



VA/DoD CLINICAL PRACTICE GUIDELINE FOR THE MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

**Department of Veterans Affairs
Department of Defense**

QUALIFYING STATEMENTS

The Department of Veterans Affairs and the Department of Defense guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

This Clinical Practice Guideline is based on a systematic review of both clinical and epidemiological evidence. Developed by a panel of multidisciplinary experts, it provides a clear explanation of the logical relationships between various care options and health outcomes while rating both the quality of the evidence and the strength of the recommendation.

Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

These guidelines are not intended to represent Department of Veterans Affairs or TRICARE policy. Further, inclusion of recommendations for specific testing and/or therapeutic interventions within these guidelines does not guarantee coverage of civilian sector care. Additional information on current TRICARE benefits may be found at www.tricare.mil by contacting your regional TRICARE Managed Care Support Contractor.

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With support from:

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&

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I. Introduction

The Department of Veterans Affairs (VA) and Department of Defense (DoD) Evidence-Based Practice Work Group (EBPWG) was established and first chartered in 2004, with a mission to advise the Health Executive Committee "... on the use of clinical and epidemiological evidence to improve the health of the population ..." across the Veterans Health Administration (VHA) and Military Health System (MHS), by facilitating the development of clinical practice guidelines (CPGs) for the VA and DoD populations.⁽¹⁾ Development and update of VA/DoD CPGs is funded by VA Evidence Based Practice, Office of Quality and Patient Safety. The system-wide goal of evidence-based CPGs is to improve patient health and well-being.

In December 2014, the VA and DoD published a CPG for the Management of Chronic Obstructive Pulmonary Disease (2014 VA/DoD COPD CPG), which was based on evidence reviewed through February 2014. Since the release of that CPG, a growing body of research has expanded the evidence base and understanding of COPD. Consequently, a recommendation to update the 2014 VA/DoD COPD CPG was initiated in 2019.

This CPG provides an evidence-based framework for evaluating and managing care for patients with COPD toward improving clinical outcomes. Successful implementation of this CPG will:

- Assess the patient's condition and collaborate with the patient, family, and caregivers to determine optimal management of patient care
- Emphasize the use of patient-centered care using individual risk factors and event history
- Minimize preventable complications and morbidity
- Optimize individual health outcomes and quality of life (QoL)

II. Background

A. Description of COPD

COPD comprises a combination of chronic and slowly progressive respiratory disorders including emphysema, small airway disease, and chronic bronchitis. Clinically, COPD can be described as persistent respiratory symptoms with significant airflow limitation, as measured by reduced maximal expiratory flow during forced exhalation.⁽²⁾ A key characteristic of COPD is the incomplete reversibility of airway obstruction, which may differ from other conditions such as asthma, in which airway obstruction is commonly reversible with bronchodilators.⁽²⁾

B. Pathology

While COPD is primarily a respiratory condition, it is associated with systemic inflammation.^(3, 4) COPD results from an inflammatory process in the distal airways possibly linked to oxidative stress.⁽²⁾ Pathologic changes occur in the large and small airways and in the terminal respiratory unit. These distal airways narrow in response to the inflammation and scarring. There are a number of additional pathophysiological changes as well, including hyperinflation and impaired gas exchanges.⁽²⁾

C. Etiology

In most cases, COPD results from prolonged exposure to lung irritants. In the United States (U.S.), exposure to cigarette smoke is the key causal factor in the development of COPD.(5, 6) Smoking has been causally linked to COPD; more than 80% of cases of COPD in the U.S. may have developed as a result of smoking.(6) Smoking is also a risk factor for COPD complications, such as pneumonia.(6) Smoking cessation results in a significant slowing of the rate of decline in lung function, but typically no substantial reversal of the established damage.(2)

Smoking is more common among military personnel than among civilians, especially in those who are younger and enlisted.(6) The VA spends billions of dollars a year to treat patients with COPD; a majority of these cases are associated with smoking.(6) Other causes of COPD include particulates and noxious inhaled substances.

Other risk factors for COPD include household, environmental and occupational air pollution, secondhand smoke, history of childhood respiratory infections, and genetic predisposition.(2) More unusual risk factors of COPD include alpha-1 antitrypsin (AAT) deficiency and other rare genetic conditions.(2)

D. Epidemiology and Impact of COPD

COPD has a considerable public health impact on the general population of the U.S. and on the health of Veterans and Service Members in particular. It is the third leading cause of death globally.(7) Global prevalence of moderate to severe COPD has been estimated to be as high as 10% of the population.(8)

As of May 2020, there were more than 16.4 million adults in the U.S. diagnosed with COPD.(9-11) In addition, COPD is thought to be frequently under-recognized and under-diagnosed. Therefore, the number of Americans with COPD may be even higher.(9) Since the 1960s, mortality rates due to COPD have climbed. Recently, there has been a shift in the population affected by COPD, and the mortality rate in women has surpassed that of men. Women have smaller lungs, and estrogen may play a role in worsening lung disease, making women more vulnerable than men to lung damage from cigarette smoke and other pollutants.(12) The condition does not affect all ethnicities equally; non-Hispanic, white males are affected more than other ethnic groups.(9) Due to the chronic and progressive nature of the condition and the long duration of exposure to tobacco smoke, the prevalence of COPD increases with age.

The condition also has important healthcare resource implications. The U.S. spent approximately \$49.9 billion on COPD, predominantly on direct healthcare expenditures.(13) In 2010, for adults over the age of 25, there were an estimated 699,000 hospitalizations for which COPD was the first diagnosis. However, there was a decline in the overall age-adjusted prevalence of those who have had COPD diagnoses, perhaps related to the overall population decrease in smoking.(11)

Veterans are at higher risk of COPD than those in the general U.S. population. According to Anderson et al. (2020), COPD affects 12.7 million individuals in the U.S., including nearly 1.25 million U.S. Veterans which is about 25% of the Veteran population.(14) Within the VA population, patients with COPD have significantly higher all-cause and respiratory-related healthcare utilization than patients without COPD.(15) Because some of their activities may pose a risk of environmental and occupational exposure, patients in the military are under particular scrutiny from their healthcare providers to look for COPD. Additionally, the physical activity associated with military life may uncover symptoms of COPD earlier among people in the

military. Patients in the military or Veterans may therefore show signs of COPD earlier in their lives than their civilian counterparts.⁽¹⁶⁾

E. Progress in Management of COPD

As previously mentioned, despite the high number of people in the U.S. that have been diagnosed with COPD, the age-adjusted prevalence has declined since 1999, possibly due to overall population decrease in smoking rates.⁽¹¹⁾ Furthermore, there has been an increase in the understanding of the disease and effective management methods. COPD is now recognized as a significant public health problem, and a greater amount of research is being conducted on the underlying mechanisms and effectiveness of various treatment methods.⁽¹⁷⁾

Pharmacologic therapy is improving with better understanding of the disease process and novel drugs. Additionally, non-pharmacologic therapy, such as pulmonary rehabilitation, is becoming increasingly recognized as an effective option.⁽¹⁷⁾ While these treatment methods may not be appropriate for all patients, they allow providers to intervene early with numerous effective treatment options. The increasing amount of COPD research leading to further understanding of the disease and effective management strategies allows patients and providers alike to be optimistic that they can manage COPD effectively to provide patients with an improved QoL.

III. Scope of this Guideline

This CPG is based on published clinical evidence and related information available through February 2020. It is intended to provide general guidance on best evidence-based practices (see [Appendix A](#) for additional information on the evidence review methodology). This CPG is not intended to serve as a standard of care.

A. Guideline Audience

This CPG is intended for use by VA and DoD primary care providers (PCPs) including physicians, nurse practitioners, physician assistants, nurses, dietitians, pharmacists, social workers, and others involved in the healthcare team caring for patients with COPD. Additionally, this CPG is intended for community-based clinicians involved in the care of Service Members, beneficiaries, or Veterans with COPD.

B. Guideline Population

The patient population of interest for this CPG is patients with COPD who are eligible for outpatient care in the VA or DoD healthcare delivery systems and those who receive outpatient care from community-based clinicians. The population includes Veterans as well as deployed and non-deployed active duty Service Members and their dependents. Regardless of care setting, any patient in the VA and DoD healthcare system should have access to this CPG's recommended interventions.

IV. Highlighted Features of this Guideline

A. Highlights in this Guideline Update

The pace of clinical research on COPD continues to grow every year with more than 30,000 publications since the release of the last guideline update in 2014.⁽¹⁸⁾ This research includes new practice-changing insights into the pathophysiology, phenotypes, progression, diagnosis, and treatment that were incorporated into these guidelines. In particular, the Work Group would like to highlight recommendations

advocating for increasing support to patients through self-management programs and telehealth, as well as changes in the recommendations for medication management that reflect increasing understanding of the various phenotypes of the disease. This research also continues to strengthen evidence for recommendations that have not changed, such as the importance of smoking cessation. Finally, the CPG highlights the areas for which more research is needed, including key aspects of care such as the use of antibiotics during COPD exacerbations.

The methodology used in developing this CPG has also been updated since the prior versions and reflects stricter standards than previous versions, which are detailed in [Appendix A](#). The result is a refined CPG that includes the most evidence-based aspects in COPD care. In order to accomplish this, the scope of the CPG has been narrowed to focus on outpatient care in the primary care setting; it does not address the specialty care of advanced COPD or the inpatient care of COPD exacerbations.

The 2021 VA/DoD COPD CPG used stricter methodology than previous iterations. For additional information on GRADE or CPG methodology, see [Appendix A](#).

B. Components of the Guideline

The 2021 VA/DoD COPD CPG is the third update to this CPG. It provides clinical practice recommendations for the care of patients with COPD (see [Recommendations](#)). In addition, the [Algorithm](#) incorporates the recommendations in the context of the flow of patient care. This CPG also includes [Research Priorities](#), which identify areas needing additional research.

To accompany this CPG, the Work Group also developed toolkit materials for providers and patients, including a provider summary, patient summary, and pocket card. These can be found at <https://www.healthquality.va.gov/index.asp>.

V. Guideline Development Team

The VA Evidence Based Practice, Office of Quality and Patient Safety, in collaboration with the Office of Evidence Based Practice, U.S. Army Medical Command, identified the following four clinicians to serve as Champions (i.e., leaders) of this CPG's Work Group: Drs. Amir Sharafkhaneh, MD, PhD and William C. (Claibe) Yarbrough, MD, MS from the VA and MAJ Nathan L. Boyer, MD, FCCS and LTC Brian M. Cohee, MD, FACP from the DoD. The Work Group comprised individuals with the following areas of expertise: pulmonology, critical care, sleep medicine, primary care medicine, emergency medicine, physical therapy, respiratory therapy, pharmacology, family medicine, internal medicine, social work, and nutrition. See [Table 1](#) for a list of Work Group members.

This CPG Work Group, led by the Champions, was tasked with:

- Determining the scope of the CPG
- Crafting clinically relevant key questions (KQs) to guide the systematic evidence review
- Identifying discussion topics for the patient focus group and considering the patient perspective
- Providing direction on inclusion and exclusion criteria for the systematic evidence review and the assessment of the level and quality of evidence
- Developing evidence-based clinical practice recommendations, including determining the strength and category of each recommendation

The Lewin Team, including The Lewin Group, ECRI, Sigma Health Consulting, Duty First Consulting, and Anjali Jain Research & Consulting, was contracted by the VA to help develop this CPG.

Table 1. Guideline Work Group and Guideline Development Team

Organization	Names*
Department of Veterans Affairs	Amir Sharafkhaneh, MD, PhD (Champion)
	William C. Yarbrough, MD, MS (Champion)
	Andrew Buelt, DO
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	Catherine Staropoli, MD
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Department of Defense	MAJ Nathan L. Boyer, MD, FCCS (Champion)
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	Mary Kate Curley, BA

*Additional contributor contact information is available in [Appendix H](#).

VI. Summary of Guideline Development Methodology

The methodology used in developing this CPG follows the *Guideline for Guidelines*, an internal document of the VA and DoD EBPWG updated in January 2019 that outlines procedures for developing and submitting VA/DoD CPGs.(19) The *Guideline for Guidelines* is available at <http://www.healthquality.va.gov/policy/index.asp>. This CPG also aligns with the National Academy of Medicine's (NAM) principles of trustworthy CPGs (e.g., explanation of evidence quality and strength, the management of potential conflicts of interest [COI], interdisciplinary stakeholder involvement, use of systematic review, and external review).(20) [Appendix A](#) provides a detailed description of the CPG development methodology.

A. Evidence Quality and Recommendation Strength

The Work Group used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to craft each recommendation and determine its strength. Per the GRADE approach, recommendations must be evidence-based and cannot be made based on expert opinion alone. The GRADE approach uses the following four domains to inform the strength of each recommendation (see [Grading Recommendations](#)):(21)

- Confidence in the quality of the evidence
- Balance of desirable and undesirable outcomes
- Patient values and preferences
- Other considerations, as appropriate, e.g.:
 - ◆ Resource use
 - ◆ Equity
 - ◆ Acceptability
 - ◆ Feasibility
 - ◆ Subgroup considerations

Using these four domains, the Work Group determined the relative strength of each recommendation (*Strong* or *Weak*). The strength of a recommendation is defined as the extent to which one can be confident that the desirable effects of an intervention outweigh its undesirable effects and is based on the framework above, which incorporates the four domains.(22) A *Strong* recommendation generally indicates *High* or *Moderate* confidence in the quality of the available evidence, a clear difference in magnitude between the benefits and harms of an intervention, similar patient values and preferences, and understood influence of other implications (e.g., resource use, feasibility).

Based on the GRADE approach, if the Work Group believes all, or almost all, informed people would recommend for or against an intervention, they develop a *Strong* recommendation.(22) If, after assessing these domains, the Work Group believes that most informed people would recommend the intervention, but a substantial number would not, it generally assigns a *Weak* designation to the recommendation.(22) Nevertheless, a *Weak* recommendation is clinically important and evidence-based.

In some instances, there is insufficient evidence on which to base a recommendation for or against a particular therapy, preventive measure, or other intervention. For example, the systematic evidence review may have found little or no relevant evidence, inconclusive evidence, or conflicting evidence for the intervention. The manner in which this is expressed in the CPG may vary. In such instances, the Work Group may include among its set of recommendations an insufficient evidence statement for an intervention that may be in common practice even though it is not supported by clinical evidence, and particularly if there may be other risks of continuing to use it (e.g., high opportunity cost, misallocation of resources). In other cases, the Work Group may decide to not include this type of statement about an intervention. For example, the Work Group may remain silent where there is an absence of evidence for a rarely used intervention. In other cases, an intervention may have a favorable balance of benefits and harms but may be a standard of care for which no recent evidence has been generated.

Using these elements, the Work Group determines the strength and direction of each recommendation and formulates the recommendation with the general corresponding text (see [Table 2](#)).

Table 2. Strength and Direction of Recommendations and General Corresponding Text

Recommendation Strength and Direction	General Corresponding Text
Strong for	We recommend ...
Weak for	We suggest ...
Neither for nor against	There is insufficient evidence to recommend for or against ...
Weak against	We suggest against ...
Strong against	We recommend against ...

It is important to note that a recommendation's strength (i.e., *Strong* versus *Weak*) is distinct from its clinical importance (e.g., a *Weak* recommendation is evidence-based and still important to clinical care). The strength of each recommendation is shown in the [Recommendations](#) section.

This CPG's use of GRADE reflects a more rigorous application of the methodology than previous iterations. For instance, the determination of the strength of the recommendation is more directly linked to the confidence in the quality of the evidence on outcomes that are critical to clinical decision-making. The confidence in the quality of the evidence is assessed using an objective, systematic approach that is independent of the clinical topic of interest. Therefore, recommendations on topics for which it may be inherently more difficult to design and conduct rigorous studies (e.g., RCTs) are typically supported by lower quality evidence and, in turn, *Weak* recommendations. Recommendations on topics for which rigorous studies can be designed and conducted may more often be *Strong* recommendations. Per GRADE, if the quality of evidence differs across the relevant critical outcomes, the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.([23](#), [24](#)) This stricter standard provides a consistent approach to determining recommendation strengths. For additional information on GRADE or CPG methodology, see [Appendix A](#).

B. Categorization of 2014 Clinical Practice Guideline Recommendations

Evidence-based CPGs should be current. Except for an original version of a new CPG, this typically requires revision of a CPG's previous versions based on new evidence or as scheduled, subject to time-based expirations.([25](#)) For example, the U.S. Preventive Services Task Force (USPSTF) has a process for

monitoring the emergence of new evidence that could prompt an update of its recommendations, and it aims to review each topic at least every five years for either an update or reaffirmation.⁽¹⁸⁾

Recommendation categories were used to track how the previous CPG's recommendations could be reconciled. These categories and their corresponding definitions are similar to those used by the National Institute for Health and Care Excellence (NICE, England).^(26, 27) Table 3 lists these categories, which are based on whether the evidence supporting a recommendation was systematically reviewed, the degree to which the previous CPG's recommendation was modified, and whether a previous CPG's recommendation is relevant in the updated CPG.

Additional information regarding these categories and their definitions can be found in [Recommendation Categorization](#). The 2021 CPG recommendation categories can be found in [Recommendations](#). [Appendix D](#) outlines the 2014 VA/DoD COPD CPG's recommendation categories.

Table 3. Recommendation Categories and Definitions^a

Evidence Reviewed	Recommendation Category	Definition
Reviewed ^b	New-added	New recommendation
	New-replaced	Recommendation from previous CPG was carried forward and revised
	Not changed	Recommendation from previous CPG was carried forward but not changed
	Amended	Recommendation from previous CPG was carried forward with a nominal change
	Deleted	Recommendation from previous CPG was deleted
Not reviewed ^c	Not changed	Recommendation from previous CPG was carried forward but not changed
	Amended	Recommendation from previous CPG was carried forward with a nominal change
	Deleted	Recommendation from previous CPG was deleted

^a Adapted from the NICE guideline manual (2012) ⁽²⁶⁾ and Garcia et al. (2014) ⁽²⁷⁾

^b The topic of this recommendation was covered in the evidence review carried out as part of the development of the current CPG.

^c The topic of this recommendation was not covered in the evidence review carried out as part of the development of the current CPG.

Abbreviation: CPG: clinical practice guideline

C. Management of Potential or Actual Conflicts of Interest

Management of COIs for the CPGs is conducted as described in the *Guideline for Guidelines*.⁽²⁸⁾ Further, the *Guideline for Guidelines* refers to details in the VHA Handbook 1004.07 Financial Relationships between VHA Health Care Professionals and Industry (November 2014, issued by the VHA National Center for Ethics in Health Care),⁽²⁹⁾ as well as to disclosure statements (i.e., the standard disclosure form that is completed at least twice by CPG Work Group members and the guideline development team).⁽²⁸⁾ The disclosure form inquires regarding any relevant financial and intellectual interests or other relationships with, e.g., manufacturers of commercial products, providers of commercial services, or other commercial interests. The disclosure form also inquires regarding any other relationships or activities that could be perceived to have influenced, or that give the appearance of potentially influencing, a respondent's contributions to the CPG. In addition, instances of potential or actual COIs among the CPG Work Group and

the guideline development team were also subject to random web-based identification via standard electronic means (e.g., Centers for Medicare & Medicaid Services Open Payments and/or ProPublica).

No COIs were identified among the CPG Work Group or the guideline development team. If an instance of potential or actual COI had been reported, it would have been referred to the VA and DoD program offices and reviewed with the CPG Work Group Champions. The VA and DoD program offices and the CPG Work Group Champions would have determined whether, and if so, what, further action was appropriate (e.g., excusing Work Group members from selected relevant deliberations or removal from the Work Group). Disclosure forms are on file with the VA Office of Quality and Patient Safety and are available upon request.

D. Patient Perspective

When developing a CPG, consideration should be given to patient perspectives and experiences, which often vary from those of providers.^(23, 29) Focus groups can be used to help collect qualitative data on patient perspectives and experiences. VA and DoD Leadership arranged a patient focus group on February 5th, 2020, at the Audie L. Murphy Memorial VA Hospital in San Antonio, Texas. The focus group aimed to gain insights from patients with COPD of potential relevance and incorporate these into the CPG as appropriate. Topics discussed included the patients' priorities, challenges they have experienced, information they have received regarding their care, and the impacts of their care on their lives.

The patient focus group comprised a convenience sample of six participants; one woman and five men. Five participants were Veterans and received care at the VA. One participant was not a Veteran or Service Member but had received healthcare within the DoD as a family member. The Work Group acknowledges this convenience sample is not representative of all patients with COPD within the VA and DoD healthcare systems and, thus, findings are not generalizable and do not comprise evidence. For more information on the patient focus group methods and findings, see [Appendix B](#). Patient focus group participants were provided the opportunity to review the final draft and provide additional feedback.

E. External Peer Review

The Work Group drafted, reviewed, and edited this CPG using an iterative process. For more information, see [Drafting and Finalizing the Guideline](#). Once the Work Group completed a near-final draft, they identified experts from the VA and DoD healthcare systems and outside organizations to review that draft. The draft was sent to those experts for a 14-business-day review and comment period. The Work Group considered all feedback from the peer reviewers and modified the CPG, where justified, in accordance with the evidence.

F. Implementation

This CPG and algorithm are designed to be adapted by individual healthcare providers with consideration of unique patient considerations and preferences, local needs, and resources. The algorithm serves as a tool to prompt providers to consider key decision points in the care for a patient with COPD. The Work Group submits suggested performance metrics for the VA and DoD to use when assessing the implementation of this CPG. Robust implementation is identified within VA and DoD internal implementation plans and policies. Additionally, implementation would entail wide dissemination through publication in the medical literature, online access, educational programs, and, ideally, electronic medical record programming in the form of clinical decision support tools at the point of care.

VII. Approach to Care in Department of Veterans Affairs and Department of Defense

A. Patient-centered Care

Guideline recommendations are intended to consider patient needs and preferences and represent a whole/holistic health approach to care that is patient-centered, culturally appropriate, and available to people with limited literacy skills and physical, sensory, or learning disabilities. VA/DoD CPGs encourage providers to use a patient-centered, whole health/holistic health approach (i.e., individualized treatment based on patient needs, characteristics, and preferences). This approach aims to treat the particular condition while also optimizing the individual's overall health and well-being.

Regardless of the care setting, all patients should have access to individualized evidence-based care. Patient-centered care can decrease patient anxiety, increase trust in clinicians, and improve treatment adherence.^(30, 31) A whole/holistic health approach (<https://www.va.gov/wholehealth/>) empowers and equips individuals to meet their personal health and well-being goals. Good communication is essential and should be supported by evidence-based information tailored to each patient's needs. An empathetic and non-judgmental approach facilitates discussions sensitive to sex, culture, ethnicity, and other differences.

The importance of palliative care has emerged in more recent years with the goal of helping the patient and family achieve the highest QoL despite the progressive nature of COPD. Palliative care is a specialty in medicine focused on treating the symptoms, pain, and stress that accompany serious illnesses like COPD. There is some evidence that palliative care programs can reduce breathlessness and improve QoL in patients with COPD.⁽³²⁾ Rather than using a mortality prognosis, "the decision to start palliative care should be based on the presence of symptoms refractory to conventional therapy, alongside the preferences of patients. Palliative care includes, among other elements, care planning communication, end-of-life decisions, limitation of aggressive treatments (intensive care unit admission, mechanical ventilation and cardiopulmonary resuscitation) and symptomatic treatment, while always considering the physical, psychosocial and spiritual aspects and preferences of patients."⁽³³⁾ Palliative care may also provide therapies to relieve the discomfort of shortness of breath or anxiety, education about lifestyle changes, and medication and disease management.⁽³⁴⁾ Regardless of disease stage or prognosis, all patients with COPD should have patient-centered, advanced care planning discussions, and shared decision making with their primary care provider.

When a patient or provider identifies a psychosocial barrier, a referral to a social worker should be considered. A social worker's primary focus is to assist patients, their families, and caregivers in resolving psychosocial, emotional, and economic barriers to health and well-being by using a "person in environment" perspective. Social workers address social determinants of health and assess the patient's psychological and emotional adjustment to illness within the context of medical diagnosis, prognosis, and treatment options. An assessment of environmental factors includes a review of the dynamics of the Veteran's support system, functional status, vocational, economic, housing, spiritual, cultural, and legal factors that influence the ability to accomplish their healthcare goals.

B. Shared Decision Making

This CPG encourages providers to practice shared decision making. Shared decision making was emphasized in *Crossing the Quality Chasm*, an Institute of Medicine (IOM) (now NAM) report, in 2001.⁽³⁵⁾ Providers must be adept at presenting information to their patients regarding individual treatments, expected risks, expected outcomes, and levels and/or settings of care, especially where there may be patient heterogeneity in risks and benefits. The VHA and MHS have embraced shared decision making. Providers are encouraged to use shared decision making to individualize treatment goals and plans based on patient capabilities, needs, and preferences.

C. Patients with Co-occurring Conditions

Co-occurring conditions can modify the degree of risk, impact diagnosis, influence patient and provider treatment priorities and clinical decisions, and affect the overall approach to the management of COPD. Many Veterans, Service Members, and their families have one or more co-occurring conditions. Because COPD is sometimes accompanied by co-occurring conditions, it is often best to manage COPD collaboratively with other care providers. Some co-occurring conditions may require early specialist consultation to determine any necessary changes in treatment or to establish a common understanding of how care will be coordinated. This may entail reference to other VA/DoD CPGs (e.g., for asthma,^a chronic insomnia disorder and obstructive sleep apnea,^b hypertension,^c obesity and overweight,^d osteoarthritis,^e and dyslipidemia.^f)

VIII. Algorithm

This CPG's algorithm is designed to facilitate understanding of the clinical pathway and decision making process used in managing patients with COPD. This algorithm format represents a simplified flow of the management of patients with COPD and helps foster efficient decision making by providers. It includes:

- An ordered sequence of steps of care
- Decisions to be considered
- Recommended decision criteria
- Actions to be taken

^a See the VA/DoD Clinical Practice Guideline for the Management of Asthma. Available at:

<https://www.healthquality.va.gov/guidelines/CD/asthma/>

^b See the VA/DoD Clinical Practice Guideline for the Management of Chronic Insomnia Disorder and Obstructive Sleep Apnea. Available at: <https://www.healthquality.va.gov/guidelines/CD/insomnia/index.asp>

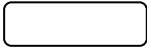



^c See the VA/DoD Clinical Practice Guideline for the Management of Hypertension in Primary Care. Available at: <https://www.healthquality.va.gov/guidelines/CD/htn/>

^d See the VA/DoD Clinical Practice Guideline for the Management of Adult Overweight and Obesity. Available at: <https://www.healthquality.va.gov/guidelines/CD/obesity/>

^e See the VA/DoD Clinical Practice Guideline for the Non-Surgical Management of Hip and Knee Osteoarthritis. Available at: <https://www.healthquality.va.gov/guidelines/CD/OA/>

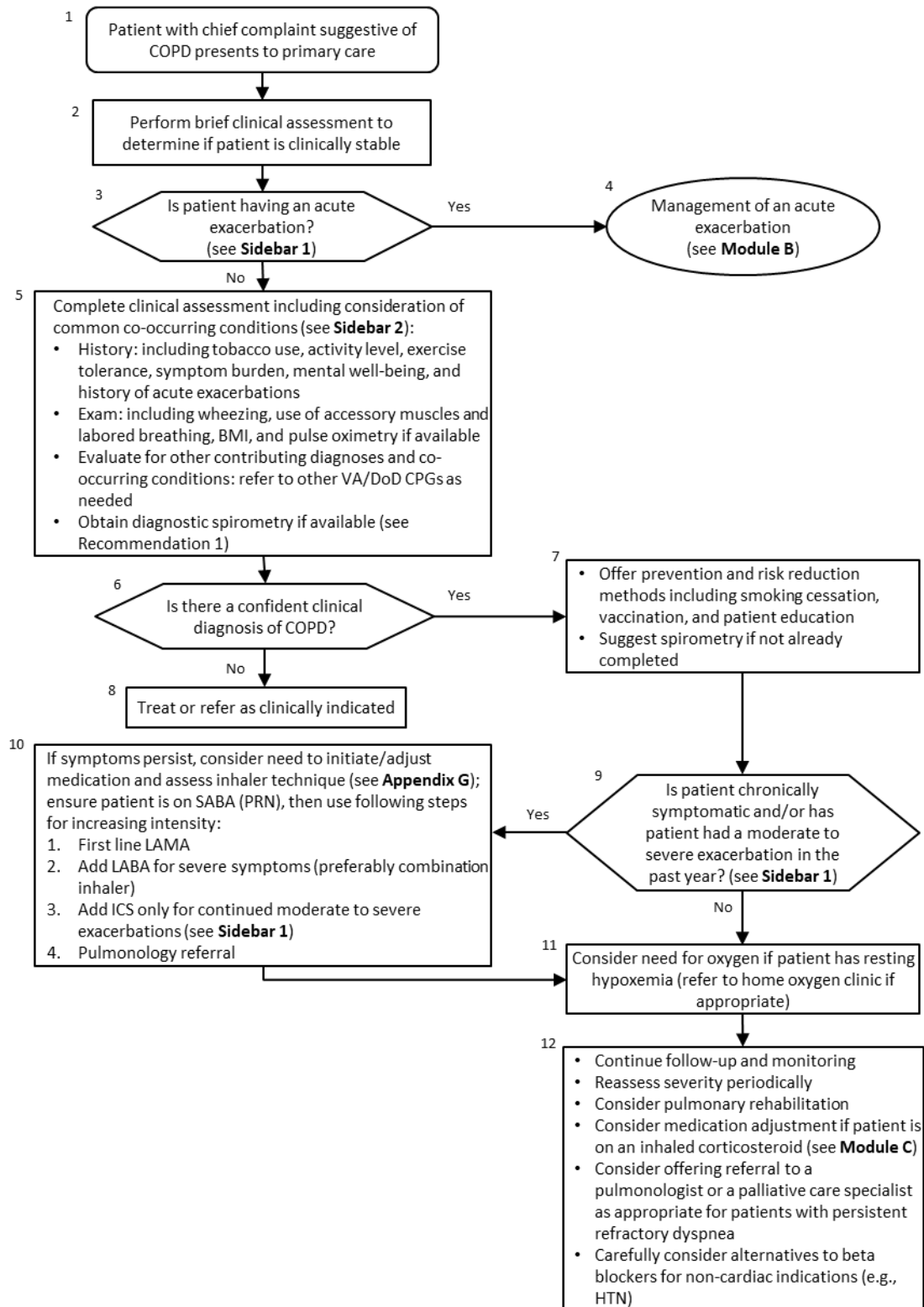
^f See the VA/DoD Clinical Practice Guideline for the Management of Dyslipidemia for Cardiovascular Risk Reduction. Available at: <https://www.healthquality.va.gov/guidelines/CD/lipids/>

The algorithm is a step-by-step decision tree. Standardized symbols are used to display each step, and arrows connect the numbered boxes indicating the order in which the steps should be followed.⁽³⁶⁾ Sidebars provide more detailed information to assist in defining and interpreting elements in the boxes.

Shape	Description
	Rounded rectangles represent a clinical state or condition
	Hexagons represent a decision point in the process of care, formulated as a question that can be answered “Yes” or “No”
	Rectangles represent an action in the process of care
	Ovals represent a link to another section within the algorithm

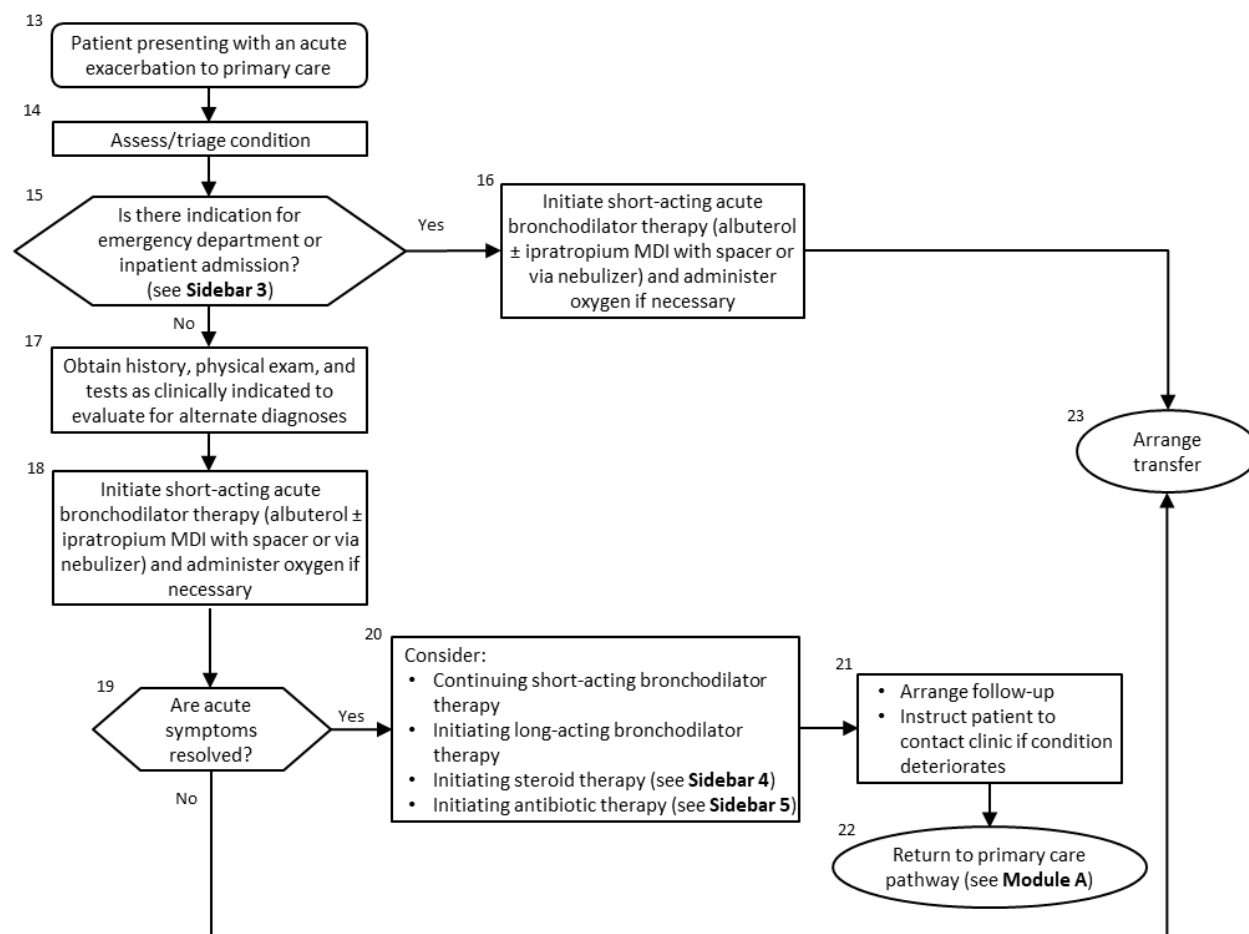
[Appendix J](#) contains alternative text descriptions of the algorithm modules.

A. Module A: Management of COPD in Primary Care



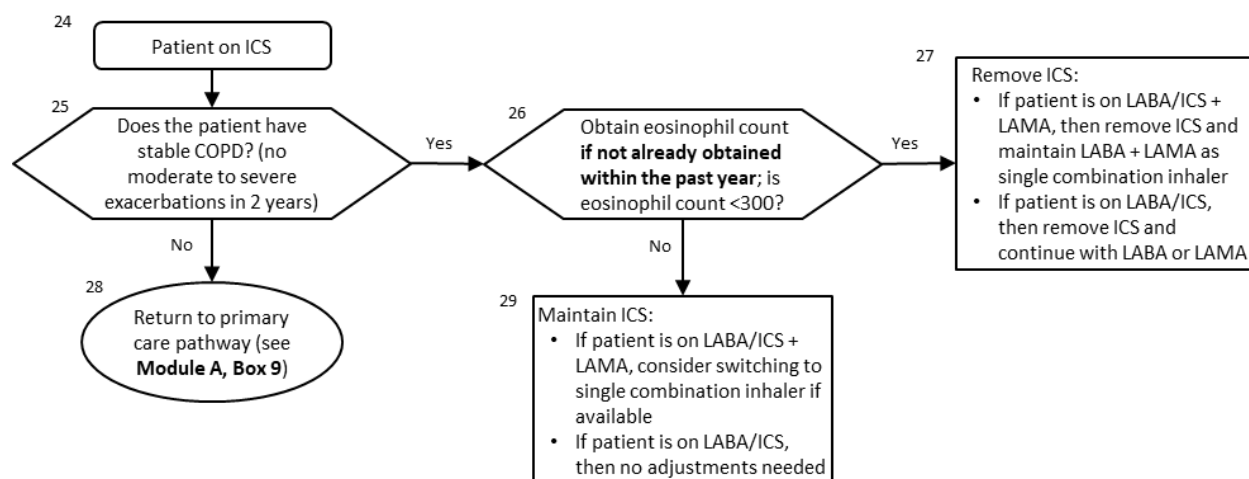
Abbreviations: BMI: body mass index; COPD: chronic obstructive pulmonary disease; CPG: clinical practice guideline; HTN: hypertension; ICS: inhaled corticosteroid; LABA: long-acting beta 2-agonist; LAMA: long-acting antimuscarinic agent; PRN: pro re nata (as needed); SABA: short-acting beta 2-agonist; VA/DoD: Department of Veterans Affairs/Department of Defense

B. Module B: Management of Acute COPD Exacerbations



Abbreviations: MDI: metered-dose inhaler

C. Module C: Inhaled Corticosteroids Usage



Abbreviations: COPD: chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; LABA: long-acting beta 2-agonist; LAMA: long-acting antimuscarinic agent

Sidebar 1: Definition of Exacerbations

Increased dyspnea above day-to-day variability with or without change in sputum amount or color. Moderate to severe exacerbations are those that require antibiotics and/or systemic corticosteroids. Patients with exacerbation within the past six months would be considered to have “severe COPD.”

Abbreviations: COPD: chronic obstructive pulmonary disease

Sidebar 2: Common Co-occurring Conditions

- CVD
- CHF
- Pulmonary embolism
- Sleep disorders
- Poor nutritional status (both under and over nutrition)
- Gastroesophageal reflux
- Depression
- Anxiety

Abbreviations: CHF: congestive heart failure; CVD: cardiovascular disease

Sidebar 3: Criteria for Possible Admission

- Accessory muscle use
- Tachypnea
- Hypoxemia or hypercapnia above baseline
- Failure to respond to initial therapy
- Clinical judgment

Sidebar 4: Initiating Steroid Therapy

Oral glucocorticoid:

- 30 – 40 mg daily prednisone equivalent for 5 – 7 days
- No benefit in higher doses
- Generally no benefit in longer duration

Abbreviations: mg: milligrams

Sidebar 5: Initiating Antibiotic Therapy

Antibiotic choices:

- Amoxicillin
- Amoxicillin/clavulanate
- Azithromycin
- Doxycycline
- Second generation cephalosporin
- Trimethoprim/sulfamethoxazole (TMP-SMX)
- Reserve broader spectrum antibiotics for severe or specific risk

Abbreviations: SMX: sulfamethoxazole; TMP: trimethoprim

IX. Recommendations

The following evidence-based clinical practice recommendations were made using a systematic approach considering four domains per the GRADE approach (see [Summary of Guideline Development Methodology](#)). These domains include: confidence in the quality of the evidence, balance of desirable and undesirable outcomes (i.e., benefits and harms), patient values and preferences, and other implications (e.g., resource use, equity, acceptability).

Topic	#	Recommendation	Strength ^a	Category ^b
Diagnosis & Classification	1.	We suggest post-bronchodilator spirometry to confirm clinical diagnosis of COPD.	Weak for	Reviewed, New-replaced
	2.	There is insufficient evidence to recommend for or against any specific clinical criteria to inform decision-making regarding advancing pharmacologic therapy for COPD.	Neither for nor against	Reviewed, New-added
Risk Reduction	3.	We recommend smoking cessation for prevention and risk reduction of COPD.	Strong for	Reviewed, New-replaced
	4.	We suggest routine vaccination for influenza and pneumococcal pneumonia for prevention and risk reduction of COPD exacerbations.	Weak for	Reviewed, New-replaced
	5.	We recommend offering inhaled long-acting muscarinic antagonists as first-line therapy in patients with symptomatic COPD.	Strong for	Reviewed, New-replaced
	6.	We recommend against offering an inhaled long-acting beta agonist as first-line therapy in patients with symptomatic COPD, unless a long-acting muscarinic antagonist is not tolerated or is contraindicated.	Strong against	Reviewed, New-added
	7.	We recommend against offering an inhaled corticosteroid in patients with symptomatic COPD as a first-line therapy.	Strong against	Not reviewed, Amended
	8.	For patients with moderate to severe obstruction who continue to report significant dyspnea or decreased quality of life despite using a long-acting muscarinic antagonist, we suggest adding a long-acting beta agonist to long-acting antimuscarinic agent therapy.	Weak for	Reviewed, New-replaced
	9.	If choosing dual therapy, we recommend against offering long-acting beta agonists with inhaled corticosteroids for patients with COPD.	Strong against	Reviewed, New-added
	10.	In patients with COPD who are on combination therapy with a long-acting antimuscarinic agent/long-acting beta agonist and continue to have COPD exacerbations, we suggest adding an inhaled corticosteroid as a third medication.	Weak for	Reviewed, New-replaced
	11.	There is insufficient evidence to recommend for or against the use of eosinophilia or suspicion of asthma-COPD overlap syndrome to guide choice of additional therapy.	Neither for nor against	Reviewed, New-added
	12.	We suggest considering withdrawal of inhaled corticosteroids in patients with COPD without moderate to severe exacerbations in the last two years.	Weak for	Reviewed, New-added

Topic	#	Recommendation	Strength ^a	Category ^b
First-line Therapy	13.	There is insufficient evidence to recommend for or against the use of N-acetylcysteine preparations available in the United States for patients with stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough).	Neither for nor against	Reviewed, Amended
	14.	There is insufficient evidence to recommend for or against the use of antibiotics for outpatient COPD exacerbations (C-reactive protein guided or not).	Neither for nor against	Reviewed, New-replaced
	15.	We recommend providing long-term oxygen therapy to patients with chronic stable resting severe hypoxemia (PaO ₂ <55 mm Hg and/or SaO ₂ ≤88%) or chronic stable resting moderate hypoxemia (PaO ₂ 56 – 59 mm Hg or SaO ₂ >88% and ≤90%) with signs of tissue hypoxia (hematocrit >55%, pulmonary hypertension, or cor pulmonale).	Strong for	Not reviewed, Not changed
	16.	We suggest against routinely offering ambulatory long-term supplemental oxygen for patients with chronic stable isolated exercise hypoxemia, in the absence of another clinical indication for supplemental oxygen.	Weak against	Reviewed, Not changed
	17.	In patients with COPD, we suggest starting or continuing cardio-selective beta-blockers only in those who have a cardiovascular indication for beta-blockers (e.g., heart failure with reduced ejection fraction or recent myocardial infarction).	Weak for	Reviewed, Amended
	18.	We suggest offering a supported self-management program that includes a written action plan with exacerbation management, smoking cessation, and exercise.	Weak for	Reviewed, New-replaced
	19.	We suggest offering telehealth support that includes telemonitoring and/or mobile applications.	Weak for	Reviewed, New-replaced

^a For additional information, see [Grading Recommendations](#).

^b For additional information, see [Recommendation Categorization](#) and [Appendix D](#).

A. Diagnosis and Classification

Recommendation

1. We suggest post-bronchodilator spirometry to confirm clinical diagnosis of COPD.
(Weak for | Reviewed, New-replaced)

Discussion

Expiratory airflow obstruction is one of the most verifiable indicators of COPD. The expiratory flow obstruction is confirmed by presence of FEV1/FVC less than 70% or less than lower limit of normal (LLN) based upon age appropriate cut-offs in post-bronchodilator spirometry. The expiratory airflow obstruction is not fully reversible in COPD.[\(37-41\)](#) However, clinical diagnosis based on history and physical assessment alone may result in under or over diagnosis of COPD. Gershon et al. (2017) showed the use of spirometry is associated with increased medication prescriptions for COPD.[\(42\)](#) Although the spirometric confirmation of COPD diagnosis is important, it may delay the diagnosis and start of therapy

Historically, the administration of a bronchodilator was needed to confirm that airway obstruction could not be completely reversed.[\(42\)](#) Post-bronchodilator spirometry improves the accuracy of COPD diagnosis over pre-bronchodilator spirometry.[\(43\)](#)

Evidence suggests that a post-bronchodilator ratio of FEV1/FVC less than 70% is acceptable confirmation of the presence of COPD in older patients without a prior history of asthma.[\(44\)](#) However, clinicians must use caution when applying this criteria to elderly patients because FEV1/FVC less than 70% can be a normal part of aging. Relying on history of exposure, history of asthma, symptoms, and the LLN of FEV1/FVC to confirm the diagnosis may be more accurate in this specific population.[\(44\)](#) Using lower FEV1/FVC threshold may exclude more patients from being considered as “obstructed” and therefore diminish the sensitivity but increase the specificity.

Reversibility to acute inhalation of short-acting bronchodilators may vary in repeated testing in COPD patients.[\(45\)](#) The absence of acute reversibility after treatment with a bronchodilator may not predict response to long-term pharmacotherapy. Thus, reversibility testing should not be used to gauge the potential benefits of treatment.[\(46-48\)](#)

The Work Group systematically reviewed evidence related to this recommendation [\(42, 43\)](#) and considered the assessment of the evidence put forth in the 2014 COPD CPG. Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group’s confidence in the quality of the evidence was very low. The body of evidence had some limitations. The limitations included lack of accessibility for testing specifically in the era of communicable respiratory infections and difficulty of doing spirometry among patients with more severe forms of COPD. The benefits of accurate diagnosis and early initiation of treatment slightly outweighed the harms of spirometry causing delay in treatment and exposure to communicable respiratory pathogens. Patient values and preferences were somewhat varied because some may not have access to spirometry, and there is a risk of exposure when a communicable respiratory disease is present. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

2. There is insufficient evidence to recommend for or against any specific clinical criteria to inform decision-making regarding advancing pharmacologic therapy for COPD.

(Neither for nor against | Reviewed, New-added)

Discussion

This recommendation is related to advancing pharmacologic therapy in outpatients with symptomatic COPD. Multiple recent guidelines and reviews have considered potential criteria for selecting patients for more advanced initial therapy at the time of diagnosis, in contrast to a stepwise approach to increasing therapy.⁽⁴⁹⁾ The Work Group examined the literature on this topic in this CPG's systematic evidence review. Based on the literature identified, the Work Group determined there is insufficient evidence to recommend any one of these criteria to inform decision-making on advancing COPD therapy. The systematic evidence review identified three efficacy trials;⁽⁵⁰⁻⁵²⁾ however, these did not address nor support a recommendation on this topic. No studies comparing different approaches for selecting patients for initial nor subsequent intensified therapy were identified. A potential benefit for an initial intensified approach to pharmacotherapy is also not excluded by this evidence review. Therefore, the Work Group identified this as a potential subject for future research efforts.

Providers use various forms of symptom assessments for advancement of therapy. The COPD treatment algorithm (see [Module A: Management of COPD in Primary Care](#)) outlines a stepwise approach to advancing therapy that is consistent with [Recommendation 5](#), [Recommendation 8](#), and [Recommendation 10](#) from this updated CPG. This exemplifies a strategy in which the therapy is matched to achieving good control of symptoms and reducing risk of exacerbations, while minimizing side effects and overuse.

The effectiveness of the medications used in advancing therapy is established; however, effectiveness of the use of clinical criteria to guide decision-making to improve outcomes has not been established. The Work Group systematically reviewed evidence related to this recommendation.⁽⁵⁰⁻⁵²⁾ Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the quality of evidence regarding establishing the criteria for advancing therapy is very low. The benefits and harms of use of the clinical criteria were balanced. The body of evidence had some limitations including lack of specificity needed to develop clear recommendations.⁽⁵¹⁾ Patient values and preferences were somewhat varied. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

B. Risk Reduction

Recommendation

3. We recommend smoking cessation for prevention and risk reduction of COPD.

(Strong for | Reviewed, New-replaced)

Discussion

Cessation of smoking tobacco and avoidance of tobacco smoke are the cornerstones of COPD treatment. Avoidance of respiratory irritants can preserve lung function and slow progression of the disease more than any available medical treatment. Individuals with COPD who stopped smoking were generally found

to have improved FEV1 the following year, a decreased rate of decline in FEV1, and reduced mortality.[\(53\)](#) Smoking cessation interventions are widely accepted and available.

The Work Group systematically reviewed evidence related to this recommendation and considered the assessment of the evidence put forth in the 2014 COPD CPG.[\(53, 54\)](#) Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of evidence was moderate. The benefits of slower decline in lung function and reduced all-cause mortality in the long term outweighed the harms associated with smoking cessation. Most patients have similar values about the contribution of smoking to illness, but many do not want to quit, have trouble quitting, and/or enjoy smoking. Smoking cessation interventions are widely available, have low resource use, and are widely accepted across providers. Thus, the Work Group decided upon a *Strong for* recommendation.

Recommendation

4. We suggest routine vaccination for influenza and pneumococcal pneumonia for prevention and risk reduction of COPD exacerbations.

(Weak for | Reviewed, New-replaced)

Discussion

Routine influenza vaccination can benefit patients with COPD by reducing exacerbations of COPD. There are no new trials since 2004; however, low quality evidence suggests influenza vaccination reduces the likelihood of a COPD exacerbation in patients with COPD.[\(55\)](#)

Pneumococcal vaccination may also be beneficial. There was moderate quality evidence for decrease in exacerbation.[\(56\)](#) However, there was low quality evidence for improvement in a variety of COPD-related outcomes including mortality and hospital admission. Patients with COPD are at increased risk of respiratory illnesses such as pneumonia, related exacerbations, and mortality. The systematic evidence review identified no evidence to recommend a specific pneumococcal vaccine.

The Work Group systematically reviewed evidence related to this recommendation [\(55, 56\)](#) and considered the assessment of the evidence put forth in the 2014 COPD CPG. Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of evidence for exacerbations was low. The body of evidence had some limitations. While the SR included had good quality methodology, the included studies were of fair quality due to unreported risks of bias.[\(55\)](#) The benefits of improved exacerbations outweighed the minimal side effects. Patient values and preferences were somewhat varied as some patient do not want to receive vaccinations. Thus, the Work Group decided upon a *Weak for* recommendation.

C. First-Line Therapy

Recommendations

5. We recommend offering inhaled long-acting muscarinic antagonists as first-line therapy in patients with symptomatic COPD.
(Strong for | Reviewed, New-replaced)
6. We recommend against offering an inhaled long-acting beta agonist as first-line therapy in patients with symptomatic COPD, unless a long-acting muscarinic antagonist is not tolerated or is contraindicated.
(Strong against | Reviewed, New-added)

Discussion

Evidence suggests that, in patients with symptomatic COPD, long-acting bronchodilators decrease dyspnea, improve QoL, and decrease exacerbations compared to placebo.[\(57-60\)](#) Additionally, long-acting muscarinic antagonists (LAMAs) and LABAs do not increase the risk of serious adverse events or total adverse events.[\(59, 61-64\)](#)

Long-acting bronchodilators do not supplant short-acting bronchodilators, which may improve lung function and decrease respiratory symptoms in patients with COPD.[\(65\)](#) Although there is a lack of high quality evidence addressing their efficacy, the Work Group acknowledges that the prescription of short-acting bronchodilators is the current standard of clinical practice in COPD. The use of short-acting bronchodilators is included in the algorithm (see [Module B: Management of Acute COPD Exacerbations](#)), but not addressed in a formal recommendation. Also, numerous patient focus group participants advocated for the symptomatic benefit and sense of security provided by short-acting bronchodilators.

LAMAs remain the first-line maintenance therapy for symptomatic patients with confirmed COPD. Chen et al. (2017) compared the efficacy of LAMAs to LABAs in an SR and demonstrated LAMAs were more effective in reducing the risk of acute exacerbations and were associated with less adverse events than LABAs.[\(66\)](#) Further supporting LAMAs over LABAs for first-line monotherapy, the SR by Maia et al. (2017) found patients treated with LAMAs had reduced risk of severe exacerbations leading to hospitalization.[\(67\)](#) The systematic evidence review carried out for this guideline update identified two SRs comparing effectiveness of various LAMAs, neither review found that one LAMA was superior to another in terms of safety or efficacy.[\(58, 60\)](#)

Despite general consistency in the evidence supporting first-line use of a LAMA over a LABA, there is some variability in patient preferences regarding this treatment. The Work Group determined that certain patient populations, such as those with glaucoma or urinary retention, may not tolerate a LAMA or may be reluctant to start a LAMA given the perceived risk of an adverse outcome. In these patient populations, a LABA could be considered as a first-line agent for symptomatic COPD.

The Work Group systematically reviewed evidence related to these recommendations [\(57-63, 66, 67\)](#) and considered the assessment of the evidence put forth in the 2014 COPD CPG.[\(64, 65\)](#) Therefore, these are *Reviewed, New-replaced* and *Reviewed, New-added* recommendations. The Work Group's confidence in the quality of the evidence was moderate. The benefits of LAMA therapy, including reduced rates of

exacerbations and hospitalizations and decreased adverse events, outweighed that harms, which were minimal. Patients have similar values and preferences for a medication that improves their symptoms and causes few side effects. Thus, the Work Group decided upon *Strong for* and *Strong against* recommendations.

Recommendation

7. We recommend against offering an inhaled corticosteroid in patients with symptomatic COPD as a first-line therapy.
(Strong against | Not reviewed, Amended)

Discussion

ICSs are not recommended for first-line therapy in COPD and are not approved by the U.S. Food and Drug Association (65) for this purpose. The effects of ICS monotherapy on lung function and QoL are inferior to monotherapy with LABAs.(68) In addition, ICS monotherapy causes more adverse events compared to placebo, including oropharyngeal candidiasis, hoarseness, bruising, and pneumonia.(69) As discussed in [Recommendations 5 and 6](#), there are more effective and safe options for first-line monotherapy for patients with symptomatic COPD (i.e., utilizing either a LAMA or, if this is not tolerated, a LABA).

The Work Group did not systematically review evidence related to this recommendation and considered the assessment of the evidence put forth in the 2014 COPD CPG.(69) Therefore, this is a *Not reviewed, Amended* recommendation. The Work Group's confidence in the quality of the evidence was moderate. The harms, including oropharyngeal candidiasis, hoarseness, bruising, and pneumonia, outweighed the benefits of an ICS as first-line monotherapy. Thus, the Work Group decided upon a *Strong against* recommendation.

Recommendation

8. For patients with moderate to severe obstruction who continue to report significant dyspnea or decreased quality of life despite using a long-acting muscarinic antagonist, we suggest adding a long-acting beta agonist to long-acting antimuscarinic agent therapy.
(Weak for | Reviewed, New-replaced)

Discussion

A meta-analysis by Oba et al. (2018) identified an SR of 11 randomized control trials (RCTs) that suggests LAMA/LABA combination therapy has a statistically significant improvement on QoL and dyspnea compared to LAMA monotherapy in individuals with moderate to severe COPD.(70) However, the change in the St. George's Respiratory Questionnaire was not clinically significant. Similarly, the Transition Dyspnea Index (TDI) was found to be statistically but not clinically significant with the addition of a LABA to a LAMA. Other studies examining the harms of LABA in combination with LAMA did not find a statistical or clinical difference in serious adverse events compared to LAMA monotherapy.

The relevant studies comparing LAMA/LABA to LAMA were of high quality with low to moderate risk of bias, and there was high confidence in the quality of the evidence.(70) Despite the statistically significant findings, the lack of clinically significant findings prevented the Work Group from including a recommendation on the optimal time to add LABA therapy to LAMA monotherapy. The FEV1 of included

individuals varied widely without a definitive cut-off. The percentage of males in the studies was as high as 96%; the percentage of individuals who currently smoked ranged from 26% to 63%; and the FEV1 predicted of individuals ranged from 37.2% to 57.4%.[\(70\)](#) This wide variation without clear cut-offs informed the Work Group's guidance regarding moderate to severe obstruction.

The Work Group systematically reviewed evidence related to this recommendation [\(70\)](#) and considered the assessment of the evidence put forth in the 2014 COPD CPG. Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was high. The benefit of combination therapy only slightly outweighed the harm, as the benefit was limited to statistically significant but not clinically significant improvement. There is some variation in patient values and preferences, as some patients may not prefer taking a second medication, while others may want to try dual therapy. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

9. If choosing dual therapy, we recommend against offering long-acting beta agonists with inhaled corticosteroids for patients with COPD.

(Strong against | Reviewed, New-added)

Discussion

An ICS plus LABA is associated with a higher risk of pneumonia compared to LAMA monotherapy.[\(70\)](#) The harm of ICSs/LABAs was not offset with potential benefit, as there was no significant difference in rates of exacerbations, QoL, dyspnea, or serious non-fatal adverse events. Although the precise risk related to pneumonia with the use of ICSs plus LABA compared to LAMA monotherapy varies based on the inclusion criteria, the number needed to harm is approximately 50.[\(70\)](#)

The Work Group determined both providers and patients would agree upon avoiding prescription of medication that causes increased harm without added benefit compared to an alternative treatment. While evidence suggests an ICS/LABA is an inferior option compared to LAMA monotherapy for the management of COPD, most studies excluded individuals with asthma or asthma-COPD overlap.[\(70\)](#) This recommendation can be applied to the population included in the studies, which were 80% male, 43% current smokers, and mean age of 65.[\(70\)](#) The applicability of this recommendation cannot adequately be extrapolated outside these inclusion criteria.

The Work Group systematically reviewed evidence related to this recommendation.[\(70\)](#) Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the quality of the evidence was moderate. Individual studies included in the SR by Oba et al. (2018) [\(70\)](#) had some limitations including smaller study sample size and larger confidence intervals (CIs).[\(71, 72\)](#) Thus, the possibility of a clinically significant benefit could not be excluded. However, the harms of increased rates of pneumonia significantly outweighed the benefits associated with an ICS/LABA compared to LAMA monotherapy, as none were identified. Patients have similar values and preferences for taking a medication that comes with harm and no benefit. Thus, the Work Group decided upon a *Strong against* recommendation.

Recommendation

10. In patients with COPD who are on combination therapy with a long-acting antimuscarinic agent/long-acting beta agonist and continue to have COPD exacerbations, we suggest adding an inhaled corticosteroid as a third medication.

(Weak for | Reviewed, New-replaced)

Discussion

Triple therapy with an ICS, LAMA, and LABA has been compared with both single and combination therapy in numerous RCTs which primarily involve patients with COPD with moderate to severe airflow obstruction and a history of one or more moderate to severe acute exacerbations (defined as exacerbations treated with antibiotics, oral corticosteroids, or those that result in hospitalization) within the prior year. Four SRs of these trials served as the evidence base for this recommendation.[\(73-76\)](#)

Triple therapy decreased the frequency of moderate to severe exacerbations, improved QoL, and improved FEV1 when compared to single or dual therapy.[\(73-76\)](#) No differences were found based on whether the inhalers are separate or combined into one device.[\(73, 76\)](#) Triple therapy did not increase the rates of serious adverse events or total adverse events. Studies inconsistently reported an association between triple therapy and an increased risk of pneumonia compared to LABA/LAMA dual therapy.[\(73, 74, 76\)](#) A meta-analysis by Cazzola et al. (2018) estimated a number needed to treat of 38 for triple therapy to prevent an acute exacerbation of COPD compared to LABA/LAMA dual therapy. Conversely, triple therapy was associated with a number needed to harm of 195 for pneumonia.[\(74\)](#)

While patient focus group participants desired improvements in their risk of exacerbations, QoL, and functional status, some heterogeneity exists among patients when weighing the risks of pneumonia and the benefits of triple therapy with an inhaled steroid. Also, the use of separate devices for triple therapy may require a patient to utilize multiple different inhaler types and techniques, and thus limit adherence to therapy. Pre-specified secondary analyses within triple therapy trials have shown benefit across all groups but suggest the magnitude of benefit was heterogeneous amongst different COPD phenotypes and may be influenced by the frequency of exacerbations, active smoking status, and/or blood eosinophil counts.[\(73-75\)](#) The Work Group determined the strength of evidence did not justify a recommendation to treat these subgroups differently. More research should be done to elucidate markers of COPD phenotypes that benefit from different therapeutic options.

The Work Group systematically reviewed evidence related to this recommendation [\(73-76\)](#) and considered the assessment of the evidence put forth in the 2014 COPD CPG. Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group's confidence in the quality of the evidence was low. The body of evidence had significant limitations including heterogeneity among the included trials as well as imprecision and limitations on the comparison of serious adverse events and pneumonia.[\(73\)](#) The benefits of increased QoL and decreased risk of exacerbations slightly outweighed the harms of increased risks of pneumonia. Patients likely have similar values and preferences for avoiding pneumonia and exacerbations. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

11. There is insufficient evidence to recommend for or against the use of eosinophilia or suspicion of asthma-COPD overlap syndrome to guide choice of additional therapy.

(Neither for nor against | Reviewed, New-added)

Discussion

One SR was identified that addressed the use of eosinophil counts to guide therapy for COPD.⁽⁷⁵⁾ Within the SR, five RCTs examined blood eosinophil counts as markers of response with the addition of ICSs, maintenance of ICSs, or withdrawal of an ICS. The SR showed no difference in ICS containing treatments and non-ICS containing treatments in the risk of moderate to severe exacerbations. Other secondary outcomes were mixed in terms of benefit of exacerbation and risk of pneumonia. None of the studies were originally designed to assess the use of eosinophil counts as a marker to guide therapy for COPD. Because the SR had mixed results with significant heterogeneity, the Work Group did not recommend for or against the use of eosinophil counts in the decision to use ICS therapy. In contrast, there is evidence for the use of eosinophil counts to inform the decision to withdraw an ICS in a patient with stable COPD. This evidence is reviewed in [Recommendation 12](#) below.

There was insufficient data to define asthma-COPD overlap syndrome. The term “syndrome” has been used by some, but a clear definition is currently not available, and, even when used, it is not clear how it might aid in decisions for therapy. The Work Group did not recommend for or against the use of this syndrome in making treatment decisions.

The Work Group systematically reviewed evidence related to this recommendation.⁽⁷⁵⁾ Therefore, this is a *Reviewed, New-added* recommendation. The Work Group’s confidence in the quality of the evidence was low. There was insufficient evidence to make a determination on the balance of potential benefits and harms. There was also insufficient data to define an overlap syndrome or determine how it might aid in the decisions of advancing therapy. There was large variation in patient values and preferences, as there is significant heterogeneity in patients with these conditions, leading to subgroup considerations. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Recommendation

12. We suggest considering withdrawal of inhaled corticosteroids in patients with COPD without moderate to severe exacerbations in the last two years.

(Weak for | Reviewed, New-added)

Discussion

Overall, moderate to high quality evidence from an SR of eight RCTs by Calzetta et al. (2017) suggested that ICS withdrawal did not differ from ICS continued for risk of exacerbations and time to exacerbation.⁽⁷⁷⁾ In addition, those weaned had a significant improvement in the QoL as measured by the St. George’s Respiratory Questionnaire. Other studies included in the SR showed a small but clinically insignificant decrease in FEV1 and no change in the adverse events or rates of exacerbation.⁽⁷⁷⁾

There was evidence from two RCTs in an SR ⁽⁷⁸⁾ which suggested an increase in risk of exacerbation in participants with higher baseline absolute blood eosinophil levels with threshold (≥ 300 cells/ μ l) in the

withdrawal groups compared to the continue groups for up to 10 months follow-up. However, evidence from another RCT in the SR showed no differences in serious adverse events.[\(78\)](#)

ICSs are not without risk of adverse events, and safely decreasing medication load is a priority for both patients and providers. There may be variability in willingness to stop withdrawing medications in stable patients, and the evidence supporting this recommendation may help patients and providers be more comfortable with weaning. There was no evidence to support a recommendation for any specific particular withdrawal protocol.

The Work Group systematically reviewed evidence related to this recommendation.[\(77, 78\)](#) Therefore, this is a *Reviewed, New-added* recommendation. The Work Group's confidence in the quality of the evidence was moderate. The body of evidence had some limitations as the increased risk of exacerbations was only found in the high eosinophil subgroup. Additionally, there was lack of repeatability/reliability of single eosinophil measure and the added complexity of requiring lab measurement to help decide treatment. The benefits of being off a steroid medication outweighed the potential harms of withdrawal, which were not significant in patients with absolute eosinophil counts of <300 cells/ μ l. Patient values and preferences were somewhat varied, as risk varied by subgroup and most patients do not want to be on steroids given the side effects. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

13. There is insufficient evidence to recommend for or against the use of N-acetylcysteine preparations available in the United States for patients with stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough).

(Neither for nor against | Reviewed, Amended)

Discussion

N-acetylcysteine is an antioxidant, anti-inflammatory, and mucolytic agent. Cysteine is one of the three amino acids that make up glutathione, the most abundant intracellular antioxidant. It was the only mucolytic agent covered in the search during the systematic evidence review carried out for this CPG update. The systematic evidence review identified an SR and meta-analysis of 12 RCTs by Fowdar et al. (2017).[\(79\)](#) There was large variability in dose and treatment duration among the included trials. NAC was found to reduce long-term (≥ 6 months) but not short-term exacerbation prevalence. However, there was no effect on exacerbation rate, FEV1, FVC, or inspiratory capacity. Adding NAC to standard therapy did not change FEV1 or incidence of adverse events compared to standard therapy alone.[\(79\)](#) For this reason, the Work Group did not recommend for or against the use of NAC in COPD treatment regimens.

The Work Group systematically reviewed evidence related to this recommendation [\(79\)](#) and considered the assessment of the evidence put forth in the 2014 COPD CPG. Therefore, this is a *Reviewed, Amended* recommendation. The Work Group's confidence in the quality of the evidence was low. The body of evidence had some limitations including large variation in the use of NAC.[\(79\)](#) Other considerations included insufficient evidence to judge the balance of potential benefits and harms. There was large variation in patient values and preferences regarding the use of NAC. Thus, the Work Group decided upon a *Neither for nor against* recommendation.

Recommendation

14. There is insufficient evidence to recommend for or against the use of antibiotics for outpatient COPD exacerbations (C-reactive protein guided or not).
(Neither for nor against | Reviewed, New-replaced)

Discussion

The efficacy and safety of antibiotic therapy for the treatment of mild to moderate outpatient COPD exacerbations remains uncertain. An SR by Vollenweider et al. (2018) evaluating the benefits and harms of antibiotic treatment for COPD exacerbations suggested, with low quality evidence, that outpatients treated with broad-spectrum antibiotic therapy have decreased risk for treatment failures up to one month following the initiation of treatment.[\(80\)](#) However, the SR also found no significant difference between antibiotic treatment and placebo in re-exacerbations in 2-6 weeks, median time to next exacerbation up to 12 months, and all-cause mortality up to two years after starting antibiotic treatment.[\(80\)](#)

Evidence from one SR and two RCTs suggests an increase in diarrhea with antibiotic therapy compared with placebo from four weeks to two years post commencement of antibiotics.[\(80-82\)](#) No significant difference was found in harms between shorter and longer durations of broad spectrum antibiotics.[\(81\)](#) Similarly, the use of C-reactive protein (CRP) point-of-care testing guided antibiotic prescription compared to usual care, had no clinically important difference in adverse effects compared to antibiotics at six months.[\(82\)](#) The Work Group did not review evidence on other specific biomarkers, such as procalcitonin, in directing the use of antibiotic therapy in COPD exacerbations.

COPD exacerbations can be triggered by environmental irritants, bacterial pathogens, and/or viral pathogens. This creates a challenge in determining the appropriateness of routine treatment of mild to moderate outpatient COPD exacerbations with antibiotics, given their effectiveness only against susceptible bacterial infections. Based on clinical judgment, antibiotic therapy may be warranted and beneficial on a case-by-case basis. Such patients could include those presenting with a moderate exacerbation, increased dyspnea and increased sputum volume/purulence, fever/chills, and leukocytosis with radiographic evidence of pneumonia.

There is large heterogeneity in the studies and methods used to capture exacerbation-related attributes (e.g., duration, severity, frequency). The studies included individuals with all levels of exacerbation severity (mild to severe), and definitions of exacerbations varied. The Work Group did not find any study that specifically evaluated antimicrobial resistance. Very few studies defined harms a priori or evaluated “serious” adverse events. The severity of adverse events was not defined, and harms were generally captured as present or absent. Lack of adequate reporting for allocation concealment, blinding of outcome assessors, poor capture, and reporting of harms were the most frequent sources of bias.

The Work Group systematically reviewed evidence related to this recommendation [\(80-82\)](#) and considered the assessment of the evidence put forth in the 2014 COPD CPG. Therefore, this is a *Reviewed, New-replaced* recommendation. The Work Group’s confidence in the quality of the evidence was low. The body of evidence had some limitations including studies with participants from both inpatient and outpatient settings and evaluation of antibiotics that are not currently in use in clinical practice. The systematic

evidence review carried out as part of this CPG update only considered studies that were conducted in outpatients and evaluated use of antibiotics currently in use within the U.S. The benefit of a decrease in treatment failure was balanced with harm of diarrhea as a side effect in some patients. Patient values and preferences for receiving antibiotics is somewhat varied. Thus the Work Group decided upon a *Neither for nor against* recommendation.

Recommendation

15. We recommend providing long-term oxygen therapy to patients with chronic stable resting severe hypoxemia ($\text{PaO}_2 < 55$ mm Hg and/or $\text{SaO}_2 \leq 88\%$) or chronic stable resting moderate hypoxemia (PaO_2 56 – 59 mm Hg or $\text{SaO}_2 > 88\%$ and $\leq 90\%$) with signs of tissue hypoxia (hematocrit $> 55\%$, pulmonary hypertension, or cor pulmonale).

(Strong for | Not reviewed, Not changed)

Discussion

Severe chronic hypoxemia is associated with significant comorbidity and mortality. There is evidence that long-term oxygen therapy (LTOT) in these clinical situations reduces mortality.[\(83-85\)](#) Chronic stable hypoxemia is defined as two measurements at least six weeks apart and at least six weeks from any acute illness resulting in hypoxemia. Effects of supplemental oxygen in moderate hypoxemia are not clear.[\(86\)](#)

There is insufficient evidence that LTOT reduces mortality in COPD patients with mild to moderate hypoxemia ($66 \text{ mmHg} < \text{PaO}_2 \leq 74 \text{ mm Hg}$) in the absence of signs of tissue hypoxia.[\(85\)](#) There is also insufficient evidence that LTOT for chronically hypoxic COPD patients improves dyspnea, QoL, hospitalization rates, or readmission rates.[\(85\)](#) Therefore, the Work Group decided to not make specific recommendations related to LTOT for these patient populations.

If transitional home oxygen is provided after an acute respiratory illness, the need for LTOT should be re-evaluated in 30 – 90 days. The RCTs found that a survival benefit among RCTs with LTOT did not measure oxygen levels or re-evaluate the need for LTOT after initial qualification.[\(83, 84\)](#) Up to 50% of these patients will not qualify for continued LTOT.[\(87\)](#) In contrast, patients with chronic stable hypoxemia who have met the criteria for LTOT prior to hospitalization do not require reassessment.[\(88\)](#) Discontinuing LTOT in these patients can result in subsequent worsening of hypoxemia.[\(88, 89\)](#) Furthermore, the safety of discontinuing LTOT under these circumstances is unknown.

The Work Group did not systematically review evidence related to this recommendation and considered the assessment of the evidence put forth in the 2014 COPD CPG.[\(83-85\)](#) Therefore, this is a *Not reviewed, Not changed* recommendation. The Work Group's confidence in the quality of the evidence was moderate. The benefits of LTOT outweighed the potential harm of adverse events, such as fire hazards for smokers. Patient values and preferences were somewhat varied. Thus, the Work Group decided upon a *Strong for* recommendation.

Recommendation

16. We suggest against routinely offering ambulatory long-term supplemental oxygen for patients with chronic stable isolated exercise hypoxemia, in the absence of another clinical indication for supplemental oxygen.

(Weak against | Reviewed, Not changed)

Discussion

Oxygen plays a pivotal role in the maintenance of cell and body function. In COPD, ventilation and oxygenation may diminish and result in hypoxemia during rest, exercise, or sleep. Thus, it may seem logical to administer supplemental oxygen to anybody who has hypoxemia during rest, exercise, or sleep. Benefits of supplemental oxygen for COPD patients with resting severe hypoxemia are proven (see [Recommendation 15](#)). However, benefits of supplemental oxygen when the patient only shows chronic stable isolated exercise hypoxemia have been a matter of debate. The evidence identified clearly argues against supplemental oxygen for this condition. The most definitive study on this topic is the Long-term Oxygen Treatment Trial (LOTT).⁽⁹⁰⁾ This is a well-designed, randomized, un-blinded but controlled trial of supplemental oxygen versus control in patients with moderate resting or exercise hypoxemia. The trial enrolled 738 patients with mean age above 68 years. Sixty-five percent of participants desaturated to less than 88% during a six-minute walk test (6MWT). Minority of participants had only resting hypoxia while less than half had only exercise-induced hypoxia. More than 60% of the participants had FEV1 less than 50% predicted. In the patients with moderate exercise-induced hypoxemia, supplemental oxygen was only given during exercise. In a time-to-event analysis, the study did not show significant reduction in time-to-death or first hospitalization. The supplemental oxygen did not provide sustained meaningful improvement in other outcomes including QoL measures.

The systematic evidence review identified a meta-analysis of seven trials by Liu and Gong (2019) evaluating the effects of supplemental oxygen compared to compressed or room air. The meta-analysis did not report improvements in dyspnea or functional capacity.⁽⁹¹⁾ Another meta-analysis by Ejiofor et al. (2016) showed that QoL and exercise capacity did not differ after six weeks of supplemental oxygen compared to compressed air. Fatigue and dyspnea domains of the Chronic Respiratory Disease Questionnaire (CRQ) improved with supplemental oxygen.⁽⁹²⁾ Ameer et al. (2014) evaluated four trials comparing supplemental oxygen with air. Exercise capacity and mortality did not differ although shortness of breath after a 6MWT was less in the oxygen group.⁽⁹³⁾ Maldonado et al. (2014) conducted a crossover RCT with 29 subjects assessing endurance test on 28% and 35% FiO₂. In this study, acute, one-time administration of various doses of oxygen did not affect the dyspnea scale, limb fatigue, or duration of constant load exercise.⁽⁹⁴⁾

The benefits and harms are balanced as supplemental oxygen is readily available; however, carrying around the oxygen container or concentrator may be cumbersome. In patients who continue to smoke, oxygen therapy also represents a potential hazard. On the other hand, benefits are unlikely, as indicated by the above studies. There may be large variation in prescription habits of practitioners and also patients' preferences in carrying around supplemental oxygen. The issues of acceptability to patients and accessibility, particularly in patients who live in rural areas, should be considered.

The Work Group systematically reviewed evidence related to this recommendation (91-94) and considered the assessment of the evidence put forth in the 2014 COPD CPG.(90) Therefore, this is a *Reviewed, Not changed* recommendation. The Work Group's confidence in the quality of the evidence was very low. Other considerations include insufficient evidence to judge the balance of potential benefits and harms. Patient values and preferences were varied as they do not want to be seen as debilitated. Thus, the Work Group decided upon a *Weak against* recommendation.

Recommendation

17. In patients with COPD, we suggest starting or continuing cardio-selective beta-blockers only in those who have a cardiovascular indication for beta-blockers (e.g., heart failure with reduced ejection fraction or recent myocardial infarction).

(Weak for | Reviewed, Amended)

Discussion

In patients with COPD with a cardiovascular (CV) indication for cardio-selective beta-blockers, such as heart failure with reduced ejection fraction (HFrEF) or recent myocardial infarction, observational data suggests that these agents are safe, improve mortality rates, and decrease COPD exacerbations.(95) While metoprolol was the only beta-blocker examined by the studies included in the systematic evidence review, the Work Group extrapolated these results to all cardio-selective beta-blockers, as they all have at least some cross-reactivity with beta2-receptors found in lung tissue.

He et al. (2017) assessed the clinical efficacy and safety of a low-dose cardio-selective beta-blocker (metoprolol) in treating acute exacerbation of COPD.(96) The RCT evaluated 100 patients with CV indications for beta-blockers and found metoprolol led to a reduction in COPD exacerbations and mortality when compared to placebo, without an increase in the incidence of adverse effects (chest tightness and lung rhonchi). However, the intended population of this study was patients with cor pulmonale with an N-terminal pro b-type natriuretic peptide level greater than 1,800 picograms/milliliter (pg/mL). While patients with reduced ejection fraction or cardiomyopathy were intended to be excluded from this trial, it is unclear how thoroughly this was evaluated by the investigators. Thus, it is difficult to elucidate the true benefit of beta-blockers in all patient populations with acute exacerbations of COPD.

Suissa et al. (2018) conducted an SR of 18 observational studies investigating the effectiveness of beta-blockers in COPD patients on major outcomes of death and COPD exacerbation.(95) Evidence from the SR suggests the use of beta-blockers in COPD patients with CV indications leads to reduced COPD exacerbations and mortality compared to non-use of beta-blockers.

The most recent attempt to provide better quality evidence on this topic was the β -Blockers (β LOCK) COPD RCT by Dransfield et al. (2019).(97) This trial evaluated the clinical efficacy and safety of a beta-blocker (metoprolol) in 532 patients with COPD who did not have CV indications for beta-blockers. The study was stopped early due to a higher risk of exacerbations and hospitalization associated with beta-blocker use.

Patient preferences were consistent in the patient focus group with high level of concern about QoL and medication-related side effects. The Work Group considered reports that patients with COPD-asthma overlap have poor outcomes on beta-blocker therapy, but there was not enough available evidence to

draw conclusions. The Work Group also considered that the harms of using cardio-selective beta-blockers in patients with COPD and hypertension without any other CV requirements outweigh the benefits.[\(97\)](#)

The Work Group systematically reviewed evidence related to this recommendation [\(95, 96\)](#) and considered the assessment of the evidence put forth in the 2014 COPD CPG. Therefore, this is a *Reviewed, Amended* recommendation. The Work Group's confidence in the quality of the evidence was very low. The body of evidence was limited to two RCTs with relatively small sample sizes.[\(95, 96\)](#) The use of beta-blockers in patients with a CV indication was associated with decreased COPD exacerbations and mortality, without an increase in adverse events. This was not the case for COPD patients without a CV indication for beta-blockers, in whom beta-blockers are associated with a higher risk of exacerbations and hospitalizations.[\(97\)](#) Patient values and preferences were similar, as all patients generally have the same desired outcomes regarding mortality benefits and adverse events when it comes to treatment with beta-blockers. Lastly, there was limited evidence evaluating beta-blockers in COPD patients with overlapping asthma. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

18. We suggest offering a supported self-management program that includes a written action plan with exacerbation management, smoking cessation, and exercise.
(Weak for | Reviewed, New-replaced)

Discussion

A supported self-management program may benefit patients with COPD. There was significant improvement in QoL when the self-management program included key components, such as written action for exacerbation management, exercise training, and smoking cessation.[\(98-100\)](#) In a meta-analysis of 10 RCTs by Lenferink et al. (2017),[\(101\)](#) subgroup analysis showed even greater QoL improvement in programs with smoking cessation. A meta-analysis of 10 RCTs by Cannon et al. (2016) showed that self-management with an exacerbation action plan, exercise training, and COPD education improved activity and physical function.[\(100\)](#) Without the key components, including written action for exacerbation management, disease education, smoking cessation, and exercise training, many studies did not have statistically significant improvement in QoL for COPD patients, no matter the level of severity.[\(99, 102-107\)](#)

The evidence reviewed consistently demonstrated supported self-management improved QoL, although there was not a significant difference in mortality or rates of worsening of adverse events, including rates of COPD-related hospitalizations. Exercise programs studied had varied functional outcomes but only two had improvement of dyspnea.[\(108, 109\)](#) In a meta-analysis of five RCTs by Paneroni et al. (2017), aerobic exercise training had clinical significance on QoL.[\(110\)](#) Exercise training varied among the studies, although most consisted of aerobic training with walking, cycling, or use of an arm crank and strength training either with weights or elastic bands. No harms were found with supported self-management.

Self-management plans have been widely used in other respiratory diseases such as asthma. Supported self-management plans allow patients to have guidance regarding concerns directly related to their chronic respiratory disease. These plans give patients clear instructions regarding therapies for worsening of symptoms, a structured plan for exercise, and strong recommendations for smoking cessation. When

written, the action plan is tailored for each patient. This was an important factor for focus group participants. Patients feel empowered and in control when they work jointly with a provider on a disease-specific, individualized, and written action plan.

The Work Group systematically reviewed evidence related to this recommendation ([98-110](#)) and considered the assessment of the evidence put forth in the 2014 COPD CPG. Therefore, this is a *Reviewed, New-replaced* recommendation. The confidence in the quality of evidence was low. The body of evidence had some limitations including variability in assessing behavioral health changes and variability between groups regarding components of usual care. The benefits varied among studies but many demonstrated improved QoL and rate of exacerbations. These benefits outweighed the harms, which were limited. The Work Group recognized the clinic resources needed to complete and regularly track participating patients. This should be a major consideration before initiating and integrating a supported self-management program in the primary care setting. Thus, the Work Group decided upon a *Weak for* recommendation.

Recommendation

19. We suggest offering telehealth support that includes telemonitoring and/or mobile applications.
(Weak for | Reviewed, New-replaced)

Discussion

The systematic evidence review evaluated telehealth interventions in the context of monitoring and supported self-management via telecommunications and digital communications technologies. ([111-127](#)) The interventions reviewed were very heterogeneous, but all of them would be considered supportive in nature and not a replacement for usual medical care. The quality of the evidence for the evaluation of telehealth support was low due to inconsistency. Most studies were either fair or poor quality, and studies varied with respect to their comparison groups and timing in which outcomes were assessed. The interventions were broadly categorized as telephone only, mobile phone/interactive web-based support, video supported and remote monitoring.

Telephone-assisted education, coaching, or rehabilitation interventions without mobile phone applications or telemonitoring showed improvement in QoL in studies that assessed outcomes immediately after the intervention but not in studies that assessed outcomes after some follow-up period. ([112, 127](#)) In one SR, interventions utilizing mobile phone/interactive web-based technology were more effective than face-to-face or documentary educational self-management support in improving QoL and increasing physical activity. ([111](#)) Individual RCTs identified through the systematic evidence review, however, did not show improvements in QoL with the use of smartphone applications for promotion of exercise and self-management. ([113-115](#)) Two SRs ([116, 117](#)) and five of six RCTs, ([118-123](#)) showed no improvements in QoL. Evidence of the effect of telemonitoring on acute healthcare utilization, emergency room (ER) visits, and hospitalizations was inconsistent. Two SRs ([116, 124](#)) showed improvement while one SR ([117](#)) and five RCTs did not. ([117-120, 122, 123](#)) Only two RCTs identified in the systematic evidence review were categorized as utilizing a video-supported intervention. ([125, 126](#)) Neither trial showed improvements in QoL.

There is likely significant variability in patient values and preferences regarding telehealth interventions. Patients also vary in their ability to use technology. Focus group participants were open to the idea of

internet or teleconferences but noted that in-person meetings, if held at accessible locations, would be preferable. Telehealth may assist with equity for patients whose access to care is limited by home-bound status or rural location. During pandemic outbreaks, telehealth may be the only safe option for the delivery of supportive programs. The feasibility of implementing telehealth support programs for patients with COPD has improved substantially since the 2014 VA/DoD COPD CPG due to improvements in technology and significant VA and DoD investment in telehealth infrastructure. National initiatives, such as the Rural Veterans Tele-Rehabilitation Initiative (RVTRI), and other programs have increased resources to facilities to offer telehealth options. The use of mobile apps and telemonitoring equipment requires more effort on the part of the patient; however, the interactive nature of these modalities may better engage patients in their care. Patients may be more likely to be physically active when monitoring activity with mobile applications or telemonitoring technology. Telemonitoring may reduce acute healthcare utilization, but the burdens telemonitoring place on patients may counter positive effects on QoL.

The Work Group systematically reviewed evidence related to this recommendation ([111-127](#)) and considered the assessment of the evidence put forth in the 2014 COPD CPG. Therefore, this is a *Reviewed, New-replaced* recommendation. The benefits increasing accessibility with telehealth support outweighed the harms. Patient values and preferences were somewhat varied but the Work Group thought most patients would welcome education, promotion of exercise, coping skills, and self-management training that is delivered remotely to their home. Technologic advances have increased feasibility of telehealth. Travel is particularly burdensome for patients with COPD and telehealth can overcome geographic barriers to care. Thus, the Work Group decided upon a *Weak for* recommendation.

X. Research Priorities

During the development of the 2021 COPD CPG, the Work Group identified areas needing additional research, including areas requiring stronger evidence to support current recommendations and research exploring new areas to guide future CPGs. Areas include triple therapy, diagnostic testing, dyspnea, exacerbations, hospitalizations, creating pathways to advance therapy, and the role of telehealth.

More research is needed on the safety of triple therapy and to better describe the subpopulations of COPD patients most likely to benefit from or be harmed by the steroid component of triple therapy and the use of eosinophils. In addition, research is needed to determine specific clinical signs and the utility of CRP and other diagnostic tests to further assist the identification of patients with a bacterial infection in which antibiotic therapy would be warranted. Studies comparing broad-spectrum versus narrow-spectrum antibiotics as well as specific antibiotic agents would be beneficial. Another area of potential research includes evaluating the efficacy and safety of self-initiated versus provider-initiated antibiotic therapy for COPD exacerbations. More research is also needed on how COPD treatment impacts dyspnea, COPD exacerbations, and COPD-related hospitalizations as well as clinical research is needed to provide clinicians with a stronger evidence with which to create treatment pathways.

Additional research is also needed to compare the effectiveness of telehealth versus face-to-face supported self-management programs. Additionally, further research is needed to clarify the role of telemonitoring in the care of patients with COPD in order to determine which variables or symptoms are the most useful to monitor and how telemonitoring data can be used by patients and providers.

Telemonitoring devices will likely become more sophisticated, wearable, and convenient over time; research on telehealth for COPD should be driven by advances in telehealth technology.

Lastly, evidence suggests additional research is needed to better understand the subtypes of COPD, the risk factors for each, and how they can be identified and treated differently, including those patients with symptoms and smoking history suggestive of COPD but without obstruction on pulmonary function tests (PFTs).

Appendix A: Guideline Development Methodology

A. Developing Key Questions to Guide the Systematic Evidence Review

To guide this CPG's systematic evidence review, the Work Group drafted 12 KQs on clinical topics of the highest priority for the VA and DoD populations. The KQs followed the population, intervention, comparison, outcome, timing, and setting (PICOTS) framework, as established by the Agency for Healthcare Research and Quality (AHRQ) (see [Table A-1](#)).

Table A-1. PICOTS (128)

PICOTS Element	Description
Population or Patients	Patients of interest. It includes the condition(s), populations or sub-populations, disease severity or stage, co-occurring conditions, and other patient characteristics or demographics.
Intervention or Exposure	Treatment (e.g., drug, surgery, lifestyle changes), approach (e.g., doses, frequency, methods of administering treatments), or diagnostic /screening test used with the patient or population.
Comparator	Treatment(s) (e.g., placebo, different drugs) or approach(es) (e.g., different dose, different frequency, standard of care) that are being compared with the intervention or exposure of interest described above.
Outcomes	Results of interest (e.g., mortality, morbidity, QoL, complications). Outcomes can include short, intermediate, and long-term outcomes.
Timing, if applicable	Duration or follow-up of interest for the particular patient intervention and outcome to occur (or not occur).
Setting, if applicable	Setting or context of interest. Setting can be a location (e.g., primary, specialty, inpatient care) or type of practice.

Abbreviation: PICOTS: population, intervention, comparison, outcome, timing, and setting; QoL: quality of life

Due to resource constraints, all KQs of interest to the Work Group could not be included in the systematic evidence review. Thus, the Work Group selected the 12 highest priority KQs for inclusion in the systematic evidence review (see [Table A-2](#)).

Using the GRADE approach, the Work Group rated each outcome on a 1 – 9 scale (7 – 9, critical for decision making; 4 – 6, important, but not critical, for decision making; and 1 – 3, of limited importance for decision making). Critical and important outcomes were included in the evidence review (see [Outcomes](#)); however, only critical outcomes were used to determine the overall quality of evidence (see [Grading Recommendations](#)).

a. Population(s)

The population of interest for all KQs included adults (≥ 18 years) who have a diagnosis of COPD that includes chronic bronchitis, emphysema, and chronic airflow limitation/obstruction. Some KQs also included additional sub-populations that were also covered per key question.

KQ Number	Sub-Population
1	Adults suspected of COPD
3, 4, 5	<ul style="list-style-type: none"> Patients with COPD and any of the following: asthma, significant changes in lung function with bronchodilator, elevated serum eosinophils (>150 cells/μl or >300 cells/μl) elevated sputum eosinophils, history of allergic rhinitis/atopy/polyps Patients with frequent exacerbations (>2/year or one hospitalization for COPD) Patients with mucopurulent bronchitis Patients with severe obstruction and/or lung hyperinflation or predominant dyspnea without exacerbations Patients with low level eosinophils (<100 cells/μl) and/or pneumonia
6	Adults \geq 18 years who have a diagnosis of COPD and clinical indications for beta-blockers
7	Adults \geq 18 years with a diagnosis of COPD who have only hypoxemia during exercise or nocturnal hypoxemia
8	Adults \geq 18 years with COPD and an acute exacerbation
11	<p>Adults \geq18 years with a diagnosis of COPD and considered high risk, which can be defined as the following:</p> <ul style="list-style-type: none"> BODE Index: Approximate 4 years survival by using BMI, FEV1, mMRC, 6MWT Refined ABCD assessment tool in COPD: Use GOLD standard, adverse events history in 1 year, COPD Assessment Test (CAT), and mMRC Patients with frequent exacerbations (>2/year or one hospitalization for COPD)
12	Adults with stable COPD on long-term inhaled corticosteroids

Abbreviations: BMI: body mass index; BODE: Body-mass index, airflow Obstruction, Dyspnea, and Exercise; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; KQ: key question; mMRC: Modified Medical Research Council

b. Interventions

KQ Number	Intervention
1	<ul style="list-style-type: none"> Spirometry or repeat spirometry Symptom severity Risk of exacerbations Comorbidities GOLD classification
2	Criteria/thresholds for moving COPD patients to intensive/advanced therapy (e.g., triple therapy, early use of steroids, antibiotics), including severity of exacerbations or frequency of exacerbations
3, 4, 5	<p>Single or combination drug therapy from the following drug or drug classes:</p> <ul style="list-style-type: none"> SABA LABA Short-acting anticholinergics Long-acting anticholinergics ICS Mucolytics
6	Beta-blockers
7	Oxygen administration

KQ Number	Intervention
8	<ul style="list-style-type: none"> • Short-term antibiotic treatment • Self-initiated antibiotics • CRP testing
9	Spacers or other optimization techniques, including nebulizers, soft-mist inhalers, DPI, or MDI
10	<p>Telehealth in the context of monitoring, supported self-management, including education and symptom management via telecommunications and digital communication technologies; examples of telehealth technologies include:</p> <ul style="list-style-type: none"> • Live video conferencing • Mobile health apps • Telephone, computer, or wearable and non-wearable devices for tele-consultation or remote patient monitoring • Secure web site or central server for data storage/transmission
11	<p>Supported self-management, which includes the following components:</p> <ul style="list-style-type: none"> • Action plans • Exercise/physical activity • Sleep/sleep hygiene • Nutrition • Stress/anxiety management • Smoking cessation • Pulmonary hygiene, breathing retraining, pulmonary exercise, breathing exercises • Medication education • Disease understanding and self-management skills • Home oxygen compliance • Mind-body medicine • Other alternative therapies
12	Tapered withdrawal

Abbreviations: COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; DPI: dry powder inhaler; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICS: inhaled-corticosteroid; KQ: key question; LABA: long-acting beta agonist; MDI: metered-doses inhalers; SABA: short-acting beta agonist

c. Comparators

KQ Number	Comparator
1	None or one or more of the other diagnostic tools/criteria
2	None or one of the other criteria/thresholds
3, 4, 5	Placebo, another medication, or combination of medications
6	No beta-blockers or alternative medication
7	No O ₂ administration
8	<ul style="list-style-type: none"> • Placebo, different antibiotic, different class of antibiotics • Physician-initiated antibiotics • No CRP testing
9	No optimization technique
10	Usual or standard of care
11	No self-management; usual or standard care
12	Immediate withdrawal or other withdrawal method

Abbreviations: CRP: C-reactive protein; KQ: key question

d. Outcomes

KQ Number	Critical Outcome(s)	Important Outcomes(s)
1	COPD diagnosis, diagnostic accuracy	Clinical classification, treatment planning, clinical adherence
2	QoL, morbidity/harms, dyspnea, exacerbation	Functional capacity, mortality
3	QoL, morbidity/harms, dyspnea, exacerbation, mortality	Functional capacity
4	QoL, morbidity/harms, dyspnea, exacerbation, mortality	Functional capacity
5	QoL, morbidity/harms, dyspnea, exacerbation, mortality	Functional capacity
6	Morbidity/harms, exacerbation, mortality	QoL, dyspnea, functional capacity
7	QoL, morbidity/harms, dyspnea, mortality	Functional capacity, exacerbation
8	Morbidity/harms, exacerbation, mortality	QoL, dyspnea, functional capacity, reduction in antibiotic use
9	Dyspnea, exacerbation, mortality	QoL, morbidity/harms, functional capacity, adherence
10	QoL, exacerbation	Morbidity/harms, dyspnea, functional capacity, mortality, healthcare utilization
11	QoL, exacerbation, dyspnea	Morbidity/harms, functional capacity, mortality, healthcare utilization
12	Morbidity/harms, exacerbation, safety	QoL, dyspnea

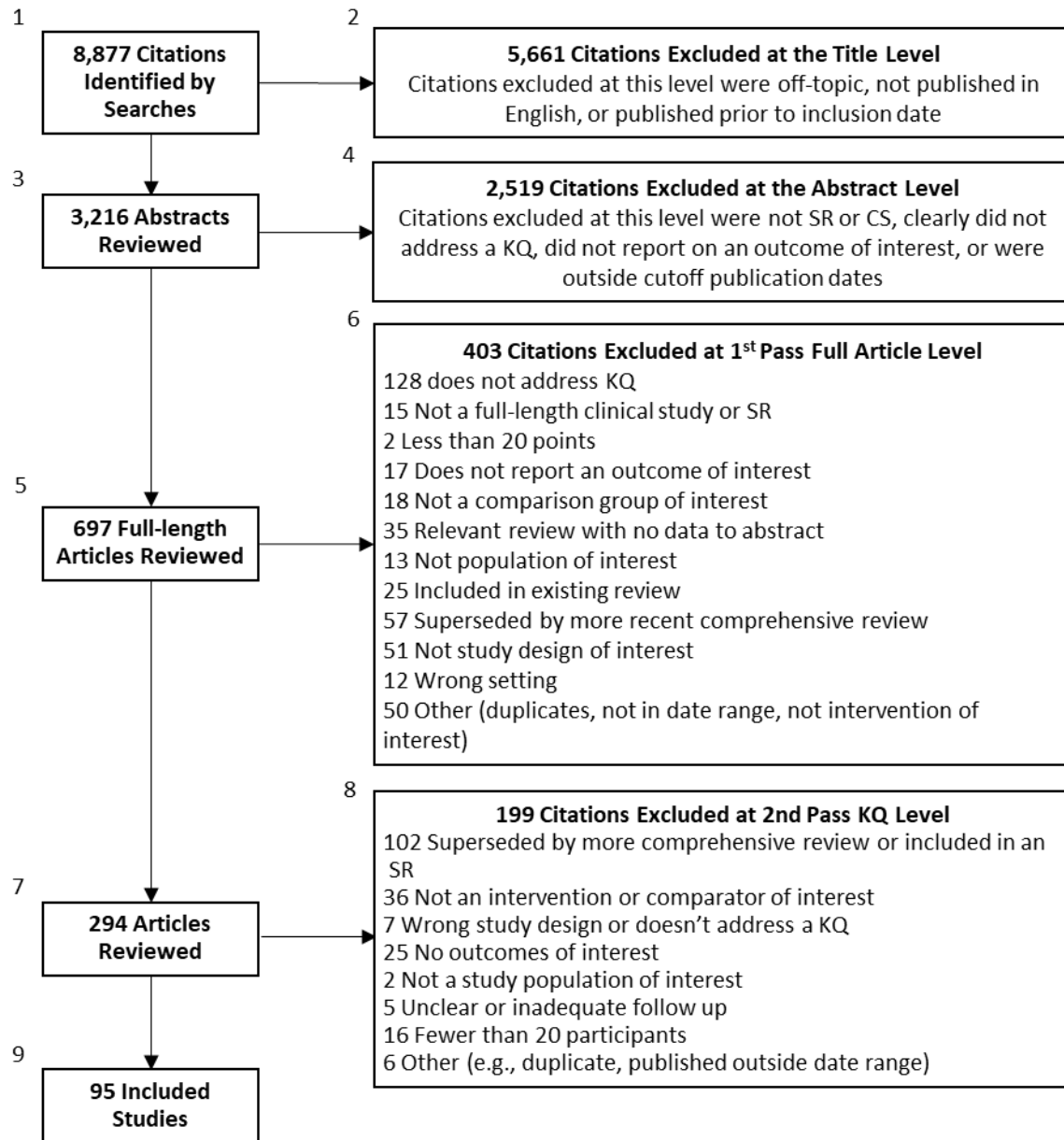
Abbreviations: COPD: chronic obstructive pulmonary disease; KQ: key question; QoL: quality of life

B. Conducting the Systematic Review

Based on the Work Group's decisions regarding the CPG's scope, KQs, and PICOTS statements, the Lewin Team produced a systematic evidence review protocol before conducting the review. The protocol detailed the KQs, PICOTS criteria, methodology to be used during the systematic evidence review, and the inclusion and exclusion criteria to be applied to each potential study, including study type and sample size. The Work Group reviewed and approved the protocol.

[Figure A-1](#) below outlines the systematic evidence review's screening process (see also the [General Criteria for Inclusion in Systematic Review](#) and [Key Question Specific Criteria](#)). In addition, [Table A-2](#) indicates the number of studies that addressed each of the questions.

Figure A-1. Study Flow Diagram



Abbreviations: CS: clinical study; KQ: key question; SR: systematic review

Alternative Text Description of Study Flow Diagram

Figure A-1. Study Flow Diagram is a flow chart with nine labeled boxes linked by arrows that describe the literature review inclusion/exclusion process. Arrows point down to boxes that describe the next literature review step and arrows point right to boxes that describe the excluded citations at each step (including the reasons for exclusion and the numbers of excluded citations).

1. Box 1: 8,877 citations identified by searches
 - a. Right to Box 2: 5,661 citations excluded at the title level

- i. Citations excluded at this level were off-topic, not published in English, or published prior to inclusion date
 - b. Down to Box 3: 3,214 abstracts reviewed
- 2. Box 3: 3,216 abstracts reviewed
 - a. Right to Box 4: 2,519 citations excluded at the abstract level
 - i. Citations excluded at this level were not an SR or clinical study, clearly did not address a KQ, did not report on an outcome of interest, or were outside cutoff publication dates
 - b. Down to Box 5: 697 full-length articles reviewed
- 3. Box 5: 697 full-length articles reviewed
 - a. Right to Box 6: 403 citations excluded at 1st pass full article level
 - i. Articles excluded at this level did not: address a KQ of interest, enroll the population of interest, meet inclusion criteria for SR or clinical study, or were a duplicate
 - b. Down to Box 7: 294 articles reviewed
- 4. Box 7: 294 articles reviewed
 - a. Right to Box 8: 199 citations excluded at 2nd pass full article level
 - i. 102 Superseded by more comprehensive review or included in a SR
 - ii. 36 Not an intervention or comparator of interest
 - iii. 7 Wrong study design or doesn't address KQ
 - iv. 25 No outcomes of interest
 - v. 2 Not a study population of interest
 - vi. 5 Unclear or inadequate follow-up
 - vii. 16 Fewer than 20 patients
 - viii. 6 Other
 - b. Down to Box 9: 95 included studies
- 5. Box 9: 95 included studies

Table A-2. Evidence Base for KQs

KQ Number	KQ	Number and Study Type
1	In patients with suspected or diagnosed COPD, what is the evidence that using spirometry or repeat spirometry, symptom severity, risk of exacerbations, GOLD classification, and comorbidities, alone or in combination, improves diagnosis, clinical classification, treatment planning, clinician adherence to treatment protocols, and diagnostic accuracy?	1 SR, 3 RCTs, 1 cohort study, 11 diagnostic studies
2	In patients with confirmed diagnosis of COPD, is there evidence to support criteria for intensive/advanced therapy?	2 RCTs, 1 cohort trial

KQ Number	KQ	Number and Study Type
3	In patients with confirmed COPD, what is the evidence that single drug therapy with the following drug classes improves outcomes? <ul style="list-style-type: none"> • Short-acting beta agonists (SABA) • Long-acting beta agonists (LABA) • Short-acting anticholinergics • Long-acting anticholinergics • Mucolytics 	10 SRs
4	In patients with confirmed COPD, what is the evidence that dual therapy with the following drug classes, or combinations, improves outcomes? <ul style="list-style-type: none"> • Short-acting beta agonists (SABA) • Long-acting beta agonists (LABA) • Short-acting anticholinergics • Long-acting anticholinergics • Inhaled corticosteroids • Mucolytics • Roflumilast 	8 SRs
5	In patients with confirmed COPD, what is the evidence that triple therapy with the following drug classes, or combinations, improves outcomes? <ul style="list-style-type: none"> • Short-acting beta agonists (SABA) • Long-acting beta agonists (LABA) • Short-acting anticholinergics • Long-acting anticholinergics • Inhaled corticosteroids • Mucolytics • Roflumilast 	4 SRs
6	In patients with confirmed COPD who have other clinical indication(s) for beta-blocker treatment, what is the evidence of benefits and/or harms with use of these agents?	1 SR, 2 RCTs
7	In patients with confirmed COPD who have hypoxemia during exercise or nocturnal hypoxemia, does administration of oxygen (oxygen) compared to no oxygen improve outcomes?	3 SRs, 2 RCTs
8	In patients with confirmed COPD and an acute exacerbation, what is the evidence that administration of short-term antibiotics are more effective than placebo in obtaining improved outcomes?	2 SRs, 2 RCTs
9	In patients with confirmed COPD does the use of spacers or other optimization of inhaler technique improve patient adherence and outcomes?	1 SR, 4 RCTs
10	In patients with confirmed COPD, what are the benefits and harms of telehealth compared to usual care for ongoing monitoring, education, and symptom management?	7 SRs, 12 RCTs
11	In patients with confirmed COPD, does supported self-management (action plans, exercise plans) improve clinical outcomes?	9 SRs, 7 RCTs
12	In patients with confirmed COPD, treated with long-term inhaled corticosteroids what is the safest and most effective way to withdraw therapy?	2 SRs
Total Evidence Base		95 studies

Abbreviations: COPD: chronic obstructive pulmonary disease; KQ: key question; RCT: randomized controlled trial; SR: systematic review

a. General Criteria for Inclusion in Systematic Evidence Review

- All studies included as evidence must have been published in English on or after January 1, 2014, to February 21, 2020.
- Publication must have been a full text clinical study or systematic review; abstracts alone were not included. Similarly, letters, editorials, and other publications that were not full-length clinical studies were not accepted as evidence.
- Study must have enrolled a patient population in which at least 85% of patients had COPD, with identifiable data for the population of interest (i.e., patients with COPD should have been identifiable in the dataset).
- Only studies assessing the efficacy of drugs that have received FDA approval for marketing in the U.S. were included in this review.
- Study must have enrolled at least 20 patients (10 per study group).
- Study must have reported on an outcome of interest.

b. Key Question Specific Criteria for Inclusion in Systematic Evidence Review

- Studies addressing KQs 2 to 12 must have been an SR of RCTs or an RCT. Observational studies were not considered as evidence for these questions. Randomized crossover trials were included only if data from the first period (prior to treatment crossover) was reported separately. Post-hoc and non-systematic pooled analyses were only included if they addressed a subpopulation or outcome not covered or reported in original study.
- For KQ 1, SRs of acceptable study designs and prospective diagnostic cohort or other prospective non-RCT studies that reported on the diagnostic characteristics (i.e., sensitivity, specificity) of the tools assessed in the question were also accepted as evidence. Retrospective case series or chart reviews were not accepted as evidence. SRs must have searched MEDLINE or EMBASE for eligible publications, performed a risk of bias assessment of included studies, and assessed the quality of evidence using a recognizable rating system, such as GRADE or something compatible (e.g., the Strength of Evidence ratings used by the Evidence-based Practice Centers for the Agency for Research and Quality). If an existing review did not assess the overall quality of the evidence, evidence from the review must have been reported in a manner that allowed judgment of the overall risk of bias, consistency, directness, and precision of evidence. Existing reviews were not used as evidence if it was not possible to assess the overall quality of the evidence in the review.
- For KQ 8, short-term antibiotic use was defined as 10 days or less.

c. Literature Search Strategy

Information regarding the bibliographic databases, date limits, and platform/provider can be found in [Table A-3](#). See [Appendix I](#) for additional information on the search strategies, including topic-specific search terms and search strategies.

Table A-3. Bibliographic Database Information

Name	Date Limits	Platform/Provider
Embase	01/01/2014 – 02/21/2020	Embase.com
Medline	01/01/2014 – 02/21/2020	Embase.com
PubMed In Process & Non-Indexed Citations	01/01/2014 – 02/21/2020	pubmed.ncbi.nlm.nih.gov

C. Developing Evidence-based Recommendations

In consultation with the VA Office of Quality and Patient Safety and the Office of Evidence Based Practice, U.S. Army Medical Command Office, the Lewin Team convened a four-day virtual recommendation development meeting on June 15, 2020, to develop this CPG's evidence-based recommendations. Two weeks before the meeting, the Lewin Team finalized the systematic evidence review and distributed the report to the Work Group; findings were also presented during the first day of the recommendation development meeting.

Led by the Champions, the Work Group interpreted the systematic evidence review's findings and developed this CPG's recommendations. Where appropriate, the Work Group carried forward and modified recommendations from the 2014 VA/DoD COPD CPG as necessary (see [Categorization of 2014 Clinical Practice Guideline Recommendations](#)). The Work Group also developed new recommendations not included in the 2014 VA/DoD COPD CPG based on the 2020 evidence review.

As the Work Group drafted recommendations, they also rated each recommendation based on a modified GRADE and USPSTF methodology. Recommendations were rated by assessing the quality of the overall evidence base, the associated benefits and harms, patient values and preferences, and other implications.

a. Grading Recommendations

Per GRADE, each recommendation's strength and direction is determined by the following four domains:[\(21\)](#)

1. Confidence in the Quality of the Evidence

Confidence in the quality of the evidence reflects the quality of the evidence base supporting a recommendation. The options for this domain include: *High*, *Moderate*, *Low*, or *Very low*. This is a direct reflection of the GRADE ratings for each relevant critical outcome in the evidence review (see [Outcomes](#)). Per GRADE, if the quality of evidence differs across the relevant critical outcomes, the lowest quality of evidence for any of the critical outcomes determines the overall quality of the evidence for a recommendation.[\(23, 24\)](#)

The recommendation strength generally aligns with the confidence in the quality of evidence. For example, *Strong* recommendations are typically supported by *High* or *Moderate* quality evidence. However, GRADE permits *Low* or *Very low* quality evidence to support a *Strong* recommendation in certain instances (e.g., life-threatening situation).[\(21\)](#)

2. Balance of Desirable and Undesirable Outcomes

The balance of desirable and undesirable outcomes (i.e., benefits and harms) refers to the relative magnitudes or tradeoffs of anticipated benefits (e.g., increased longevity, reduced morbidity, improved

QoL, decreased resource use) and harms (e.g., decreased longevity, increased complications, impaired QoL). The options for this domain include: *benefits outweigh harms/burden*, *benefits slightly outweigh harms/burden*, *benefits and harms/burdens are balanced*, *harms/burdens slightly outweigh benefits*, and *harms/burdens outweigh benefits*. This domain assumes most clinicians will offer patients an intervention if its advantages exceed the harms. The Work Group's understanding of the benefits and harms associated with the recommendation influenced the recommendation's strength and direction.

3. Patient Values and Preferences

Patient values and preferences is an overarching term that includes patients' perspectives, beliefs, expectations, and goals for health and life as they may apply to the intervention's potential benefits, harms, costs, limitations, and inconvenience. The options for this domain include: *similar values*, *some variation*, or *large variation*. For instance, there may be *some variation* in patient values and preferences for a recommendation on the use of acupuncture, as some patients may dislike needles. When patient values seem homogeneous, this domain may increase the recommendation's strength. Alternatively, when patient values seem heterogeneous, this domain may decrease a recommendation's strength. As part of this domain, the Work Group considered the findings from the patient focus group carried out as part of this CPG update (see [Appendix B](#)).

4. Other Implications

Other implications encompass the potential consequences or other impacts that might affect the strength or direction of the recommendation. The options for this domain include resource use, equity, acceptability, feasibility, and subgroup considerations. The following are example implications related to equity and subgroup considerations, respectively: some of the indicated population may be geographically remote from an intervention (e.g., complex radiological equipment); a drug may be contraindicated in a subgroup of patients.

Table A-4. GRADE Evidence to Recommendation Framework

Decision Domain	Questions to Consider	Judgment
Confidence in the quality of the evidence	Among the designated critical outcomes, what is the lowest quality of relevant evidence? How likely is further research to change the confidence in the estimate of effect?	High Moderate Low Very low
Balance of desirable and undesirable outcomes	What is the magnitude of the anticipated desirable outcomes? What is the magnitude of the anticipated undesirable outcomes? Given the best estimate of typical values and preferences, are you confident that benefits outweigh harms/burdens or vice versa?	Benefits outweigh harms/burdens Benefits slightly outweigh harm/burden Benefits and harms/burdens are balanced Harms/burdens slightly outweigh benefits Harms/burdens outweigh benefits
Patient values and preferences	What are the patients' values and preferences? Are values and preferences similar across the target population? Are you confident about typical values and preferences?	Similar values Some variation Large variation

Decision Domain	Questions to Consider	Judgment
Other implications (e.g., resource use, equity, acceptability, feasibility, subgroup considerations)	What are the costs per resource unit? Is this intervention generally available? What is the variability in resource requirements across the target population and settings? Are the resources worth the expected net benefit from the recommendation? Is this intervention and its effects worth withdrawing or not allocating resources from other interventions?	Various considerations

b. Recommendation Categorization

A summary of the recommendation categories and definitions is available in [Table 3](#).

1. Categorizing Recommendations with an Updated Review of the Evidence

Reviewed refers to recommendations on topics included in this CPG's systematic evidence review.

Reviewed, New-added recommendations are original, new recommendations (i.e., not included in the previous CPG). These recommendations are based entirely on evidence included in the current CPG's systematic evidence review.

Reviewed, New-replaced recommendations were in the previous CPG but revised based on the updated evidence review. These recommendations may have clinically relevant edits. *Reviewed, Not changed* recommendations were carried forward from the previous CPG unchanged. *Reviewed, Amended* recommendations were carried forward from the previous CPG with a nominal change. This allowed for the recommendation language to reflect GRADE approach and any other not clinically meaningful edits deemed necessary. These recommendations can be based on a combination of evidence included in the current CPG's systematic evidence review and the evidence base that supported the recommendation in the previous CPG.

Reviewed, Deleted refers to recommendations from the previous CPG that were deleted after a review of the evidence. This may occur if the evidence supporting the recommendation is outdated (e.g., there is no longer a basis to recommend use of an intervention and/or new evidence suggests a shift in care), rendering the recommendation obsolete.

2. Categorizing Recommendations without an Updated Review of the Evidence

There were also cases in which it was necessary to carry forward recommendations from the previous CPG without an updated review of the evidence. Given time and resource constraints, the systematic evidence review carried out for this CPG update could not cover all available evidence on COPD; therefore, its KQs focused on new or updated research or areas not covered in the previous CPG.

For areas in which the relevant evidence was not changed and for which recommendations made in the previous CPG were still relevant, recommendations could have been carried forward to the updated CPG without an updated review of the evidence. The evidence supporting these recommendations was thus also carried forward from the previous CPG. These recommendations were categorized as *Not reviewed*. If evidence had not been reviewed, recommendations could have been categorized as *Not changed*, *Amended*, or *Deleted*. *Not reviewed, Not changed* recommendations were carried forward from the previous CPG unchanged. *Not reviewed, Amended* recommendations were modified from the previous

CPG with a nominal change. *Not reviewed, Deleted* recommendations were determined by the Work Group to not be relevant. A recommendation may not be relevant if it, for example, pertained to a topic (e.g., population, care setting, treatment) outside of the updated CPG's scope or if it was determined to be common practice.

The recommendation categories for the current CPG are noted in the [Recommendations](#). The recommendation categories from the 2014 VA/DoD COPD CPG are noted in [Appendix D](#).

D. Drafting and Finalizing the Guideline

The Work Group wrote, reviewed, and edited three drafts of the CPG using an iterative review process to solicit feedback on and make revisions to the CPG. The first and second drafts were posted online for 20 and 14 business days, respectively, for the Work Group to provide feedback. Draft 3 was made available for a 14-day peer review and comment (see [External Peer Review](#)). The Work Group reviewed all feedback submitted during each review period and made appropriate revisions to the CPG. Following the Draft 3 review and comment period, the Work Group reviewed external feedback and created a final draft of the CPG. The Champions then presented the CPG to the EBPWG for approval. The Work Group considered the EBPWG's feedback and revised the CPG as appropriate to create the final version. To accompany the CPG, the Work Group produced toolkit products, including a provider summary, pocket card, and patient summary. The EBPWG approved the final CPG and toolkit products in April 2021.

Appendix B: Patient Focus Group Methods and Findings

A. Methods

VA and DoD Leadership recruited participants for the focus group, with support from the Champions, other Work Group members, and individuals at the patient focus group location as needed. While participant recruitment focused on eliciting a range of perspectives likely to be relevant and informative in the CPG development process, patient focus group participants were not intended to be a representative sample of VA and DoD patients. Participants were not incentivized for their participation or reimbursed for travel expenses.

The Work Group, with support from the Lewin Team, identified topics on which patient input was important to consider in developing the CPG. The Lewin Team developed, and the Work Group approved, a patient focus group guide covering these topics. The focus group facilitator led the discussion using the guide to elicit the patients' perspectives about their treatment and overall care. Given the limited time and the range of interests of the focus group participants, not all questions were addressed.

B. Patient Focus Group Findings

a. Participants indicated that providers should consider activities of daily living when assessing a patient's pulmonary functioning to better understand the practical impact of COPD on a patient's life.

- Participants thought pulmonary function testing should include activities of daily living instead of just walking.
- Participants expressed concern that their providers did not consider the practical aspects of managing their COPD and the impact it has on their lives.

b. Participants were concerned about the practicality and weight of supplemental oxygen equipment and expressed unanimous support for rescue inhalers.

- Participants agreed that their supplemental oxygen tanks were too heavy and expressed a desire for lighter and more portable equipment. Although participants wanted lighter oxygen equipment, they found the smaller oxygen concentrators to be too expensive.
- Many participants disliked the single strap design of oxygen cylinder bags because it is uncomfortable, impractical, and restricts them from carrying other items.
- Participants were hesitant to use oxygen on a regular basis. Many agreed it is easy to become dependent on it.
- All participants valued the portability of rescue inhalers and most carried at least one with them at all times.

c. Participants valued self-management and alternative medicine treatment options.

- Participants valued exercise as a self-management tool because it improved their symptoms and provided social stimulation.

- Most participants thought a COPD support group would be helpful for social interaction and sharing of treatment options.
 - Participants were open to trying alternative medicine and turned to naturopathic options when the care they received was inadequate.
- d. Participants varied in their trust of the medical system and sought more consistent care from providers who knew them and their medical issues.***
- VA participants expressed frustration with scheduling appointments and receiving follow-up from their providers.
 - Participants sought consistent care from the same team of providers.
- e. Participants stressed the importance of shared decision making in discussing treatment options with their providers. Patients sought providers who considered an individual's comorbidities when discussing treatment options and were mindful that patients vary in their preferences for and tolerance of different treatments.***
- Participants valued providers who use shared decision making to understand a patient's needs, values, and treatment preferences.
 - Participants received inconsistent care from providers. While some of their providers utilized shared decision making to individualize their care, others did not.

Appendix C: Evidence Table

Table C-1. Evidence Table^{a,b,c,d}

Recommendation	2014 Strength of Recommendation	Evidence	2021 Strength of Recommendation	Recommendation Category
1. We suggest post-bronchodilator spirometry to confirm clinical diagnosis of COPD.	Strong for	(42 , 43) Additional References: (37-41 , 44-48)	Weak for	Reviewed, New-replaced
2. There is insufficient evidence to recommend for or against any specific clinical criteria to inform decision-making regarding advancing pharmacologic therapy for COPD.	N/A	(50-52) Additional References: (49)	Neither for nor against	Reviewed, New-added
3. We recommend smoking cessation for prevention and risk reduction of COPD.	Strong for	(53 , 54)	Strong for	Reviewed, New-replaced
4. We suggest routine vaccination for influenza and pneumococcal pneumonia for prevention and risk reduction of COPD exacerbations.	Strong for	(55 , 56)	Weak for	Reviewed, New-replaced
5. We recommend offering inhaled long-acting muscarinic antagonists as first-line therapy in patients with symptomatic COPD.	Weak for Strong for	(57-67)	Strong for	Reviewed, New-replaced
6. We recommend against offering an inhaled long-acting beta agonist as first-line therapy in patients with symptomatic COPD, unless a long-acting muscarinic antagonist is not tolerated or is contraindicated.	N/A	(57-67)	Strong against	Reviewed, New-added

^a 2014 Strength of Recommendation column: The 2014 VA/DoD COPD CPG was developed using the GRADE approach to determine the strength of each recommendation. Inclusion of more than one 2014 strength of recommendation indicates that more than one 2014 VA/DoD COPD CPG recommendation is covered by the 2021 recommendation. “Not applicable” indicates that the 2014 VA/DoD COPD CPG recommendation was a new recommendation, and therefore does not have an associated 2014 strength of recommendation.

^b Evidence column: The first set of references listed in each row in the evidence column constitutes the evidence base for the recommendation. To be included in the evidence base for a recommendation, a reference needed to be identified through a systematic evidence review carried out as part of the initial development or update of this CPG. The second set of references in the evidence column (called “Additional References”) includes references that provide additional information related to the recommendation, but which were not identified through a systematic evidence review. These references were, therefore, not included in the evidence base for the recommendation and did not influence the strength and direction of the recommendation.

^c 2021 Strength of Recommendation column: The 2021 VA/DoD COPD CPG was developed using the GRADE approach to determine the strength of each recommendation. Refer to the Grading Recommendations section for more information.

^d Recommendation Category column: Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.

Recommendation	2014 Strength of Recommendation	Evidence	2021 Strength of Recommendation	Recommendation Category
7. We recommend against offering an inhaled corticosteroid in patients with symptomatic COPD as a first-line therapy.	Strong against	(69) Additional References: (68)	Strong against	Not reviewed, Amended
8. For patients with moderate to severe obstruction who continue to report significant dyspnea or decreased quality of life despite using a long-acting muscarinic antagonist, we suggest adding a long-acting beta agonist to long-acting antimuscarinic agent therapy.	Strong for	(70)	Weak for	Reviewed, New-replaced
9. If choosing dual therapy, we recommend against offering long-acting beta agonists with inhaled corticosteroids for patients with COPD.	N/A	(70) Additional References: (71, 72)	Strong against	Reviewed, New-added
10. In patients with COPD who are on combination therapy with a long-acting antimuscarinic agent/long-acting beta agonist and continue to have COPD exacerbations, we suggest adding an inhaled corticosteroid as a third medication.	Weak for	(73-76)	Weak for	Reviewed, New-replaced
11. There is insufficient evidence to recommend for or against the use of eosinophilia or suspicion of asthma-COPD overlap syndrome to guide choice of additional therapy.	N/A	(75)	Neither for nor against	Reviewed, New-added
12. We suggest considering withdrawal of inhaled corticosteroids in patients with COPD without moderate to severe exacerbations in the last two years.	N/A	(77, 78)	Weak for	Reviewed, New-added
13. There is insufficient evidence to recommend for or against the use of N-acetylcysteine preparations available in the United States for patients with stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough).	N/A	(79)	Neither for nor against	Reviewed, Amended
14. There is insufficient evidence to recommend for or against the use of antibiotics for outpatient COPD exacerbations (C-reactive protein guided or not).	N/A	(80-82)	Neither for nor against	Reviewed, New-replaced
15. We recommend providing long-term oxygen therapy to patients with chronic stable resting severe hypoxemia ($\text{PaO}_2 < 55$ mm Hg and/or $\text{SaO}_2 \leq 88\%$) or chronic stable resting moderate hypoxemia ($\text{PaO}_2 56 - 59$ mm Hg or $\text{SaO}_2 > 88\%$ and $\leq 90\%$) with signs of tissue hypoxia (hematocrit $> 55\%$, pulmonary hypertension, or cor pulmonale).	Strong for	(83-85) Additional References: (86-89)	Strong for	Not reviewed, Not changed

Recommendation	2014 Strength of Recommendation	Evidence	2021 Strength of Recommendation	Recommendation Category
16. We suggest against routinely offering ambulatory long-term supplemental oxygen for patients with chronic stable isolated exercise hypoxemia, in the absence of another clinical indication for supplemental oxygen.	Weak against	(90-94)	Weak against	Reviewed, Not changed
17. In patients with COPD, we suggest starting or continuing cardio-selective beta-blockers only in those who have a cardiovascular indication for beta-blockers (e.g., heart failure with reduced ejection fraction or recent myocardial infarction).	Weak for	(95, 96) Additional References: (97)	Weak for	Reviewed, Amended
18. We suggest offering a supported self-management program that includes a written action plan with exacerbation management, smoking cessation, and exercise.	Weak for	(98-110)	Weak for	Reviewed, New-replaced
19. We suggest offering telehealth support that includes telemonitoring and/or mobile applications.	Weak for	(106, 111-126)	Weak for	Reviewed, New-replaced

Appendix D: 2014 Recommendation Categorization Table

Table D-1. 2014 COPD CPG Recommendation Categorization Table^{a,b,c,d,e,f}

2014 CPG Recommendation #	2014 CPG Recommendation Text	2014 CPG Strength of Recommendation	2021 CPG Recommendation Category	2021 CPG Recommendation #
1	We recommend that spirometry, demonstrating airflow obstruction (post-bronchodilator forced expiratory volume in one second/forced vital capacity [FEV1/FVC] <70%, with age adjustment for more elderly individuals), be used to confirm all initial diagnoses of chronic obstructive pulmonary disease (COPD).	Strong for	Reviewed, New-replaced	1
2	We have no recommendations regarding utilization of existing clinical classification systems at this time.	N/A	Not reviewed, Deleted	N/A
3	We suggest classification of patients with COPD into two groups: Patients who experience frequent exacerbations (two or more/year, defined as prescription of corticosteroids, prescription of antibiotics, hospitalization, or emergency department [ED] visit); and Patients without frequent exacerbations.	Weak for	Not reviewed, Deleted	N/A

^a 2014 CPG Recommendation # column: This indicates the recommendation number of the recommendation in the 2014 VA/DoD COPD CPG.

^b 2014 CPG Recommendation Text column: This contains the wording of each recommendation from the 2014 VA/DoD COPD CPG.

^c 2014 CPG Strength of Recommendation column: The 2014 VA/DoD COPD CPG used the GRADE approach to determine the strength of each recommendation. The strength of recommendations in the 2014 VA/DoD COPD CPG were: Strong for, Weak for, N/A, Weak against, or Strong against.

^d 2014 CPG Recommendation Category column: This is the recommendation category assigned during the development of the 2014 VA/DoD COPD CPG. Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.

^e 2021 CPG Recommendation Category column: This is the recommendation category assigned during the development of the 2021 VA/DoD COPD CPG. Refer to the Recommendation Categorization section for more information on the description of the categorization process and the definition of each category.

^f 2021 CPG Recommendation # column: For recommendations that were carried forward from the 2014 VA/DoD COPD CPG, this column indicates the new recommendation(s) to which they correspond.

2014 CPG Recommendation #	2014 CPG Recommendation Text	2014 CPG Strength of Recommendation	2021 CPG Recommendation Category	2021 CPG Recommendation #
4	We recommend offering prevention and risk reduction efforts including smoking cessation and vaccination. <i>Modified from the 2007 CPG without an updated systematic review of the evidence.</i>	Strong for	Reviewed, New-replaced	3, 4
5	We recommend investigating additional comorbid diagnoses particularly in patients who experience frequent exacerbations (two or more/year, defined as prescription of corticosteroids, prescription of antibiotics, hospitalization, or ED visit) using simple tests and decision rules (cardiac ischemia [troponin, electrocardiogram], congestive heart failure [B-type natriuretic peptide (BNP), pro-BNP], pulmonary embolism [D-dimer plus clinical decision rule], and gastroesophageal reflux).	Strong for	Not reviewed, Deleted	N/A
6	We suggest that patients with COPD and signs or symptoms of a sleep disorder have a diagnostic sleep evaluation. <i>Modified from the 2007 CPG without an updated systematic review of the evidence.</i>	Weak for	Not reviewed, Deleted	N/A
7	We suggest that patients presenting with early onset COPD or a family history of early onset COPD be tested for alpha-1 antitrypsin (AAT) deficiency. <i>Modified from the 2007 CPG without an updated systematic review of the evidence.</i>	Weak for	Not reviewed, Deleted	N/A
8	We recommend that patients with AAT deficiency be referred to a pulmonologist for management of treatment. <i>Modified from the 2007 CPG without an updated systematic review of the evidence.</i>	Strong for	Not reviewed, Deleted	N/A
9	We recommend prescribing inhaled short-acting beta 2-agonists (SABAs) to patients with confirmed COPD for rescue therapy as needed. <i>Modified from the 2007 CPG without an updated systematic review of the evidence.</i>	Strong for	Not reviewed, Deleted	N/A
10	We suggest using spacers for patients who have difficulty actuating and coordinating drug delivery with metered-dose inhalers (MDIs). <i>Modified from the 2007 CPG without an updated systematic review of the evidence.</i>	Weak for	Reviewed, Deleted	N/A
11	We recommend offering long-acting bronchodilators to patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough).	Strong for	Reviewed, Deleted	N/A
12	We suggest offering the inhaled long-acting antimuscarinic agent (LAMA) tiotropium as first-line maintenance therapy in patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough).	Weak for	Reviewed, Deleted	5

2014 CPG Recommendation #	2014 CPG Recommendation Text	2014 CPG Strength of Recommendation	2021 CPG Recommendation Category	2021 CPG Recommendation #
13	We recommend inhaled tiotropium as first-line therapy for patients with confirmed, stable COPD who have respiratory symptoms (e.g., dyspnea, cough) and severe airflow obstruction (i.e., post bronchodilator FEV1 <50%) or a history of COPD exacerbations.	Strong For	Reviewed, New-replaced	5
14	For clinically stable patients with a confirmed diagnosis of COPD and who have not had exacerbations on short-acting antimuscarinic agents (SAMAs), we suggest continuing with this treatment, rather than switching to long-acting bronchodilators. <i>Modified from the 2007 CPG without an updated systematic review of the evidence.</i>	Weak For	Not reviewed, Deleted	N/A
15	For patients treated with a SAMA who are started on a LAMA to improve patient outcomes, we suggest discontinuing the SAMA. <i>Modified from the 2007 CPG without an updated systematic review of the evidence.</i>	Weak For	Not reviewed, Deleted	N/A
16	We recommend against offering an inhaled corticosteroid (ICS) in symptomatic patients with confirmed, stable COPD as a first-line monotherapy.	Strong Against	Not reviewed, Amended	7
17	We recommend against the use of inhaled long-acting beta 2-agonists (LABAs) without an ICS in patients with COPD who may have concomitant asthma.	Strong Against	Not reviewed, Deleted	N/A
18	In patients with confirmed, stable COPD who are on inhaled LAMAs (tiotropium) or inhaled LABAs alone and have persistent dyspnea on monotherapy, we recommend combination therapy with both classes of drugs.	Strong For	Reviewed, New-replaced	8
19	In patients with confirmed, stable COPD who are on combination therapy with LAMAs (tiotropium) and LABAs and have persistent dyspnea or COPD exacerbations, we suggest adding ICS as a third medication.	Weak For	Reviewed, New replaced	10
20	We suggest against offering roflumilast in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist.	Weak Against	Not reviewed, Deleted	N/A
21	We suggest against offering chronic macrolides in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist.	Weak Against	Not reviewed, Deleted	N/A
22	We suggest against offering theophylline in patients with confirmed, stable COPD in primary care without consultation with a pulmonologist.	Weak Against	Not reviewed, Deleted	N/A

2014 CPG Recommendation #	2014 CPG Recommendation Text	2014 CPG Strength of Recommendation	2021 CPG Recommendation Category	2021 CPG Recommendation #
23	There is insufficient evidence to recommend for or against the use of N-acetylcysteine (120) preparations available in the U.S. in patients with confirmed, stable COPD who continue to have respiratory symptoms (e.g., dyspnea, cough).	N/A	Reviewed, Amended	13
24	We suggest not withholding cardio-selective beta-blockers in patients with confirmed COPD who have a cardiovascular indication for beta-blockers.	Weak For	Reviewed, Amended	17
25	We suggest using non-pharmacologic therapy as first-line therapy and using caution in prescribing hypnotic drugs for chronic insomnia in primary care for patients with COPD, especially for those with hypercapnea or severe COPD. <i>Modified from the 2007 CPG without an updated systematic review of the evidence.</i>	Weak For	Not reviewed, Deleted	N/A
26	For patients with COPD and anxiety, we suggest consultation with a psychiatrist and/or a pulmonologist to choose a course of anxiety treatment that reduces, as much as possible, the risk of using sedatives/anxiolytics in this population. <i>Modified from the 2007 CPG without an updated systematic review of the evidence.</i>	Weak For	Not reviewed, Deleted	N/A
27	We recommend providing long-term oxygen therapy (LTOT) to patients with chronic stable resting severe hypoxemia (partial pressure of oxygen in arterial blood [PaO ₂] <55 mm Hg and/or peripheral capillary oxygen saturation [SaO ₂] ≤88%) or chronic stable resting moderate hypoxemia (PaO ₂ of 56-59 mm Hg or SaO ₂ >88% and ≤90%) with signs of tissue hypoxia (hematocrit >55%, pulmonary hypertension, or cor pulmonale). <i>Modified from the 2007 CPG without an updated systematic review of the evidence.</i>	Strong For	Not reviewed, Not changed	15
28	We recommend that patients discharged home from hospitalization with acute transitional oxygen therapy are evaluated for the need for LTOT within 30-90 days after discharge. LTOT should not be discontinued if patients continue to meet the above criteria. <i>Modified from the 2007 CPG without an updated systematic review of the evidence.</i>	Strong For	Reviewed, Deleted	N/A
29	We suggest against routinely offering ambulatory LTOT for patients with chronic stable <i>isolated</i> exercise hypoxemia, in the absence of another clinical indication for supplemental oxygen.	Weak Against	Reviewed, Not changed	16

2014 CPG Recommendation #	2014 CPG Recommendation Text	2014 CPG Strength of Recommendation	2021 CPG Recommendation Category	2021 CPG Recommendation #
30	For patients with COPD and hypoxemia and/or borderline hypoxemia (SaO ₂ <90%) who are planning to travel by plane, we suggest a brief consultation or an e-consult with a pulmonologist. <i>Modified from the 2007 CPG without an updated systematic review of the evidence.</i>	Weak For	Reviewed, Deleted	N/A
31	When other causes of nocturnal hypoxemia have been excluded, we suggest against routinely offering LTOT for the treatment of outpatients with stable, confirmed COPD and <i>isolated</i> nocturnal hypoxemia.	Weak Against	Not reviewed, Deleted	N/A
32	In the absence of other contributors (e.g., sleep apnea), we suggest referral for a pulmonary consultation in patients with stable, confirmed COPD and hypercapnea.	Weak For	Not reviewed, Deleted	N/A
33	We suggest supported self-management for selected high risk patients with COPD.	Weak For	Reviewed, New-replaced	18
34	We suggest against using action plans <i>alone</i> in the absence of supported self-management.	Weak Against	Not reviewed, Deleted	N/A
35	We suggest using telehealth for ongoing monitoring and support of the care of patients with confirmed COPD.	Weak For	Reviewed, New-replaced	19
36	We recommend offering pulmonary rehabilitation to stable patients with exercise limitation despite pharmacologic treatment and to patients who have recently been hospitalized for an acute exacerbation.	Strong For	Not reviewed, Deleted	N/A
37	We suggest offering breathing exercise (e.g., pursed lip breathing, diaphragmatic breathing, or yoga) to patients with dyspnea that limits physical activity.	Weak For	Not reviewed, Deleted	N/A
38	We suggest referral to a dietitian for medical nutritional therapy recommendations (such as oral calorie supplementation) to support patients with severe COPD who are malnourished (body mass index [BMI] <20 kg/m ²).	Weak For	Not reviewed, Deleted	N/A
39	We recommend that any patient considered for surgery for COPD (lung volume reduction surgery [LVRS] and lung transplant) be first referred to a pulmonologist for evaluation. <i>Modified from the 2007 CPG without an updated systematic review of the evidence.</i>	Strong For	Not reviewed, Deleted	N/A

2014 CPG Recommendation #	2014 CPG Recommendation Text	2014 CPG Strength of Recommendation	2021 CPG Recommendation Category	2021 CPG Recommendation #
40	We recommend antibiotic use for patients with COPD exacerbations who have increased dyspnea and increased sputum purulence (change in sputum color) or volume.	Strong For	Not reviewed, Deleted	N/A
41	We suggest basing choice of antibiotic on local resistance patterns and patient characteristics. a. First-line antibiotic choice may include doxycycline, trimethoprim/sulfamethoxazole (TMP-SMX), second-generation cephalosporin, amoxicillin, amoxicillin/clavulanate, and azithromycin. b. Despite the paucity of evidence regarding the choice of antibiotics, we suggest reserving broader spectrum antibiotics (e.g., quinolones) for patients with specific indications such as: i. Critically ill patients in the intensive care unit (ICU); ii. Patients with recent history of resistance, treatment failure, or antibiotic use; and iii. Patients with risk factors for healthcare associated infections.	Weak For	Not reviewed, Deleted	N/A
42	For outpatients with acute COPD exacerbation who are treated with antibiotics, we recommend a five-day course of the chosen antibiotic.	Strong For	Not reviewed, Deleted	N/A
43	There is insufficient evidence to recommend for or against procalcitonin-guided antibiotic use for patients with acute COPD exacerbations.	N/A	Reviewed, New-replaced	14
44	For acute COPD exacerbations, we recommend a course of systemic corticosteroids (oral preferred) of 30-40 mg prednisone equivalent daily for 5-7 days.	Strong For	Not reviewed, Deleted	N/A
45	We suggest use of airway clearance techniques utilizing positive expiratory pressure (PEP) devices for patients with COPD exacerbations and difficulty expectorating sputum.	Weak For	Not reviewed, Deleted	N/A
46	We recommend the early use of non-invasive ventilation (12) in patients with acute COPD exacerbations to reduce intubation, mortality, and length of hospital stay.	Strong For	Not reviewed, Deleted	N/A
47	We recommend the use of NIV to support weaning from invasive mechanical ventilation and earlier extubation of intubated patients with COPD.	Strong For	Not reviewed, Deleted	N/A

Appendix E: Pharmacotherapy

Refer to current product information for additional prescribing information.

Table E-1. Short-Acting Beta 2-agonist (SABA) Products

	Product	Delivery	Strength	Dosing	Doses per Unit
Hand-held Devices	Albuterol ProAir Respiclick	DPI	90 mcg	2 inhalations every 4 – 6 hours as needed (Max: 2 inhalations every 4 hours)	200
	Albuterol ProAir HFA Proventil HFA Ventolin HFA	MDI			
	Levalbuterol Xopenex HFA	MDI	45 mcg	1 or 2 inhalations every 4 – 6 hours as needed (Max: 2 inhalations every 4 hours)	
Nebulizers	Albuterol sulfate solution	Neb	2.5 mg/3 mL	Inhale contents of one vial every 6 – 8 hours as needed over 5 – 15 minutes (Max: 10 mg/day)	30
	Levalbuterol solution Xopenex	Neb	0.63 mg/3 mL	Inhale contents of one vial every 6 – 8 hours as needed for 3 doses/day (Max: 3.75 mg/day)	25
			1.25 mg/3 mL		

Abbreviations: DPI: dry powder inhaler; HFA: hydrofluoroalkane; mcg: microgram; MDI: metered-dose inhaler; mg: milligram; mL: milliliter; Neb: nebulized solution; SABA: short-acting beta 2-agonist

Table E-2. Short-Acting Antimuscarinic (129) Products

	Product	Delivery	Strength	Dosing	Doses per Unit
Hand-held Devices	Ipratropium Atrovent HFA	MDI	17 mcg	2 inhalations 4 times/day (Max: 12 inhalations/day)	200
Nebulizers	Ipratropium bromide solution	Neb	500 mcg/2.5 mL	Inhale contents of one vial every 6 – 8 hours (Max: 2000 mcg/day)	30

Abbreviations: HFA: hydrofluoroalkane; mcg: microgram; MDI: metered-dose inhaler; mg: milligram; mL: milliliter; Neb: nebulized solution; SAMA: short-acting antimuscarinic

Table E-3. Short-Acting Beta 2-agonist (SABA) + Short-Acting Antimuscarinic (129) Products

	Product	Delivery	Strength	Dosing	Doses per Unit
Hand-held Devices	Ipratropium/Albuterol Combivent Respimat	SMI	20/100 mcg	1 inhalation 4 times/day (Max: 6 inhalations/day)	120
Nebulizers	Ipratropium/Albuterol solution DuoNeb	Neb	0.5/3 mg/3 mL	Inhale contents of one vial (3 mL) every 6 hours (Max: 3/18 mg/day)	30

Abbreviations: mcg: microgram; mg: milligram; mL: milliliter; Neb: nebulized solution; SABA: short-acting beta 2-agonist; SAMA: short-acting anticholinergic; SMI: soft mist inhaler

Table E-4. Long-Acting Beta 2-Agonist (LABA) Products

	Product	Delivery	Strength	Dosing	Doses per Unit
Hand-held Devices	Indacaterol Arcapta Neohaler	DPI	75 mcg	Inhale contents of one capsule once daily (Max: 300 mcg/day)	30
	Olodaterol Striverdi Respimat	SMI	2.5 mcg	2 inhalations once daily (Max: 5 mcg/day)	60
	Salmeterol Serevent Diskus	DPI	50 mcg	1 inhalation twice daily (Max: 100 mcg/day)	60
Nebulizers	Arformoterol solution Brovana	Neb	15 mcg/2 mL	Inhale contents of one vial twice daily (Max: 30 mcg/day)	60
	Formoterol solution Perforomist	Neb	20 mcg/2 mL	Inhale contents of one vial twice daily (Max: 40 mcg/day)	60

Abbreviations: DPI: dry powder inhaler; LABA: long-acting beta 2-agonist; mcg: microgram; mg: milligram; mL: milliliter; Neb: nebulized solution; SMI: soft mist inhaler

Table E-5. Long-Acting Muscarinic Antagonists (LAMA) Products

	Product	Delivery	Strength	Dosing	Doses per Unit
Hand-held Devices	Acclidinium Tudorza Pressair	DPI	400 mcg	1 inhalation twice daily (Max: 800 mcg/day)	60
	Tiotropium Spiriva Handihaler	DPI	18 mcg	Inhale contents of one capsule once daily (Max: 18 mcg/day)	30
	Tiotropium Spiriva Respimat	SMI	2.5 mcg	2 inhalations once daily (Max: 5 mcg/day)	60
	Umeclidinium Incruse Ellipta	DPI	62.5 mcg	1 inhalation once daily (Max: 62.5 mcg/day)	30

	Product	Delivery	Strength	Dosing	Doses per Unit
Nebulizers	Glycopyrrolate solution Lonhala Magnair*	Neb	25 mcg/mL	Inhale contents of one vial twice daily (Max: 25 mcg twice daily)	60
	Revefenacin solution Yupelri	Neb	175 mcg/3 mL	Inhale contents of one vial once daily (Max: 175 mcg/day)	30

*Must be used with the proprietary Magnair nebulizer

Abbreviations: DPI: dry powder inhaler; mcg: microgram; mL: milliliters; Neb: nebulized solution; SMI: soft mist inhaler

Table E-6. Long-Acting Muscarinic Antagonists (LAMA) + Long-Acting Beta 2-Agonist (LABA) Products

	Product	Delivery	Strength	Dosing	Doses per Unit
Hand-held devices	Acclidinium/Formoterol Duaklir Pressair	DPI	400/12 mcg	1 inhalation twice daily (Max: 2 inhalations/day)	60
	Glycopyrrolate/Formoterol Bevespi Aerosphere	MDI	9/4.8 mcg	2 inhalations twice daily (Max: 4 inhalations/day)	120
	Tiotropium/Olodaterol Stiolto Respimat	SMI	2.5/2.5 mcg	2 inhalations once daily (Max: 2 inhalations/day)	60
	Umeclidinium/Vilanterol Anoro Ellipta	DPI	62.5/25 mcg	1 inhalation once daily (Max: 1 inhalation/day)	30

Abbreviations: DPI: dry powder inhaler; LABA: long-acting beta 2-agonist; LAMA: long-acting anticholinergic; mcg: microgram; MDI: metered-dose inhaler; mg: milligram; mL: milliliter; SMI: soft mist inhaler

Table E-7. Inhaled Corticosteroids (ICS) Products*

	Product	Delivery	Strength	Dosing	Potency of Steroid	Doses per Unit
Hand-held devices	Beclomethasone Qvar ReditHaler	MDI	40 mcg	1 or 2 inhalations twice daily	Low	120
			80 mcg	1 or 2 inhalations twice daily (Max: 320 mcg twice daily)	Low/Med/ High	
	Budesonide Pulmicort Flexhaler	DPI	90 mcg	1 or 2 inhalations twice daily	Low	60
			180 mcg	1 or 2 inhalations twice daily (Max: 720 mcg twice daily)	Low/Med/ High	120
	Ciclesonide Alvesco HFA	MDI	80 mcg	1 or 2 inhalations twice daily	Low/Med	60
			160 mcg	1 or 2 inhalations twice daily (Max: 320 mcg twice daily)	Med/High	
	Fluticasone furoate Arnuity Ellipta	DPI	100 mcg	1 or 2 inhalations once daily (Max: 200 mcg/day)	Low/High	30
			200 mcg	1 inhalation once daily (Max: 200 mcg/day)	High	

Product	Delivery	Strength	Dosing	Potency of Steroid	Doses per Unit
Hand-held devices (cont.)	DPI	55 mcg	1 or 2 inhalations twice daily	Low	60
		113 mcg	1 or 2 inhalations twice daily (Max: 223 mcg twice daily)	Low/Med	
		232 mcg	1 inhalation twice daily (Max: 223 mcg twice daily)	Med	
		50 mcg	1 or 2 inhalations twice daily	Low	
		100 mcg	1 or 2 inhalations twice daily	Low/Med	
		250 mcg	1 or 2 inhalations twice daily (Max: 1000 mcg twice daily)	Med/High	
	MDI	44 mcg	1 or 2 inhalations twice daily	Low	120
		110 mcg	1 or 2 inhalations twice daily	Low/Med	
		220 mcg	1 or 2 inhalations twice daily (Max: 880 mcg twice daily)	Med/High	
	MDI DPI	100 mcg	1 or 2 inhalations twice daily	Low	120
		200 mcg	1 or 2 inhalations twice daily (Max: 800 mcg/day)	Med/High	
		110 mcg	1 or 2 inhalations daily	Low	60
		220 mcg	1 or 2 inhalations daily (Max: 440mcg/day)	Low/Med	
Nebulizers	Neb	0.25 mg/2 mL	Inhale contents of one respule once daily	Low	30
		0.5 mg/2 mL	Inhale contents of one or two respules once or twice daily	Med/High	

*Not to be used alone in COPD; use in combination for LABA or LAMA+LABA

Abbreviations: DPI: dry powder inhaler; HFA: hydrofluoroalkane; mcg: microgram; Med: medium; MDI: metered-dose inhaler; mg: milligram; mL: milliliter; Neb: nebulized solution

Table E-8. Inhaled Corticosteroids (ICS) + Long-Acting Beta 2-Agonist (LABA) + Long-Acting Muscarinic Antagonists (LAMA) Products

Product	Delivery	Strength	Dosing	Potency of Steroid	Doses per Unit
Hand-held devices	MDI	80/4.5 mcg	2 inhalations twice daily	Low	120
		160/4.5 mcg	2 inhalations twice daily (Max: 320/9 mcg twice daily)	Med	
	DPI	100/25 mcg	1 inhalation once daily	Low	30
		200/25 mcg	1 inhalation once daily (Max: 200/25 mcg daily)	High	

	Product	Delivery	Strength	Dosing	Potency of Steroid	Doses per Unit
Hand-held devices (cont.)	Fluticasone propionate/ Salmeterol Advair Diskus Wixela Inhub Authorized generic	DPI	100/50 mcg	1 inhalation twice daily	Low	60
			250/50 mcg	1 inhalation twice daily (Max: 250/50 mcg twice daily (COPD))	Med	
			500/50 mcg	1 inhalation twice daily (Max: 500/50 mcg twice daily (asthma))	High	
	Fluticasone propionate/ Salmeterol Advair HFA	MDI	45/21 mcg	2 inhalations twice daily	Low	120
			115/21 mcg	2 inhalations twice daily	Med	
			230/21 mcg	2 inhalations twice daily (Max: 460/42 mcg twice daily)	High	
	Mometasone/ Formoterol Dulera	MDI	100/5 mcg	2 inhalations twice daily	Med	120
			200/5 mcg	200/5 mcg: 2 inhalations twice daily (Max: 400/10 mcg twice daily)	High	

Abbreviations: DPI: dry powder inhaler; HFA: hydrofluoroalkane; ICS: inhaled corticosteroid; LABA: long-acting beta 2-agonist; mcg: microgram; MDI: metered-dose inhaler; mg: milligram; mL: milliliter

Table E-9. Inhaled Corticosteroids (ICS) + Long-Acting Beta 2-Agonist (LABA) + Products

	Product	Delivery	Strength	Dosing	Potency of Steroid	Doses per Unit
Single Inhaler	Budesonide/Glycopyrrolate/ Formoterol fumarate Breztri Aerosphere	MDI	160/9/ 4.8 mcg	2 inhalations twice daily	Med	30
	Fluticasone furoate/Vilanterol/ Umeclidinium Trelegy Ellipta	DPI	100/25/ 62.5 mcg	1 inhalation once daily	Low	30
Multiple Inhalers*	Fluticasone furoate Arnuity Ellipta + Tiotropium/Olodaterol Stiolto Respimat	DPI	100 mcg	1 inhalation once daily	Low	30
		SMI	2.5/2.5 mcg	2 inhalations once daily		60
	Fluticasone propionate Flovent Diskus + Umeclidinium/Vilanterol Anoro Ellipta	DPI	100 mcg	1 or 2 inhalations twice daily	Low/Med	60
		DPI	62.5/25 mcg	1 inhalation once daily		30

	Product	Delivery	Strength	Dosing	Potency of Steroid	Doses per Unit
Multiple Inhalers (cont.)*	Mometasone AsmanexTwisthaler + Tiotropium/Olodaterol Stiolto Respimat	DPI	220 mcg	1 or 2 inhalations daily	Low/Med	60
		SMI	2.5/2.5 mcg	2 inhalations once daily		60

* Less costly 3-drug therapy can be achieved by using a 2-drug fixed-dose combination (LAMA+LABA preferred in COPD) + a single inhaler (ICS preferred in COPD) (e.g., see below [NOT all-inclusive list])

Abbreviations: COPD: chronic obstructive pulmonary disease; DPI: dry powder inhaler; ICS: inhaled corticosteroid; LABA: long-acting beta 2-agonist; LAMA: long-acting anticholinergic; mcg: microgram; SMI: soft mist inhaler

Table E-10. Low, Medium, and High Daily Inhaled Corticosteroids (ICS) Doses for Adults

ICS Drug	Low	Medium	High
Beclomethasone	100 – 200 mcg	>200 – 400 mcg	>400 mcg
Budesonide	200 – 400 mcg	>400 – 800 mcg	>800 mcg
Ciclesonide (HFA)	80 – 160 mcg	>160 – 320 mcg	>320 mcg
Fluticasone furoate (DPI)	100 mcg	N/A	200 mcg
Fluticasone propionate (DPI and HFA)	100 – 250 mcg	>250 – 500 mcg	>500 mcg
Mometasone	110 – 220 mcg	440 mcg	>440 mcg

Abbreviations: DPI: dry powder inhaler; HFA: hydrofluoroalkane; ICS: inhaled corticosteroid; mcg: microgram

Table E-11. Comments by Drug Class*

Drug Class	Comments
Beta 2-agonists	LABAs increase the risk of asthma-related death; do not use as monotherapy in asthma May cause palpitations, chest pain, rapid heart rate, increased blood pressure, tremor, nervousness Decreases in potassium levels have occurred SABAs are used for acute treatment of bronchospasm; LABAs are used for chronic treatment of bronchospasm Formoterol and indacaterol: capsules are for oral inhalation only; capsules should not be swallowed; administer using supplied inhalation device only
Antimuscarinic Agents	Use with caution in patients with narrow angle glaucoma, prostatic hyperplasia, or bladder neck obstruction Caution patient to getting product in eyes; temporary blurred vision may result For relief of dry mouth, suggest use of saliva substitute, practice of good oral hygiene, rinsing of mouth after inhalation; instruct patient to take sips of water frequently, suck on ice chips or sugarless hard candy, or chew sugarless gum Tiotropium: capsules are for oral inhalation only; capsules should not be swallowed; administer using supplied inhalation device only
Inhaled Glucocorticoids	Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported Advise patients to rinse mouth after inhalation to reduce risk of oral fungal infections (e.g., oropharyngeal candidiasis)

Note: Each drug class has agents available in a dry powder formulation. Dry powder formulations contain lactose and small amounts of milk proteins; do not use in patients with severe hypersensitivity to milk proteins.

* Table not intended as a comprehensive list of all warnings, precautions, and risks.

Abbreviations: LABA: long-acting beta 2-agonist; SABA: short-acting beta 2-agonist

Appendix F: Standardized Questionnaires

Standardized questionnaires may help clinicians assess symptom burden. Two commonly used questionnaires are the modified Medical Research Council Questionnaire (mMRC) and the COPD Assessment Test (CAT). The mMRC is a simple tool that can be used to assesses dyspnea in multiple medical conditions.⁽¹³⁰⁾ The CAT is a more complex questionnaire that is specific to COPD.⁽¹³¹⁾


A. Modified Medical Research Council Questionnaire

Table F-1. mMRC ⁽¹³⁰⁾

Grade	Description of Breathlessness
Grade 0	I only get breathless with strenuous exercise
Grade 1	I get short of breath when hurrying on level ground or walking up a slight hill
Grade 2	On level ground, I walk slower than people of the same age because of breathlessness, or I have to stop for breath when walking at my own pace on the level
Grade 3	I stop for breath after walking about 100 yards or after a few minutes on level ground
Grade 4	I am too breathless to leave the house or I am breathless when dressing

B. COPD Assessment Test

Figure F-1. CAT (131)



Your name:

Today's date:

How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment.

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

Example: I am very happy 0 ☒ 1 2 3 4 5 I am very sad

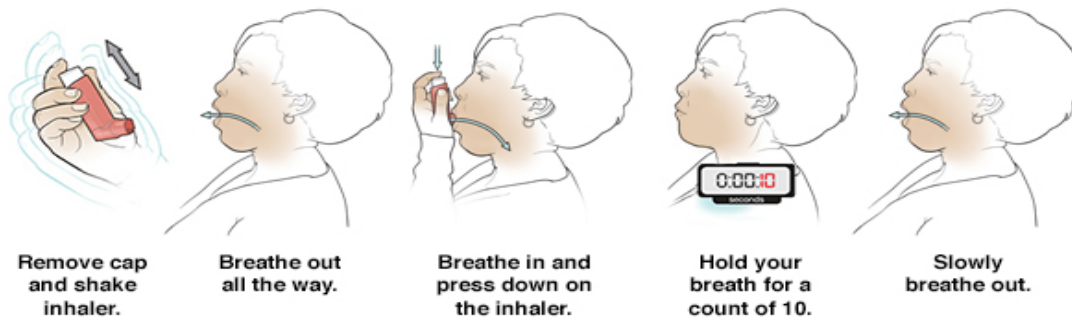
I never cough		0 1 2 3 4 5					I cough all the time		SCORE
I never cough		0 1 2 3 4 5					I cough all the time		↓
I have no phlegm (mucus) in my chest at all		0 1 2 3 4 5					My chest is completely full of phlegm (mucus)		↓
My chest does not feel tight at all		0 1 2 3 4 5					My chest feels very tight		↓
When I walk up a hill or one flight of stairs I am not breathless		0 1 2 3 4 5					When I walk up a hill or one flight of stairs I am very breathless		↓
I am not limited doing any activities at home		0 1 2 3 4 5					I am very limited doing activities at home		↓
I am confident leaving my home despite my lung condition		0 1 2 3 4 5					I am not at all confident leaving my home because of my lung condition		↓
I sleep soundly		0 1 2 3 4 5					I don't sleep soundly because of my lung condition		↓
I have lots of energy		0 1 2 3 4 5					I have no energy at all		↓
<small>COPD Assessment Test and the CAT logo are trademarks of the GlaxoSmithKline group of companies. © 2009 GlaxoSmithKline. All rights reserved.</small>									TOTAL SCORE <div style="border: 1px solid black; width: 40px; height: 30px; margin: 0 auto;"></div>

Appendix G: Inhaler Techniques

It is very common to discover patients not using their inhaler(s) as they are designed. Incorrect inhaler technique can lead to an assumption of treatment failure. It is critical to assess a patient's inhaler technique before the determination of treatment failure.

A. Metered-Dose Inhaler

Figure G-1. How to correctly use a metered-dose inhaler (MDI) ([132](#))



Alternative Text Description of MDI (Figure G-1)

Step 1: Remove cap and shake inhaler (about 5 seconds)

Step 2: Sitting or standing up straight, take a deep breath and breathe out all the way

Step 3: Bring the inhaler to the mouth; seal lips tightly around the mouthpiece and begin breathing in slowly; press down on the inhaler ONCE and continue to breathe in SLOWLY AND DEEPLY for about 3 to 5 seconds

Step 4: Remove the inhaler from the mouth and hold your breath a count of 10 seconds, or as long as able to comfortably with mouth closed

Step 5: Slowly breathe out

Repeat the steps above for each inhalation, waiting at least 60 seconds between puffs

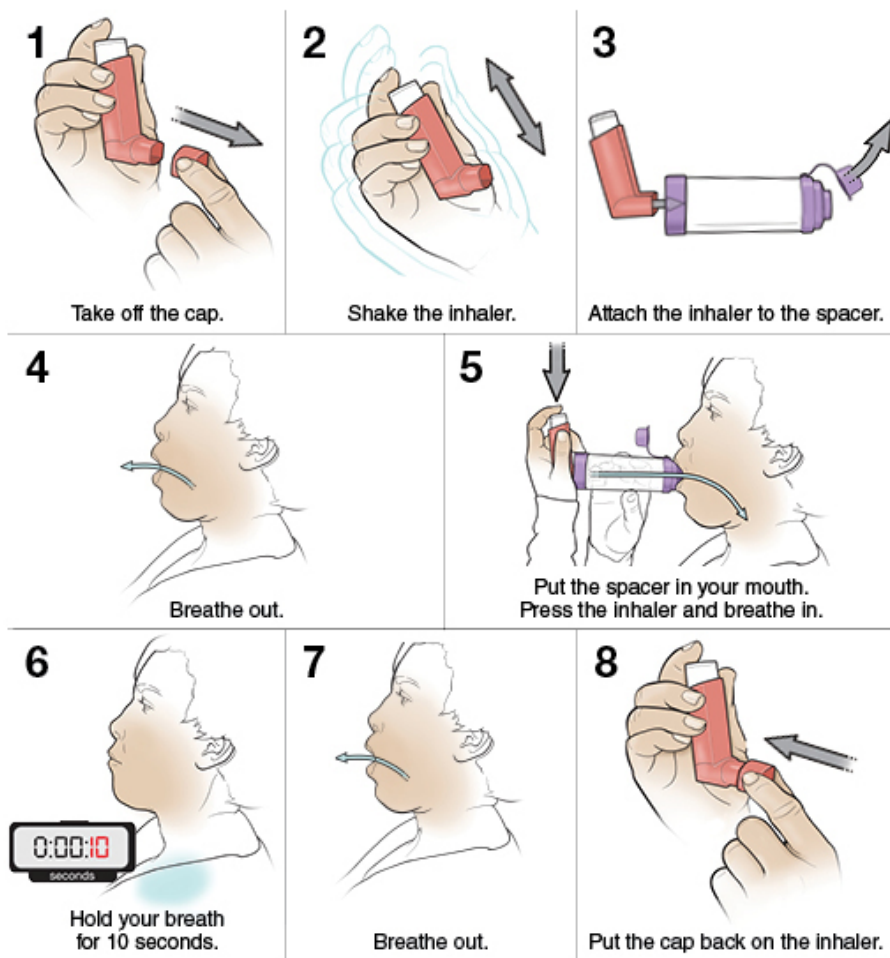
Step 6: Replace cap and store in a safe place

Important

- Wash hands
- Check expiration date and the counter of the inhaler, if there is one
- Ensure the metal canister is placed correctly in the plastic holder
- Prime the inhaler on the first use
- Clean the plastic mouthpiece and cap frequently, after removing the metal canister, under warm water and allow to dry completely
- Always rinse mouth with water, swishing and gargling, and spit out after using inhaled corticosteroids; do not swallow

B. Metered-Dose Inhaler with a Spacer

Figure G-2. How to correctly use an MDI with a spacer (133)



Alternative Text Description of MDI with a spacer (Figure G-2)

Step 1: Take off the cap

Step 2: Shake the inhaler (about 5 seconds)

Step 3: Attach the inhaler to the spacer and remove the cap from the spacer

Step 4: Sitting or standing up straight, take a deep breath and breathe out completely

Step 5: Put the spacer in your mouth; seal lips tightly around the mouthpiece; press down on the inhaler canister ONCE and breathe in SLOWLY AND DEEPLY for about 5 to 10 seconds; the spacer may make a whistling sound if the breathing is too quick

Step 6: Remove the spacer from the mouth and hold your breath for 10 seconds, or as long as able to comfortably with mouth closed

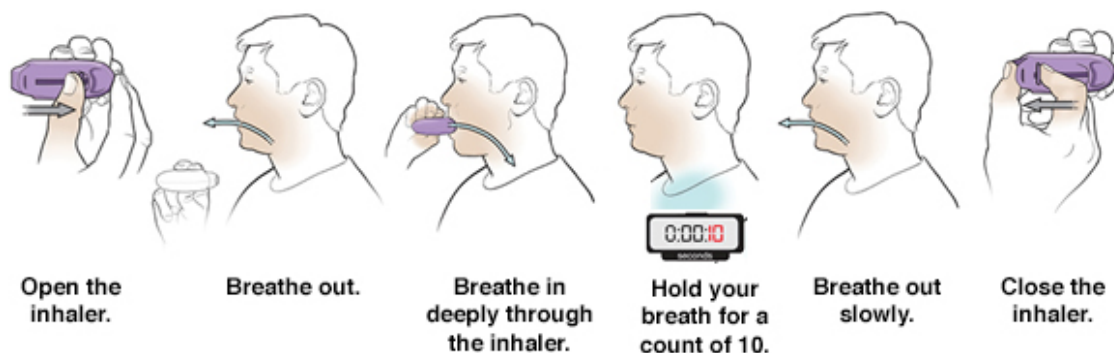
Step 7: Breathe out slowly

Repeat the steps above for each inhalation, waiting at least 60 seconds between puffs

Step 8: Put the cap back on the inhaler and store in a safe place

C. Dry Powder Inhalers

Figure G-3. How to correctly use a dry powder inhaler (DPI) ([134](#))



Alternative Text Description of DPIs (Figure G-3)

Step 1: Open, load, and hold the inhaler following the manufacturer's directions

Step 2: Sitting or standing up straight, take a deep breath and breathe out completely

Step 3: Bring the inhaler to the mouth; seal lips tightly around the mouthpiece and breathe in QUICKLY AND DEEPLY through the inhaler for about 3 to 5 seconds

Step 4: Remove the inhaler from the mouth and hold your breath for a count of 10 seconds, or as long as able to comfortably with mouth closed

Step 5: Breathe out slowly away from the inhaler

Repeat the steps above for each inhalation, waiting at least 60 seconds between puffs

Step 6: Close the inhaler and store in a cool, dry and safe place

Important

- Wash hands
- Check expiration date and the counter of the inhaler, if there is one
- Do not wash with soap and water; to clean, wipe mouthpiece with a dry cloth at least once a week or as needed
- Always rinse mouth with water, swishing and gargling, and spit out after using inhaled corticosteroids; do not swallow

D. Respimat Inhalers

a. First Time Use – Prepare

Figure G-4. How to prepare Respimat Inhaler ([135](#))

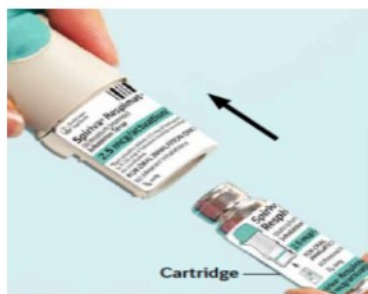
Step 1



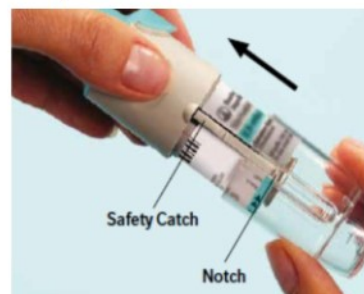
Step 2



Step 3



Step 4



Alternative Text Description of preparing Respimat Inhaler (Figure G-4)

Step 1: Press down on the safety catch and firmly pull off the clear base with the other hand.

Step 2: Write the discard by date on the label; the discard by date is 3 months from the date the cartridge is inserted into the inhaler

Step 3: Insert the narrow end of the cartridge into the inhaler, pressing down on a firm surface; about 1/8 of an inch will remain visible when the cartridge is correctly inserted; do not remove the cartridge once it has been inserted into the inhaler

Step 4: Click the clear base back into place; do not remove the clear base again.

b. First Time Use – Prime

It is important to follow these steps to ensure the dosing system is filled for first time use. Priming is necessary to make sure the correct amount of medicine is delivered. It will not affect the number of doses available.

Figure G-5. How to prime RespiMat Inhaler (135)

Step 1



Step 2



Step 3



Alternative Text Description of priming RespiMat Inhaler (Figure G-5)

Step 1: Hold the inhaler upright with the cap closed; turn the clear base in the direction of the arrows on the label until it clicks

Step 2: Open the cap

Step 3: Point the inhaler to the ground; press the dose release button; close the cap.

Repeat Steps 1, 2, and 3 until a cloud of mist is visible. Once the cloud of mist is visible, repeat Steps 1, 2, and 3 three more times to ensure the inhaler is prepared for use.

c. Daily Use

Figure G-6. Daily use of RespiMat Inhaler (135)

Step 1



Step 2



Step 3



Alternative Text Description of daily use of RespiMat Inhaler (Figure G-6)

Step 1: TURN

Keep cap closed; turn clear base in the direction of the arrow on the label until it clicks

Step 2: OPEN

Open the cap until it snaps fully open; sitting or standing up straight, take a deep breath and breathe out slowly and completely

Step 3: PRESS

Bring the inhaler to the mouth with it pointing to the back of the throat; close lips tightly around the mouthpiece, without covering the air vents; begin inhaling slowly while pressing the dose release button; continue to breathe in SLOWLY AND DEEPLY for about 3 to 5 seconds

Remove the inhaler from the mouth; hold breath for 10 seconds, or as long as able to comfortably with mouth closed; breathe out slowly

Repeat the steps above for each inhalation. Wait at least 60 seconds between inhalations.

These steps should be performed TWO TIMES to receive the proper dose of medicine.

When both inhalations are completed, close the cap and store in a safe place.

Appendix H: Participant List

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Appendix I: Literature Review Search Terms and Strategy

Table I-1. COPD Search Strategy for OVID (Medline, EMBASE databases)

Set #	Concept	Strategy
1	COPD	'chronic obstructive lung disease'/de OR 'chronic airflow limitation' OR 'chronic airflow obstruction*' OR 'chronic obstructive airway disease' OR 'chronic obstructive lung disease' OR 'chronic obstructive pulmonary disease' OR 'chronic obstructive respiratory disease' OR 'chronic pulmonary dysfunction' OR 'chronic pulmonary dysfunction' OR 'chronic respiratory disease' OR 'chronic respiratory insufficien*' OR coad OR copd*
2	Chronic Bronchitis	'chronic bronchitis'/de OR 'chronic bronchitis'
3	Emphysema	'emphysema'/exp OR emphysema
4	Problem	#1 OR #2 OR #3
5	KQ1 – Spirometry	'lung function test'/exp OR 'spirometry'/exp OR 'bronchodilator respons*' OR 'lung function test*' OR 'pulmonary function test*' OR 'respiratory function test*' OR spirometry
6	KQ1 – Disease Severity	'disease severity'/exp OR ((disease OR symptom*) NEAR/2 (severe OR severity))
7	KQ1 – Exacerbations	'disease exacerbation'/de OR 'exacerbation'/de OR exacerbat*
8	KQ1 – Comorbidities	'comorbidity'/de OR comorbid*
9	KQ1 – GOLD Classification	GOLD near/2 classif*
10	KQ1 – Interventions	#5 OR #6 OR #7 OR #8 OR #9
11	KQ1 Combined Set	#4 AND #10
12	KQ2 – Intensive/Advanced Therapy	#4 AND (advanced OR intensive) NEAR/3 (therap* OR treatment*)
13	KQ3-6 – Stepped Therapy	'combination drug therapy'/exp OR 'drug combination'/exp OR ((combin* OR dual OR multi* OR step* OR tripl*) NEAR/2 (drug* OR pharm* OR therap* OR treatment*))
14	KQ3-6 – LABA/SABA	'beta adrenergic receptor stimulating agent'/exp OR 'long acting beta agonist'/de OR 'short acting beta agonist'/de OR LABA OR SABA OR ((longacting OR 'long acting' OR shortacting OR 'short acting') NEAR/2 ('beta agonist*')) OR aformoterol* OR albuterol* OR formoterol* OR indacaterol* OR levalbuterol* OR olodaterol* OR salmeterol* OR vilanterol*
15	KQ3-6 – LA/SA Anticholinergics	(longacting OR 'long acting' OR shortacting OR 'short acting') AND ('cholinergic receptor blocking agent'/exp OR 'anti cholinergic*' OR anticholinergic*)
16	KQ3-6 – Corticosteroids, Glucocorticoids	'corticosteroid'/exp OR Alvesco* OR 'Arnuity* Ellipta*' OR Asmanex* OR beclomethasone OR budesonide* OR ciclesonide* OR corticosteroid* OR Flovent* OR fluticasone* OR methylprednisolone OR mometasone* OR prednisone* OR Pulmicort* OR Qvar*
17	KQ3-6 – Beta-blockers	'beta adrenergic receptor blocking agent'/exp OR (beta NEAR/2 (antagonist* OR block*))
18	KQ3-6 – Bronchodilators	'bronchodilating agent'/exp OR aclidinium* OR glycopyrrolate* OR ipratropium* OR olodaterol* OR revefenacin* OR tiotropium* OR 'Trelegy* Ellipta*' OR umeclidinium*
19	KQ3-6 – PDE 4 Inhibitors	roflumilast*

Set #	Concept	Strategy
20	KQ3-6 – Mucolytics	'mucolytic agent'/exp OR acetylcysteine* OR ambroxol OR carbocysteine* OR erdosteine* OR mucolytic* OR 'N-acetylcysteine'
21	KQ3-6 – LAMA	aclidinium* OR tiotropium* OR umeclidinium*
22	KQ3-6 – Other Drugs	guaifenesin OR theophylline
23	KQ3-6 – Interventions	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
24	KQ3-6 Combine	#4 AND #23
25	KQ7 – Hypoxemia	'hypoxemia'/exp OR hypox*
26	KQ7 – Oxygen Therapy	'oxygen'/exp OR “nocturnal ventilation” OR oxygen
27	KQ 7 Combine	#4 AND #25 AND #26
28	KQ8 – Antibiotics	'antibiotic agent'/exp OR antibiotic* OR azithromycin* OR erythromycin* OR levofloxacin* OR moxifloxacin* OR doxycycline* OR amoxicillin*
29	KQ8 – CRP Testing	'c reactive protein'/de AND (level* OR test*) OR (('c reactive protein' OR crp) NEAR/3 (level* OR test*))
30	KQ8 Combine	#4
31	KQ9 – MDI Optimization	'inhaler'/exp OR 'metered dose inhaler'/exp OR 'nebulizer'/exp OR dpi OR 'dry powder' OR inhaler* OR 'inhalation therap*' OR 'metered dose' OR mdi OR nebuliz* OR optimiz* OR 'soft mist' OR spacer*
32	KQ9 – Combine	#4 AND #31
33	KQ10 – Telehealth	'internet'/exp OR 'mobile application'/exp OR 'mobile health application'/exp OR 'mobile phone'/exp OR 'online monitoring'/exp OR 'social media'/exp OR 'teleconsultation'/exp OR 'telehealth'/exp OR 'telemedicine'/exp OR 'telemonitoring'/exp OR 'text messaging'/exp OR cellphone* OR 'e-health*' OR ehealth* OR 'm health*' OR mhealth* OR 'mobile device*' OR 'mobile health*' OR mobilephone* OR phone* OR remote* OR smartphone* OR 'smart phone*' OR telehealth* OR telemonitor* OR telephone*
34	KQ10 Combine	#4 AND #33
35	KQ11 – Self-management	'self care'/exp OR 'smoking cessation'/exp OR 'smoking cessation program'/exp OR 'action plan*' OR 'disease understanding' OR 'exercise plan*' OR 'self-care' OR 'self-manage*' OR 'smoking cessation' OR 'pulmonary rehabilitation'/exp OR 'breathing retraining' OR 'lung rehab*' OR 'medication education' OR 'pulmonary exercise*' OR 'pulmonary hygiene' OR 'pulmonary rehab*'
36	KQ11 – Physical Activity	'aerobic exercise'/exp OR 'cardio respiratory fitness' OR 'exercise'/exp OR 'exercise intensity'/exp OR 'fitness'/exp OR 'high intensity interval training'/exp OR 'jogging'/exp OR 'martial art'/exp OR 'moderate intensity continuous training'/exp OR 'physical activity'/exp OR 'physical activity, capacity and performance'/exp OR 'pilates'/exp OR 'resistance training'/exp OR 'stretching exercise'/exp OR 'swimming'/exp OR 'tai chi'/exp OR 'training'/exp OR 'treadmill'/exp OR 'treadmill exercise'/exp OR 'walking'/exp OR 'weight lifting'/exp OR 'yoga'/exp OR bicycle* OR bike* OR biking OR cardio OR cycling OR exercis* OR fitness OR jog* OR hike* OR hiking OR 'martial art*' OR pilates OR ran OR run OR runner OR runs OR running OR sport* OR swim* OR 'tai chi' OR treadmill* OR walk* OR 'weight training' OR workout* OR ((work NEXT/1 out*)) OR yoga OR ((aerobic* OR physical*) NEAR/2 (exercis* OR fitness))

Set #	Concept	Strategy
37	KQ11 – Other Interventions	'alternative medicine'/exp OR 'breathing exercise'/de OR 'mind body medicine'/de OR 'nutrition'/exp OR 'sleep hygiene'/de OR 'stress management'/de OR 'breathing exercis*' OR nutrition OR 'sleep hygiene' OR ((anxiety OR stress) NEAR/2 manage*) OR (oxygen NEAR/2 complian*) OR ((alternative OR complementary) NEAR/2 (medicine OR therap*))
38	KQ11 Combine	#4 AND (78) OR #36 OR #37
39	KQ12 – Corticosteroids Withdrawal	(corticosteroid* OR steroid*) NEAR/2 (decrease* OR 'step down' OR taper* OR withdraw*)
40	KQ12 Combine	#4 AND #39
41	All KQs	#11 OR #12 OR #24 OR #27 Or #30 OR #32 OR #34 OR #38 OR #40
42	Date Limit	#41 AND [31-12-2013]/sd NOT [23-2-2020]/sd
43	Remove unwanted publication types	#42 NOT (abstract:nc OR annual:nc OR 'book'/exp OR 'case study'/exp OR conference:nc OR 'conference abstract':it OR 'conference paper'/exp OR 'conference paper':it OR 'conference proceeding':pt OR 'conference review':it OR congress:nc OR 'editorial'/exp OR editorial:it OR 'erratum'/exp OR letter:it OR 'note'/exp OR note:it OR meeting:nc OR sessions:nc OR 'short survey'/exp OR symposium:nc OR [conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [letter]/lim OR [note]/lim OR [short survey]/lim OR comment:ti OR book:pt OR 'case report'/de OR 'case report':ti OR 'a case':ti OR 'a patient':ti OR 'year old':ti,ab)
Study Type Hedges Applied as Needed	Limit to meta-analyses and systematic reviews	AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR cochrane OR 'meta analysis' OR 'meta analyses' OR metaanalysis OR metaanalyses OR search* OR systematic:ti)
	Limit to randomized controlled trials	AND ('randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de OR random*:ab,ti OR nct* OR [randomized controlled trial]/lim)
	Limit to diagnostic studies	AND ('diagnostic test accuracy study'/de OR 'diagnostic test accuracy'/de OR 'differential diagnosis'/exp OR 'sensitivity and specificity':de OR ('sensitivity AND specificity'):ti OR 'accuracy':de OR 'precision'/exp OR 'prediction and forecasting'/exp OR likelihood:ti OR 'predictive value'/exp OR 'predictive value':ti OR diagnos*:ti OR 'diagnostic accuracy')

Appendix J. Alternative Text Descriptions of Algorithm

A. Module A: Management of COPD in Primary Care

1. Module A starts with Box 1, in the shape of a rounded rectangle: “Patient with chief complaint suggestive of COPD presents to primary care”
2. Box 1 connects to Box 2, in the shape of a rectangle: “Perform brief clinical assessment to determine if patient is clinically stable”
3. Box 2 connects to Box 3, in the shape of a hexagon, asks the question: “Is the patient having an acute exacerbation? (see Sidebar 1)”
 - a. If the answer is “Yes” to Box 3, then Box 4, in the shape of an oval: “Management of an acute exacerbation (see Module B)”
 - b. If the answer is “No” to Box 3, then Box 5, in the shape of a rectangle: “Complete clinical assessment including consideration of common co-occurring conditions (see Sidebar 2):
 - i. History: including tobacco use, activity level, exercise tolerance, symptom burden, mental well-being, and history of acute exacerbations
 - ii. Exam: including wheezing, use of accessory muscles and labored breathing, BMI, and pulse oximetry if available
 - iii. Evaluate for other contributing diagnoses and comorbid conditions: refer to other VA/DoD CPGs as needed
 - iv. Obtain diagnostic spirometry if available (see Recommendation 1)”
4. Box 5 connects to Box 6, in the shape of a hexagon, asks the question: “Is there a confident clinical diagnosis of COPD?”
 - a. If the answer is “Yes” to Box 6, then Box 7, in the shape of a square: “Offer prevention and risk reduction methods including smoking cessation, vaccination, and patient education; suggest spirometry if not already completed”
 - b. If the answer is “No” to Box 6, then Box 8, in the shape of a square: “Treat or refer as clinically indicated”
5. Box 7 connects to Box 9, in the shape of a hexagon, asks the question: “Is patient chronically symptomatic and/or has patient had a moderate to severe exacerbation in the past year? (see Sidebar 1)”
 - a. If the answer is “Yes” to Box 9, then Box 10, in the shape of a square: “If symptoms persist, consider need to initiate/adjust medication and assess inhaler techniques (see Appendix G); ensure patient is on SABA (PRN), then use following steps for increasing intensity:
 - i. First line LAMA
 - ii. Add LABA for severe symptoms (preferably combination inhaler)
 - iii. Add ICS only for continued moderate to severe exacerbations (see Sidebar 1)

- iv. Pulmonology referral”
- v. Box 10 connects to Box 11
- b. If the answer is “No” to Box 9, then Box 11, in the shape of a square: “Consider need for oxygen if patient has resting hypoxemia (refer to home oxygen clinic if appropriate)”
- 6. Box 11 connects to Box 12, in the shape of a square: “Continue follow-up and monitoring; reassess severity periodically; consider pulmonary rehabilitation; consider medication adjustment if patient is on an inhaled corticosteroid (see Module C); consider offering referral to a pulmonologist or a palliative care specialist as appropriate for patients with persistent refractory dyspnea; carefully consider alternatives to beta blockers for non-cardiac indications (e.g., HTN)”

B. Module B: Management of Acute COPD Exacerbations

1. Module B begins with Box 13, in the shape of a rounded rectangle: “Patient presenting with an acute exacerbation to primary care”
2. Box 13 connects to Box 14, in the shape of a rectangle: “Assess/triage condition”
3. Box 14 connects to Box 15, in the shape of a hexagon, asks the question: “Is there indication for emergency department or inpatient admission? (see Sidebar 3)”
 - a. If the answer is “Yes” to Box 15, then Box 16, in the shape of a rectangle: “Initiate short-acting acute bronchodilator therapy (albuterol ± ipratropium MDI with spacer or via nebulizer) and administer oxygen if necessary”
 - i. Box 16 then connects to Box 23, in the shape of an oval: “Arrange transfer”
 - b. If the answer is “No” to Box 15, then Box 17, in the shape of a rectangle: “Obtain history, physical exam, and tests as clinically indicated to evaluate for alternate diagnoses”
4. Box 17 connects to Box 18, in the shape of a rectangle: “Initiate short-acting acute bronchodilator therapy (albuterol +/- ipratropium MDI with spacer or via nebulizer) and administer oxygen if necessary”
5. Box 18 connects to Box 19, in the shape of a hexagon, asks the question: “Are acute symptoms resolved?”
 - a. If the answer is “Yes” to Box 19, then Box 20, in the shape of a rectangle: “Consider:
 - i. Continuing short-acting bronchodilator therapy
 - ii. Initiating long-acting bronchodilator therapy
 - iii. Initiating steroid therapy (see Sidebar 4)
 - iv. Initiating antibiotic therapy (see Sidebar 5)”
 - b. If the answer is “No” to Box 19, then Box 23, in the shape of an oval: “Arrange transfer”
6. Box 20 connects to Box 21, in the shape of a rectangle: “Arrange follow-up; instruct patient to contact clinic if condition deteriorates”
7. Box 21 connects to Box 22, in the shape of an oval: “Return to primary care pathway (see Module A)”

C. Module C: Inhaled Corticosteroid Usage

1. Module C begins with Box 24, in the shape of a rounded rectangle: “Patient on ICS”
2. Box 24 connects to Box 25, in the shape of a hexagon, which asks the question: “Does the patient have stable COPD? (no moderate to severe exacerbations in 2 years)”
 - a. If the answer is “Yes” to Box 25, then Box 26, in the shape of a hexagon, asks the question: “Obtain eosinophil count if not already obtained within the past year; Is eosinophil count <300?”
 - i. If the answer is “Yes” to Box 26, then Box 27, in the shape of a rectangle: “Remove ICS:
 - If patient is on LABA/ICS + LAMA, then remove ICS and maintain LABA + LAMA as single combination inhaler
 - If patient is on LABA/ICS, then remove ICS and continue with LABA or LAMA”
 - ii. If the answer is “No” to Box 26, then Box 29, in the shape of a rectangle: “Maintain ICS:
 - If patient is on LABA/ICS+LAMA, consider switching to a single combination inhaler if available
 - If patient is on LABA/ICS, then no adjustments needed”
 - b. If the answer is “No” to Box 25, then Box 28, in the shape of an oval: “Return to primary care pathway (see Module A, Box 9)”

Appendix K: Abbreviations

Abbreviation	Definition
AAT	alpha-1 antitrypsin
AHRQ	Agency for Healthcare Research and Quality
ATS	American Thoracic Society
BMI	body mass index
BNP	B-type natriuretic peptide
BODE	body mass index, airflow obstruction, dyspnea, and exercise capacity
CAT	COPD Assessment Test
CHF	congestive heart failure
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPG	clinical practice guideline
DoD	Department of Defense
DPI	dry powder inhaler
EBPWG	Evidence-Based Practice Working Group
FDA	U.S. Food and Drug Administration
FEV1	forced expiratory volume in one second
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Pulmonary Disease
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Hg	mercury
ICS	inhaled corticosteroid
ICU	intensive care unit
kg	kilogram
KQ	key question
LABA	long-acting beta 2-agonist
LAMA	long-acting antimuscarinic agent
LLN	lower limit of normal
LOTT	Long-term Oxygen Treatment Trial
LTOT	long-term oxygen therapy
LVRS	lung volume reduction surgery
MDI	metered-dose inhaler
m	meter
mcg	microgram
mg	milligram
mm	millimeter
mMRC	modified Medical Research Council
NAC	N-acetylcysteine
NIV	non-invasive ventilation

Abbreviation	Definition
O₂	oxygen
PaO₂	partial pressure of oxygen in arterial blood
PICOTS	population, intervention, comparison, outcome, timing, and setting
PRN	as needed
PO	orally
QoL	quality of life
RCT	randomized controlled trial
SABA	short-acting beta 2-agonist
SAMA	short-acting antimuscarinic agent
SaO₂	peripheral capillary oxygen saturation
SMI	soft mist inhaler
TMP-SMX	trimethoprim/sulfamethoxazole
U.S.	United States
USPSTF	U.S. Preventive Services Task Force
VA	Department of Veterans Affairs

References

1. U.S. Department of Veterans Affairs/Department of Defense Health Executive Committee (HEC). Evidence Based Practice Work Group Charter [updated January 9, 2017]. Available from: www.healthquality.va.gov/documents/EvidenceBasedPracticeWGCharter123020161.pdf.
2. Evans L. Book Review: Harrison's Pulmonary and Critical Care Medicine. Joseph Loscalzo. New York: McGraw-Hill Medical. 2010. Soft cover, 592 pages, illustrated, \$74.95. *Respiratory Care*; 2011.
3. Agusti A, Thomas A, Neff lecture. Chronic obstructive pulmonary disease: A systemic disease. *Proc Am Thorac Soc*. 2006;3(6):478-81. Epub 2006/08/22. doi: 10.1513/pats.200603-058MS. PubMed PMID: 16921116.
4. Nussbaumer-Ochsner Y, Rabe KF. Systemic manifestations of COPD. *Chest*. 2011;139(1):165-73. Epub 2011/01/07. doi: 10.1378/chest.10-1252. PubMed PMID: 21208876.
5. Macdonald G, Fauci AS, Kasper DL, Longo DL, Braunwald E, Hauser SL, Jameson JL, Loscalzo J. Harrison's Internal Medicine, 17th edition. *Internal Medicine Journal*. 2008;38(12):932-. doi: 10.1111/j.1445-5994.2008.01837.x.
6. Wedge R, Bondurant S. Combating tobacco use in military and Veteran populations: National Academies Press; 2009.
7. Telehealth and Telemedicine AAFP: AAFP. Available from: <https://www.aafp.org/about/policies/all/telehealth-telemedicine.html>.
8. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (The BOLD Study): A population-based prevalence study. *Lancet*. 2007;370(9589):741-50. Epub 2007/09/04. doi: 10.1016/s0140-6736(07)61377-4. PubMed PMID: 17765523.
9. American Lung Association. Learn About COPD [updated January 25, 2021; cited 2020 September 1]. Available from: <https://www.lung.org/lung-health-diseases/lung-disease-lookup/copd/learn-about-copd>.
10. American Lung Association. Estimated prevalence and incidence of lung disease: American Lung Association Epidemiology and Statistics Unit - *Research and Health Education* [updated May 13, 2020; cited 2020 September 5]. Available from: <https://www.lung.org/research/trends-in-lung-disease/prevalence-incidence-lung-disease>.
11. Ford ES, Croft JB, Mannino DM, Wheaton AG, Zhang X, Giles WH. COPD surveillance--United States, 1999-2011. *Chest*. 2013;144(1):284-305. Epub 2013/04/27. doi: 10.1378/chest.13-0809. PubMed PMID: 23619732.
12. The University of Chicago. COPD [cited 2021 April 13]. Available from: <http://asthma.bsd.uchicago.edu/sample-page/chronic-obstructive-pulmonary-lung-disease-copd/>.
13. American Lung Association. Chronic Obstructive Pulmonary Disease (COPD). Available from: <https://www.lung.org/lung-health-diseases/lung-disease-lookup/copd>.
14. Anderson E, Wiener RS, Resnick K, Elwy AR, Rinne ST. Care coordination for Veterans with COPD: A positive deviance study. *The American Journal of Managed Care*. 2020;26(2):63-8. PubMed PMID: 32059093.
15. Sharafkhaneh A, Petersen NJ, Yu HJ, Dalal AA, Johnson ML, Hanania NA. Burden of COPD in a government health care system: A retrospective observational study using data from the US Veterans Affairs population. *Int J Chron Obstruct Pulmon Dis*. 2010;5:125-32. Epub 2010/05/13. doi: 10.2147/copd.s8047. PubMed PMID: 20461144.
16. Morris MJ, Lucero PF, Zanders TB, Zacher LL. Diagnosis and management of chronic lung disease in deployed military personnel. *Ther Adv Respir Dis*. 2013;7(4):235-45. Epub 2013/03/09. doi: 10.1177/1753465813481022. PubMed PMID: 23470637.
17. Barnes PJ, Celli BR. Chronic obstructive pulmonary disease: reasons for optimism. *Therapy*. 2009;6(6):769-70.
18. U.S. Preventive Services Task Force. Standards for Guideline Development June 2018.

19. U.S. Department of Veteran Affairs, Department of Defense. Guideline for Guidelines. Veterans Health Administration, Office of Quality & Performance, Evidence Review Subgroup; Revised January 29, 2019.
20. Ransohoff DF, Pignone M, Sox HC. How to decide whether a clinical practice guideline is trustworthy. *JAMA*. 2013;309(2):139-40. Epub 2013/01/10. doi: 10.1001/jama.2012.156703. PubMed PMID: 23299601.
21. Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *J Clin Epidemiol*. 2013;66(7):726-35. Epub 2013/04/11. doi: 10.1016/j.jclinepi.2013.02.003. PubMed PMID: 23570745.
22. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y, et al. GRADE guidelines: 14. Going from evidence to recommendations: The significance and presentation of recommendations. *J Clin Epidemiol*. 2013;66(7):719-25. Epub 2013/01/15. doi: 10.1016/j.jclinepi.2012.03.013. PubMed PMID: 23312392.
23. Schunemann HJ, Fretheim A, Oxman AD. Improving the use of research evidence in guideline development: 10. Integrating values and consumer involvement. *Health Res Policy Syst*. 2006;4:22. Epub 2006/12/07. doi: 10.1186/1478-4505-4-22. PubMed PMID: 17147811.
24. Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, et al. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol*. 2011;64(4):395-400. Epub 2011/01/05. doi: 10.1016/j.jclinepi.2010.09.012. PubMed PMID: 21194891.
25. Newberry SJ, Ahmadzai N, Motala A, Tsertsvadze A, Maglione M, Ansari MT, et al. AHRQ Methods for Effective Health Care. *Surveillance and identification of signals for updating systematic reviews: Implementation and early experience*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2013.
26. National Institute for Health and Care Excellence. *The guidelines manual*. London: National Institute for Health and Care Excellence, 2012.
27. Martinez Garcia L, McFarlane E, Barnes S, Sanabria AJ, Alonso-Coello P, Alderson P. Updated recommendations: An assessment of NICE clinical guidelines. *Implement Sci*. 2014;9:72. Epub 2014/06/13. doi: 10.1186/1748-5908-9-72. PubMed PMID: 24919856.
28. U.S. Department of Veteran Affairs, Department of Defense. Guideline for Guidelines: Veterans Health Administration, Office of Quality & Performance, Evidence Review Subgroup [updated January 29, 2019]. Available from: <http://www.healthquality.va.gov/policy/index.asp>.
29. Clinical practice guidelines we can trust. Washington, DC: National Academies Press, 2011.
30. Robinson JH, Callister LC, Berry JA, Dearing KA. Patient-centered care and adherence: Definitions and applications to improve outcomes. *J Am Acad Nurse Pract*. 2008;20(12):600-7. Epub 2009/01/06. doi: 10.1111/j.1745-7599.2008.00360.x. PubMed PMID: 19120591.
31. Stewart M, Brown JB, Donner A, McWhinney IR, Oates J, Weston WW, et al. The impact of patient-centered care on outcomes. *J Fam Pract*. 2000;49(9):796-804. Epub 2000/10/14. PubMed PMID: 11032203.
32. Higginson IJ, Bausewein C, Reilly CC, Gao W, Gysels M, Dzingina M, et al. An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: A randomised controlled trial. *The Lancet Respiratory Medicine*. 2014;2(12):979-87.
33. Almagro P, Yun S, Sangil A, Rodríguez-Carballeira M, Marine M, Landete P, et al. Palliative care and prognosis in COPD: A systematic review with a validation cohort. *International Journal of Chronic Obstructive Pulmonary Disease*. 2017;12:1721.
34. Palliative Care and COPD: American Lung Association [updated February 27, 2020 September 4, 2020]. Available from: <https://www.lung.org/lung-health-diseases/lung-disease-lookup/copd/treating/palliative-care-and-copd>.
35. Institute of Medicine. *Crossing the quality chasm: A new health system for the 21st century*. Washington DC: National Academies Press, 2001.

36. Society for Medical Decision Making Committee on Standardization of Clinical Algorithms. Proposal for clinical algorithm standards. *Med Decis Making*. 1992;12(2):149-54. Epub 1992/04/01. PubMed PMID: 1573982.
37. Qaseem A, Snow V, Shekelle P, Sherif K, Wilt TJ, Weinberger S, et al. Diagnosis and management of stable chronic obstructive pulmonary disease: A clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2007;147(9):633-8. Epub 2007/11/03. PubMed PMID: 17975186.
38. Jones RC, Price D, Ryan D, Sims EJ, von Ziegenweidt J, Mascarenhas L, et al. Opportunities to diagnose chronic obstructive pulmonary disease in routine care in the UK: A retrospective study of a clinical cohort. *Lancet Respir Med*. 2014;2(4):267-76. Epub 2014/04/11. doi: 10.1016/s2213-2600(14)70008-6. PubMed PMID: 24717623.
39. Hill K, Goldstein RS, Guyatt GH, Blouin M, Tan WC, Davis LL, et al. Prevalence and underdiagnosis of chronic obstructive pulmonary disease among patients at risk in primary care. *CMAJ*. 2010;182(7):673-8. Epub 2010/04/08. doi: 10.1503/cmaj.091784. PubMed PMID: 20371646.
40. Ghattas C, Dai A, Gemmel DJ, Awad MH. Over diagnosis of chronic obstructive pulmonary disease in an underserved patient population. *International Journal of Chronic Obstructive Pulmonary Disease*. 2013;8:545. PubMed PMID: 24348030.
41. Strong M, Green A, Goyder E, Miles G, Lee AC, Basran G, et al. Accuracy of diagnosis and classification of COPD in primary and specialist nurse-led respiratory care in Rotherham, UK: A cross-sectional study. *Primary Care Respiratory Journal*. 2014;23(1):67-73. PubMed PMID: 24477772.
42. Gershon A, Mecredy G, Croxford R, To T, Stanbrook MB, Aaron SD. Outcomes of patients with chronic obstructive pulmonary disease diagnosed with or without pulmonary function testing. *CMAJ*. 2017;189(14):E530-E8. PubMed PMID: 28396329.
43. Kronborg T, Hangaard S, Cichosz SL, Hejlesen O. Increased accuracy after adjustment of spirometry threshold for diagnosing COPD based on pre-bronchodilator FEV1/FVC. *Respiratory Care*. 2019;64(1):85-90. PubMed PMID: 30578360.
44. Tan WC, Bourbeau J, Hernandez P, Chapman K, Cowie R, FitzGerald MJ, et al. Canadian prediction equations of spirometric lung function for Caucasian adults 20 to 90 years of age: Results from the Canadian Obstructive Lung Disease (COLD) study and the Lung Health Canadian Environment (LHCE) study. *Can Respir J*. 2011;18(6):321-6. Epub 2011/12/22. doi: 10.1155/2011/540396. PubMed PMID: 22187687.
45. Hanania NA, Sharafkhaneh A, Celli B, Decramer M, Lystig T, Kesten S, et al. Acute bronchodilator responsiveness and health outcomes in COPD patients in the UPLIFT trial. *Respiratory Research*. 2011;12(1):6. PubMed PMID: 21219660.
46. National Institute for Health and Care Excellence. *Chronic obstructive pulmonary disease: Management of chronic obstructive pulmonary disease in adults in primary and secondary care*. 2004.
47. Hanania NA, Celli BR, Donohue JF, Martin UJ. Bronchodilator reversibility in COPD. *Chest*. 2011;140(4):1055-63. Epub 2011/10/06. doi: 10.1378/chest.10-2974. PubMed PMID: 21972384.
48. Tashkin D, Kesten S. Long-term treatment benefits with tiotropium in COPD patients with and without short-term bronchodilator responses. *Chest*. 2003;123(5):1441-9. Epub 2003/05/13. doi: 10.1378/chest.123.5.1441. PubMed PMID: 12740259.
49. Global Initiative for Chronic Obstructive Lung Disease. 2021. Available from: <https://goldcopd.org/>.
50. Stolz D, Hirsch HH, Schilter D, Louis R, Rakic J, Boeck L, et al. Intensified therapy with inhaled corticosteroids and long-acting β 2-agonists at the onset of upper respiratory tract infection to prevent chronic obstructive pulmonary disease exacerbations. A multicenter, randomized, double-blind, placebo-controlled trial. *American Journal of Respiratory and Critical Care Medicine*. 2017;197(9):1136-46. doi: 10.1164/rccm.201709-1807OC. PubMed PMID: 29266965.

51. Betsuyaku T, Kato M, Fujimoto K, Kobayashi A, Hayamizu T, Hitosugi H, et al. A randomized trial of symptom-based management in Japanese patients with COPD. *International Journal of Chronic Obstructive Pulmonary Disease*. 2018;13:2409-23. doi: 10.2147/COPD.S152723. PubMed PMID: 30147307.
52. Vetrano DL, Zucchelli A, Bianchini E, Cricelli C, Piraino A, Zibellini M, et al. Triple inhaled therapy in COPD patients: Determinants of prescription in primary care. *Respiratory Medicine*. 2019;154:12-7. doi: <https://doi.org/10.1016/j.rmed.2019.05.022>. PubMed PMID: 31202120.
53. Scanlon PD, Connett JE, Waller LA, Altose MD, Bailey WC, Buist AS, et al. Smoking cessation and lung function in mild-to-moderate chronic obstructive pulmonary disease. The Lung Health Study. *Am J Respir Crit Care Med*. 2000;161(2 Pt 1):381-90. Epub 2000/02/15. doi: 10.1164/ajrccm.161.2.9901044. PubMed PMID: 10673175.
54. Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE. The effects of a smoking cessation intervention on 14.5-year mortality: A randomized clinical trial. *Ann Intern Med*. 2005;142(4):233-9. Epub 2005/02/16. doi: 10.7326/0003-4819-142-4-200502150-00005. PubMed PMID: 15710956.
55. Kopsaftis Z, Wood-Baker R, Poole P. Influenza vaccine for chronic obstructive pulmonary disease (COPD). *Cochrane Database of Systematic Reviews*. 2018(6). doi: 10.1002/14651858.CD002733.pub3. PubMed PMID: CD002733.
56. Walters JAE, Tang JNQ, Poole P, Wood-Baker R. Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*. 2017(1). doi: 10.1002/14651858.CD001390.pub4. PubMed PMID: CD001390.
57. Donohue JF, Betts KA, Du EX, Altman P, Goyal P, Keininger DL, et al. Comparative efficacy of long-acting β 2-agonists as monotherapy for chronic obstructive pulmonary disease: A network meta-analysis. *International Journal of Chronic Obstructive Pulmonary Disease*. 2017;12:367-81. doi: 10.2147/COPD.S119908. PubMed PMID: 28176892.
58. Oba Y, Lone NA. Comparative efficacy of long-acting muscarinic antagonists in preventing COPD exacerbations: a network meta-analysis and meta-regression. *Therapeutic Advances in Respiratory Disease*. 2015;9(1):3-15. doi: 10.1177/1753465814565624. PubMed PMID: 25586493.
59. Zou Y, Xiao J, Yang DH, Li J, Chen Q. Efficacy and safety of an aclidinium bromide treatment for 12 weeks or longer in patients with moderate-to-severe COPD: A meta-analysis. *COPD: Journal of Chronic Obstructive Pulmonary Disease*. 2016;13(4):499-508. doi: 10.3109/15412555.2015.1074172. PubMed PMID: 26846588.
60. Ismaila AS, Huisman EL, Puneekar YS, Karabis A. Comparative efficacy of long-acting muscarinic antagonist monotherapies in COPD: A systematic review and network meta-analysis. *International Journal of Chronic Obstructive Pulmonary Disease*. 2015;10:2495-517. doi: 10.2147/COPD.S92412. PubMed PMID: 26604738.
61. Ni H, Htet A, Moe S. Umeclidinium bromide versus placebo for people with chronic obstructive pulmonary disease (COPD). *Cochrane Database Syst Rev*. 2017;6(6):CD011897. Epub 2017/06/21. doi: 10.1002/14651858.CD011897.pub2. PubMed PMID: 28631387.
62. Lee HW, Kim H-J, Lee C-H. The impact of olodaterol on the risk of mortality and serious adverse events: A systematic review and meta-analysis. *British Journal of Clinical Pharmacology*. 2017;83(6):1166-75. doi: 10.1111/bcp.13210. PubMed PMID: 27957746.
63. Geake JB, Dabscheck EJ, Wood-Baker R, Cates CJ. Indacaterol, a once-daily beta2-agonist, versus twice-daily beta2-agonists or placebo for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*. 2015(1). doi: 10.1002/14651858.CD010139.pub2. PubMed PMID: CD010139.
64. Kew KM, Mavergames C, Walters J. Long-acting beta2-agonists for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*. 2014. doi: 10.1002/14651858.CD010177. PubMed PMID: 24127118.
65. Wadbo M, Löfdahl C-G, Larsson K, Skoogh BE, Tornling G, Arweström E, et al. Effects of formoterol and ipratropium bromide in COPD: A 3-month placebo-controlled study. *European Respiratory Journal*. 2002;20(5):1138-46. doi: 10.1183/09031936.02.00301702. PubMed PMID: 12449166.

66. Chen W-C, Huang C-H, Sheu C-C, Chong I-W, Chu K-A, Chen Y-C, et al. Long-acting beta2-agonists versus long-acting muscarinic antagonists in patients with stable COPD: A systematic review and meta-analysis of randomized controlled trials. *Respirology*. 2017;22(7):1313-9. doi: 10.1111/resp.13100. PubMed PMID: 28654201.
67. Maia IS, Pincelli MP, Leite VF, Amadera J, Buehler AM. Long-acting muscarinic antagonists vs. long-acting β 2 agonists in COPD exacerbations: A systematic review and meta-analysis. *Jornal Brasileiro de Pneumologia*. 2017;43(4):302-12. PubMed PMID: 28767773.
68. Kew KM, Dias S, Cates CJ. Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: A network meta-analysis. *Cochrane Database Syst Rev*. 2014(3):Cd010844. Epub 2014/03/29. doi: 10.1002/14651858.CD010844.pub2. PubMed PMID: 24671923.
69. Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*. 2012(7). PubMed PMID: 22786484.
70. Oba Y, Keeney E, Ghatehorde N, Dias S. Dual combination therapy versus long-acting bronchodilators alone for chronic obstructive pulmonary disease (COPD): A systematic review and network meta-analysis. *The Cochrane Database of Systematic Reviews*. 2018;12(12):CD012620-CD. doi: 10.1002/14651858.CD012620.pub2. PubMed PMID: 30521694.
71. Cazzola M, Andò F, Santus P, Ruggeri P, Di Marco F, Sanduzzi A, et al. A pilot study to assess the effects of combining fluticasone propionate/salmeterol and tiotropium on the airflow obstruction of patients with severe-to-very severe COPD. *Pulmonary Pharmacology & Therapeutics*. 2007;20(5):556-61. doi: <https://doi.org/10.1016/j.pupt.2006.06.001>. PubMed PMID: 16914336.
72. Hoshino M, Ohtawa J. Effects of tiotropium and salmeterol/fluticasone propionate on airway wall thickness in chronic obstructive pulmonary disease. *Respiration*. 2013;86(4):280-7. Epub 2013/07/25. doi: 10.1159/000351116. PubMed PMID: 23880883.
73. Zayed Y, Barbarawi M, Kheiri B, Haykal T, Chahine A, Rashdan L, et al. Triple versus dual inhaler therapy in moderate-to-severe COPD: A systematic review and meta-analysis of randomized controlled trials. *The Clinical Respiratory Journal*. 2019;13(7):413-28. PubMed PMID: 30947394.
74. Cazzola M, Rogliani P, Calzetta L, Matera MG. Triple therapy versus single and dual long-acting bronchodilator therapy in COPD: A systematic review and meta-analysis. *European Respiratory Journal*. 2018;52(6). PubMed PMID: 30309975.
75. Langham S, Lewis J, Pooley N, Embleton N, Langham J, Han MK, et al. Single-inhaler triple therapy in patients with chronic obstructive pulmonary disease: A systematic review. *Respiratory Research*. 2019;20(1):1-13. PubMed PMID: 31684965.
76. Lai C-C, Chen C-H, Lin CYH, Wang C-Y, Wang Y-H. The effects of single inhaler triple therapy vs single inhaler dual therapy or separate triple therapy for the management of chronic obstructive pulmonary disease: A systematic review and meta-analysis of randomized controlled trials. *International Journal of Chronic Obstructive Pulmonary Disease*. 2019;14:1539. PubMed PMID: 31371939.
77. Calzetta L, Matera MG, Braido F, Contoli M, Corsico A, Di Marco F, et al. Withdrawal of inhaled corticosteroids in COPD: A meta-analysis. *Pulmonary Pharmacology & Therapeutics*. 2017;45:148-58. PubMed PMID: 28606478.
78. Oshagbemi OA, Odiba JO, Daniel A, Yunusa I. Absolute blood eosinophil counts to guide inhaled corticosteroids therapy among patients with COPD: Systematic review and meta-analysis. *Current Drug Targets*. 2019;20(16):1670-9. PubMed PMID: 31393244.
79. Fowdar K, Chen H, He Z, Zhang J, Zhong X, Zhang J, et al. The effect of N-acetylcysteine on exacerbations of chronic obstructive pulmonary disease: A meta-analysis and systematic review. *Heart Lung*. 2017;46(2):120-8. Epub 2017/01/23. doi: 10.1016/j.hrtlng.2016.12.004. PubMed PMID: 28109565.

80. Vollenweider DJ, Frei A, Steurer-Stey CA, Garcia-Aymerich J, Puhan MA. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*. 2018(10). doi: 10.1002/14651858.CD010257.pub2. PubMed PMID: CD010257.
81. Stolbrink M, Amiry J, Blakey JD. Does antibiotic treatment duration affect the outcomes of exacerbations of asthma and COPD? A systematic review. *Chronic Respiratory Disease*. 2018;15(3):225-40. PubMed PMID: 29232988.
82. Butler CC, Gillespie D, White P, Bates J, Lowe R, Thomas-Jones E, et al. C-reactive protein testing to guide antibiotic prescribing for COPD exacerbations. *New England Journal of Medicine*. 2019;381(2):111-20. PubMed PMID: 31291514.
83. Nocturnal Oxygen Therapy Trial Group. Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: A clinical trial. *Ann Intern Med*. 1980;93(3):391-8. Epub 1980/09/01. PubMed PMID: 6776858.
84. Report of the Medical Research Council Working Party. Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. *Lancet*. 1981;1(8222):681-6. Epub 1981/03/28. PubMed PMID: 6110912.
85. COPD Working Group. Pulmonary rehabilitation for patients with chronic pulmonary disease (COPD): An evidence-based analysis. *Ont Health Technol Assess Ser*. 2012;12(6):1-75. Epub 2012/10/18. PubMed PMID: 23074434.
86. Ekström M. Clinical usefulness of long-term oxygen therapy in adults. *N Engl J Med*. 2016;375(17):1683-4. PubMed PMID: 27783914.
87. Oba Y, Salzman GA, Willsie SK. Reevaluation of continuous oxygen therapy after initial prescription in patients with chronic obstructive pulmonary disease. *Respir Care*. 2000;45(4):401-6. Epub 2000/04/26. PubMed PMID: 10780035.
88. Standards for the diagnosis and management of patients with COPD. American Thoracic Society, 2004.
89. O'Donohue WJ, Jr. Effect of oxygen therapy on increasing arterial oxygen tension in hypoxemic patients with stable chronic obstructive pulmonary disease while breathing ambient air. *Chest*. 1991;100(4):968-72. Epub 1991/10/11. PubMed PMID: 1914613.
90. COPD Working Group. Long-term oxygen therapy for patients with chronic obstructive pulmonary disease (COPD): An evidence-based analysis. *Ontario Health Technology Assessment Series*. 2012;12(7):1. PubMed PMID: 23074435.
91. Liu Y, Gong F. Determination of whether supplemental oxygen therapy is beneficial during exercise training in patients with COPD: A systematic review and meta-analysis. *Experimental and Therapeutic Medicine*. 2019;18(5):4081-9.
92. Ejiofor SI, Bayliss S, Gassamma A, Turner AM. Ambulatory oxygen for exercise-induced desaturation and dyspnea in chronic obstructive pulmonary disease (COPD): Systematic review and meta-analysis. *Chronic Obstructive Pulmonary Diseases: Journal of the COPD Foundation*. 2016;3(1):419. PubMed PMID: 28848863.
93. Ameer F, Carson KV, Usmani ZA, Smith BJ. Ambulatory oxygen for people with chronic obstructive pulmonary disease who are not hypoxaemic at rest. *Cochrane Database of Systematic Reviews*. 2014(6). PubMed PMID: 24957353.
94. Maldonado D, González-García M, Barrero M, Jaramillo C, Casas A. Exercise endurance in chronic obstructive pulmonary disease patients at an altitude of 2640 meters breathing air and oxygen (FIO₂ 28% and 35%): A randomized crossover trial. *COPD: Journal of Chronic Obstructive Pulmonary Disease*. 2014;11(4):401-6. PubMed PMID: 24111929.
95. Suissa S, Ernst P. Beta-blockers in COPD: A methodological review of the observational studies. *COPD: Journal of Chronic Obstructive Pulmonary Disease*. 2018;15(5):520-5. PubMed PMID: 30822238.

96. He W. Clinical efficacy and safety of cardio-selective β -receptor blocker in management of AECOPD complicated with right heart failure. *Biomedical Research*. 2017.
97. Dransfield MT. *Beta Blockers for the Prevention of Acute Exacerbations of COPD*. University of Alabama at Birmingham Birmingham United States, 2019.
98. Hegelund A, Andersen IC, Andersen MN, Bodtger U. The impact of a personalised action plan delivered at discharge to patients with COPD on readmissions: A pilot study. *Scandinavian Journal of Caring Sciences*. 2019. PubMed PMID: 31865631.
99. Lenferink A, van der Palen J, van der Valk PD, Cafarella P, van Veen A, Quinn S, et al. Exacerbation action plans for patients with COPD and comorbidities: A randomised controlled trial. *European Respiratory Journal*. 2019;54(5). PubMed PMID: 31413163.
100. Cannon D, Buys N, Sriram KB, Sharma S, Morris N, Sun J. The effects of chronic obstructive pulmonary disease self-management interventions on improvement of quality of life in COPD patients: A meta-analysis. *Respiratory Medicine*. 2016;121:81-90. PubMed PMID: 27888996.
101. Lenferink A, Brusse-Keizer M, van der Valk PD, Frith PA, Zwerink M, Monninkhof EM, et al. Self-management interventions including action plans for exacerbations versus usual care in patients with chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*. 2017(8). PubMed PMID: 28777450.
102. Liang J, Abramson MJ, Russell G, Holland AE, Zwar NA, Bonevski B, et al. Interdisciplinary COPD intervention in primary care: A cluster randomised controlled trial. *European Respiratory Journal*. 2019;53(4):1801530. PubMed PMID: 30792342.
103. Sánchez-Nieto JM, Andújar-Espinosa R, Bernabeu-Mora R, Hu C, Gálvez-Martínez B, Carrillo-Alcaraz A, et al. Efficacy of a self-management plan in exacerbations for patients with advanced COPD. *International Journal of Chronic Obstructive Pulmonary Disease*. 2016;11:1939. PubMed PMID: 27574418.
104. Wang T, Tan J-Y, Xiao LD, Deng R. Effectiveness of disease-specific self-management education on health outcomes in patients with chronic obstructive pulmonary disease: An updated systematic review and meta-analysis. *Patient Education and Counseling*. 2017;100(8):1432-46. PubMed PMID: 28318846.
105. Benzo R, Vickers K, Novotny PJ, Tucker S, Hoult J, Neuenfeldt P, et al. Health coaching and chronic obstructive pulmonary disease rehospitalization. A randomized study. *American Journal of Respiratory and Critical Care Medicine*. 2016;194(6):672-80. PubMed PMID: 26953637.
106. Jolly K, Sidhu M, Bates E, Majothi S, Sitch A, Bayliss S, et al. Systematic review of the effectiveness of community-based self-management interventions among primary care COPD patients. *NPJ Primary Care Respiratory Medicine*. 2018;28(1):1-8. PubMed PMID: 30470741.
107. Rose L, Istamboulian L, Carriere L, Thomas A, Lee H-B, Rezaie S, et al. Program of integrated care for patients with chronic obstructive pulmonary disease and multiple comorbidities (PIC COPD+): A randomised controlled trial. *European Respiratory Journal*. 2018;51(1). PubMed PMID: 29326330.
108. Liao W-H, Chen J-W, Chen X, Lin L, Yan H-Y, Zhou Y-Q, et al. Impact of resistance training in subjects with COPD: A systematic review and meta-analysis. *Respiratory Care*. 2015;60(8):1130-45. doi: 10.4187/respcare.03598. PubMed PMID: 26015595.
109. McKeough ZJ, Velloso M, Lima VP, Alison JA. Upper limb exercise training for COPD. *Cochrane Database of Systematic Reviews*. 2016(11). doi: 10.1002/14651858.CD011434.pub2. PubMed PMID: CD011434.
110. Paneroni M, Simonelli C, Vitacca M, Ambrosino N. Aerobic exercise training in very severe chronic obstructive pulmonary disease: A systematic review and meta-analysis. *American Journal of Physical Medicine & Rehabilitation*. 2017;96(8):541-8. PubMed PMID: 28099192.
111. McCabe C, McCann M, Brady AM. Computer and mobile technology interventions for self-management in chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*. 2017(5). PubMed PMID: 28535331.

112. Deng N, Gu T, Zhao Q, Zhang X, Zhao F, He H. Effects of telephone support on exercise capacity and quality of life in patients with chronic obstructive pulmonary disease: A meta-analysis. *Psychology, Health & Medicine*. 2018;23(8):917-33. PubMed PMID: 29320895.
113. Park SK, Bang CH, Lee SH. Evaluating the effect of a smartphone app-based self-management program for people with COPD: A randomized controlled trial. *Applied Nursing Research*. 2020;151231. PubMed PMID: 31955942.
114. Demeyer H, Louvaris Z, Frei A, Rabinovich RA, de Jong C, Gimeno-Santos E, et al. Physical activity is increased by a 12-week semiautomated telecoaching programme in patients with COPD: A multicentre randomised controlled trial. *Thorax*. 2017;72(5):415-23. PubMed PMID: 28137918.
115. Vorrink SN, Kort HS, Troosters T, Zanen P, Lammers J-WJ. Efficacy of an mHealth intervention to stimulate physical activity in COPD patients after pulmonary rehabilitation. *European Respiratory Journal*. 2016;48(4):1019-29. PubMed PMID: 27587557.
116. Hong Y, Lee SH. Effectiveness of tele-monitoring by patient severity and intervention type in chronic obstructive pulmonary disease patients: A systematic review and meta-analysis. *International Journal of Nursing Studies*. 2019;92:1-15. PubMed PMID: 30690162.
117. Sul A-R, Lyu D-H, Park D-A. Effectiveness of telemonitoring versus usual care for chronic obstructive pulmonary disease: A systematic review and meta-analysis. *Journal of Telemedicine and Telecare*. 2020;26(4):189-99. PubMed PMID: 30541375.
118. Nguyen HQ, Moy ML, Liu I-LA, Fan VS, Gould MK, Desai SA, et al. Effect of physical activity coaching on acute care and survival among patients with chronic obstructive pulmonary disease: A pragmatic randomized clinical trial. *JAMA Network Open*. 2019;2(8):e199657-e. doi: 10.1001/jamanetworkopen.2019.9657. PubMed PMID: 31418811.
119. Kessler R, Casan-Clara P, Koehler D, Tognella S, Viejo JL, Dal Negro RW, et al. COMET: A multicomponent home-based disease-management programme versus routine care in severe COPD. *European Respiratory Journal*. 2018;51(1):1701612. doi: 10.1183/13993003.01612-2017. PubMed PMID: 29326333.
120. Soriano JB, García-Río F, Vázquez-Espinosa E, Conforto JI, Hernando-Sanz A, López-Yepes L, et al. A multicentre, randomized controlled trial of telehealth for the management of COPD. *Respiratory Medicine*. 2018;144:74-81. doi: 10.1016/j.rmed.2018.10.008. PubMed PMID: 30366588.
121. Lilholt PH, Udsen FW, Ehlers L, Hejlesen OK. Telehealthcare for patients suffering from chronic obstructive pulmonary disease: Effects on health-related quality of life: Results from the Danish 'TeleCare North' cluster-randomised trial. *BMJ Open*. 2017;7(5):e014587.
122. Wan ES, Kantorowski A, Homsy D, Teylan M, Kadri R, Richardson CR, et al. Promoting physical activity in COPD: Insights from a randomized trial of a web-based intervention and pedometer use. *Respiratory Medicine*. 2017;130:102-10.
123. Bernocchi P, Vitacca M, La Rovere MT, Volterrani M, Galli T, Baratti D, et al. Home-based telerehabilitation in older patients with chronic obstructive pulmonary disease and heart failure: A randomised controlled trial. *Age and Ageing*. 2018;47(1):82-8.
124. Yang F, Xiong Z-F, Yang C, Li L, Qiao G, Wang Y, et al. Continuity of care to prevent readmissions for patients with chronic obstructive pulmonary disease: A systematic review and meta-analysis. *COPD: Journal of Chronic Obstructive Pulmonary Disease*. 2017;14(2):251-61.
125. Tupper OD, Gregersen TL, Ringbaek T, Brøndum E, Frausing E, Green A, et al. Effect of tele-health care on quality of life in patients with severe COPD: A randomized clinical trial. *International Journal of Chronic Obstructive Pulmonary Disease*. 2018;13:2657.
126. Tsai LLY, McNamara RJ, Moddel C, Alison JA, McKenzie DK, McKeough ZJ. Home-based telerehabilitation via real-time videoconferencing improves endurance exercise capacity in patients with COPD: The randomized controlled TeleR Study. *Respirology*. 2017;22(4):699-707.

127. Jolly K, Sidhu MS, Hewitt CA, Coventry PA, Daley A, Jordan R, et al. Self management of patients with mild COPD in primary care: Randomised controlled trial. *BMJ*. 2018;361:k2241. Epub 2018/06/15. doi: 10.1136/bmj.k2241. PubMed PMID: 29899047.
128. Agency for Health Research and Quality. The effective health care program stakeholder guide Appendix D: Research questions & PICO(TS) 2011. Available from: <https://www.ahrq.gov/research/findings/evidence-based-reports/stakeholderguide/appendixc.html>.
129. Ogasawara T, Sakata J, Aoshima Y, Tanaka K, Yano T, Kasamatsu N. Bronchodilator effect of tiotropium via Respimat administered with a spacer in patients with chronic obstructive pulmonary disease (COPD). *Internal Medicine*. 2017;advpub. doi: 10.2169/internalmedicine.8255-16.
130. Global Initiative for Chronic Obstructive Lung Disease. *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2018*. Available from: <https://goldcopd.org/wp-content/uploads/2016/04/GOLD-2018-WMS.pdf>.
131. Jones PW HG, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD assessment test. *Eur Respir J*. 2009;34:648-54.
132. Using an Inhaler Veterans Health Library[3/30/2021]. Available from: https://www.veteranshealthlibrary.va.gov/Search/142,82457_VA.
133. Using an Inhaler with a Spacer [03/31/21]. Available from: https://www.veteranshealthlibrary.va.gov/Search/142,90331_VA.
134. Using Dry-Powder Inhalers (DPIs) [03/30/21]. Available from: https://www.veteranshealthlibrary.va.gov/Search/142,86203_VA.
135. SPIRIVA RESPIMAT [03/30/21]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207070s000lbl.pdf.