



Effective Health Care Treatments for Chronic Obstructive Pulmonary Disease Exacerbation

Results of Topic Selection Process & Next Steps

The nominator, the American Academy of Family Physicians (AAFP), wanted to acquire a rigorously conducted systematic review to inform recommendations for a new clinical practice guideline that will broadly cover management of exacerbations of Chronic Obstructive Pulmonary Disease (COPD).

The topic will go forward for refinement as a new systematic review. The scope of this topic, including populations, interventions, comparators, and outcomes, will be further developed in the refinement phase. When key questions have been drafted, they will be posted on the AHRQ Web site and open for public comment. To sign up for notification when this and other Effective Health Care (EHC) Program topics are posted for public comment, please go to <https://effectivehealthcare.ahrq.gov/email-updates>.

Topic Brief

Topic Name: Treatments for Chronic Obstructive Pulmonary Disease Exacerbation

Topic #: 0739

Nomination Date: May 1, 2017

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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Summary of Key Findings:

- This topic meets all selection criteria.
- The scope was narrowed because of an in-process review for a clinical practice guideline by another group
- The scope of a new review would likely be small to medium.

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Introduction

In 2014, Chronic Obstructive Pulmonary Disease (COPD) was the third leading cause of death in the United States with over 15 million people diagnosed with the condition.¹ Many people suffer from this disease for years and die prematurely of it or its complications. Among patients with COPD, acute exacerbations are a leading cause of deterioration of pulmonary function and quality of life.^{2,3} Unfortunately, the true incidence of COPD exacerbations is quite difficult to assess because about half of exacerbations are not reported by patients.⁴ COPD exacerbations are also associated with substantially higher risk for mortality. Estimates of hospital mortality rates for patients admitted with an COPD exacerbation vary from 4%–30%⁵ and the 3-month mortality rate after hospitalization in the UK is approximately 15%.^[5] COPD is also a costly disease. In developed countries, exacerbations of COPD account for the greatest burden on the health care system. In the United States in 2010, the total national medical costs attributable to COPD including exacerbations were \$32.1 billion.⁶

Therapeutic management of COPD exacerbations range from pharmacologic agents such as short-acting/long-acting inhaled bronchodilators, systemic corticosteroids and other anti-inflammatory drugs (e.g. phosphodiesterase-4 inhibitors), and antibiotic therapy to non-pharmacologic measures such as supplemental oxygen therapy, non-invasive mechanical ventilation (NIV), home-based management, and pulmonary rehabilitation.⁷⁻⁹ In addition, several new pharmacologic agents with novel mechanisms of action in early stages of development may be of potential benefit to COPD patients including those in acute exacerbation.¹⁰ However, the comparative benefits and harms of these varied treatment approaches including the optimal combination or sequencing of these treatments to mitigate COPD exacerbation is unclear.

Nominator and Stakeholder Engagement

Topic nomination #0739 was received on May 1, 2017. The nominator, the American Academy of Family Physicians (AAFP), wanted to acquire a rigorously conducted systematic review to inform recommendations for a new clinical practice guideline that will broadly cover management of stable COPD and COPD exacerbations. Based on a search of practice guidelines on the AAFP website, the most recent guideline related to COPD endorsed by AAFP is the 2012 American College of Physicians (ACP) Guideline on Diagnosis and Management of Stable COPD.¹¹

We identified a systematic review in development to inform a practice guideline by another organization. With this information and nominator consultation we narrowed the scope to an area outside the scope of the in-process review, on pharmacologic and non-pharmacologic treatments for COPD exacerbation.

The key questions for this nomination are:

Key Question 1. In adult patients who have COPD, what are the benefits and harms of pharmacologic therapies for treatment of exacerbation of symptoms?

Key Question 2. In adult patients who have COPD, what are the benefits and harms of non-pharmacologic therapies for treatment of exacerbation of symptoms?

To define the inclusion criteria for the key questions we specify the population, interventions, comparators, and outcomes (PICO) of interest. See Table 1.

Table 1. Key Questions and PICOTs

Key Questions	1. In adult patients who have COPD, what are the benefits and harms of pharmacologic therapies for treatment of exacerbation of symptoms?	2. In adult patients who have COPD, what are the benefits and harms of non-pharmacologic therapies for treatment of exacerbation of symptoms?
Population	Adults with acute exacerbation of COPD	Adults with acute exacerbation of COPD
Interventions	Pharmacologic interventions include: <ul style="list-style-type: none"> • <i>Beta adrenergic agonists</i> • <i>Anticholinergic agents</i> • <i>Glucocorticoid therapy</i> • <i>Antibiotics</i> • <i>Combinations of the above</i> • <i>Others</i> 	Non-pharmacologic interventions include: <ul style="list-style-type: none"> • <i>Oxygen therapy</i> • <i>Mechanical ventilation</i> <ul style="list-style-type: none"> ◦ <i>Non-invasive ventilation</i> ◦ <i>Invasive ventilation</i> • <i>Chest physiotherapy</i> • <i>Nutritional support</i> • <i>Others</i>
Comparators	Pharmacologic treatments compared to each other and to non-pharmacologic treatments	Non-pharmacologic treatments compared to each other and to pharmacologic treatments
Outcomes	Primary outcomes: <i>Resolution of exacerbation/treatment failure; Relapse/recurrence; Mortality; Adverse effects (harms)</i> Secondary outcomes: <i>Symptom scores; Lung function (pre- and post-bronchodilator including FEV1, FVC), PEF; Quality of Life; Physical capacity (timed walking tests, endurance tests); Duration of hospitalization; Duration of assisted ventilation</i>	Primary outcomes: <i>Resolution of exacerbation/treatment failure; Relapse/recurrence; Mortality; Adverse effects (harms)</i> Secondary outcomes: <i>Symptom scores; Lung function (pre- and post-bronchodilator including FEV1, FVC), PEF; Quality of Life; Physical capacity (timed walking tests, endurance tests); Duration of hospitalization; Duration of assisted ventilation</i>
Timing	All	All

Abbreviations: PICO=Populations, Interventions, Comparators, Outcomes, Timing; COPD= Chronic Obstructive Pulmonary Disease; FEV1= Forced Expiratory Volume measured during the first second of forced breath; FVC= Forced Vital Capacity; PEF= Peak Expiratory Flow

Methods

To assess topic nomination #0739 *Treatments for COPD Exacerbation*, for priority for a systematic review or other AHRQ EHC report, we used a hierarchical process using established selection criteria (Appendix A). Assessment of each criteria determined the need for evaluation of the next one.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last five years pertaining to the key questions of the nomination. See Appendix B for sources searched.

Impact of a New Evidence Review

The impact of a new evidence review was assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a literature search in PubMed from October 2012 and October 2017. Due to the large number of articles identified, we reviewed a random sample of 200 titles and abstracts for inclusion and classified identified studies by study design, to assess the size and scope of a potential evidence review. We then calculated the projected total number of included studies based on the proportion of studies included from the random sample. We then applied the Cochrane RCT filter to identify RCTs that were not included in the first sample. See Appendix C for the PubMed search strategy and links to the ClinicalTrials.gov search.

Value

We assessed the nomination for value. We considered whether or not the clinical, consumer, or policymaking context had the potential to respond with evidence-based change; and if a partner organization would use this evidence review to influence practice.

Compilation of Findings

We constructed a table with the selection criteria and our assessments (see Appendix A).

Results

Appropriateness and Importance

This is an appropriate and important topic. The topic represents a significant burden. In 2014, COPD was the third leading cause of death in the United States with over 15 million people diagnosed with the condition. Estimates of mortality due to exacerbation ranges from 4-30%. It affects health care decisions for a large, vulnerable population. In the United States in 2010, the total national medical costs attributable to COPD including exacerbations was estimated to be \$32.1 billion.¹

Desirability of New Review/Duplication

A new evidence review on COPD exacerbations would not be duplicative of an existing product. We identified a guideline with a systematic review that is relevant to both Key Questions 1 and 2.¹³ However, the review did not provide enough detail to be of use to the nominator and the search range ended in November 2015. Our search also found an additional systematic review relevant for Key Question 1 focused solely on bronchodilators.¹⁴ See Table 2 for citations for the relevant reviews.

Impact of a New Evidence Review

A new systematic review on COPD exacerbations may have a high impact due to practice variation among providers due to conflicting data/opinion on a multitude of available treatment strategies.

Feasibility of a New Evidence Review

A new evidence review examining is feasible. We have low confidence that the total size of the relevant literature from October 2012 to the present may be approximately 50 studies across the two key questions. We identified 26 relevant trials on ClinicalTrials.gov and project an additional 60 RCTs after reviewing 10% of titles and abstracts resulting from the use of the Cochrane RCT filter. The scope aligns with a small- to medium-sized systematic review. See Table 2, Feasibility column for the citations of relevant studies.

Table 2. Key questions and relevant evidence reviews and original research

Key Question	Duplication (Completed or In-Process Evidence Reviews)	Feasibility (Published and Ongoing Original Research)
KQ 1: In adult patients who have COPD, what are the benefits and harms of pharmacologic therapies for treatment of exacerbation of symptoms?	Total number of completed and in-progress systematic reviews: 2 <ul style="list-style-type: none">• Cochrane - 1¹⁴• Other - 1¹³	<u>Size/scope of review</u> Relevant Studies Identified: 4 <ul style="list-style-type: none">• RCT – 3¹⁵⁻¹⁷• Retrospective Cohort - 1¹⁸ Projected Total: 20 <u>ClinicalTrials.gov</u> Relevant Trials: 9 <ul style="list-style-type: none">• Recruiting – 3¹⁹⁻²¹• Active, not recruiting – 2^{22, 23}• Completed - 4²⁴⁻²⁷ <u>Cochrane RCT filter</u> Relevant Studies Identified: 5 ²⁸⁻³² Projected Total: 50

Key Question	Duplication (Completed or In-Process Evidence Reviews)	Feasibility (Published and Ongoing Original Research)
KQ 2: In adult patients who have COPD, what are the benefits and harms of non-pharmacologic therapies for treatment of exacerbation of symptoms?	Total number of completed and in-progress systematic reviews: 1 <ul style="list-style-type: none"> Other - 1¹³ 	<u>Size/scope of review</u> Relevant Studies Identified: 6 <ul style="list-style-type: none"> RCT – 5³³⁻³⁷ Retrospective Cohort - 1³⁸ Projected Total: 30 <u>ClinicalTrials.gov</u> Relevant Trials: 17 <ul style="list-style-type: none"> Recruiting – 10³⁹⁻⁴⁸ Active, not recruiting – 1⁴⁹ Completed – 6⁵⁰⁻⁵⁵ <u>Cochrane RCT filter</u> Relevant Studies Identified: 1 ⁵⁶ Projected Total: 10

Abbreviations: KQ=Key Question; RCT=Randomized Controlled Trial; COPD=Chronic Obstructive Pulmonary Disease

Value

The potential for value is high given that this topic will inform clinical decision-making on treating patients suffering from COPD exacerbations across community and clinical settings. AAFP will use a new systematic review to formulate a new guideline.

Summary of Findings

- This nomination meets all selection criteria.
- The scope was narrowed because of an in-process review for a clinical practice guideline by another group.
- Appropriateness and importance: The nomination is both appropriate and important.
- Duplication: We identified two relevant systematic reviews but one did not include sufficient detail and was not sufficiently up to date; the other did not cover the entire scope of the nomination.
- Feasibility: A new review is feasible. The projected evidence base is likely small to medium.
- Impact: A new systematic review would have high impact.
- Value: The potential for value is high.

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51. Effectiveness and Feasibility of Delivering an Education Program to Patients With an Acute Exacerbation of COPD; <https://clinicaltrials.gov/show/NCT02321215>.
52. Respiratory Rehabilitation Exercises in Older Adults With Acute Exacerbations of Chronic Obstructive Pulmonary Disease; <https://clinicaltrials.gov/show/NCT02329873>.
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Appendix A. Selection Criteria Summary

Selection Criteria	Supporting Data
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes, this topic represents a health care drug and intervention available in the U.S.
1b. Is the nomination a request for a systematic review?	Yes, this topic is a request for a systematic review.
1c. Is the focus on effectiveness or comparative effectiveness?	The focus of this review is on both effectiveness and comparative effectiveness.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes, it is biologically plausible. Yes, it is consistent with what is known about the topic.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes, this topic represents a significant burden. In 2014, COPD was the third leading cause of death in the United States with over 15 million people diagnosed with the condition. Estimates of mortality due to exacerbation ranges from 4-30%.
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, this topic affects health care decisions for a large, vulnerable population.
2c. Represents important uncertainty for decision makers	Yes, this topic represents important uncertainty for decision makers.
2d. Incorporates issues around both clinical benefits and potential clinical	Yes, this nomination addresses both benefits and potential harms of prevention interventions, pharmacological interventions, and non-pharmacological treatments for COPD exacerbation.
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes. In the United States in 2010, the total national medical costs attributable to COPD including exacerbations was estimated to be \$32.1 billion.
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	We identified a guideline with a systematic review that is relevant to both Key Questions 1 and 2. ¹³ However, the review did not provide enough details to be of use to the nominator and the search range ended in November 2015. Our search also found an additional systematic review relevant for Key Question 1 focused solely on bronchodilators. ¹⁴
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes, the standard of care is unclear due to a multitude of available treatment strategies. Recommendations among authors and experts differ.

Selection Criteria	Supporting Data
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes, there is practice variation due to conflicting data/opinion and existing recommendations.
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	<i>Size/scope of review:</i> We estimate that the total size of the relevant literature (October 2012 – present) may be approximately 50 studies across key questions (low confidence). Scope of the review is likely medium. <i>ClinicalTrials.gov:</i> We identified 26 relevant trials on ClinicalTrials.gov. <i>Cochrane RCT filter results:</i> We project an additional 60 RCTs potentially covering interventions for COPD exacerbation after reviewing 10% of titles and abstracts.
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	Yes, this topic will inform clinical decision-making on treating patients suffering from COPD exacerbations across community and clinical settings.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes, AAFP will use a systematic review to formulate a new guideline. It is an area of interest to other clinicians.

Abbreviations: COPD=Chronic Obstructive Pulmonary Disease; AAFP=American Academy of Family Physicians; AHRQ=Agency for Healthcare and Research Quality; RCT=Randomized Controlled Trial;

Appendix B. Search for Evidence Reviews (Duplication)

Listed are the sources searched.

Source
Search date: October 1, 2012 to October 1, 2017
AHRQ: Evidence reports and technology assessments, USPSTF recommendations
VA Products: PBM, and HSR&D (ESP) publications, and VA/DoD EBCPG Program
Cochrane Systematic Reviews and Protocols http://www.cochranelibrary.com/
PubMed Health http://www.ncbi.nlm.nih.gov/pubmedhealth/
HTA (CRD database): Health Technology Assessments http://www.crd.york.ac.uk/crdweb/
PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/
CADTH (Canadian Agency for Drugs and Technologies in Health) https://www.cadth.ca/
DoPHER (Database of promoting health effectiveness reviews) http://eppi.ioe.ac.uk/webdatabases4/Intro.aspx?ID=9
Secondary Sources checked on an as needed basis
Campbell Collaboration http://www.campbellcollaboration.org/
McMaster Health System Evidence https://www.healthsystemevidence.org/
Robert Wood Johnson http://www.rwjf.org/
Systematic Reviews (Journal) : protocols and reviews http://systematicreviewsjournal.biomedcentral.com/
UBC Centre for Health Services and Policy Research http://chspr.ubc.ca/
WHO Health Evidence Network http://www.euro.who.int/en/data-and-evidence/evidence-informed-policy-making/health-evidence-network-hen
CINAHL (EBSCO)

Appendix C. Search Strategy & Results (Feasibility)

Topic: Treatments for Chronic Obstructive Pulmonary Disease Exacerbation Date: October 13, 2017 Database Searched: PubMed	
Concept	Search String
Chronic Obstructive Pulmonary Disease	((COPD[MeSH Terms] OR COPD[Title]) OR "Chronic Obstructive Pulmonary Disease"[Title])
AND	
Treatment	((Therapeutics[Mesh] OR treatment[Title/Abstract]) OR therapeutic[Title/Abstract]) OR intervention[Title/Abstract])
AND	
Exacerbation	exacerbation[Title/Abstract]
NOT	
Not Editorials, etc.	(((((("Letter"[Publication Type]) OR "News"[Publication Type]) OR "Patient Education Handout"[Publication Type]) OR "Comment"[Publication Type]) OR "Editorial"[Publication Type])) OR "Newspaper Article"[Publication Type]
Limit to last 5 years, Human, English	Filters activated: published in the last 5 years, Humans, English.
N=984	
Systematic Review N=86	PubMed subsection "Systematic [sb]"
Randomized Controlled Trials N=603	Cochrane Sensitive Search Strategy for RCT's "(((((((groups[tiab]) OR (trial[tiab])) OR (randomly[tiab])) OR (drug therapy[sh])) OR (placebo[tiab])) OR (randomized[tiab])) OR (controlled clinical trial[pt])) OR (randomized controlled trial[pt]))"
Other N=295	

Clinicaltrials.gov Searched on October 13, 2017

Recruiting

72 studies found for: COPD Exacerbation | studies received on or after 10/01/2012

https://clinicaltrials.gov/ct2/results?cond=COPD+Exacerbation&sfpd_s=10%2F01%2F2012&Search=Apply&recrs=a&age_v=&gndr=&type=&rslt=

Active, not recruiting

12 studies found for: COPD Exacerbation | studies received on or after 10/01/2012

https://clinicaltrials.gov/ct2/results?cond=COPD+Exacerbation&sfpd_s=10%2F01%2F2012&Search=Apply&recrs=d&age_v=&gndr=&type=&rslt=

Completed

47 studies found for: COPD Exacerbation | studies received on or after 10/01/2012

https://clinicaltrials.gov/ct2/results?cond=COPD+Exacerbation&sfpd_s=10%2F01%2F2012&Search=Apply&recrs=e&age_v=&gndr=&type=&rslt=