality of evidence, patient values and preferences, and feasibility (16).

A strong recommendation would have been made for an intervention if the panel was certain that the desirable consequences of the intervention outweigh the undesirable consequences, just as a strong recommendation would have been made against an intervention if the panel was certain that the undesirable consequences of the intervention outweigh the desirable consequences. A strong recommendation would have indicated that most well-informed patients would choose to have or not to have the intervention.

A conditional recommendation was made for an intervention when the panel was uncertain that the desirable consequences of the intervention outweigh the undesirable consequences, just as a conditional recommendation was made against an intervention if the panel was uncertain that the undesirable consequences of the intervention outweigh the desirable consequences. Reasons for uncertainty included low or very low overall quality of evidence (determined from the outcomes a priori defined as "critical"), the desirable and undesirable consequences being finely balanced, or the underlying values and preferences playing an important role. A conditional recommendation indicates that well-informed patients may make different choices regarding whether to have or not have the intervention.

Manuscript preparation

The initial draft of the manuscript was prepared by the co-chairs, methodologists, and one panellist (MM). The lead methodologist wrote the content for the online supplement, which

was edited by the co-chairs. Both the manuscript and the online supplement were reviewed, edited, and approved by all panel members prior to submission.

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