Topic Brief: Prescribing and Treatment in Chronic Obstructive Pulmonary Disease (COPD)

Date: 08/28/2019
Nomination Number: 0863

Purpose: This document summarizes the information addressing a nomination submitted on 6/07/2019 through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

Issue: Chronic obstructive pulmonary disease (COPD) is a common and preventable condition which carries a significant social and economic burden. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) program is considered the standard of care for management of COPD[1], however adherence to the guideline recommendations among practitioners remains suboptimal. Furthermore, little is known regarding the relative benefits and harms associated with the GOLD guideline concordant care compared to non-guideline concordant management of COPD.

Program Decision:

Though the scope of this topic met all EHC Program selection criteria and was considered for a systematic review or a rapid review. However, it was not selected.

Key Findings

We found no systematic reviews addressing this nomination. We identified nine primary studies[2-10] assessing adherence to the GOLD guideline recommendations by the U.S. primary care providers. Each study examined the levels of adherence to the GOLD recommended pharmacotherapies by class and type of inhalers and assessed relative benefits and harms associated with the GOLD guideline concordant treatment of COPD compared to non-GOLD guideline concordant treatment. The evidence base might be larger because our estimate was based on a narrowly targeted search. Also, some non-US based studies which were not included in our search may also be contributory.

Background

COPD is a group of debilitating respiratory conditions including emphysema, chronic bronchitis and chronic obstructive asthma. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2019 Report defines COPD as a common, preventable and treatable disease characterized by progressive irreversible airflow limitation secondary to chronic lung inflammation related to tobacco use and other toxic exposures.[1] COPD manifests as dyspnea,

chronic cough and periodic exacerbations[11-13], is most prevalent among elderly populations and is frequently complicated by one or more comorbid conditions.[14]

COPD is the third leading cause of death worldwide, impacting close to 380 million people, nearly 10% of the world's population[15]. It is the fourth leading cause of death in the United States, impacting an estimated 15.7 million or approximately 6.4% of Americans[16, 17]. COPD is a costly disease responsible for significant total economic expenditures and healthcare utilization costs. In 2010 alone the total economic costs of COPD in the U.S. were estimated to be $49.9 billion, including 29.5 billion of direct medical care costs.[18]

Despite its high morbidity and mortality, COPD is treatable. Several national and international evidence-based guidelines have been developed to guide the diagnosis and management of COPD, including the 2019 Global Strategy for the Diagnosis, Management and Prevention of COPD by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) program[1], the 2011 joint Clinical Practice Guideline for Diagnosis and Management of Stable COPD by the American College of Physicians, American College of Chest Physicians, American Thoracic Society and European Respiratory Society[19] and the 2014 VA/DoD Clinical Practice Guideline for Management of COPD[20], among others. The most widely used GOLD guideline provides comprehensive evidence-based guidance for diagnosis, treatment and prevention of COPD. It categorizes COPD patients into ABCD groups based on symptom burden and exacerbation risk to guide treatment recommendations standardized based on the group[1].

However, studies assessing adherence to the GOLD guideline in clinical practice demonstrate suboptimal compliance with the guideline recommendations both within the U.S. and in other countries. One recent retrospective review of COPD management practices among the U.S. primary care providers showed that few patients received recommended diagnostic testing, 31% were misdiagnosed as having COPD and only 42% were prescribed pharmacotherapies recommended by the guideline[2]. A number of studies showed that low adherence to the guideline recommendations leads to both under and overtreatment of COPD symptoms. Simeone at al found that as many as 60% of patients were inappropriately prescribed inhaled corticosteroids, a practice that can lead to negative long-term patient outcomes[4].

Presently little is known regarding how suboptimal adherence to the GOLD guideline recommendations impacts patient outcomes. Gaining a better understanding of the relative benefits and harms of the GOLD guideline concordant treatment compared to the guideline discordant treatment is one of the aims of this nomination. Overall, the goal of this nomination is three-fold: 1) to understand the level of adherence to the GOLD guideline recommendations for management of stable COPD in the U.S., 2) to assess comparative benefits and harms associated with the GOLD guideline concordant vs guideline discordant treatment of COPD and 3) to identify any non-GOLD guideline concordant COPD management practices that may be associated with improved patient outcomes.

Nomination Summary

The original nomination focused on assessing the overall adherence to the GOLD guideline recommendations by health care providers in the U.S. Through discussions with the nominator, we narrowed the scope to adherence to the GOLD guideline recommendations for pharmacologic treatment of stable COPD by U.S. primary care providers and pulmonologists in the outpatient setting.

The Boehringer Ingelheim Group is planning to utilize the findings from this potential systematic review or rapid review to inform the COPD clinician and research community regarding the impact of GOLD guideline adherence on patient outcomes and to impact practice change through educational outreach using its existing collaboration with the National Heart, Lung and Blood Institute (NHLBI) through the COPD National Action Plan.

Scope

1) For adults with COPD (GOLD Groups ABCD) what are the relative benefits and harms associated with GOLD guideline concordant pharmacologic treatment of stable COPD compared to guideline discordant treatment?

Table 1. Questions and PICOTS (population, intervention comparator, outcome, timing and setting)

Questions	The relative benefits and harms associated with GOLD guideline concordant pharmacologic treatment for stable COPD
Population	American adults with COPD, GOLD Groups ABCD
Interventions	GOLD guideline concordant pharmacotherapy for stable COPD, categorized by inhaler class and type
Comparators	GOLD guideline discordant pharmacologic treatment of stable COPD
Outcomes	Adherence to GOLD guideline concordant care Clinical outcomes: • Moderate[1] COPD exacerbations/year • Severe[2] COPD exacerbation/year • All COPD related hospitalizations/year • Mortality Quality of life related outcomes: • COPD – Related Quality of Life • TDI (Transition Dyspnea Index) • St. George's Respiratory Questionnaire[3] (SGRQ) Physiological outcomes: • Change from baseline FEV1 after 3+ months of treatment Total healthcare utilization costs: • Outpatient visits • ED visits • Inpatient hospitalizations Medication costs

[1] Moderate COPD exacerbation – worsening respiratory status requiring treatment with systemic glucocorticoids, antibiotics or both.

[2] Severe COPD exacerbation – worsening respiratory status requiring inpatient hospitalization.

[3] St. George's Respiratory Questionnaire – COPD specific instrument measuring impact of COPD on overall health, daily life and perceived well-being.

Timing	3+ months of outpatient COPD treatment
Setting	Outpatient primary care and subspecialty pulmonology clinics

Abbreviations: COPD=chronic obstructive pulmonary disease; ED=emergency department; FEV1=forced expiratory volume in one second; GOLD=Global Initiative for Chronic Obstructive Lung Disease; TDI=transition dyspnea index;

Assessment Methods

See Appendix A.

Summary of Literature Findings

We found no systematic reviews addressing the subject of this nomination. We found a total of nine primary studies[2-10] assessing adherence to the GOLD guideline recommendations for management of stable COPD among the U.S. primary care providers and pulmonologists.

Ten studies were retrospective health record reviews and medical and pharmacy claims data analyses and one study (Mannino et al) was a secondary analysis of the TICARI (Tiotropium in COPD Patients with Acute Respiratory Infection) trial. The studies included between 101 and 33,558 individual patient records, included predominantly elderly individuals (mean 63.1 – 70 years of age) and approximately equal distribution of males and females, except Rhine et al which was a retrospective review of medical and pharmacy records of 130 of Veterans Administration (VA) hospitals and had a 96.6% male population.

Each of the studies categorized patient data by COPD severity using the GOLD guideline recommended classification by ABCD Groups and the majority of the studies also distinguished whether the COPD diagnoses were based on spirometric testing (in accordance with the guideline recommendations) or made clinically. Each of the studies assessed the treatment patterns by COPD Group and class and type of prescribed inhalers and to what extent prescribed pharmacotherapies adhered to the GOLD guideline recommendations.

In addition to the GOLD guideline concordance, a subset of studies also looked at appropriate use of pharmacotherapies, such as inhaled corticosteroids and triple therapy. Other outcomes included frequency of COPD exacerbations and annual healthcare and pharmacy costs stratified by COPD ABCD Group.

See Appendix B for detailed assessments of all EPC selection criteria.

Summary of Selection Criteria Assessment

This topic addresses an important issue that might affect outcomes for people treated for COPD. The literature base is small; we found no systematic reviews and nine primary studies addressing adherence with the GOLD guideline. As a part of the COPD National Action Plan sponsored by NHLBI, a new systematic review could be used by the nominator to inform educational activities aimed at providers about the impact of GOLD guideline-concordant care on patient outcomes.

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.

Related Resources

We identified seventeen additional primary studies[21-37] which evaluated adherence to the GOLD guideline by health care providers in countries outside the U.S. While these studies did not meet

our feasibility search criteria having been conducted outside the U.S., they may nevertheless be a valuable resource to the nominator. Some of the findings from these studies, such as the impact of the GOLD guideline concordant care on outcomes for patients with COPD would likely be informative for the potential evidence review.

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Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

Desirability of New Review/Absence of Duplication

We searched for high-quality, completed or in-process evidence reviews published in the last three years 8/16/2016 – 8/16/2019 on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
    - AHRQ Evidence Reports https://www.ahrq.gov/research/findings/evidence-based-reports/index.html
    - EHC Program https://effectivehealthcare.ahrq.gov/
    - US Preventive Services Task Force https://www.uspreventiveservicestaskforce.org/
    - AHRQ Technology Assessment Program https://www.ahrq.gov/research/findings/ta/index.html
- US Department of Veterans Affairs Products publications
    - Evidence Synthesis Program https://www.hsrd.research.va.gov/publications/esp/
    - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program https://www.healthquality.va.gov/
- Cochrane Systematic Reviews https://www.cochranelibrary.com/
- PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/
- PubMed https://www.ncbi.nlm.nih.gov/pubmed/
- Epistemonikos
- Health System Evidence
- PDQ Evidence
- EvidenceNOW
- PCORI

Impact of a New Evidence Review

The impact of a new evidence review was qualitatively 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 various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review

We conducted a limited literature search in PubMed for the last five years from September 11, 2014 through September 11, 2019.We identified and reviewed a total of 318 abstracts. It should be noted that we conducted two searches. The original literature search was too narrow and yielded no relevant findings. We then broadened our search strategy and the repeat search identified nine primary studies which addressed the nominator's question.

Search strategy
Question: What are the relative benefits and harms associated with GOLD guideline concordant treatment for stable COPD?

#	**Searches**
1	pulmonary disease, chronic obstructive/ or bronchitis, chronic/ or pulmonary emphysema/
2	(chronic obstructive pulmonary disease or COPD or chronic airflow obstruction or COAD or chronic obstructive lung).ti,ab,kf.
3	or/1-2
4	("Global Initiative for Chronic Obstructive Lung Disease" or (GOLD adj2 guideline*)).ti,ab,kf.
5	Guideline Adherence/
6	(guideline* adj5 (adher* or nonadher* or complian* or noncomplian* or implement* or uptake)).ti,ab,kf.
7	or/4-6
8	and/3,7
9	limit 8 to observational study
10	retrospective studies/ or "chart review".ti,ab,kf.
11	or/9-10
12	8 and 11
13	limit 12 to yr="2014 -Current"

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.

Appendix B. Selection Criteria Assessment

Selection Criteria	Assessment
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
1b. Is the nomination a request for an evidence report?	Yes
1c. Is the focus on effectiveness or comparative effectiveness?	Yes
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
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	COPD is the third leading cause of death worldwide, affecting approximately 380 million people, nearly 10% of the world's population. COPD is the fourth leading cause of death and the second most common cause of disability in the United States, affecting an estimated 16.7 million (6.4%) of Americans.
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	Improving management of COPD and optimizing functional status of individuals affected by this condition is important for improving patient care outcomes and may result in reduction of the significant economic costs attributable to COPD. The GOLD guideline for management of COPD is considered the standard of care, however adherence to the guideline recommendations by clinicians remains variable [7, 8, 38]. As of current, there had been no evidence-based review to assess the correlation between adherence to the GOLD recommendations and outcomes for patients with COPD.
2c. Incorporates issues around both clinical benefits and potential clinical harms	Yes
2d. 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. COPD carries significant economic and social burden. Costs attributable to COPD and its sequela are substantial and are projected to increase in the future. In 2010, total national medical costs attributable to COPD and its sequela were estimated at $32.1 billion and total absenteeism costs for $3.9 billion, for total burden of COPD attributable costs of $36.9 billion. An estimated 16.4 million days of work were lost because of COPD. National medical costs are projected to increase from $32.1 billion in 2010 $249.0 billion in 2020.[18]
3. Desirability of a New Evidence Review/Absence of Duplication	
3. A recent high-quality systematic review or other evidence review is not available on this topic	Yes, a new evidence review would not be redundant. We did not identify any relevant high-quality systematic reviews.
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, clinical practice guidelines to optimize pharmacotherapy for patients with COPD are updated regularly however the adherence to these guidelines in real world clinical practice remains low. Few studies to date assessed the patient outcome related benefits and harms associated with the GOLD-guideline concordant COPD treatment compared to the non-GOLD guideline concordant treatment.
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, the limited available evidence shows that the GOLD guideline recommendations are not being consistently followed. However, the consequences of suboptimal adherence to the guideline for patient outcomes remain largely unknown.
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)	While the literature base is small it could be feasible for a small systematic review or a rapid review. We used a targeted search, and it is likely the evidence base is larger. In addition, non-US studies were excluded. We identified a total of nine primary studies[2-10] that assessed to what extent the real-world COPD management practices by the U.S. primary care providers and pulmonologists adhere to the GOLD guideline recommendations. Eight studies were retrospective health record reviews and medical and pharmacy claims data analyses and one study (Mannino et al) was a secondary analysis of the TICARI (Tiotropium in COPD Patients with Acute Respiratory Infection) trial. The studies included between 101 and 33,558 individual patient records, included predominantly elderly individuals (mean 63.1 – 70 years of age) and approximately equal distribution of males and females, except Rhine et al which was a retrospective review of medical and pharmacy records of 130 of Veterans Administration (VA) hospitals and had a 96.6% male population. Each of the studies categorized patient data by COPD severity using the GOLD guideline recommended classification by ABCD Groups and the majority of the studies also distinguished whether the COPD diagnoses were based on spirometric testing (in accordance with the guideline recommendations) or made clinically. Each of the studies assessed the treatment patterns by COPD Group and class and type of prescribed inhalers and to what extent prescribed pharmacotherapies adhered to the GOLD guideline recommendations. The studies found that on average only half of COPD patients received guideline concordant management for stable COPD regardless the level of severity. Suboptimal adherence to the guideline recommendations was seen not only among primary care providers but also among

	pulmonologists (Wallace et al). Non-GOLD guideline concordant treatment included both under-treatment and over-treatment. For example, Simeone et al found that only 29.3% of all patients diagnosed with COPD were receiving any maintenance medications, 25.5% of these patients were receiving triple therapy and a substantial percentage of patients receiving triple therapy (consisting of long-acting beta two agonists (LABA), muscarinic receptor antagonists (LAMA) and inhaled corticosteroids (ICS)) were patients with GOLD Grades 1 and 2, suggesting inappropriate inhaled corticosteroid prescribing. Other outcomes assessed in the identified studies included frequency of COPD exacerbations and whether it corresponded with non-GOLD guideline adherent treatment and annual healthcare and pharmacy costs stratified by GOLD guideline-based classification of COPD severity into ABCD Groups.
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	Yes, there is a Federally-funded effort to promote practice change in the treatment of COPD. NHLBI launched the COPD National Action Plan in 2017. This was developed at the request of Congress and provides a framework for action on the part of researchers, Federal partners, providers, advocacy groups, and patients[39].
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	The nominator, Boehringer Ingelheim sees this systematic review and/or rapid review by AHRQ as an important and unbiased evidence-based resource to inform the broader COPD community. Specifically, the nominator plans to utilize its field-based clinical teams to disseminate the findings of this potential review among the COPD stakeholder community. Additionally, the nominator has established connections with the National Heart, Lung and Blood Institute (NHLBI) with which the nominator has been collaborating around implementation of the COPD National Action Plan focused on clinician education.

Abbreviations: AHRQ=Agency for Healthcare Research and Quality; COPD=chronic obstructive pulmonary disease; GOLD guideline = The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2019 Report; NHLBI=National Heart, Lung, and Blood Institute