# CLINICAL PRACTICE GUIDELINES FOR THE MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

*Published on November 8, 2023*

# Disclaimer

This clinical practice guideline (CPG) is intended to be used by primary care workers in the primary care facility who manage possible and diagnosed COPD patients within the universal healthcare (UHC) framework of the Philippines. Adherence to this guideline is encouraged by the Department of Health (DOH), however, it should not restrict the clinicians in using their clinical judgment and considering patient's values, needs, and preferences while handling individual cases. Clinicians and relevant stakeholders must always exercise sound clinical decision-making as the individual patient's history, current physical status, and their responses to treatment may vary.

Payors and policymakers, including hospital administrators and employers, can also utilize this CPG. Policymakers may be guided on resource prioritization and allocations (i.e. national and local government unit funding, UHC or Philhealth package development) to facilitate and ensure better respiratory health outcomes for COPD patients. Nonconformance to this document should not be the sole basis for granting or denying financial assistance or insurance claims. Recommendations from this CPG should not be treated as strict rules to base legal action.

Developers of this CPG are aware of its limitations. Evidence summaries are based on the best available scientific evidence at the time of its formulation. As such, certain aspects of the interventions or diagnostic tests may not be completely addressed by the included studies.

This CPG is not intended to cover the entirety of the management of chronic obstructive pulmonary disease (COPD). It provides recommendations on interventions where variability in clinical practice and some controversies in decision-making exist.

You may contact us through email at research@lcp.gov.ph or secretariat@philchest.com for any questions or clarifications on the outputs and process of this CPG.

# Acknowledgements

We would like to acknowledge the effort and participation of the following key stakeholders: (1) Department of Health as the funding agency; (2) University of the Philippines-National Institutes for Health as the lead technical guide; and, (3) Lung Center of the Philippines as the lead developer. We also like to send our gratitude to these institutions for providing their clinical expertise and experience which helped create this CPG: Philippine College of Chest Physicians, Philippine College of Physicians, LCP COPD Support Group, Philippine Nurses Association, Philippine Academy of Family Physicians, Philippine Society of General Internal Medicine, Regional Lung Center - Vicente Sotto Memorial Medical Center, and Association of Municipal Health Officers of the Philippines.

The COPD CPG Task Force, NIH, and DOH would like to give special acknowledgement to the significant contribution of Dr. Aldrin Loyola+, the technical adviser of the task force, in the protocol development and evidence review process of this CPG development project.

# Participating Societies, Organizations, Agencies, and/or Institutions

Department of Health

University of the Philippines

UP-Institute of Clinical Epidemiology

Lung Center of the Philippines

Philippine Nurses Association

Philippine Academy of Family Physicians

Philippine College of Chest Physicians

Philippine Society of General Internal Medicine

Philippine College of Physicians

Association of Municipal Health Officers of the Philippines

Regional Lung Center - Vicente Sotto Memorial Medical Center

LCP COPD Support Group

# List of Abbreviations

| | |
|---|---|
| AOR | Adjusted odds ratio |
| CDQ | COPD Diagnostic Questionnaire |
| CHF | Congestive heart failure |
| CI | Confidence interval |
| COPD | Chronic obstructive pulmonary disease |
| COPD-PS | COPD Population Screener |
| CRQ | Chronic Respiratory Disease Questionnaire |
| FEV | Forced expiratory volume |
| GOLD | Global Initiative for Chronic Obstructive Lung Disease |
| ICS | Inhaled corticosteroid |
| IHD | Ischemic heart disease |
| LABA | Long-acting beta-agonists |
| LABD | Long-acting bronchodilator |
| LAMA | Long-acting muscarinic antagonists |
| LFQ | Lung Function Questionnaire |
| LTOT | Long-term oxygen therapy |
| MCID | Minimal clinically important difference |
| mmRC | Modified Medical Research Council |
| NICE | National Institute for Care and Excellence |
| NPG | National Practice Guidelines |
| NRA | Nicotine receptor antagonists |
| NRT | Nicotine replacement therapy |
| OR | Odds ratio |
| PNDF | Philippine National Drug Formulary |
| QALY | Quality-adjusted life years |
| QOL | Quality of life |
| RCT | Randomized controlled trial |
| RR | Relative risk |
| SABA | Short-acting beta-agonists |
| SAMA | Short-acting muscarinic antagonists |
| SGRQ | St. George's Respiratory Questionnaire |
| SR/MA | Systematic review and meta-analysis |
| VAS | Visual Analog Scale |

# Content

# List of Tables

# List of Figures

# Executive Summary

Chronic obstructive pulmonary disease (COPD) continues to be a primary burden to Filipino patients and our healthcare system. There are varying practices in the management of patients with COPD. Primary care management of COPD is important for early diagnosis, initial management and prompt referral to specialists to slow the progression of symptoms, reduce exacerbations, and improve survival of these patients. This clinical practice guideline (CPG) aims to (1) improve the respiratory health outcomes of COPD patients, specifically their quality of life, symptoms of breathlessness, exercise capacity, exacerbations, hospitalizations, mortality, and lung function and (2) ensure adherence of primary care providers to the COPD CPG in the primary care setting. This guideline is intended to be used by primary care workers in the primary care facility who manage possible and diagnosed COPD patients within the universal healthcare (UHC) framework of the Philippines. Its target beneficiaries are COPD patients and indirectly the whole of society in the Philippines. Policymakers may also be guided on resource prioritization and allocations (i.e. national and local government unit funding, UHC or Philhealth package development) to facilitate and ensure better respiratory health outcomes for COPD patients.

This is the fourth clinical practice guideline on the management of COPD among Filipinos. The first three guidelines were all initiated by the Philippine College of Chest Physicians (PCCP) Council on COPD and Pulmonary Rehabilitation last 2009, 2014, and 2021. The latest (2021) guideline was done in collaboration with the Philippine Academy of Family Physicians (PAFP) which aims to provide a simple guide to all health care workers who manage possible COPD patients within the UHC framework of the Philippines and the presence of COVID-19 infection.[7]

This CPG covers key clinical issues in the primary care setting and were classified into 4 domains: (1) prevention, screening and diagnosis of copd; (2) management of stable copd; (3) management of copd exacerbation; and, (4) referral systems, non-pharmacologic management, and palliative care. There are 11 questions with 24 of recommendations in this guideline (see Table 1). Majority of the recommendations have strong strength of recommendation and were based not only on the certainty of evidence but also on other equally important factors such as equity, feasibility, cost, and patient's values and preferences. Further research may have an impact on the estimates of the effect of each intervention or accuracy of the diagnostic tests included in this CPG.

# Summary of Recommendations

Table 1. Summary of Recommendations

| No. | Recommendations | Certainty of Evidence | Strength of Recommendation |
|---|---|---|---|
| 1A | Among smokers, we recommend smoking cessation to prevent COPD | Moderate | Strong |
| 1B | Among patients with COPD who are smokers, we recommend smoking cessation to prevent COPD-related morbidity and mortality | Moderate | Strong |
| 1C | Among households using biomass fuels, we recommend shifting to clean fuel (i.e., gas or electricity) to reduce the risk for COPD | Very low | Strong |
| 2A | Among probable COPD patients, we recommend against the use of clinical scoring system alone compared to facility-based spirometry in confirming the diagnosis of COPD in the primary care setting | Low | Strong |
| 2B | Among probable COPD patients, we suggest the use of clinical scoring system to identify patients who may need further confirmatory testing | Low | Weak |
| 2C | Among probable COPD patients, we recommend against the use of peak flow meter alone in confirming the diagnosis of COPD in the primary care setting | Very low | Strong |
| 2D | Among probable COPD patients, we recommend against the use of handheld spirometer alone in confirming the diagnosis of COPD in the primary care setting | Very low | Strong |
| 2E | Among probable COPD patients, we suggest the use of combined clinical scoring system and handheld spirometer as an alternative to facility-based spirometry in confirming the diagnosis of COPD in the primary care setting | Very low | Weak |
| 2F | Among probable COPD patients, we | Low | Weak |

| | | | |
|---|---|---|---|
| | suggest against use of combined clinical scoring system and peak flow meter compared to facility-based spirometry in confirming the diagnosis of COPD in the primary care setting | | |
| 3A | Among stable COPD patients in the primary care setting with FEV1<80% or mMRC≥2* and are not in exacerbation, we recommend the use of LABA/LAMA combination therapy over LAMA or LABA monotherapy | Low | Strong |
| 3B | Among stable COPD patients in the primary care setting with FEV1<80% or mMRC≥2* and are not in exacerbation, we suggest the use of LAMA over LABA | Low | Weak |
| 3C | Among stable COPD patients in the primary care setting with FEV1≥80% or mMRC<2* and are not in exacerbation, we suggest the use of LAMA monotherapy over LABA monotherapy or LABA/LAMA combination therapy | Very low | Weak |
| 4 | Among stable COPD patients in the primary care setting with FEV1<80% or mMRC≥2* with increased risk for exacerbations and absence of concurrent respiratory infection**, we recommend the use of inhaled corticosteroids in combination with inhaled long-acting bronchodilators | Low | Strong |
| 5A | Among stable COPD patients in the primary care setting, we recommend the use of inhaled long-acting bronchodilator over oral methylxanthines | Very low | Strong |
| 5B | Among stable COPD patients in the primary care setting, we recommend the use of oral methylxanthines versus no treatment if inhaled long-acting bronchodilator is not available | Very low | Strong |
| 5C | Among stable COPD patients in the primary care setting, we recommend against adding oral methylxanthines to inhaled long-acting bronchodilator | Very low | Strong |
| 6 | Among patients with COPD, we | Very low | Strong |

| | | | |
|---|---|---|---|
| | recommend the use of SABA+SAMA (combination therapy) in the management of acute exacerbation. In situations where SABA+SAMA is not readily available, SABA may be used | | |
| 7 | Among COPD patients in acute exacerbation with worsening symptoms and not responding to bronchodilators, we recommend the use of short course*** oral steroids in the primary care setting | Low | Strong |
| 8 | Among outpatients with COPD, we recommend initiation of oral antibiotics in the presence of at least two of the following symptoms: increased dyspnea, increased frequency of cough, increased sputum volume or purulence | Low | Strong |
| 9A | Among COPD patients managed at the primary level, we recommend referral of any of the following conditions that are associated with higher risk of moderate to severe exacerbation to higher level of care: prior history of exacerbation, presence of comorbidities, and severe or very severe airflow limitation | Very low | Strong |
| 9B | Among COPD patients managed at the primary level, we recommend referral of any of the following conditions that are associated with higher risk of mortality to higher level of care: presence of uncontrolled diabetes or cardiovascular disease, previous hospitalization for acute exacerbation within the past year, hospital readmission within 30 days, and use of long-term oxygen therapy | Very low | Strong |
| 10 | Among stable COPD patients, we recommend the use of guided self-management utilizing COPD action plan in primary care setting | Low | Strong |
| 11A | Among symptomatic COPD patients with moderate to severe breathlessness,**** who are not hypoxemic, and does not fulfill criteria for long-term oxygen therapy (LTOT), we suggest using low flow oxygen therapy for relief of dyspnea with caution and | Low | Weak |

| | | | |
|---|---|---|---|
| | close supervision of attending physician | | |
| 11B | Among patients with advanced-stage or end-stage COPD and/or refractory dyspnea, we suggest to consider the use of opioids with close supervision to relieve dyspnea that persists despite maximized medical management | Very low | Weak |

**The Modified Medical Research Council (mmRC) Dyspnea Scale stratifies severity of dyspnea in respiratory diseases, particularly COPD: [mmRC of 0] Dyspnea only with strenuous exercise; [mmRC of 1] Dyspnea when hurrying or walking up a slight hill; [mmRC of 2] Walks slower than people of the same age because of dyspnea or has to stop for breath when walking at own pace; [mmRC of 3] Stops for breath after walking 100 yards (91 m) or after a few minutes; [mmRC of 4] Too dyspneic to leave house or breathless when dressing.*
***Based on included RCTS in this review, addition of ICS to long-acting bronchodilator was indicated for patients with recurrent history of exacerbations. However, concurrent respiratory infection was identified as a contraindication.*
****The duration of short course is 5-10 days. Referral to higher level of care may be done upon discretion of the primary care physician at any time for non-responders or for those with incomplete response.*
*****Moderate to severe breathlessness is defined as mMRc of 3-4 (3 stops for breath after walking 100m or stops after a few minutes walking on the level; 4 Too breathless to leave the house or breathless on dressing or undressing)*

# Introduction

## Background

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, causing 3.23 million deaths in 2019.[1] In the Philippines, chronic lower respiratory diseases, including COPD, continue to be part of the top 10 causes of mortality.[2] Aside from its impact on mortality, COPD causes compromised quality of life among its survivors. COPD patients experience persistent and progressive respiratory symptoms, including difficulty in breathing, cough and phlegm production making them at risk for exacerbations and hospitalizations. The COPD burden is projected to increase in the coming decades because of continued exposure to COPD risk factors and aging of the population.[3] In the latest study on the burden of COPD in a rural setting in the Philippines in 2011, the prevalence of COPD in the rural setting was 20.8%, which was higher than that determined previously for an urban area. This may be attributed to smoking, exposure to wood fuels and a high prevalence of tuberculosis in the community.[4]

## Objectives

The ultimate or long-term goal of this clinical practice guideline (CPG) development is improved respiratory health outcomes of COPD patients, specifically improving their quality of life, reducing symptoms of breathlessness, increasing exercise capacity, reducing exacerbations, hospitalizations, mortality, and improving lung function. Short term goal is the adherence of primary care providers to the COPD CPG in the primary care setting.

The following are the objectives of this CPG in order to achieve the aforementioned long term and short term goals: (1) to develop an evidence-based and consensus recommendations involving key stakeholders, specifically on the following domains in the primary care setting: (a) prevention, screening and diagnosis; (b)management of stable COPD; (c) management of COPD exacerbations; and, (d) and referral systems, non-pharmacologic management, and palliative care. This CPG also aims to provide consensus recommendations for the monitoring of uptake, adherence, and outcomes and the updating of this guideline.

## Target Population

## Intended Users

This document serves as a guide to standard of care and clinical decisions of primary care workers in the primary care facility who manage possible and diagnosed COPD patients within the universal healthcare (UHC) framework of the Philippines. Under UHC, primary care worker refers to a health care worker, who may be a health professional or community health worker/volunteer certified by DOH to provide primary care services, while primary care facility refers to the institution that primarily delivers primary care services which shall be licensed or registered by the DOH.[5]

Its target beneficiaries are COPD patients and will cover all genders, ≥ 40yo, across disease status and stages (stable or in exacerbation and GOLD A,B,C,D), and those with or without comorbidities. Since this is a primary care CPG, patients managed in the hospital setting were excluded.

Policymakers may also be guided on resource prioritization and allocations (i.e. national and local government unit funding, UHC or Philhealth package

development) to facilitate and ensure better respiratory health outcomes for COPD patients.

## Key Clinical Issues and Questions

Table 2 below shows the list of key questions included in this CPG and each question PICO.

**Table 2. List of Guideline Questions**

| **Question 1: Among adult patients exposed to tobacco smoke and biomass fuel, what is the efficacy and safety of risk reduction strategies in the prevention of onset of COPD and COPD related morbidity and mortality?** | |
|---|---|
| **Population** | Patients with risk factors for COPD<br>(smoking, biomass fuel exposure) |
| **Intervention/ Treatment** | Risk reduction interventions (smoking cessation, non biomass fuel alternatives/non use of biomass fuel) |
| **Comparison** | Usual care/No intervention |
| **Outcomes** | Efficacy<br>Reduction in the incidence of COPD<br>Delay in onset of COPD related symptoms<br>Delay in lung function decline or improvement of lung function (FEV1, FEV1/FVC)<br>COPD related morbidity and mortality<br>Safety<br>Adverse events |
| **Subgroups (if any)** | None |

| **Question 2: Among probable COPD patients, how accurate and safe is the use of clinical scoring system and/or peak flow meter and/or handheld spirometer as compared to facility-based spirometer in the diagnosis of COPD in the primary care setting?** | |
|---|---|
| **Population** | Probable COPD |
| **Index Test** | Clinical scoring system and/or peak flow meter and/or handheld spirometer |
| **Reference Standard** | Facility-based spirometer |
| **Outcomes** | Diagnosis of COPD |

| | |
|---|---|
| | Accuracy (Sensitivity, Specificity, PPV, NPV, LR)<br>Safety (Adverse events) |
| **Subgroups (if any)** | None |

| **Question 3: Among stable COPD patients in the primary care settings, how effective and safe are inhaled long-acting bronchodilators (LABA or LAMA alone or LAMA/LABA combination) in improving symptoms and preventing exacerbations, hospitalization, and death?** | |
|---|---|
| **Population** | Stable COPD<br>Operational definition: COPD patients who are not in exacerbation.<br>(Exacerbation: worsening of the patient's respiratory symptoms that is beyond the normal day by day variation and leads to a change in medication; any of the following: Change in sputum character or purulence, Increase in sputum production, Increase in dyspnea) |
| **Intervention/ Treatment** | LABA versus LAMA<br>LABA versus LABA/LAMA combination<br>LAMA versus LABA/LAMA combination |
| **Comparison** | |
| **Outcomes** | COPD-related quality-of-life (HRQoL), Functional Capacity, Exercise Capacity, Exacerbations, Treatment Failure, COPD-related Hospitalization, All-cause Mortality, COPD-Related Mortality, Lung Function, Length of Recovery, Adverse Event |
| **Subgroups (if any)** | COPD stage or severity (ABCD) |

| **Question 4:** Among stable COPD patients in the primary care setting, how effective and safe are inhaled corticosteroids (with vs without inhaled long acting bronchodilator) in improving symptoms and preventing exacerbations, hospitalization, and death? | |
|---|---|
| **Population** | Stable COPD<br>Operational definition: COPD patients who are not in exacerbation.<br>(Exacerbation: worsening of the patient's respiratory symptoms that is beyond the normal day by day variation and leads to a change in medication; any of the following: Change in sputum |

| | |
|---|---|
| | character or purulence, Increase in sputum production, Increase in dyspnea) |
| **Intervention/ Treatment** | Inhaled Corticosteroid + Inhaled Long-Acting Bronchodilator |
| **Comparison** | Inhaled Long-Acting Bronchodilator |
| **Outcomes** | COPD-related quality-of-life (HRQoL), Functional Capacity, Exercise Capacity, Exacerbations, Treatment Failure, COPD-related Hospitalization, All-cause Mortality, COPD-Related Mortality, Lung Function, Length of Recovery, Adverse Events |
| **Subgroups (if any)** | COPD stage or severity |

| | |
|---|---|
| **Question 5:** Among stable COPD patients in the primary care setting, how effective and safe are oral methylxanthines (alone or in combination with inhaled long-acting bronchodilator) in improving symptoms, preventing exacerbations, hospitalization, and death? | |
| **Population** | Stable COPD<br>Operational definition: COPD patients who are not in exacerbation.<br>(Exacerbation: worsening of the patient's respiratory symptoms that is beyond the normal day by day variation and leads to a change in medication; any of the following: Change in sputum character or purulence, Increase in sputum production, Increase in dyspnea) |
| **Intervention/ Treatment** | Oral Methylxanthine with or without Inhaled Long-acting bronchodilator |
| **Comparison** | Inhaled Long-acting bronchodilator |
| **Outcomes** | COPD-related quality-of-life (HRQoL), Functional Capacity, Exercise Capacity, Exacerbations, Treatment Failure, COPD-related Hospitalization, All-cause Mortality, COPD-Related Mortality, Lung Function, Length of Recovery, Adverse Event |
| **Subgroups (if any)** | Specific type of methylxanthine (doxofylline, theophylline, etc.)<br>COPD stage or severity |

| |
|---|
| **Question 6:** Among patients with COPD exacerbation in the primary care setting, |

| | |
|---|---|
| how effective and safe are SABA+SAMA vs SABA alone in improving symptoms and preventing recurrence, hospitalization, and death? | |
| **Population** | COPD patients in exacerbation |
| **Intervention/ Treatment** | SABA+SAMA |
| **Comparison** | SABA |
| **Outcomes** | Symptom Improvement, Recurrence, Hospitalization, Death<br>Safety/Adverse events |
| **Subgroups (if any)** | Setting (primary care vs hospital); Route (via inhaler vs nebulization); Severity of exacerbation (mild, moderate, severe) |
| | |

| | |
|---|---|
| **Question 7:** Among COPD patients in exacerbation, how effective and safe are steroids in improving symptoms and preventing recurrence, hospitalization and death? | |
| **Population** | COPD patients in exacerbation |
| **Intervention/ Treatment Comparison (Main Question)** | Steroids<br>No steroids |
| **Intervention/ Treatment Comparison (Sub Question)** | Short course (<7 days)<br>Extended duration (>7 days) |
| **Outcomes** | Symptom Improvement, Recurrence, Hospitalization, Death, safety/adverse event |
| **Subgroups (if any)** | Severity of exacerbation (mild, moderate, severe) |
| | |

| | |
|---|---|
| **Question 8:** Among COPD patients in exacerbation, how effective and safe are initiation of antibiotics in improving symptoms and preventing recurrence, hospitalization and death? | |
| **Population** | COPD patients in exacerbation |
| **Intervention/ Treatment** | Antibiotics |

| | |
|---|---|
| **Comparison** | None |
| **Outcomes** | Symptom Improvement, Recurrence, Hospitalization, Death, safety/adverse event |
| **Subgroups (if any)** | Setting (primary care vs hospital); Route (oral vs intravenous); Severity of exacerbation (mild, moderate, severe); Indications when to initiate antibiotics (empiric, symptom/criteria based) |

| **Question 9:** Among COPD patients managed by primary care physicians, what are the conditions that warrant referral to specialists to improve their symptoms and quality of life and to prevent COPD related morbidity and mortality? | |
|---|---|
| **Population** | COPD patients managed by primary care physicians |
| **Intervention** | Referral to specialists of certain conditions |
| **Comparison** | Usual care |
| **Outcomes** | Symptom improvement<br>Quality of life<br>COPD related morbidity and mortality |
| **Subgroups (if any)** | None |

| **Question 10:** Among stable COPD patients managed in the primary care setting, how effective and safe is guided self-management utilizing a COPD action plan in improving their symptoms and quality of life, reducing exacerbations, and prevention of hospitalization and death? | |
|---|---|
| **Population** | Stable COPD patients managed in the primary care setting<br>Operational definition: COPD patients who are not in exacerbation.<br>(Exacerbation: worsening of the patient's respiratory symptoms that is beyond the normal day by day variation and leads to a change in medication; any of the following: Change in sputum character or purulence, Increase in sputum production, Increase in dyspnea) |
| **Intervention/ Treatment** | Guided self-management (includes COPD action plan) |
| **Comparison** | Usual care |
| **Outcomes** | Symptom Improvement, Quality of life, exacerbations, Hospitalization, Death, Safety/Adverse event |

| | |
|---|---|
| **Subgroups (if any)** | Quantify the benefit of each component/combinations (smoking cessation, symptom diary and COPD action plan, inhaler technique, vaccination, physical activity)<br><br>COPD stage specific guided self-management strategies<br><br>Implementation strategies in the primary care setting |

| **Question 11:** Among end-stage or advanced-stage COPD patients, how effective and safe are primary care palliative services in improving quality of life? | |
|---|---|
| **Population** | End-stage or advanced-stage COPD patients (no more aggressive measures) |
| **Intervention/ Treatment** | Primary care palliative services/strategies (oxygen, opioids) |
| **Comparison** | Usual care |
| **Outcomes** | Quality of life (Symptom relief, comfort, quality of dying) |
| **Subgroups (if any)** | Palliative care strategies<br>- Symptom based (opiates, oxygen inhalation) |

# CPG Development Methodology

The COPD CPG followed the methodology prescribed by the DOH and employed the de novo mode of CPG development.[6] This CPG focused on primary care setting and complied with the national practice guideline development standards.

The COPD CPG Task Force is composed of the following working groups: COI Review Committee, Steering Committee, Evidence Review Experts, and Consensus Panel. They are experts in the field of pulmonology and public health who are affiliated with different organizations (Appendix G).

The COI review committee is composed of 2 members who are not involved in the COPD guideline development. They reviewed the COI declarations of all the members of the task force and assessed their eligibility to assume the assigned role (Appendix H).

The steering committee was tasked to convene the task force and oversee the entire CPG development process. It is composed of 7 members representing the lead developer, Lung Center of the Philippines, and other stakeholders: Philippine College of Chest Physicians, Philippine College of Physicians, Philippine Society of General Internal Medicine, and Philippine Academy of Family Physicians.

The consensus panel prioritized the critical and important outcome measures prior to finalizing the PICO questions (rating of outcomes), reviewed the evidence summaries and drafts recommendations prior to an en banc CP meeting, and voted on the recommendations of the CPG during the en banc CP meeting. There are 12 members of the consensus panel and they are composed of members from different stakeholders: Lung Center of the Philippines, Philippine College of Chest Physicians, Philippine College of Physicians, Philippine Academy of Family Physicians, Association of Municipal Health Officers of the Philippines (Sorsogon, South Cotabato), Regional Lung Center - Vicente Sotto Memorial Medical Center (Cebu), Philippine Nurses Association, and patient advocate and patient representative from the LCP COPD Support Group.

The technical working group (TWG) was under the oversight of a technical adviser from NIH and was led by the 2 technical coordinators, who are both methodologists/clinical epidemiologists. The technical coordinators supervised the 11 evidence review experts in their evidence synthesis. A technical facilitator was also employed to moderate and facilitate all the consensus panel meetings. The technical writer ensured documentation of the consensus issues and consistency of the entries in the entire manuscript.

## Evidence Synthesis

### Search Methods and Strategies

A specific and clearly focused population, intervention/exposure, comparator, and outcome (PICO) of each guideline or clinical question formed the basis for search strategy and the eligibility criteria. This facilitated an explicit, reproducible search strategy that resulted in a comprehensive, exhaustive, and systematic search for original articles and other information sources. A systematic search of at least, but not limited to, two medical databases (National Library of Medicine's

MEDLINE database, Cochrane Central Register of Controlled Trials (CENTRAL), clinicaltrials.gov, Health Research and Development Information Network (HERDIN), and Google Scholar) were explored and included eligible studies covered by the latest database search (may vary per question from February 2023 to July 2023). This was decided upon by the technical coordinators and technical advisers. Cross referencing, as well as exploration of grey literature was done. Studies written in English language and those with available free full text copy were prioritized. However, efforts to retrieve the English version or full-text copy from authors were sought as necessary and deemed feasible. The search yield was limited to studies that are indexed in the databases mentioned in the review methods. HERDIN was also searched for local COPD studies during the scoping review but the yield was low, not aligned with the PICO, and were older studies. Refer to Appendix A for the search terms and search strategy of each clinical question.

Inclusion and Exclusion Criteria

Two evidence reviewers independently did the study selection guided by the inclusion and exclusion criteria. Refer to Appendix A for the inclusion and exclusion criteria of each clinical question. The characteristics of the included studies for each question can be found in Appendix B

Study Quality Assessment

Two evidence reviewers did the critical appraisal of the studies. Assessment of the risk of bias (ROB) was done using the appropriate tool per study design. Table 3 below lists the tools that were used. The study quality assessment of the included studies for each question is found in Appendix D.

**Table 3. Tools used to assess the risk of bias**

| Tool used | Type of article |
|---|---|
| Quadas-2 | Diagnostic studies |
| Cochrane ROB version 2 | Intervention/therapy studies |
| AMSTAR | Systematic review and meta-analysis |
| Newcastle-Ottawa scale | Observational studies |

Data Synthesis

A systematic synthesis (qualitative or quantitative using Review Manager version 5.4), reporting, and presentation of the characteristics and findings of the included studies and the pooled results were done (Appendix E).

## Formulating Recommendations

Certainty of Evidence and Strength of Recommendations

The Consensus Panel was guided by the two categories of grading the strength of recommendations, weak or strong. Figure 1 below suggests implications of strong or weak recommendations that follow from the recommendations. This provided clear direction to patients, clinicians, and policy-makers.[9]

| | Strong Recommendation | Weak Recommendation |
|---|---|---|
| **For patients** | Most individuals in this situation would want the recommended course of action and only a small proportion would not. | The majority of individuals in this situation would want the suggested course of action, but many would not. |
| **For clinicians** | Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences. | Recognize that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision. |
| **For policy makers** | The recommendation can be adapted as policy in most situations including for the use as performance indicators. | Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place. |

**Figure 1.** Implications of Recommendations[9]

Patients' Views and Preferences

Most of the guideline questions do not have direct and local evidence on patients' values and preferences. The panel was guided by indirect evidence coming from foreign studies, by their own experience with their patients, and the valuable inputs from patient advocate and patient representative during the actual consensus panel meetings.

Resource Implications

Most of the guideline questions do not have direct and local evidence on cost effectiveness of interventions. The panel was guided by indirect evidence coming from foreign studies, by their own experience with their patients, by the valuable inputs from patient advocate and patient representative, and by existing cost estimates during the time of evidence review or panel discussion.

Rating of Outcomes

The appraised evidence that was gathered was assessed for quality using the GRADE methodology which included: (1) rating of outcomes, (2) estimating of effect for each outcome, and (3) rating quality of evidence for each outcome. Figure 2 outlines the certainty of evidence.[6] The results of the systematic evidence review done for each PICO question are summarized in an evidence profile and summary of findings using the GRADEPro Guideline Development Tool (GDT) (Appendix C).

| QUALITY | DEFINITION | IMPLICATIONS |
|---|---|---|
| **High** | The group is very confident that the true effect lies close to that of the estimate of the effect | Further research is very unlikely to change confidence in the estimate of effect |
| **Moderate** | The group is moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different | Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate |
| **Low** | Confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the true effect | Further research is very likely to have an important impact on confidence in the estimate of effect and is unlikely to change the estimate |
| **Very low** | The group has very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect | Any estimate of effect is very uncertain |

**Figure 2.** Certainty of evidence table[6]

Consensus Process

The formulation of of recommendations was guided by the Evidence to Decision framework of Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.[6] The multi-sectoral consensus panel followed the GRADE process in creating their recommendations: (1) rating the overall quality of evidence (Appendix C), and (2) grading the strength of recommendation based on the following primary considerations: (a) quality of evidence (b) balance between benefits and harms (c) values preferences, and burden on patients, (d) cost and resource use. Equity, as well as human rights, and social determinants of health was also considered.[8]

The task force had a total of 9 virtual consensus panel meetings. Each meeting followed the guidance on the quorum and consensus for the remote en banc consensus panel meetings set by NIH (see table below).

| | | | | | |
|---|---|---|---|---|---|
| Total CP of COPD CPG | 10 | | | | |
| Quorum | 6 | | | | |
| Voting in attendance | 10 | 9 | 8 | 7 | 6 |
| Consensus | 7 | 6 | 6 | 6 | 6 |

Each meeting met the quorum or the minimum number of voting consensus panelists in attendance that when all are in agreement, it reaches the simple majority of the entire consensus panel membership. For the COPD CPG with 10 consensus panelists, the quorum is set at 6 voting members, for the meeting to proceed. Each recommendation met the required consensus. The consensus was defined as an agreement among 75% of the present voting members in attendance, as long as this number is at least a simple majority of the entire/full consensus panel membership.

A technical facilitator ensured that the conduct of the consensus building adheres to the DOH Manual of CPG development wherein each member is requested to cast their vote and all ideas were discussed.

## Guideline Dissemination

The final CPG manuscript shall be submitted to the National Practice Guidelines Clearinghouse of the DOH for quality appraisal. Once quality standards are met and the CPG is approved to be adopted as a national practice guideline, the dissemination of the CPG shall be done. Launching of the CPG shall be done in an official DOH-initiated event and followed by dissemination in specialty societies-initiated conferences. Relevant factors and issues captured by the domains, guideline questions, and management algorithms shall be emphasized for each launching activity to ensure understanding and guidance in their adoption and implementation. DOH shall be in-charge of the dissemination, producing the official online copy, and the mass reprinting of the manuscript for dissemination to the stakeholders.

## Guideline Monitoring and Evaluation

The steering committee recommends DOH-led monitoring of short term outcomes (adherence to recommendations as reflected in the algorithms as indicators or measures) and long term outcomes (improved respiratory health outcomes in terms of the following measures or indicators: quality of life, symptoms of breathlessness, exercise capacity, exacerbations, hospitalizations, mortality, and lung function). Quality of care studies and program evaluation research may aid and facilitate the monitoring and evaluation of the implementation of this CPG. May refer to the research implications section for the specific research studies.

## External Review

The CPG manuscript was handed to two external reviewers, both are non pulmonologists. One is an infectious disease specialist and clinical epidemiologist and the other one is a family medicine specialist. The intention of the external review was to improve the manuscript's quality by gathering feedback on recommendations, applicability, feasibility, and dissemination plans. The external reviewers were given AGREE-REX Tool as their assessment tool. The overall outcome provided by external reviewers was that the guideline was well-written, comprehensive, and applicable to outpatient settings for primary care providers. Specific comments and suggestions were: (1) to mention the role of policy makers and the impact of this CPG in Philhealth benefit package development and in resource allocation, (2) to mention efforts to search for local studies especially for patient's values and preferences, (3) to resolve applicability issues by specifying how will the CPG be articulated to ensure that primary care workers would understand and effectively disseminate the CPG, and (4) clarification on the scope of the CPG if home care management was included (not included in this CPG) and if management of nicotine dependence using NRTs was included (to be addressed in a separate CPG). The steering committee discussed these reviews and addressed them accordingly in the manuscript.

## Guideline Updating

The PCCP Council on COPD shall assist DOH in evaluating the need to update the CPG every 3 years or earlier as deemed necessary. Factors that may trigger update of the guideline include: (1) novel drugs, interventions, and technology that warranted investigation for inclusion in the standard of care of COPD patients, (2) noted practice variations that needs to be resolved, or (3) new evidences or global or local events that could affect the direction and strength of recommendations of the specific recommendation statement/s in the CPG. A formal letter of request for update shall be sent by the PCCP Council on COPD to DOH (Disease Prevention and Control Bureau, Evidence Generation Department) stating the rationale for the requested update. The DOH shall evaluate the request, provide corresponding response, and allocate funding if the update request was deemed valid.

## Editorial Independence

Funding Source

This COPD CPG development is funded by the DOH. The views or interest of the DOH have not influenced the content of the guideline and the final recommendations.

Management of Conflicts of Interest

The University of the Philippines National Institutes of Health (UP NIH) provided the electronic conflict of interest (eCOI) form aligned with the prescribed COI form of the DOH NPG Program. Nominated or provisional members of the COPD CPG Task Force accomplished the eCOI. Two COI review committee members of the COPD CPG Task Force, who were not involved in the COPD CPG development convened to examine, assess, and manage the conflicts of interest of all the members of the task force. They ensured the collation and proper documentation of all decisions. Any disagreement between the two COI review committee members was resolved by a third party coming from the UP NIH. The

recommendations of the COI review committee were discussed with the Steering Committee.

The process of COI evaluation was guided by the COI algorithm (Figure 3) crafted by the UP-NIH. Each task force member was designated the following status depending on the COI review committee's evaluation of their eCOI declaration, curriculum vitae, and actual interrogation or clarification: Status A – Non-financial COI (approved with no constraint), Status B – Non-financial COI (Broadcast conflict at discussion), Status C – Indirect Financial COI (CP: cannot vote for certain question), and Status D – Indirect Financial COI (ERE: disqualified for specific questions); Indirect/Direct Financial COI (SC, Coordinator, Facilitator - Disqualified) (Appendix H)

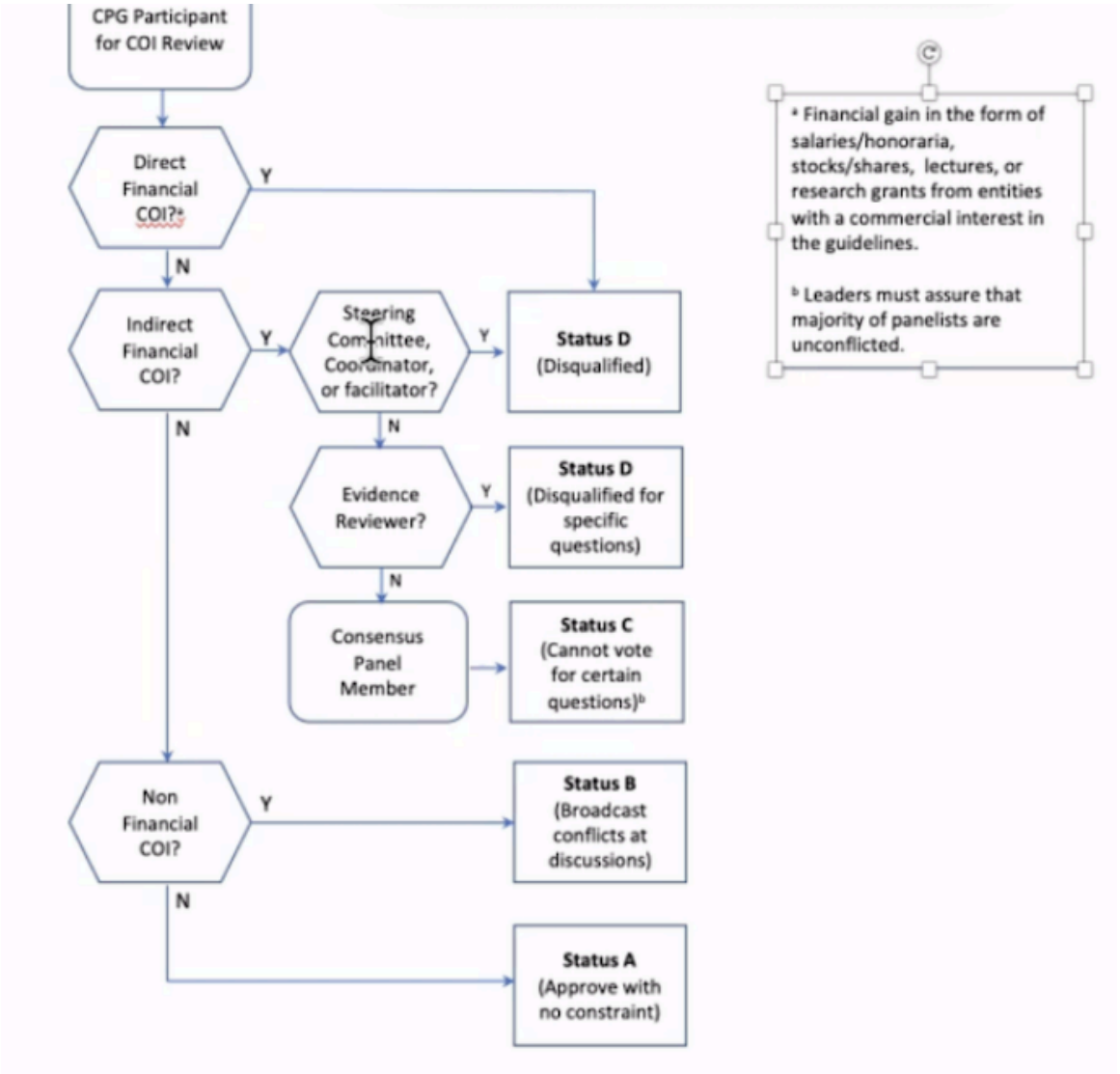



**Figure 3.** COI Management Algorithm

The COIs of the COI Review Committee were evaluated by the UHC-CPG Project Lead and Technical Committee and processed in the same manner as above. The COI of the CPF TF members are found in Appendix H. No major competing interests of guideline development group members have been encountered during the consensus discussions.

# Recommendations and Evidence Summaries

## DOMAIN 1. PREVENTION, SCREENING AND DIAGNOSIS OF COPD IN THE PRIMARY CARE SETTING

**Clinical Question No. 1.** Among adult patients exposed to tobacco smoke and biomass fuel, what is the efficacy and safety of risk reduction strategies in the prevention of onset of COPD and COPD related morbidity and mortality?

| *Recommendation No. 1A* |
| --- |
| **Among smokers, we recommend smoking cessation to prevent COPD** *(Moderate certainty of evidence, Strong recommendation)* |

| *Recommendation No. 1B* |
| --- |
| **Among patients with COPD who are smokers, we recommend smoking cessation to prevent COPD-related morbidity and mortality** *(Moderate certainty of evidence, Strong recommendation)* |

| *Recommendation No. 1C* |
| --- |
| **Among households using biomass fuels, we recommend shifting to clean fuel (i.e., gas or electricity) to reduce the risk for COPD** *(Very low certainty of evidence, Strong recommendation)* |

### Key Findings

- Findings from one large randomized clinical trial showed that smoking cessation interventions significantly reduced all-cause mortality and decline in lung function. Likewise, two randomized trials on community based interventions for smoking cessation also reduced all-cause mortality. Safety data showed adverse events when using medications for smoking cessation compared to using placebo. However, when these are compared with the use of behavioral therapy alone, the difference is insignificant. Additionally, there were more serious adverse events when using a higher dose of nicotine patch, using nicotine replacement for a longer duration, use of combination of NRTs, as well as use of preloading strategy in using nicotine replacement. Overall certainty of evidence was moderate.
- Findings from 11 observational studies also showed association biomass fuel exposure and COPD. In one large observational study, the PURE Study, noted association of biomass fuel exposure to be significant in the development of COPD. The studies considered had good methodologic quality, but overall certainty of evidence was very low.

### Consensus Issues

Evidence on smoking cessation consistently highlights its favorable impact on preventing COPD and reducing associated morbidity. Moreover, smoking cessation promotes a multitude of health benefits, particularly for individuals at

risk for or afflicted with COPD. The crucial practice of quitting smoking has already gained traction at the primary care level, owing to its practical viability as an intervention. Likewise, it is important to recognize that the strategies aimed at facilitating smoking cessation should be carefully individualized for each patient based on their distinctive attributes, level of tobacco dependence, and concurrent health conditions. In the realm of clinical application, a noteworthy trend emerges: a significant majority of patients, especially those afflicted with COPD, exhibit a remarkable commitment to sustaining their smoke-free status. This steadfast dedication is often underpinned by the stark and often severe consequences they have encountered subsequent to their decision to quit smoking.

Biomass fuels continue to be extensively utilized as a household cooking modality, particularly in rural regions, owing to their cost-effectiveness relative to electricity or gasoline (e.g., liquefied petroleum gas) and their widespread availability. The practice of cooking with biomass fuels typically occurs in open kitchens situated outside the household. Nevertheless, the residue and smoke stemming from the use of these fuels tend to permeate indoor spaces, often settling on rooftops. This prevalent practice is significantly associated with an elevated risk of developing COPD and subsequent mortality.

Despite the existing evidence bearing a degree of uncertainty, a strong recommendation was given to use clean or non-polluting fuels for cooking (i.e., electricity or gasoline) to reduce the risk for developing COPD. Encouraging the transition to clean or non-polluting fuels is imperative, given the potential health hazards associated with biomass fuel usage. A key strategy entails ensuring widespread access, availability, and affordability of clean fuels, particularly in marginalized and underserved areas. Here, the role of governments is pivotal; concerted efforts should be made to facilitate the provision of clean or non-polluting fuel options to safeguard the health and well-being of communities.

## Introduction

Chronic Obstructive Pulmonary Disease (COPD) has been reported as being one of the 10 leading causes of death in the Philippines since 2000 until the present. It is a disease that has chronic respiratory manifestations that are often due to airway and alveolar abnormalities leading to progressive and persistent airflow obstruction. This disease has been directly linked to tobacco smoking and exposure to toxic fumes from air pollution, with the importance of non-smoking COPD being reiterated. Most of the interventions that are aimed towards the management of the disease are done to those patients who already have symptoms and documented airflow limitation. However, COPD can be prevented, and smoking cessation has been found to influence its progression. There are limited studies on prevention of COPD, and the latest guidelines propose attention to ‘early COPD’ and ‘pre-COPD’. This guideline question aims to determine whether interventions have an effect to prevent COPD and COPD related morbidity and mortality in patients exposed to smoke and biomass fuel.

## Review Methods

A comprehensive search was done from 20 January 2023 to 07 July 2023 in MEDLINE, Cochrane Library ClinicalTrials.gov, medRxiv, and bioRxiv. Free text and

medical subject headings (MeSH terms) with the terms: chronic obstructive pulmonary disease, respiratory function test, biomass fuel, mortality, and smoking cessation were used.

The studies considered were initially limited to only randomized controlled trials (RCTs) however it was extended to include cohort studies due to a lack of available trials for the association of biomass fuels and COPD. Likewise, the search was extended to include those with subjects who were smokers, both with and without diagnosed COPD. Interventions that were considered were limited to relationships of outcomes with smoking and smoking cessation. Outcomes which were considered include change in lung function (FEV1, FEV1/FVC ratio), incidence of COPD, and mortality related to COPD. Refer to Appendix A, Question 2 for the search strategies that were used.

## Evidence

**Efficacy and Safety of Smoking Cessation on COPD-related Outcomes**

Twelve observational studies (n=779,553) related to the association of smoking and development of COPD were found.[10-21] Results showed that smoking is strongly associated with the development of COPD (OR 2.55; 95% CI 1.95, 3.33). Subgroup analysis showed that active smokers had even higher odds of developing COPD (OR 2.95; 95% CI 2.43, 3.59) than individuals passively exposed to cigarette or tobacco smoke (OR 1.53; 95% CI 1.20, 1.96).

Two RCTs and four cohort studies (n=21,466) evaluated the efficacy and and safety of smoking cessation strategies and COPD-related outcomes. [22-27] The RCT included in this review was a follow-up study of the Lung Health Study which enrolled patients from the general population.[22-23] Interventions for smoking cessation significantly reduced all-cause mortality among adult patients with airflow obstruction over a period of 14.5 years (RR 0.85; 95% CI 0.85, 0.98) according to one RCT.[24] Combination of the studies of community based interventions with smoking cessation shows reduced all-cause mortality compared to those continuing to smoke (RR 0.85; 95% CI 0.75,0.96).[22-24]

Studies have shown that the use of medications such as nicotine replacement therapy (NRT) (i.e., gums, lozenges, sprays, patches) and nicotine receptor antagonists (NRA) which include varenicline, cytisine, and dianicline have increased the quit rate of smoking. Behavioral therapy and other medications (i.e., bupropion, antidepressants, clonidine, naltrexone, and lobeline) also showed to have this effect.[22-25] The use of NRTs over placebo showed increased quit rate (RR 2.6; 95% CI1.29,1.54) (OR 2.2 95% CI 1.9,2.6), as well as use of NRA (OR 2.7 95% CI 2.3,3.2) and bupropion (RR 2.03; 95% CI 1.263.28) (OR 2.1; 95% CI 1.8,2.6), (OR 1.52; 95% CI 1.22,1.89).[22-24] The combination of bupropion with NRT or with NRA also had better odds for quitting smoking (OR 3.8; 95% CI 2.3, 6.2), and (OR 4.0; 95% CI 2.1, 7.7).[22] Addition of varenicline specifically to bupropion and NRT showed benefit as well (OR 2.0; 95% CI 1.11, 3.61), and (OR 1.84; 95% CI 1.07-3.18).[25] Table 5 below summarizes the efficacy and safety of smoking cessation on COPD-related outcomes

Table 5**.** Summary of Findings on the Efficacy and Safety of Smoking Cessation on COPD-related Outcomes

| Outcomes | Basis | Effect Estimate | 95% Confidence Interval | Interpretation | Certainty of Evidence |
|---|---|---|---|---|---|
| Community-based Integrated Interventions | | | | | |
| Risk of COPD | 2 RCT (n=1,535) | OR 0.69 | 0.49, 0.96 | Benefit | High |
| Data from Lung Health Study with Community based Interventions | | | | | |
| Mortality | 3 Randomized trial (n=7,767) | RR 0.85 | 0.75, 0.96 | Benefit | High |
| FEV1 Decline (SI only) | 1 Randomized trial (n=2,728) | MD -61.00 mL | -79.10, -42.90 | Benefit | High |

A network meta-analysis done in 2021 comparing efficacy and safety of these interventions showed that the odds ratio for adverse events when using different interventions for smoking cessation against behavioral therapy was not significant. The interventions compared with placebo which have significant odds ratio for risk include use of single NRT (OR 1.6; 95% CI 1.2, 2.2) combination NRT (OR 2.8; 95% CI 1.2, 6.3), and NRA (OR 1.7; 95% CI 1.3, 2.2). Higher probability for adverse events was also seen with the use of bupropion and an NRA (OR 6.0; 95% CI 1.2, 38.0) against placebo and the use of naltrexone (OR 12; 95%CrI 2.7-58).[22]

A review on the adverse effects of different manners of delivery of nicotine replacement and effects of different dosages showed an increased risk of serious adverse events with longer NRT treatment duration (26 weeks vs 8 weeks) (RR: 1.63; 95% CI 0.60, 4.42). Likewise, comparison of overall serious adverse events, there was a risk ratio of 4.44 (95% CI 0.76-25.85) comparing single with combination NRT use. Increasing the dosage (42/44mg against 21/22mg patches) of 24-hour nicotine patches have an increased RR 5.01 (95% CI 0.87-28.82) for serious adverse events. Preloading, or the use of NRT while smoking, was shown to have increased risk for serious adverse events compared to regular use of NRT RR 1.11 (95% CI 0.59-2.09).[23] Table 6 summarizes the safety of smoking cessation interventions.

Table 6**.** Safety of Smoking Cessation Interventions

| Outcomes | Basis | Effect Estimate | 95% Confidence Interval | Interpretation | Certainty of Evidence |
|---|---|---|---|---|---|
| Adverse events of using bupropion and NRA against placebo | 97 Randomized trial (n=47,407) | OR 6.0 | 1.2, 38.0 | Harm | Moderate |
| Adverse events of using combined NRT | 97 Randomized trial | OR 2.8 | 1.2, 6.3 | Harm | Moderate |

| | | | | | |
|---|---|---|---|---|---|
| against placebo | (n=47,407) | | | | |
| Adverse events of using NRA against placebo | 97 Randomized trial (n=47,407) | OR 1.7 | 1.3, 2.2 | Harm | Moderate |
| Adverse events of using single NRT against placebo | 97 Randomized trial (n=47,407) | OR 1.6 | 1.2, 2.2 | Harm | Moderate |
| Adverse events of using naltrexone against placebo | 97 Randomized trial (n=47,407) | OR 12 | 2.7, 58.0 | Harm | Moderate |

Results from two RCTs that examined the effect of community-based integrated interventions (n=1,535) showed that community-based integrated interventions performed in the community i.e., systematic health education on COPD and work environment, intensive individualized interventions, which included smoking cessation with nicotine replacement therapy, behavioral counseling significantly reduced the risk of developing COPD (RR 0.69; 95% CI 0.49, 0.96).[26-27] Refer to Table 5 above for the summary of findings on community-based integrated interventions.

In terms of lung function, decline in forced expiratory volume (FEV1) was significantly less in the smoking intervention group (mean decline 188 mL±246 mL) when compared with usual care (mean decline 249 mL±236 mL). Difference in mean decline was significant between smoking intervention and usual care (MD -61.00 mL; 95% CI -79.10 mL, -42.90 mL).[29]

**Association of Biomass Fuel Exposure and Development of COPD**

For the association of biomass fuel exposure and development of COPD, there were eleven observational studies (n=32,181) which showed that biomass exposure is associated with the development of COPD (OR 1.74; 95% CI 1.39, 2.17; Very low certainty).[32-42] This included one study done in a rural area in the Philippines.[34] Likewise, findings from one observational study on the biomass exposure smoke from wood and coal during cooking and/or heating showed that use of solid fuel is associated with the development of COPD, compared to a population using gas or electricity for cooking (HR 1.31; 95% CI 1.05, 1.63). Further, patients who use solid fuel for household cooking note a risk towards mortality against those using gas or electricity (HR 1.24 95% CI, 1.15, 1.34).[42] Table 7 below summarizes the data for studies on biomass fuel exposure.

Table 7. Summary of Findings on Biomass Fuel Exposure

| Outcomes | Basis | Effect Estimate | 95% Confidence Interval | Interpretation | Certainty of Evidence |
|---|---|---|---|---|---|
| Data from Observational Studies on Biomass Fuel Exposure | | | | | |
| Any Biomass Fuel Exposure | 11 Observational studies (n=32,181) | OR 1.74 | 1.39, 2.17 | Harm | Very Low |
| Solid Fuel use | 1 Observational study (n=91,350) | HR 1.31 | 1.05, 1.63 | Harm | Very Low |
| Mortality | 1 Observational study (n=91,350) | HR 1.24 | 1.15, 1.34 | Harm | Very Low |

## Recommendations from Other Groups

The GOLD 2023 guidelines emphasize the importance of smoking cessation as this has the greatest capacity to alter the natural history of COPD. The improvement of ventilation and use of non-polluting stoves are recommended as well. There was no mention of specific strategies of intervention to at risk patients before development of COPD.[44]

| Group | Recommendation | Strength of recommendation and certainty of evidence |
|---|---|---|
| GOLD 2023 | Smoking Cessation Interventions should be actively pursued in patients with COPD | A |
| GOLD 2023 | Efficient Ventilation, non-polluting cooking stoves, and similar interventions should be recommended | B |

## Ongoing Trials and Research Gaps

A search on trials at ClinicalTrials.gov website of the US National Library of Medicine yielded two studies that explore interventions to influence development of chronic diseases. The first aims to assess impact of lifestyle modification (diet, physical activity, alcohol and smoking consumption) towards the development of dementia, diabetes, cardiovascular disease, cancer, and COPD.[305] Another study aims to see whether a preventive program can identify individual risk for lifestyle related disease (Type 2 DM, CVD, COPD) and if targeted preventive services will have an impact in changing behavior.[306]

## Additional Considerations for Evidence to Decision Phase

The country has implemented laws that prohibit the sale of tobacco products especially towards the youth in 2003 and there are other policies that help curb smoking and its accessibility (e.g., restructuring of excise tax on tobacco products, use of graphic health warnings on tobacco products, provision of smoke free environments). The DOH has partnered with multiple organizations for the implementation of the policies in place and a Quitline hotline has been in place for those needing assistance in quitting smoking.[45]

**Cost**

There have been a number of cost analysis in implementation of smoking cessation programs and they range from USD 1, 132 to USD 2, 892 per quit.[46-47] A study in a third world country in 2002 showed an average cost per life year saved of USD 1, 311 to USD 6, 032 for men and USD 2, 052 to USD 9, 777 for women.[48] At these costs, it is still cost-effective in secondary stroke prevention as well as when considered in terms of yield in additional life added after smoking cessation.[49]

The cost of upgrading to modern cooking stoves ranges from Php 983 to as much as Php 5,455.86, depending on the number of stoves and source of fuel (gas/electricity). Yearly expenditures for cooking water based food were Php 151.78 to Php 958.83 when using wood as a source of energy, while use of electricity (Php 3,314.35 to 3,838.44) and LPG (Php 4,813.62 to P6,893.73) are higher.[50]

**Patient's Values and Preference, Equity, Acceptability, and Feasibility**

Analysis of the 2015 GATS data showed that the price increase affected smoking by preventing initiation of smoking rather than reducing the intensity of smoking tobacco products after the implementation of the Sin Tax Law. It also revealed two 'typologies' of smokers in the country – 'potential quitters' who are more likely to quit and decrease smoking volume and those who are 'unlikely to quit'. The potential quitters are often female, students, with low nicotine dependence, and smoke 3 sticks a day fewer than their counterparts. Nicotine dependence prompted those who are unlikely to quit to employ price-minimization strategies such as bulk buying, switching brands, and looking for other sources of products.[51]

The country is below the percentage of households with access to clean cooking fuel sources compared to Southeast and East Asian neighbors. 28% of rural households have access to clean fuel compared to 68% in neighboring countries. Urban households on the other hand, have 69% who have access to clean cooking compared to 91% among East and Southeast Asia. Initial cost for upgrading household kitchen setups, as well as lack of information on safety of LPG are identified barriers against shift to clean fuel sources. Furthermore, the traditions and flavors brought about by smoke and charcoal remain important values in our country.[52-53]

**Clinical Question No. 2.** Among probable COPD patients, how accurate and safe is the use of clinical scoring system and/or peak flow meter and/or handheld spirometer as compared to facility-based spirometer in the diagnosis of COPD in the primary care setting?

| *Recommendation No. 2A* |
| --- |
| **Among probable COPD patients, we recommend against the use of clinical scoring system alone compared to facility-based spirometer in confirming the diagnosis of COPD in the primary care setting** *(Low certainty of evidence, Strong recommendation)* |

| *Recommendation No. 2B* |
| --- |
| **Among probable COPD patients, we suggest the use of clinical scoring system to identify patients who may need further confirmatory testing** *(Low certainty of evidence, Weak recommendation)* |

| *Recommendation No. 2C* |
| --- |
| **Among probable COPD patients, we recommend against the use of peak flow meter alone in confirming the diagnosis of COPD in the primary care setting** *(Very low certainty of evidence, Strong recommendation)* |

| *Recommendation No. 2D* |
| --- |
| **Among probable COPD patients, we recommend against the use of handheld spirometry alone in confirming the diagnosis of COPD in the primary care setting** *(Very low certainty of evidence, Strong recommendation)* |

| *Recommendation No. 2E* |
| --- |
| **Among probable COPD patients, we suggest the use of combined clinical scoring system and handheld spirometer as an alternative to facility-based spirometry in confirming the diagnosis of COPD in the primary care setting** *(Very low certainty of evidence, Weak recommendation)* |

| *Recommendation No. 2F* |
| --- |
| **Among probable COPD patients, we suggest against use of combined** |

**clinical scoring system and peak flow meter compared to facility-based spirometry in confirming the diagnosis of COPD in the primary care setting** *(Low certainty of evidence, Weak recommendation)*

### Key Findings

- Findings from 29 cross-sectional studies with a total of 47,495 patients demonstrated that the use of clinical scoring systems, i.e., COPD Diagnostic Questionnaire (CDQ), COPD Population Screener (COPD-PS), Lung Function Questionnaire (LFQ) and COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk (CAPTURE) Screening Tool yielded a weakly positive and negative likelihood ratio while the use of handheld spirometer or peak flow meter yielded moderately positive and weakly negative likelihood ratio. The combined use of a clinical scoring system with handheld spirometer and clinical scoring system with peak flow meter yielded a strongly positive and weakly negative likelihood ratio. There were no reported adverse events.

- The overall certainty of evidence was very low for sensitivity due to serious risk of bias, inconsistency and imprecision. The overall certainty of evidence was low for specificity due to serious risk of bias and inconsistency.

### Consensus Issues

The use of combined clinical scoring system with handheld spirometer is preferred over the use of combined clinical scoring system with peak flow meter, and the use of either clinical scoring system alone, peak flow meter alone, and handheld spirometer alone in confirming the diagnosis of COPD in the primary care setting. A strong recommendation against the use of clinical scoring system alone, peak flow meter alone, and handheld spirometer alone in confirming the diagnosis of COPD in the primary care setting was given on the basis of low sensitivity and high false positivity of these tests when compared to facility-based spirometry. The use of a test with low sensitivity could result in underdiagnosis, i.e., high number of missed cases, while the use of a test with high false positivity could lead to unnecessary treatment initiation, higher treatment costs, and potential treatment complications.

In areas where peak flow meters and facility-based spirometry are unavailable, primary care providers in the panel suggested using clinical criteria, i.e., patient-related risk factors and history, cough frequency, presence of dyspnea, sputum production, and sputum purulence, in identifying patients with probable COPD. Clinical scoring systems are recommended as an initial tool to identify symptoms and to correlate these symptoms with ensuing symptom progression and/or improvement. Thus, clinical scoring systems are highly useful in identifying patients (screening) at the primary care level who may need to be referred to a higher level facility for confirmatory testing. Through this screening strategy, unwarranted referrals to higher level (e.g., Levels 2 or 3) health facilities could be avoided. Careful interpretation of findings from clinical scoring systems should be emphasized as these findings could be prone to bias (subjectivity) necessitating further confirmatory testing using facility-based spirometry. At present, there are no locally validated versions of the clinical scoring systems (i.e., COPD Diagnostic

Questionnaire, COPD Population Screener, Lung Function Questionnaire, and CAPTURE Screening Tool) included in this review. The decision on which of the aforementioned clinical scoring systems to use is left to the discretion of the primary care provider.

Facility-based spirometry is used to confirm the diagnosis of COPD and is preferred by pulmonologists in the panel. However, facility-based spirometry could still be costly with additional expenses on single-use (individual) mouthpieces. Referral to higher level facilities for facility-based spirometry is necessary as this test is not widely accessible in the primary care setting, i.e., especially in Level 1 health care facilities and in provinces as compared to urban areas.

Handheld spirometers are not standardized and their use requires technical training (i.e., technical skills on test performance and quality assurance processes) of primary care providers. While handheld spirometry and peak-flow meters might seem like viable alternatives, they do not fully substitute facility-based spirometry in terms of accuracy and comprehensive assessment (i.e., correlation of handheld spirometry or peak flow meter results and clinical findings). Unfortunately, these two tests are also not widely available locally, which further hinder their use as practical alternatives to facility-based spirometry.

Addressing these challenges requires concerted efforts from healthcare authorities and policymakers to increase the availability and accessibility of facility-based spirometry in primary care settings, especially in underserved areas. Standardizing equipment and providing proper training to healthcare professionals will enhance the accuracy and reliability of spirometry tests, ultimately improving COPD diagnosis and patient care. Additionally, investing in research and development of affordable, portable, and accurate diagnostic tools that can be utilized in resource-limited settings would be beneficial. This approach would allow for more comprehensive COPD screening and diagnosis, bridging the gap between rural and urban healthcare access and ultimately improving the management of COPD on a broader scale.

## Introduction

There is a need to improve case finding approach to guide strategy on identifying people at risk and people with COPD symptoms in order to reduce COPD progression. COPD is considered in any patient who has symptoms such as dyspnea, persistent cough, or sputum production. To screen for unreported COPD symptoms, clinical scoring systems such as the COPD Questionnaire (CDQ), an 8-item tool; COPD Population Screener (COPD-PS), a 5-item tool; Lung Function Questionnaire (LFQ) a 5-item tool, and COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk (CAPTURE) screening tool, a 5-item tool with peak expiratory flow measurement, were developed. To confirm the diagnosis of COPD, the presence of non-fully reversible airflow limitation (i.e., FEV1/FVC 0.7 post-bronchodilation) determined by facility-based spirometry is required. Handheld spirometer or peak flow meter were tested versus facility-based spirometry to help screen for patients with COPD.

## Review Methods

A systematic search was conducted using Medline, Cochrane Library and Herdin Plus from inception to 06 February 2023. Studies that investigate the use of the pre-specified COPD clinical scoring systems using questionnaires to establish the target condition, COPD, using the reference standard of facility-based spirometry were included. The outcomes of interest were sensitivity, specificity, and positive and negative likelihood ratio and adverse events. Likelihood ratios were interpreted as following the table below.[54]

Table 8. Likelihood Ratios Interpretation

| **Positive Likelihood Ratio (LR +)** | | **Negative Likelihood Ratio (LR -)** | |
|---|---|---|---|
| > 10.0 | Strongly positive | < 0.1 | Strongly negative |
| 3.0 -10.0 | Moderately positive | 0.3 – 0.1 | Moderately negative |
| < 3.0 | Weakly positive | > 0.3 | Weakly negative |

Contingency tables (2x2 tables) were obtained and, if not stated, derived using Review Manager 5.4 calculator. Prespecified subgroup analysis were done for studies with the following pre-specified cutoffs: ≥ 16.5 and 19.5 for COPD Diagnostic Questionnaire (CDQ), ≥ 4 and 5 for COPD Population Screener (COPD-PS), ≤ 18 for Lung Function Questionnaire (LFQ), score 5-6 or 2-5 with peak expiratory flow rate < 350 L/min (males) or < 250 L/min for (females) for CAPTURE and FEV1/FEV6 ratio <0.70 and <0.73 for handheld spirometer. Pooled outcome data were generated using the midas package in STATA 14 if with four or more relevant studies. For less than four studies, metaDTA v2.01 (17th August 2021) was used. Each study was appraised for risk of bias using QUADAS-2 tool. The quality of evidence for each outcome was evaluated following the GRADE guidelines.

## Evidence

### COPD Diagnostic Questionnaire (CDQ)

The pooled sensitivity from twelve cross sectional studies (n=42, 980) was 0.75 (95% CI 0.65, 0.84) and pooled specificity was 0.61 (95% CI 0.47, 0.73).[54-66] The test showed weakly positive likelihood ratio (LR+ 1.90; 95% CI 1.50, 2.40) and weakly negative likelihood ratio (LR- 0.41; 95% CI 0.33, 0.50). Subgroup analysis of five studies (n=2,863) using the cutoff of ≥ 16.5 yielded pooled sensitivity of 0.81(95% CI 0.71, 0.89) and pooled specificity of 0.44 (95% CI 0.28, 0.62). The test showed weakly positive likelihood ratio (LR+ 1.46; 95% CI 1.18, 1.82) and weakly negative likelihood ratio (LR- 0.42; 95% CI 0.35, 0.51). Using the cutoff of ≥ 19.5, based on five cross sectional studies (n=5,197) yielded pooled sensitivity of 0.67(95% CI 0.59, 0.74) and pooled specificity of 0.65 (95% CI 0.57, 0.73). The test showed weakly positive likelihood ratio (LR+ 1.90; 95% CI 1.60, 2.30) and weakly negative likelihood ratio (LR- 0.51; 95% CI 0.43, 0.62). Certainty of evidence was low due to serious risk of bias to index test and inconsistency.

### COPD Population Screener (COPD-PS)

The pooled sensitivity of COPD-PS based on eleven cross-sectional studies was was 0.68 (95% CI 0.51, 0.81) and pooled specificity was 0.72 (95% CI 0.57, 0.83).[65, 67-75] The test showed weakly positive likelihood ratio (LR+ 2.40; 95% CI 1.80, 3.30) and weakly negative likelihood ratio (LR- 0.45; 95% CI 0.32, 0.62). Subgroup analysis of six studies (n=11,825) using the cutoff of ≥ 4 yielded pooled sensitivity of 0.74 (95%

CI 0.51, 0.89) and pooled specificity of 0.66 (95% CI 0.44, 0.83). The test showed weakly positive likelihood ratio (LR+ 2.20; 95% CI 1.50, 3.20) and weakly negative likelihood ratio (LR- 0.38; 95% CI 0.24, 0.61). Using the cutoff of ≥ 5, based on five cross sectional studies (n=6,459) yielded pooled sensitivity of 0.61 (95% CI 0.44, 0.75) and pooled specificity of 0.75 (95% CI 0.65, 0.83). The test showed weakly positive likelihood ratio (LR+ 2.40; 95% CI 1.60, 3.60) and weakly negative likelihood ratio (LR- 0.52; 95% CI 0.35, 0.78). Certainty of evidence was downgraded to low due to serious risk of bias to index test and inconsistency.

**Lung Function Questionnaire (LFQ)**

The pooled sensitivity of LFQ based on eight cross-sectional studies (n=16,233) was 0.67 (95% CI 0.49, 0.82) and pooled specificity was 0.72 (95% CI 0.54, 0.85).[56, 65, 73, 76-78] The test showed weakly positive likelihood ratio (LR+ 2.40; 95% CI 1.70, 3.50) and weakly negative likelihood ratio (LR- 0.45; 95% CI 0.33, 0.62). Certainty of evidence was low due to serious risk of bias to index test and inconsistency.

**CAPTURE screening Tool**

The pooled sensitivity of CAPTURE screening tool according to three cross-sectional studies (n=15, 978) was 0.54 (95% CI 0.48, 0.60) and pooled specificity was 0.81 (95% CI 0.74, 0.87).[60, 78, 79] The test showed weakly positive likelihood ratio (LR+ 2.90; 95% CI 2.10, 4.10) and weakly negative likelihood ratio (LR- 0.56; 95% CI 0.50, 0.63). Certainty of evidence was moderate due to inconsistency.

**Handheld Spirometer**

The pooled sensitivity of handheld spirometer based on twelve cross-sectional studies was 0.68 (95% CI 0.54, 0.80) and pooled specificity was 0.87 (95% CI 0.78, 0.93).[60, 70-72, 80-87] The test showed moderately positive likelihood ratio (LR+ 5.30; 95% CI 3.20, 8.90) and weakly negative likelihood ratio (LR- 0.37; 95% CI 0.25, 0.54). The certainty of evidence was low due to serious risk of bias to index test and inconsistency.

Subgroup analysis of six studies (n=2,849) using the cutoff of ≤ 0.70 yielded pooled sensitivity of 0.55 (95% CI 0.33, 0.74) and pooled specificity of 0.93 (95% CI 0.80, 0.98). The test showed a moderately positive likelihood ratio (LR+ 7.90; 95% CI 2.70, 23.00) and weakly negative likelihood ratio (LR- 0.49; 95% CI 0.31, 0.78). The certainty of evidence was very low for sensitivity due to serious risk of bias to index test, inconsistency and imprecision. The certainty of evidence was low for specificity due to serious risk of bias to index test and inconsistency.

Subgroup analysis of three studies (n=559) using the cutoff of ≤ 0.73 yielded pooled sensitivity of 0.77 (95% CI 0.51, 0.92) and pooled specificity of 0.83 (95% CI 0.78, 0.87). The test showed a moderately positive likelihood ratio (LR+ 4.50; 95% CI 3.45, 5.86) and weakly negative likelihood ratio (LR- 0.28; 95% CI 0.11, 0.68). The certainty of evidence was very low for sensitivity due to serious risk of bias to index test, inconsistency and imprecision. The certainty of evidence was low for specificity due to serious risk of bias to index test and inconsistency.

**Peak Flow Meter**

The pooled sensitivity of flowmeter was 0.61 (95% CI 0.31, 0.84) and pooled specificity is 0.87 (95% CI 0.67, 0.96) according to four cross-sectional studies.[60, 71, 74,

[88] The test showed moderately positive likelihood ratio (LR+ 4.70; 95% CI 2.60, 8.40) and weakly negative likelihood ratio (LR- 0.45; 95% CI 0.25, 0.81). The certainty of evidence was very low for sensitivity due to serious risk of bias to index test, inconsistency and imprecision. The certainty of evidence was low for specificity due to serious risk of bias to index test and inconsistency.

**Combined Clinical Scoring System and Handheld Spirometry**

The pooled sensitivity of combined clinical scoring system and handheld spirometry was 0.64 (95% CI 0.39, 0.83) and pooled specificity was 0.94 (95% CI 0.85, 0.98) based on four cross-sectional studies (n=4,635).[60, 64, 74, 88] The test showed strongly positive likelihood ratio (LR+ 10.7; 95% CI 5.00, 23.30) and weakly negative likelihood ratio (LR- 0.39; 95% CI 0.21, 0.70). The certainty of evidence was very low for sensitivity due to serious risk of bias to index test, inconsistency and imprecision. The certainty of evidence was low for specificity due to serious risk of bias to index test and inconsistency.

**Combined Clinical Scoring System and Peak Flow Meter**

The pooled sensitivity of combined clinical scoring system and handheld spirometry was 0.54 (95% CI 0.40, 0.68) and pooled specificity was 0.95 (95% CI 0.91, 0.97) according to two cross-sectional studies (n=8,580).[60, 74] The test showed strongly positive likelihood ratio (LR+ 11.32; 95% CI 4.83, 26.10) and weakly negative likelihood ratio (LR- 0.48; 95% CI 0.34, 0.68). The certainty of evidence was low for sensitivity due to serious risk of bias to index test and inconsistency. The certainty of evidence was moderate for specificity due to inconsistency.

There were no studies that reported adverse events. The pooled estimates of sensitivity and specificity have very high heterogeneity. The overall certainty of evidence was downgraded to very low for sensitivity due to risk of bias, inconsistency and imprecision. The overall certainty of evidence was downgraded to low for specificity due to risk of bias and inconsistency. Refer to Tables 9 and 10 below for the summary of diagnostic accuracy of various index tests.

Table 9. Diagnostic Accuracy Outcomes of Various Index Test Compared to Facility-based Spirometry at Pretest Probability of *13.8%*

| Index Test | Cutoff | No. of Studies | Population | Sensitivity 95% CI | Specificity 95% CI | Estimates per 1,000 tested # diagnosed \| # missed range | | Certainty of Evidence (Sensitivity) | Certainty of Evidence (Specificity) |
|---|---|---|---|---|---|---|---|---|---|
| CDQ | ALL | 12 | 11,944 | **0.75** 0.65, 0.84 | **0.61** 0.47, 0.73 | **104** 90, 116 | **34** 22, 48 | Low | Low |
| | ≥ 16.5 | 5 | 2,863 | **0.81** 0.71, 0.89 | **0.44** 0.28, 0.62 | **11** 10, 12 | **3** 2, 4 | Low | Low |
| | ≥ 19.5 | 5 | 5,197 | **0.67** 0.59, 0.74 | **0.65** 0.57, 0.73 | **9** 8,10 | **5** 4,6 | Low | Low |
| COPD-PS | ALL | 11 | 15,738 | **0.68** 0.51, 0.81 | **0.72** 0.57, 0.83 | **9** 7,11 | **5** 3, 7 | Low | Low |
| | ≥ 4 | 6 | 11,825 | **0.74** 0.51, 0.89 | **0.66** 0.44, 0.83 | **10** 7, 12 | 4 2, 7 | Low | Low |
| | ≥ 5 | 6 | 6,459 | **0.61** 0.44, 0.75 | **0.75** 0.65, 0.83 | **8** 6, 10 | **6** 4, 8 | Low | Low |
| LFQ | ≤ 18 | 8 | 16,233 | **0.67** 0.49, 0.82 | **0.72** 0.54, 0.85 | **9** 7, 11 | **5** 3,7 | Low | Low |
| CAPTURE | ALL | 3 | 15,978 | **0.54** 0.48, 0.60 | **0.81** 0.74, 0.87 | **75** 66, 83 | **63** 55, 72 | Moderate | Moderate |
| Handheld spirometer | ALL | 12 | 6,353 | 0.68 0.54, 0.80 | 0.87 0.78, 0.93 | 9 5, 11 | 5 9,3 | Low | Low |
| | < 0.70 | 6 | 2,849 | 0.55 0.33, 0.74 | 0.93 0.80, 0.98 | 8 5, 10 | 6 4, 9 | Very Low | Low |
| | < 0.73 | 3 | 559 | 0.77 0.51, 0.92 | 0.83 0.78, 0.87 | 106 70, 127 | 32 11, 68 | Very Low | Low |
| Peak Flow Meter | ALL | 4 | 10,158 | 0.61 0.31, 0.84 | 0.87 0.67, 0.96 | 84 43, 116 | 54 22, 95 | Very Low | Low |
| Combined Clinical Scoring System and Handheld Spirometer | Various | 4 | 4,635 | 0.64 0.39, 0.83 | 0.94 0.85, 0.98 | 9 5, 11 | 5 3, 9 | Very Low | Low |
| Combined Clinical Scoring System and Flow Meter | Various | 2 | 8,580 | 0.54 0.40, 0.68 | 0.95 0.91, 0.97 | 75 55, 94 | 63 44, 83 | Low | Moderate |

Table 10. Diagnostic Accuracy Outcomes of Various Index Test Compared to Facility-based Spirometry at Pretest Probability of *20.8%*

| Index Test | Cutoff | No. of Studies* | Population | Sensitivity 95% CI | Specificity 95% CI | Estimates per 1000 tested # diagnosed \| # missed range | | Certainty of Evidence (Sensitivity) | Certainty of Evidence (Specificity) |
|---|---|---|---|---|---|---|---|---|---|
| CDQ | ALL | 12 | 11,944 | 0.75<br>0.65, 0.84 | 0.61<br>0.47, 0.73 | 156<br>135, 175 | 52<br>33, 73 | Low | Low |
| | ≥ 16.5 | 5 | 2,863 | 0.81<br>0.71, 0.89 | 0.44<br>0.28, 0.62 | 17<br>15, 19 | 4<br>2, 6 | Low | Low |
| | ≥ 19.5 | 5 | 5,197 | 0.67<br>0.59, 0.74 | 0.65<br>0.57, 0.73 | 14<br>12, 15 | 7<br>6, 9 | Low | Low |
| COPD-PS | ALL | 11 | 15,738 | 0.68<br>0.51, 0.81 | 0.72<br>0.57, 0.83 | 14<br>11, 17 | 7<br>4, 10 | Low | Low |
| | ≥ 4 | 6 | 11,825 | 0.74<br>0.51, 0.89 | 0.66<br>0.44, 0.83 | 15<br>11, 19 | 6<br>2, 10 | Low | Low |
| | ≥ 5 | 6 | 6,459 | 0.61<br>0.44, 0.75 | 0.75<br>0.65, 0.83 | 13<br>9, 16 | 8<br>5, 12 | Low | Low |
| LFQ | ≤ 18 | 8 | 16,233 | 0.67<br>0.49, 0.82 | 0.72<br>0.54, 0.85 | 14<br>10, 17 | 7<br>4, 11 | Low | Low |
| CAPTURE | ALL | 3 | 15,978 | 0.54<br>0.48, 0.60 | 0.81<br>0.74, 0.87 | 112<br>100, 125 | 96<br>83, 108 | Moderate | Moderate |
| Handheld spirometer | ALL | 12 | 6,353 | 0.68<br>0.54, 0.80 | 0.87<br>0.78, 0.93 | 13<br>8, 17 | 8<br>4, 13 | Low | Low |
| | < 0.70 | 6 | 2,849 | 0.55<br>0.33, 0.74 | 0.93<br>0.80, 0.98 | 11<br>7, 15 | 10<br>6, 14 | Very Low | Low |
| | < 0.73 | 3 | 559 | 0.77<br>0.51, 0.92 | 0.83<br>0.78, 0.87 | 160<br>91, 106 | 48<br>17, 1012 | Very Low | Low |
| Peak Flow Meter | ALL | 4 | 10,158 | 0.61<br>0.31, 0.84 | 0.87<br>0.67, 0.96 | 127<br>64, 175 | 81<br>33, 144 | Very Low | Low |
| Combined Clinical Scoring System and Handheld Spirometer | Various | 4 | 4,635 | 0.64<br>0.39, 0.83 | 0.94<br>0.85, 0.98 | 13<br>8, 17 | 8<br>4, 13 | Very Low | Low |
| Combined Clinical Scoring System and Flow Meter | Various | 2 | 8,580 | 0.54<br>0.40, 0.68 | 0.95<br>0.91, 0.97 | 112<br>83, 141 | 96<br>67, 125 | Low | Moderate |

## Recommendations from Other Groups

There were no specific recommendations on the use of clinical questionnaires and scoring systems, peak flow meter and handheld spirometer in the diagnosis of COPD. Clinical scoring systems were mentioned in the recent Global Initiative for Chronic Obstructive Lung Disease report to identify mild or minimally symptomatic disease with modest sensitivity and specificity.

| Group or Agency | Recommendation | Strength of recommendation and certainty of evidence |
|---|---|---|
| Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2023[89] | A diagnosis of COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease but forced spirometry that demonstrates the presence of a post-bronchodilator FEV1/FVC < 0.7 is mandatory to establish the diagnosis of COPD. | Not Stated |
| | In asymptomatic individuals without any significant exposures to tobacco or other risk factors, screening spirometry is probably not indicated; whereas in those with symptoms or risk factors (e.g., > 20 pack years of smoking, recurrent chest infections, early life events), the diagnostic yield for COPD is relatively high and spirometry should be considered as a method for early case finding. | Not Stated |
| | In a variety of settings case-finding has been able to identify previously | |

| | | |
|---|---|---|
| | undiagnosed COPD. In general, these tools identify a high proportion of patients with mild or minimally symptomatic disease, exhibiting modest sensitivity and specificity. | |
| National Institute for health and Care Excellence (NICE) 2018[90] | Measure post-bronchodilator spirometry to confirm the diagnosis of COPD. | Not Stated |
| US Preventive Services Task Force 2021[91] | The USPSTF recommends against screening for chronic obstructive pulmonary disease in asymptomatic adults. | Moderate Certainty of Evidence |

## Ongoing Trials and Research Gaps

There were no pertinent ongoing studies found on clingovtrials.com and Herdin Plus as of 04 March 2023. COPD screening studies were abundant but included harm outcomes were negligible.

## Additional Considerations for Evidence to Decision Phase

**Cost**

The use of clinical scoring systems has no cost and may be self-administered. In a county based COPD screening study among COPD high risk (COPD-PS ≥ 5), early screening cause an increase in quality-adjusted life years (QALYs) by 0.28 compared to no screening.[92] However, in a study that included portable spirometer comparing with both screening with COPD questionnaire and no screening, portable spirometer was cost saving with an incremental cost-effectiveness ratio of -5026 per QALY when compared to COPD questionnaire and -1766 per QALY when compared to no screening. Peak flow meter may cost from Php 633.50 to Php 745.00.

**Patient's Values and Preference, Equity, Acceptability, and Feasibility**

In a survey regarding patient preference about spirometry, majority found spirometry acceptable even if they have limited knowledge on how they will undergo the test.[93] Respondents rated "getting a diagnosis" as second highest after "knowledge improvement on lung function."

COPD diagnosis brings stigma to patients. COPD was described as a self-inflicted disease leading to self-blaming, shame, and guilt.[94, 95] They also tend to hide the diagnosis as they perceive it to be a humiliating disease. Patients expressed that employment was limited due to potential negative impact on employers' health insurance cost for employees.

There were no studies about values and preference, acceptability, and feasibility on COPD clinical scoring systems or questionnaires.

## DOMAIN 2. MANAGEMENT OF STABLE COPD IN THE PRIMARY CARE SETTING

**Clinical Question No. 3.** Among stable COPD patients in the primary care settings, how effective and safe are inhaled long-acting bronchodilators (LABA or LAMA alone or LAMA/LABA combination) in improving symptoms and preventing exacerbations, hospitalization, and death?

| *Recommendation No. 3A* |
| --- |
| **Among stable COPD patients in the primary care setting with FEV1<80% or mmRC≥2* and are not in exacerbation, we recommend the use of LABA/LAMA combination therapy over LAMA or LABA monotherapy** *(Low certainty of evidence, Strong recommendation)* |

| *Recommendation No. 3B* |
| --- |
| **Among stable COPD patients in the primary care setting with FEV1<80% or mmRC≥2* and are not in exacerbation, we suggest the use of LAMA over LABA** *(Low certainty of evidence, Weak recommendation)* |

| *Recommendation No. 3C* |
| --- |
| **Among stable COPD patients in the primary care setting with FEV1≥80% or mmRC<2* and are not in exacerbation, we suggest the use of LAMA monotherapy over LABA monotherapy or LABA/LAMA combination therapy** *(Very low certainty of evidence, Weak recommendation)* |

**The Modified Medical Research Council (mmRC) Dyspnea Scale stratifies severity of dyspnea in respiratory diseases, particularly COPD: [mmRC of 0] Dyspnea only with strenuous exercise; [mmRC of 1] Dyspnea when hurrying or walking up a slight hill; [mmRC of 2] Walks slower than people of the same age because of dyspnea or has to stop for breath when walking at own pace; [mmRC of 3] Stops for breath after walking 100 yards (91 m) or after a few minutes; [mmRC of 4] Too dyspneic to leave house or breathless when dressing.*

### Key Findings

- There are 39 randomized clinical trials included in this analysis that investigated the efficacy and safety of LABA, LAMA and LABA/LAMA combination bronchodilators amongst stable COPD.

- This review showed that treatment with Long-acting Muscarinic Receptor Antagonist (LAMA) provided a lower incidence of moderate to severe exacerbations and adverse events, and a significant improvement in FEV1 compared to Long-acting Beta Agonists agents (LABA). The overall quality of evidence was moderate for all outcomes.

- This review also showed that treatment with dual LABA/LAMA therapy is superior to either LABA or LAMA monotherapy in reducing moderate to severe exacerbations and dyspnea, improving quality of life and FEV1. In terms of safety, the current evidence remains to be inconclusive if dual

therapy has lower rates of adverse events than monotherapy. The overall quality of evidence was high for reducing dyspnea, and moderate for improving quality of life and patient's FEV1 values. It is important to note that the reduction in moderate-to-severe exacerbations was seen only when dual therapy was compared to LABA monotherapy with a low quality of evidence.

- Most of the included studies have a low to unclear risk of bias. Studies that have high risk of bias are open-label studies, and those with high attrition rates. Almost all studies are industry funded, this conflict of interest has been disclosed a priori. No available evidence can be pooled for the following outcomes: Exercise capacity and treatment failure.

- The evidence was downgraded because of issues in inconsistency for results with high I2 value, and of issues in imprecision for results with wide confidence interval.

- Findings from one randomized controlled trial and two cohort studies showed that among patients with mild COPD, the use of LAMA monotherapy significantly reduced the risk of exacerbation and hospitalization when compared to placebo and significantly reduced risk of exacerbation when compared with LABA monotherapy. Overall certainty of evidence was downgraded to very low due to risk of bias and imprecision.

### Consensus Issues

Research findings have consistently demonstrated that the synergistic effect of combining LABA/LAMA yields substantial benefits. This includes notable reductions in exacerbation frequency and dyspnea, accompanied by improvements in FEV1 values and overall quality of life for patients. As a result of these positive outcomes, medical experts widely recommend the employment of the LABA/LAMA combination, particularly for individuals displaying symptoms and those affected by moderate to severe COPD.

In cases where combination therapy is not accessible, the expert panel advocates for the utilization of LAMA as opposed to LABA monotherapy. This preference stems from the remarkable advantages of LAMA, notably in terms of reducing hospitalization rates, influencing FEV1 values positively, and mitigating exacerbation occurrences. Moreover, LAMA has fewer adverse events, and it presents a more cost-effective alternative compared to LABA. Acknowledging that monotherapy is used for patients with mild COPD as the primary treatment approach, it's essential to assess the patient's treatment response within 2-4 weeks following the commencement of therapy.

Disparities in the availability and accessibility of various LABA/LAMA formulations, as well as standalone LABA or LAMA treatments, are discernible between rural and urban areas. While LAMA monotherapy options do exist in rural regions, they are not as prevalent as combination therapies. Conversely, urban locales offer a broader spectrum of choices, encompassing both monotherapy and combination approaches. There is also a lack of availability of LABA monotherapy in the country. The average retail price for combination therapy falls within the range of

Php 2,430.00 to Php 2,895.00, whereas LAMA monotherapy costs range from Php 300.00 to Php 2,700.00.

In the absence of established universal guidelines, primary care physicians rely on their wealth of clinical experience and expertise to navigate patient care. Employing a dynamic two-way referral system with specialists, they ensure that complex cases receive the specialized attention they require. When initial treatment efforts fail to yield improvement, primary care practitioners initiate treatment themselves and, if deemed necessary, facilitate referrals to higher-level medical facilities. This approach underscores the importance of a patient-centered approach, where the foremost concern is the patient's well-being and timely access to appropriate care.

Healthcare providers play a pivotal role in meticulously evaluating the patient's medical condition to determine the most fitting treatment approach. This assessment encompasses a comprehensive understanding of the patient's medical history, current health status, and any potential contraindications. Equally crucial is the transparent and thorough communication of the available treatment options to the patient. By providing clear explanations, healthcare providers empower patients to make informed decisions about their own healthcare journey. Inclusion of the patient in the decision-making process is an essential aspect of patient-centered care. This collaborative approach not only promotes trust between the patient and healthcare provider but also enhances the likelihood of treatment adherence and successful outcomes.

In summary, primary care physicians' adept use of clinical judgment and their flexible referral system with specialists, coupled with the meticulous evaluation of treatment choices and patient involvement in decision-making, collectively contribute to a comprehensive and patient-centric healthcare paradigm.

## Introduction

Both long-acting B2-agonists (LABAs) and long-acting antimuscarinic antagonists (LAMAs) are used in the chronic management of COPD.  Both classes of medications have been shown to improve FEV1, lung volumes, dyspnea, and health-related quality of life. Further, several LABA/LAMA combinations are now available for clinical use in COPD. However, it is not clear which group of above-mentioned inhalers is most effective. There is uncertainty on the optimal first-line therapy for symptomatic COPD. Even with the current guidelines, it is still not clear if dual therapy with LABA/LAMA is superior to monotherapy, or if LAMA monotherapy is superior to LABA monotherapy for symptomatic COPD.

## Review Methods

A systematic search was done from the date of the last search January 31, 2023 using Cochrane Library, Google Scholar and Pubmed. The Combined MeSh and free text search used the following terms chronic obstructive pulmonary disease, long-acting muscarinic antagonists, adrenergic beta-2 receptor agonists, LABA or LAMA. Specific examples of LABA or LAMA that include but are not limited to olodaterol, vilanterol, indacaterol, etc., were also included in the search. References of current clinical guidelines and latest meta-analyses were reviewed to ensure all studies related to the topic are included. (see Appendix 1 for full search history). Only randomized controlled trials that compared (1) LABA vs

LAMA monotherapy and, (2) LABA/LAMA Dual therapy vs either LABA or LAMA monotherapy with duration of at least 12 weeks were included in this review. No limits were placed on age, COPD severity and dosing of bronchodilators.

Due to expected clinical heterogeneity, the specific inhaler monotherapy type (LABA or LAMA) compared to dual therapy in a priori chosen subgroups was evaluated. A post-hoc sensitivity analysis on outcomes when significant heterogeneity was noted, and possibly attributable to outlier study data was also conducted. The studies included were appraised using the Cochrane risk of bias assessment criteria. The effect estimates were pooled using Revman ver 5.3. Data were pooled per outcome for the eligible studies using Mantel-Haenszel (MH) random-effects (RE) and inverse variance meta-analytical approaches for both the dichotomous and continuous data. Dichotomous outcomes were reported as relative risks (RR) or odds ratios (OR), and continuous outcomes were reported as mean differences (MD) unless otherwise specified. Sensitivity analyses were performed to assess the contribution of each study to the pooled estimate by excluding individual studies one at a time and recalculating the pooled RR or OR or MD estimates for the remaining studies (one-study removed meta-analysis).

## Evidence

**Mortality**

There is inconclusive evidence from twenty RCTs that either LABA or LAMA Monotherapy can reduce mortality (RR 0.93, CI 0.74, 1.18, P 0.57, $I_2$ = 0%, FE). Certainty of evidence was downgraded to moderate because of imprecision (wide confidence interval).[96-115]

There is also inconclusive evidence that supports that LABA+LAMA Dual therapy is superior to LAMA (RR 0.92, [0.81, 1.17], p = 0.78, $I_2$ = 0%, FE) or LABA (RR 1.07 [0.70, 1.63], p = 0.77, I2 = 0%, FE) in reducing mortality among stable COPD patients. Test for subgroup interactions was p = 0.70, indicating no significant differences in pooled estimates for dual vs LABA and dual vs LAMA. Certainty of evidence was downgraded to moderate because of imprecision (wide confidence interval).

**Moderate to Severe Exacerbations**

Data from fifteen RCTs showed that LAMA monotherapy is superior to LABA monotherapy in reducing moderate to severe exacerbations (RR 0.92, [0.86, 0.98], p = 0.01, I2 = 52%, RE).[98- 103, 106-108, 110, 112-114, 116, 117] These findings suggest that when choosing a mono-bronchodilator for patients with COPD, LAMA may be a better option than LABA, especially in patients at risk of frequent exacerbations. Certainty of evidence was downgraded to moderate due to inconsistency (substantial heterogeneity).

Pooled analysis of 12 RCTs showed that dual therapy of LABA+LAMA bronchodilators is superior to LABA monotherapy (RR 0.78 [0.62, 0.97], p = 0.03, I2 = 71%, RE) in reducing moderate to severe exacerbations. Certainty of evidence was downgraded to low due to risk of bias and inconsistency (substantial heterogeneity). A sensitivity analysis wherein removed all studies with outlier data were removed by eyeballing the forest plot. This reduces the I2 to 0%. This analysis also changed the effect estimate to also become inconclusive (RR 0.94, CI 0.86, 1.03, P= 0.18).

The evidence also remains to be inconclusive when dual therapy of LABA+LAMA bronchodilators is compared to LAMA monotherapy in reducing exacerbations (RR 0.99, CI 0.88, 1.11, p = 0.87, I2 = 67%, RE). Certainty of evidence was downgraded to moderate due to inconsistency (substantial heterogeneity).

Hospitalizations, all cause

There is inconclusive evidence to show that either LABA or LAMA monotherapy ( RR 0.94, CI 0.58, 1.51, p = 0,79, I2 = 51%, RE).[118-120] Certainty of evidence was downgraded to low due to imprecision and inconsistency. The results of the studies were imprecise because of the wide confidence interval.

There is also inconclusive evidence to favor dual therapy of LABA+LAMA over LAMA monotherapy (RR 0.93, CI 0.86, 1.01, p = 0.07. I2 = 0%, FE) or LABA monotherapy (RR O.93, CI 0.70, 1.23, p = 0.61, I2 = 16%, FE) in reducing all causes of hospitalizations. Certainty of evidence was downgraded to moderate due to imprecision (wide confidence interval). Test for subgroup differences was p = 0.98, indicating there is no significant difference in pooled estimates for dual vs LABA and dual vs LAMA.

Hospitalizations, COPD-Related

Findings from four RCTs showed that LAMA monotherapy is superior to LABA monotherapy in reducing COPD-related hospital admissions (RR 0.89, CI 0.80, 0.99, p = 0.03, I2 = 0%, FE).[99, 101, 116, 118,] Certainty of evidence was high.

Quality of Life

All the studies included used the SGRQ score to objectively measure QOL outcome. A total score is calculated from 0 (no health impairment) to 100 (maximum health impairment). Analysis of fifteen RCTs showed that the mean change in the SGRQ score was not statistically different between LABA or LAMA monotherapy in improving the quality of life of COPD patients (MD 0.29 -0.33, 0.91, p = 0.36, I2 = 64%).[97, 111, 103, 104, 106-108, 115, 117, 119-121,] Certainty of evidence was downgraded to low due to inconsistency and imprecision. Substantial heterogeneity can be attributed due to difference in time points of measurement, differences in study duration and methodologies. The wide confidence interval can be explained by the subjective component, despite validation, of SGRQ.

There is noted improved scores in SGRQ for patients who are treated with dual LABA+LAMA therapy compared to those patients who are treated with LAMA (MD-1.33, -1.73, 0.93, P < 0.00001, I2 = 5%) or LABA monotherapy (MD -1.07, -1.63, -0.5, p = 0.0002, I2 = 0%). The MD was smaller than the four units that is considered clinically important. A decrease of 4 units, after a medical intervention, in the SGRQ score is generally accepted in the literature to be a valid threshold value of beneficial treatment. Certainty of evidence was downgraded to moderate due to imprecision. Test for subgroup differences was p = 0.46, indicating there is no significant difference in pooled estimates for dual vs LABA and dual vs LAMA.

Dyspnea

All of the included studies used for this analysis used the Transitional Dyspnea Index (TDI). Results from fourteen RCTs did not show any statistical difference in the TDI score change from the baseline between the LAMA and LABA treatment in improving the dyspnea score of COPD patients (MD – 0.03, -0.12, 0.06, p = 0.51,

I2 = 15%, FE).[103-105, 108-110, 113, 115-117, 119, 120, 122,] Certainty of evidence was downgraded to moderate due to imprecision.

On the other hand, dual therapy of LABA+LAMA showed a statistically significant improvement over both LABA (MD 0.32, 0.22, 0.42, P< 0.00001, I2 = 11%, FE) or LAMA (MD 0.33, 0.24, 0.42, P< 0.00001, I2 = 5%, FE) monotherapy in improving dyspnea. However, these results did not reach the minimal clinically important difference (MCID) of the TDI which is a total score of one unit. Certainty of evidence was high. Test for subgroup differences is p = 0.84, indicating there is no significant difference in pooled estimates for dual vs LABA and dual vs LAMA.

**FEV1 change**

Analysis showed that the use of either monotherapy or dual therapy significantly improves FEV1 values amongst stable COPD patients. The pooled results from fifteen RCTs showed that LAMA monotherapy is superior to LABA monotherapy in improving FEV1 values (MD 0.02, 0.01, 0.03, P< 0.00001, I2 = 50%).[96, 103, 106- 108, 110, 112-115, 120, 122] The actual difference of 10 to 30 mL is very small and below the 50 to 100 mL level of MCID for which the index is usually used for a comparison with placebo. The difference in the trough FEV1 did not cause a significant change in the patient's QOL and symptoms evaluated by the SGRQ and TDI score. Certainty of evidence was downgraded to moderate due to imprecision.

Dual therapy with LABA and LAMA was shown to be superior to both LAMA (MD 0.06, 0.05, 0.08, P< 0.00001, I2 = 90%) and LABA (MD 0.06, 0.04, 0.08,P < 0.00001, I2 = 95%) monotherapy. These results have moderate strength of evidence, downgraded once because of inconsistency from a very heterogeneous population. Certainty of evidence was downgraded to moderate due to inconsistency. Test for subgroup differences is P=0.69, indicating there is no significant difference in pooled estimates for dual vs LABA and dual vs LAMA.

**Total Adverse Events**

Concerning the safety components, the analysis showed a small but significantly lower incidence of total adverse events in LAMA compared to LABA. Analysis of 20 RCTs showed that LAMA monotherapy was shown to have reduced incidence of adverse events than LABA monotherapy (RR 0.92, CI0.86, 0.98,P=0.002, I2 = 82%, RE).[97, 103, 104, 106-111, 113, 115, 119, 120,] Certainty of evidence was downgraded to moderate due to inconsistency.

However, the evidence remains to be inconclusive to show whether dual therapy with LABA+LAMA has lesser or more adverse events than monotherapy with either LABA (RR 0.96, CI 0.91, 1.01, P=0.16, I2 0%) or LAMA (RR 1.00, CI 0.97, 1.02, P=0.77, I2 = 0%, FE). Certainty of evidence was downgraded to moderate due to imprecision. Test for subgroup differences is P=0.23, indicating there is no significant difference in pooled estimates for dual vs LABA and dual vs LAMA.

**Serious Adverse Events Related to COPD**

The evidence from fifteen RCTs was inconclusive to show that either LAMA or LABA is superior in reducing COPD-related SAE (RR 0.97, [0.76, 1.23], p = 0.79, I2 = 93%, RE).[97, 98, 104, 105, 110, 113, 115, 117, 119,122-126] Certainty of evidence was downgraded to low due to imprecision and inconsistency.

This finding is also consistent when dual therapy of LABA+LAMA was compared with monotherapy. The evidence remains to be inconclusive to suggest that dual therapy is superior to either LAMA monotherapy (RR 1.02, CI 0.89, 1.17, P=0.78, I2=0 %) or LABA monotherapy (RR 1.09, CI 0.85, 1.39, P=0.52, I2 = 0%). Certainty of evidence was downgraded to moderate due to imprecision . Test for subgroup differences is p = 0.67, indicating there is no significant difference in pooled estimates for dual vs LABA and dual vs LAMA.

**Additional Data for Mild COPD**

There were three articles on stable mild COPD comparing LABA or LAMA monotherapy or LABA or LAMA monotherapy versus combination therapy. Critical outcomes that were looked into are: symptom improvement, risk for exacerbation, risk for hospitalization, and risk for mortality.[127-129]

Findings for LAMA as tiotropium versus placebo from one RCT showed a significant benefit with LAMA in reducing the risk for any exacerbation, moderate exacerbation, and hospitalization form any cause.[127] Certainty of evidence was downgraded to moderate due to potential publication bias as results were obtained from a single study. In the same study, LAMA as tiotropium when compared with placebo showed inconclusive effect in terms of exacerbation leading to hospitalization. Certainty of evidence was downgraded to low due to imprecision and potential publication bias as results were obtained from a single study. However, findings for LAMA as tiotropium versus placebo showed significant harm with LAMA for minor adverse events such as oropharyngeal discomfort, dry mouth, and pharyngeal discomfort. Table 11 below summarizes the comparison of tiotropium and placebo.

Table 11. Comparison of Tiotropium and Placebo

| Critical OUTCOMES | BASIS (No and Type Of Studies, Total Participants) | EFFECT SIZE | 95% CI | INTERPRETATION | CERTAINTY OF EVIDENCE |
|---|---|---|---|---|---|
| Any Exacerbation | 1 RCT (n=841) | RR 0.63 | 0.47, 0.85 | Benefit with LAMA | Moderate |
| Moderate or Worse Severity Exacerbation | 1 RCT (n=841) | RR 0.63 | 0.45, 0.86 | Benefit with LAMA | Moderate |
| Hospitalization from Any Cause | 1 RCT (n=841) | RR 0.38 | 0.19, 0.78 | Benefit with LAMA | Moderate |
| Exacerbation Resulting to Hospitalization | 1 RCT (n=841) | RR 0.60 | 0.33, 1.09 | Inconclusive (Trend to LAMA) | Low |
| Adverse Events | 1 RCT (n=841) | RR 2.22 | 1.46, 3.39 | Harm with LAMA | Moderate |

Findings for LAMA versus LABA from one cohort study showed inconclusive effect in terms of exacerbations. However, among patients with one or more previous exacerbations, risk of another exacerbation was significantly reduced with LAMA.[128] Certainty of evidence was downgraded to very low due to imprecision (for any exacerbation) and potential publication bias as results were obtained from a single study. Table 12 below shows the comparison of LABA and LAMA in terms of exacerbations.

Table 12. LABA versus LAMA for Exacerbations

| **Critical OUTCOMES** | **BASIS (No and Type Of Studies, Total Participants)** | **EFFECT SIZE** | **95% CI** | **INTERPRETATION** | **CERTAINTY OF EVIDENCE** |
|---|---|---|---|---|---|
| Exacerbation in all patients | 1 cohort study (n=51,218) | aOR 0.96 | 0.90, 1.02 | Inconclusive | Very Low |
| Exacerbation stratified by presence of prior COPD exacerbation | | | | | |
| One or more previous exacerbation | 1 cohort study (n=14,456) | aOR 0.88 | 0.80, 0.96 | Benefit with LAMA | Very Low |
| Two or more previous exacerbation | 1 cohort study (n=4,098) | aOR 0.89 | 0.78, 1.01 | Inconclusive (Trend to LAMA) | Very Low |

Findings for LAMA versus LAMA/LABA combination therapy form one cohort study showed inconclusive effects on risk for exacerbation, risk for hospitalization, and risk for mortality among mild COPD patients.[129] Certainty of evidence was downgraded to very low due to imprecision and potential publication bias as results were obtained from a single study. Table 13 below shows the comparison of LABA and LAMA in terms of its risk for exacerbation, risk for hospitalization, and risk for mortality among mild COPD patients.

Table 13. Comparison of LABA versus LAMA and its risk for exacerbation, hospitalization, and mortality

| **Critical OUTCOMES** | **BASIS (No and Type Of Studies, Total Participants)** | **EFFECT SIZE** | **95% CI** | **INTERPRETATION** | **CERTAINTY OF EVIDENCE** |
|---|---|---|---|---|---|
| Exacerbation | 1 cohort study (n=273) | OR 1.28 | 0.70, 2.33 | Inconclusive | Very Low |
| Hospitalization | 1 cohort study (n=273) | OR 1.07 | 0.49, 2.32 | Inconclusive | Very Low |

| | | | | | |
|---|---|---|---|---|---|
| Mortality | 1 cohort study (n=273) | OR 0.41 | 0.02, 8.12 | Inconclusive | Very Low |

A post hoc sensitivity analysis for all outcomes was conducted by removing studies with high risk of bias (open labeled, high attrition rate). The pooled effect estimate did not significantly change for all outcomes except when dual therapy was compared to LABA in reducing moderate to severe exacerbations. Sensitivity analyses that reduced the heterogeneity of the trials resulted into the current evidence to be inconclusive. The same outcome has low certainty of evidence because of inconsistency and imprecision; hence this can only suggest the use of dual therapy in patients with high risk of exacerbations.

The tables below summarizes the comparison of mono and dual therapy using LABA and LAMA.

Table 14. LABA Monotherapy vs LAMA Monotherapy in COPD

| **Critical OUTCOMES** | **BASIS (No and Type Of Studies, Total Participants)** | **EFFECT SIZE** | **95% CI** | **INTERPRETATION** | **CERTAINTY OF EVIDENCE** |
|---|---|---|---|---|---|
| All-cause Mortality | 20 RCTS<br>N = 27635 | RR 0.93<br>p = 0.56<br>I2 = 0% | [0.74, 1.18] | Inconclusive | Moderate |
| Moderate to Severe Exacerbation | 15 RCTs<br>N = 23572 | RR 0.92<br>p = 0.01<br>I2 = 52% | [0.86, 0.98] | Favors LAMA | Moderate |
| Hospitalization, all cause | 3 RCTs<br>N = 3509 | RR 0.94<br>p = 0.79<br>I2 = 51% | [0.58, 1.51] | Inconclusive | Low |
| Hospitalization due to COPD | 4 RCTs<br>N = 24935 | RR 0.89<br>p = 0.03<br>I2 = 0% | [0.80, 0.99] | Favors LAMA | High |
| Quality of Life | 15 RCTs<br>N = 16224 | MD 0.29<br>p = 0.36<br>I2 = 64% | [-0.33, 0.91] | Inconclusive | Low |
| Dyspnea | 14 RCTs<br>N = 17043 | MD -0.03<br>p = 0.51<br>I2 = 15% | [-0.12, 0.06] | Inconclusive | Moderate |
| Adverse Events (any) | 20 RCTs<br>N = 29179 | RR 0.92<br>p = 0.008<br>I2 = 82% | [0.86, 0.98] | Favors LAMA | Moderate |
| COPD SAE | 15 RCTs<br>N = 27635 | RR 0.97<br>p = 0.79<br>I2 = 93% | [0.76, 1.23] | Inconclusive | Low |
| FEV1 change | 16 RCTs | MD 0.02 | [0.01, 0.03] | Favors LAMA | Moderate |

| | | | | | |
|---|---|---|---|---|---|
| | N = 13635 | p = <0.00001<br>I2 = 50% | | | |

Table 15. LABA+LAMA Dual Therapy vs LAMA Monotherapy in COPD

| **Critical OUTCOMES** | **BASIS (No and Type Of Studies, Total Participants)** | **EFFECT SIZE** | **95% CI** | **INTERPRETATION** | **CERTAINTY OF EVIDENCE** |
|---|---|---|---|---|---|
| All-cause Mortality | 32 RCTs<br>N = 32703 | RR 0.97<br>p = 0.78<br>I2 = 0% | (0.81, 1.17) | Inconclusive | Moderate |
| Moderate to Severe Exacerbation | 15 RCTs<br>N = 20051 | RR 0.99<br>p = 0.87<br>I2 = 67% | [0.88, 1.11] | Inconclusive | Moderate |
| Hospitalization, all cause | 6 RCTs<br>N = 13504 | RR = 0.93<br>p = 0.07<br>I2 = 0% | (0.86, 1.01) | Inconclusive | Moderate |
| Quality of Life | 20 RCTs<br>N = 17760 | MD – 1.33<br>P <0.00001<br>I2 = 5% | (-1.73, -0.93) | Favors DUAL therapy | Moderate |
| Dyspnea | 20 RCTs<br>N = 20583 | MD = 0.33<br><br>P < 0.00001<br>I2 = 6% | (0.2, 0.42) | Favors DUAL therapy | High |
| Adverse Events (any) | 31 RCTs<br><br>N = 31960 | RR 1.00<br><br>P 0.77<br>I2 = 0% | (0.97, 1.02) | Equivalent | High |
| COPD SAE | 23 RCTS<br>N = 20385 | RR 1.02<br><br>p = 0.78<br>I2 = 0 % | [0.89, 1.17] | Inconclusive | Moderate |
| FEV1 change | 29 RCTs<br>N = 22142 | MD = 0.06<br><br>I2 = 90%<br>p <0.00001 | (0.05, 0.08) | Favors DUAL therapy | Moderate |

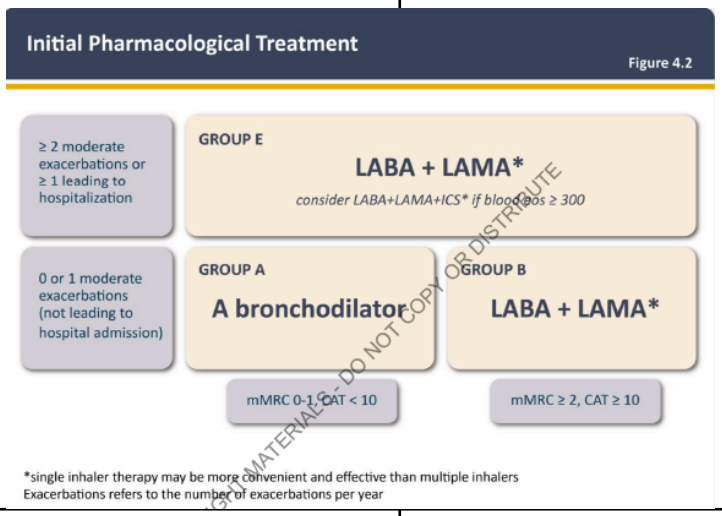
Table 16. LABA+LAMA Dual Therapy vs LABA Monotherapy in COPD

| **Critical OUTCOMES** | **BASIS (No and Type Of Studies, Total Participants)** | **EFFECT SIZE** | **95% CI** | **INTERPRETATION** | **CERTAINTY OF EVIDENCE** |
|---|---|---|---|---|---|
| All-cause | 18 RCTs | RR 1.06 | (0.70, 1.62) | Inconclusive | Moderate |

| | | | | | |
|---|---|---|---|---|---|
| Mortality | N = 12715 | p = 0.77<br>I2 = 0% | | | |
| Moderate to Severe Exacerbation | 13 RCTs<br>N = 6266 | RR 0.78<br>p = 0.03<br>I2 = 71% | (0.62, 0.97) | Favors DUAL therapy | Low |
| Hospitalization, all cause | 4 RCTs<br>N = 4280 | RR = 0.93<br>p = 0.61<br>I2 = 13% | (0.70, 1.23) | Inconclusive | Moderate |
| Quality of Life | 10 RCTs<br>N = 7838 | MD – 1.07<br>p = 0.0002<br>I2 = 0% | (-1.63, -0.5) | Favors DUAL therapy | Moderate |
| Dyspnea | 11 RCTs<br>N = 8122 | MD 0.32<br>P <0.00001<br>I2 = 11% | (0.22,0.42) | Favors DUAL therapy | High |
| Adverse Events (any) | 18 RCTs<br>N = 11982 | RR = 0.96<br>p = 0.16<br>I2 = 0% | (0.91, 1.01) | Inconclusive | Moderate |
| COPD SAE | 7 RCTs | RR 1.09<br>p = 0.52<br>I2 = 0% | [0.85, 1.39] | Inconclusive | Moderate |
| FEV1 change | 14 RCTs<br>N = 9966 | MD 0.06<br>P <0.00001<br>I2 = 95% | (0.04, 0.08) | Favors DUAL therapy | Moderate |

## Recommendations from Other Groups

| **Group or Agency** | **Recommendation** | **Strength of recommendation and certainty of evidence** |
|---|---|---|
| Pharmacologic Management of Chronic Obstructive Pulmonary Disease An Official American Thoracic Society Clinical Practice Guideline[130] | In patients with COPD who complain of dyspnea or exercise intolerance, we recommend LABA + LAMA combination therapy over LABA or LAMA monotherapy. | Strong Recommendation, Moderate Certainty Evidence |
| GOLD 2023[131] | • LAMAs have a greater effect on exacerbation reduction compared with LABAs and | Strong Recommendation, Moderate Certainty Evidence |

| | | |
|---|---|---|
| | decrease hospitalization (Evidence B).<br>● Combination treatment with a LABA and a LAMA increases FEV1 and reduces symptoms compared to monotherapy (Evidence A)<br>● Combination treatment with a LABA+LAMA reduces exacerbations compared to monotherapy (Evidence B).<br>● When initiating treatment with long-active bronchodilators the preferred choice is a combination of a long-acting muscarinic antagonist and a long-acting B2 agonist. (Evidence A).<br>  <br><br> | |
| Canada Thoracic Society 2019[132] | We recommend an inhaled long-acting bronchodilator, either LAMA or LABA | Strong Recommendation, Moderate Certainty Evidence |

| | | |
|---|---|---|
| | monotherapy, to reduce dyspnea, improve exercise tolerance, and improve health status. LAMA is preferred over LABA therapy to prevent AECOPD.<br><br>We recommend an inhaled LAMA/LABA dual therapy in patients who experience persistent dyspnea, exercise intolerance, and/or poor health status despite the use of LAMA or LABA monotherapy. Shortness of breath and exercise tolerance improve with LAMA/LABA dual therapy over monotherapy; health status has not been addressed as a primary outcome. | Weak Recommendation, Low Certainty Evidence |
| NICE guidelines: COPD 2019[133] | Offer LAMA+LABA to people who:<br>● Do not have asthmatic features/features suggesting steroid responsiveness and<br>● Remain breathless or have exacerbations despite:<br>o Having used or been offered treatment for tobacco dependence if they smoke and<br>o Optimized non-pharmacological management and relevant vaccinations and | Not stated |

## Ongoing Trials and Research Gaps

There is an ongoing study entitled "Efficiency of Twice Daily Formoterol Versus Once Daily Tiotropium in Patients With GOLD A/B COPD (FACT)," however it is not yet recruiting participants.

## Additional Considerations for Evidence to Decision Phase

**Cost**

In a recently published prospective cross-sectional study by Ang, et al done in a tertiary hospital in the Philippines, mean hospitalization cost for COPD exacerbation is 28,200 against the PhilHealth provision of only Php 12,200.00.[134]

Table 17. Cost of LABA and LAMA

| Long-Acting Bronchodilator available in the Philippines | Average Retail Cost per month | Average Retail Cost per Day |
|---|---|---|
| LABA/LAMA Dual Therapy | | |
| Indacaterol/Glycopyrronium (Ultibro or Glycoair) | P 2430 | P 81 |
| Olodaterol/Tiotropium (Spiolto) | P 2565 | P 85.5 |
| Umeclidinium/Vilanterol (Anoro) | P 2895 | P 96.50 |
| Aclidinium/Formoterol (Duaklir Genuari) | Not available | Not available |
| LABA Monotherapy | | |
| Indacaterol (Onbrez) | Not available | Not available |
| Olodaterol (Striverdi) | Not available | Not available |
| Aformoterol | Not available | Not available |
| Formoterol (Easyhaler/Foradil/Oxis) | Not available | Not available |
| Salmeterol (serevent) | Not available | Not available |
| LAMA Mono therapy | | |
| Tiotropium 18mcg Handihaler | P 305 for the inhaler device<br>P 2700 for the capsules<br>Total: 3005 | P 100 |
| Tiotropium Respimat (Spiriva) | P 2980 | P 99 |
| Umeclidinium (Incruse) | Not available | Not available |
| Glycopyrronium (seebri) | Not available | Not available |
| Aclidinium | Not available | Not available |

**Patient's Values and Preference, Equity, Acceptability, and Feasibility**

There are no local studies available regarding COPD patients values on available treatment. The latest available evidence was published last 2021 that conducted interviews amongst COPD patients in the UK, US and Germany. In this study by Shroeder et al., their results indicate that for patients with COPD in these countries, efficacy and safety remain priorities, whilst also revealing the importance of ease and frequency of use, and number of inhalers required.[135] In a similar study done earlier by Kawata et al., their results showed that attributes such as decreased use of rescue medication, ease of use for inhaler, and being able to feel a medication begin to work quickly are aspects beyond safety and efficacy that patients consider in evaluating preference for a COPD maintenance

medication.[136] There is a scarcity of studies regarding the stigma of COPD. The latest available study done by Johnsons et al 50. in 2007 noted that the stigma arises because people are held responsible for their disease, are noted to have engaged in a stigmatized behavior (smoking), are marked with oxygen equipment and bodily changes, and experience a disruption in their social interactions.[137]

**Clinical Question No. 4**. Among stable COPD patients in the primary care setting, how effective and safe are inhaled corticosteroids (with vs without inhaled long acting bronchodilator) in improving symptoms and preventing exacerbations, hospitalization, and death?

| *Recommendation No. 4* |
| --- |
| **Among stable COPD patients in the primary care setting with FEV1<80% or mmRC≥2* with increased risk for exacerbations and absence of concurrent respiratory infection*, we recommend the use of inhaled corticosteroids in combination with inhaled long-acting bronchodilators** *(Low certainty of evidence, Strong recommendation)* |

**Based on included RCTS in this review, addition of ICS to long-acting bronchodilator was indicated for patients with recurrent history of exacerbations. However, concurrent respiratory infection was identified as a contraindication.*

## Key Findings

- There were 56 RCTs that investigated the effect of inhaled corticosteroid (ICS) with long-acting bronchodilator (LABD) compared with LABD alone (non ICS-containing therapy) among patients with stable moderate-to-very severe chronic obstructive pulmonary disease (COPD).

- The use of ICS with LABD when compared with LABD alone showed benefits in terms of reduction in all-cause mortality, health status improvement using St. George's Respiratory Questionnaire (SRGQ), dyspnea reduction and reduction in the risk of COPD exacerbation. However, the use of ICS with LABD when compared with LABD alone showed inconclusive effects on the risk for COPD-related hospitalization.

- The use of ICS with LABD when compared with LABD alone showed harm in terms of increased risk for developing pneumonia.

- Overall certainty of evidence was strong. Certainty of evidence were voted by the panel to be strong after deliberation.

## Consensus Issues

The integration of inhaled corticosteroids (ICS) into inhaled long-acting bronchodilator (LABD) regimens offers a significant array of benefits, encompassing improvements in mortality rates, overall quality of life, exacerbation occurrences, and the alleviation of dyspnea. Hence, it was given a strong recommendation despite the low certainty of evidence. The addition of ICS to LABD was beneficial in terms of mortality, improvement of quality of life and in reducing exacerbation and dyspnea.

ICS is typically added as a step-up to bronchodilator therapy if symptoms remain uncontrollable. However, it is crucial to acknowledge that while ICS exhibit the potential to curtail the frequency and intensity of exacerbations, their appropriateness might not extend to all individuals afflicted by COPD.

Selecting the appropriate treatment course hinges on a thorough assessment of the patient's condition. Patients who exhibit a recurring pattern of exacerbations,

coupled with persistent and evident dyspnea, particularly within the stable range of moderate to severe COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages 2-4, FEV1 < 80%), stand to derive substantial advantages from the combination of ICS and inhaled LABD.

This amalgamation of therapies signifies a strategic intervention tailored to address the unique needs of patients who fall within this specific profile. The triple therapy of LABA, LAMA and ICS is used especially for patients with severe COPD. By merging the anti-inflammatory effects of ICS with the bronchodilatory properties of long-acting agents, healthcare providers aim to not only alleviate symptoms but also improve overall health outcomes. The careful selection of patients who stand to gain the most from this combined treatment underscores the importance of precision medicine in managing COPD.

Nonetheless, it's important to acknowledge that the utilization of both ICS and inhaled LABD carries the potential for overuse, which in turn can result in an increased risk for pneumonia. Furthermore, the concomitant administration of these two medications has been associated with an increased susceptibility to pneumonia. To navigate these potential challenges, vigilant and systematic monitoring is imperative, coupled with the implementation of comprehensive measures aimed at minimizing the risk of pneumonia development. Striking a delicate equilibrium between the advantages and potential drawbacks is paramount for healthcare providers when considering the prescription of this combined drug regimen.

While the combined use of ICS and inhaled LABD can offer substantial benefits in terms of symptom management and improved lung function, it's essential to exercise caution in their administration. Overuse of these medications might lead to unintended complications, possibly exacerbating existing health issues or giving rise to new concerns. This underscores the significance of accurate dosing, patient education, and ongoing evaluation to ensure that the treatment remains aligned with the patient's evolving needs and condition. Additionally, the heightened risk of pneumonia associated with this combined therapy warrants proactive measures to mitigate its occurrence. Implementing strategies such as vaccination, meticulous oral hygiene, and frequent review of treatment plans can help mitigate this risk and enhance patient safety.

When considering the initiation of ICS and inhaled LABD, healthcare providers play a pivotal role in assessing the potential benefits against the possible risks for each patient. This decision-making process necessitates a comprehensive evaluation of the patient's medical history, current health status, and susceptibility to specific complications. In doing so, physicians can tailor the treatment plan to each patient's unique circumstances, maximizing therapeutic benefits while minimizing potential adverse effects.

In conclusion, the utilization of the two drugs presents a duality of possibilities—promising symptom relief on one hand, but carrying the potential for overuse and pneumonia on the other. With careful monitoring, risk mitigation strategies, and a judicious balance between advantages and potential drawbacks, healthcare providers can harness the benefits of this combination while safeguarding patient well-being.

The pricing of inhalers containing ICS varies. Diverse formulations and combinations of ICS and long-acting bronchodilators are readily accessible. Notably, the combination of LABA/ICS + LAMA/LABA, while potentially more expensive than other preparations, presents a comprehensive approach that addresses multiple aspects of COPD management. The introduction of the triple inhaler (LABA/LAMA/ICS) in June 2023 signifies a recent advancement in COPD treatment options. However, as with any newly launched medication, accessibility might be influenced by factors such as distribution channels, insurance coverage, and regional availability.

The cost variation in ICS-containing inhalers reflects a range of factors, including the specific formulation, brand, and dosing regimen. This diversity in pricing allows patients and healthcare providers to select options that align with individual budget constraints and therapeutic needs.

In conclusion, the cost variability of ICS-containing inhalers and different combinations of ICS and long-acting bronchodilators provides patients and healthcare providers with choices that cater to individual preferences and financial considerations. The emergence of the triple inhaler represents a significant step forward in COPD management, although its availability may initially differ due to its recent introduction. It is imperative for patients and healthcare professionals to collaboratively explore treatment options and consider factors beyond cost, such as therapeutic benefits and individual treatment goals.

## Review Methods

A systematic literature search was conducted in Medline, Cochrane Library and clinicaltrials.gov databases on the use of inhaled corticosteroids in combination with other bronchodilators in patients with stable COPD from inception to January 2023. Only randomized controlled trials that compared ICS-containing inhaler therapy versus non-ICS containing inhaler therapy were included. RCTs that compared ICS-containing therapy to placebo only were excluded. Studies with asthma-COPD overlap in diagnosis were also excluded. Last date of search was January 15, 2023. The retrieved titles and abstracts were independently screened by two reviewers for inclusion. Studies which used inhaled corticosteroids in stable COPD were retrieved for full text review. The quality of the included RCTs were evaluated using Cochrane Risk of Bias Tool. Critical outcomes identified for this review were all-cause mortality, health status using SGRQ, COPD exacerbation, COPD-related hospitalization and occurrence of pneumonia. Important outcome seen was dyspnea reduction. Outcomes with at least two studies were pooled via a meta-analysis. Meta-analysis was performed using a random or fixed effects model with risk-ratio as effect size estimate of dichotomous outcomes and mean difference for continuous outcomes. Heterogeneity was estimated using I2 statistics. Outcome-specific level of certainty of evidence was evaluated using the GRADEpro GDT tool.

## Introduction

Inhaled corticosteroids in combination with other bronchodilators (usually a LAMA or a LABA or both) is used in the management of chronic obstructive pulmonary disease, to those with > 2 moderate exacerbations of COPD per year, history of hospitalization for exacerbations of COPD, blood eosinophils >300 cell/uL (GOLD 2023). ICS reduce inflammation in the airways and can help improve lung function, reduce symptoms and decrease the frequency of COPD

exacerbations. In vitro studies for inhaled corticosteroids demonstrated that endothelial colony-forming cells exhibit reduced senescence thereby reducing chemokines from cell apoptosis. A recent meta-analysis on the use of ICS vs non-ICS combination therapy in COPD, reported lower exacerbations in ICS therapy and improvement in quality-of life scores among COPD patients. This evidence review aims to compare the patient-related outcomes of ICS-containing combination therapy compared to non-ICS containing therapy in the treatment of stable COPD.

## Evidence

### All-cause Mortality

Pooled results from forty two RCTs showed (N= 81,705) that analyzed the risk for all-cause mortality with the use of ICS-containing inhalers when compared with non-ICS-containing inhalers showed that the use of ICS-containing inhaler significantly reduced all-cause mortality (RR 0.80; 95% CI 0.74, 0.87; I2=0%). [138-178] The cause of death, however, were mostly cardiovascular in nature and were adjudicated to be unrelated to study medication. In one study, more pneumonia-related deaths were recorded than anticipated in the ICS-containing treatment arm. Low body mass index, older age (i.e., >65 years old) and current smoking were noted to be associated with pneumonia. Certainty of evidence was high.

### Health Status Using SGRQ

Pooled results from 29 RCTs (N= 57, 200) that analyzed the patients' health status using the SGRQ, an instrument designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease showed that the use of ICS-containing inhalers reduced SGRQ scores when compared with non-ICS-containing inhalers (MD -1.28; 95% CI -1.63, -0.93; I2=100%).[138-144, 146, 147, 149-153, 155, 156, 161-164, 166-169, 172-177, 179] Minimum clinically important difference stated in the studies included was -4.00. Certainty of evidence was low due to high heterogeneity.

### Effect of Treatment on Dyspnea

Pooled results from four RCTs (N= 5,277) showed a between group mean difference of -0.08 points (95% CI -0.10, -0.07).[145, 164, 166, 170] Certainty of evidence was downgraded to moderate due to substantial heterogeneity (I2=85%).

### Risk for Exacerbation

Pooled results from forty-nine RCTs (N=66,487) showed that the use of ICS-containing inhaler significantly reduced exacerbations (RR 0.88; 95% CI 0.84, 0.93; I2=85%) when compared with the use of non-ICS containing inhalers.[138-155, 157-177, 180-188] Certainty of evidence was downgraded to moderate due to inconsistency from substantial heterogeneity.

### Risk for Developing Pneumonia

Pooled results from forty three RCTs (N= 75,511) showed that the use of ICS-containing inhaler significantly increased the risk of developing pneumonia (RR 1.58; 95% CI 1.47, 1.70; I2=9%) when compared with the use of non-ICS containing inhalers.[138-168, 170-177, 183, 185, 187] Certainty of evidence was high.

**Risk for COPD-related Hospitalization**

Pooled results from fifteen RCTs (N=18,238) showed that ICS-containing inhalers has inconclusive effect when compared with non-ICS-containing inhalers (RR 0.91; 95% CI 0.82, 1.01; I2=36%).[138, 148-155, 159, 170-172, 177, 178, 185]

Analysis of COPD exacerbation and SGRQ scores yielded a high degree of heterogeneity (I2 85% and 100%, respectively) thus giving a serious grade on inconsistency. This resulted to a moderate certainty of evidence for COPD exacerbation and low certainty for SGRQ scores. Table 18 below shows the summary of findings on the comparison of the efficacy of ICS and non-ICS containing inhalers.

Table 18. Summary of Findings of the Efficacy and Safety of ICS-containing versus non-ICS-containing Inhalers

| **OUTCOMES** | **Basis (No. and Type of Studies, Total Participants)** | **Effect Size** | **95% CI** | **Interpretation** | **Certainty of Evidence** |
|---|---|---|---|---|---|
| CRITICAL OUTCOMES | | | | | |
| All-cause mortality | 42 RCTs (n=81,705) | RR 0.80 | 0.74, 0.87 | Benefit (Favors ICS) | High |
| Health status using SGRQ | 29 RCTs (n=57,200) | MD -1.28 | -1.63, -0.93 | Benefit (Not Clinically Significant) | Low |
| Risk for COPD exacerbation | 49 RCTS (n=66,487) | RR 0.88 | 0.84, 0.93 | Benefit (Favors ICS) | Moderate |
| Risk for Pneumonia (as Serious Adverse Event) | 43 RCT (n=75,511) | RR 1.58 | 1.47,1.70 | Harm | High |
| COPD-related hospitalization | 15 RCTs (n=18,238) | RR 0.91 | 0.82, 1.01 | Inconclusive | Low |
| IMPORTANT OUTCOME | | | | | |
| Dyspnea Reduction | 4 RCTS (n=5377) | MD -0.08 | -0.10, -0.07 | Benefit (Favors ICS) | Moderate |

## Recommendations from Other Groups

| **Group or Agency** | **Recommendation** | **Strength of recommendation and certainty of evidence** |
|---|---|---|
| Global Strategy for Prevention, Diagnosis and Management of COPD[189]: 2023 Report (as of December 10, 2022) | • An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations | Evidence A |

| | | |
|---|---|---|
| | in patients with exacerbations and moderate to very severe COPD<br><br>● Regular treatment with ICS increases the risk of pneumonia especially with severe disease<br><br>● Lower blood and sputum eosinophils are associated with greater presence of proteobacteria, notably Haemophilus, increased bacterial infections and pneumonia<br><br>● Independent of ICS use, there is evidence that a blood eosinophil count of <2% increased the risk of pneumonia<br><br>● Triple inhaled therapy of LABA+LAMA+ICS improves lung function, symptoms and health status and reduces exacerbations, compared to LABA+ICS, LABA+LAMA or LAMA monotherapy (Evidence A). Recent data suggest a beneficial effect of triple inhaled therapy versus fixed-dose LABA+LAMA combinations on mortality in symptomatic COPD patients with a history of frequent and/or severe exacerbations<br><br>● Single inhaler therapy may be more convenient and effective than multiple inhalers | Evidence A<br><br>Evidence C |

| | | |
|---|---|---|
| American Thoracic Society: Pharmacologic Management of Chronic Obstructive Pulmonary Disease[190] (2020) | ● In patients with COPD who complain of dyspnea or exercise intolerance despite dual therapy with LABA/LAMA, suggests the use of triple therapy with ICS/LABA/LAMA over dual therapy with LABA/LAMA in those patients with a history of one or more exacerbations in the past year requiring antibiotics or oral steroids or hospitalization.<br>● In patients with COPD who are receiving triple therapy (ICS/LABA/LAMA), suggests that the ICS can be withdrawn if the patient has had no exacerbations in the past year.<br>● Does not make a recommendation for or against ICS as an additive therapy to long-acting bronchodilators in patients with COPD and blood eosinophilia, except for those patients with a history of one or more exacerbations in the past year requiring antibiotics or oral steroids or hospitalization, for whom we suggest ICS as an additive therapy. | Conditional, Moderate Certainty<br><br>Conditional, Moderate Certainty<br><br>Conditional, Moderate Certainty |
| Canada Thoracic Society Clinical Practice Guideline on pharmacotherapy in patients with COPD – 2019 update of evidence[191] | ● Suggests LAMA/LABA/ICS triple therapy in COPD patients with persistent dyspnea and poor health status in the last year despite the use of | Grade 2A |

| | | |
|---|---|---|
| | inhaled LAMA/LABA dual therapy. | |

## Ongoing Trials and Research Gaps

There are 2 studies currently on going that incorporates inhaled corticosteroids in a triple regimen-single device, namely: TRICOLON and TETRIS.[307] These two trials are estimated to be completed in year 2024.

## Additional Considerations for Evidence to Decision Phase

**Cost**

COPD generates substantial costs for the patient and healthcare system, mainly related to moderate to severe stages and the exacerbations and complications seen. Out-of-pocket expense of hospitalized patients with acute exacerbation of COPD in a Philippine tertiary care center was found to be at 22,000-51,000 pesos with a mean stay of 8 days.[192] If we consider more rapid decline in lung function for every COPD exacerbation, the cost of exacerbations of COPD is greater than the cost of maintenance inhaler therapy (800-2500 Php depending on device).[193] It is important to note that while ICS can help reduce the frequency and severity of exacerbations, they may not be appropriate for all COPD patients.

Table 19. Cost of ICS and non-ICS containing inhalers

| | **ICS-containing Inhaler** | **Non-ICS-containing Inhaler** |
|---|---|---|
| Cost | 400-2615Php[a] | 1500-2900 Php[b] |

[a]Reference for price range (include generic and common branded inhalers)
[b]Reference for price range (include generic and common branded inhalers)

**Patient's Values and Preference, Equity, Acceptability, and Feasibility**

COPD is associated with substantial health, emotional and social impact to patients. A longitudinal aging study done in a Dutch population showed slower walking speeds and lower perception of health compared to non-COPD counterparts. COPD patients were found to have more impaired disease-specific health status, were less likely to have a partner, more socially deprived and receives less emotional support than non-COPD counterparts.[194] A standardized approach to treatment of COPD cannot be done due to its heterogenous pathobiology. A management with patient preference in consideration is important. A study by Tervonen in 2020 showed that patients with COPD prefer medications with fast onset of action, preferably with a once-daily dosing on pressurized inhaler forms with lower rate of exacerbations yearly. This study also found that the more symptomatic the patient is (CAT score >30), the more patients value medications with faster onset of action than reduction in exacerbations. On the other hand, patients with better control of their disease (CAT<20), reduction of risk for potential ICS adverse events was more important.[195]

**Clinical Question No. 5.** Among stable COPD patients in the primary care setting, how effective and safe are oral methylxanthines (alone or in combination with inhaled long-acting bronchodilator) in improving symptoms, preventing exacerbations, hospitalization, and death?

| *Recommendation No. 5A* |
| --- |
| **Among stable COPD patients in the primary care setting, we recommend the use of inhaled long-acting bronchodilator over oral methylxanthines** *(Very low certainty of evidence, Strong recommendation)* |

| *Recommendation No. 5B* |
| --- |
| **Among stable COPD patients in the primary care setting, we recommend the use of oral methylxanthines versus no treatment if inhaled long-acting bronchodilator is not available** *(Very low certainty of evidence, Strong recommendation)* |

| *Recommendation No. 5C* |
| --- |
| **Among stable COPD patients in the primary care setting, we recommend against adding oral methylxanthines to inhaled long-acting bronchodilator** *(Very low certainty of evidence, Strong recommendation)* |

## Key Findings

- There were four RCTs included in this evidence review which determined the efficacy of oral methylxanthine with or without inhaled long-acting bronchodilator compared with long-acting bronchodilator (LABD) in stable COPD. Two additional studies (one meta-analysis and one case-control study) were included to ascertain safety of methylxanthine use.

- Methylxanthine when used with or without LABD shows no improvement in symptoms and dyspnea score, reduction in exacerbation, hospitalization, mortality, and exercise capacity. The overall effect of methylxanthine in lung function shows equivalence when compared to LABD. Methylxanthine does not increase the risk of adverse events (arrhythmia, insomnia, headache and dyspepsia) but has shown increased risk for nausea.

- The certainty of evidence was downgraded to very low due to serious risk of performance and detection biases in two studies. In addition, issues on inconsistencies and imprecision were present. Two studies have few reported events for hospitalization and mortality. Inconsistencies in results were likewise described in outcomes of dyspnea score, exacerbations and adverse events. Outcomes in dyspnea score, hospitalization, and exercise

capacity showed high suspicion for publication bias. The overall effect of evidence was very low.

### Consensus Issues

The panel strongly recommended the use of inhaled LABD over oral methylxanthines despite the very low certainty of evidence. This recommendation was based on the benefits that inhaled LABDs offer, including notable decrease in mortality rate, decrease in risk of exacerbation, lung function and symptoms improvement, and significant reduction in COPD-related hospitalizations. The preference for inhaled LABDs is underpinned by their more direct and targeted delivery to the lungs, facilitating more effective bronchodilation and symptom relief. This administration route circumvents the challenges associated with the metabolism and adverse events (i.e., arrhythmia, nausea, dyspepsia, insomnia, and headache) observed with oral methylxanthines, resulting in a more efficacious and safer treatment option. Furthermore, the compelling evidence supporting the advantages of inhaled LABDs in various domains of COPD management strengthens the rationale behind this recommendation. The positive impact on mortality, exacerbations, lung function, symptom control, exercise capacity, and hospitalizations collectively underscores the comprehensive benefits that inhaled LABDs can provide to individuals with COPD.

Healthcare professionals have also consistently observed positive outcomes when inhaled LABDs are chosen over oral methylxanthines. Notably, the use of oral methylxanthines entails certain drawbacks, such as their narrow therapeutic index. This characteristic means that achieving the desired effect with oral methylxanthines might necessitate higher doses compared to inhaled LABDs. However, opting for higher doses of oral methylxanthines comes with an elevated risk of adverse events, underscoring the importance of prudent dosing and vigilant monitoring.

On the contrary, oral methylxanthines present a viable option, particularly in cases where inhaledLABDs are not accessible. This avenue gains prominence, serving as a bridge when inhaled LABDs are not yet introduced. However, when contemplating the augmentation of inhaled LABDs with oral methylxanthines, caution is advised as this amalgamation might not yield additional benefits. Rather, it could elevate both risks and financial costs.

The deployment of oral methylxanthines, especially at higher dosages, is often accompanied by side effects like tremors, arrhythmia, nausea and insomnia. These unwanted effects can be mitigated by moderating the dosage, highlighting the importance of personalized treatment approaches that factor in individual tolerances and responses.

The selection between inhaled LABDs and oral methylxanthines rests upon a meticulous evaluation of the benefits and potential drawbacks, taking into account patients' unique characteristics and symptomatology. Physicians play a pivotal role in this deliberative process, offering expert guidance while recognizing the patient's preferences and priorities. Involving patients in the decision-making journey fosters a collaborative healthcare environment, further enhancing treatment adherence and overall outcomes.

Oral methylxanthines are significantly cheaper than inhaled LABD whose price ranges from Php 15.00 to Php 23.75 per tablet. The cost of inhaled LABD ranges from Php 64.21 to Php 957.00 per inhaler. In addition, oral methylxanthines can be procured per piece which is more equitable for the patient.

In conclusion, despite the limited certainty of evidence, the collective consensus among healthcare experts is resoundingly in favor of prioritizing inhaled LABD over oral methylxanthines. This is due to the array of benefits offered by inhaled LABDs, their favorable safety profile, and the potential risks associated with the use of oral methylxanthines. This approach, grounded in evidence-based practice, represents a steadfast commitment to optimizing the well-being of individuals grappling with COPD.

## Review Methods

A systematic search was done to examine available published studies on the efficacy and safety of oral methylxanthines alone or in combination with long-acting bronchodilators in the management of stable COPD. A comprehensive search was done in PubMed, Cochrane Library, ClinicalTrials.gov, Google Scholar and the Health Research and Development Information Network (HERDIN) from inception until 01 February 2023. Search terms used were "pulmonary disease, chronic obstructive" (MeSH descriptor) OR "stable COPD", "methylxanthine" OR "doxofylline" OR "theophylline", "long-acting bronchodilator" OR "LABA" OR "LAMA". Studies filtered were clinical practice guidelines, systematic reviews and meta-analysis, and randomized controlled trials. The search was expanded to include observational studies for the safety outcomes of methylxanthine without direct comparison to a long-acting bronchodilator.
The study population was limited to well-controlled COPD without exacerbation in the past 4-6 weeks, without history of atopy or clinical diagnosis of bronchial asthma. Critical outcomes in this review included all-cause mortality, COPD-related quality of life, exacerbation prevention. Hospitalization, presence of adverse events, symptom improvement and lung function were considered important but not critical outcomes.
Included studies were assessed for risk of bias using Cochrane Risk of Bias Tool v1 for RCTs, AMSTAR-2 for systematic review and meta-analysis, and Newcastle Ottawa Quality Assessment for the observational study.

## Evidence

**Symptom improvement**

Results from two RCTs have used varying dyspnea score systems as measures of symptom improvement and both studies showed inconclusive improvement in symptom using CAT score when methylxanthine is used with tiotropium (MD -0.98; 95% CI -1.90, -0.06) after 6 months of intervention; and in UK MRC score when methylxanthine is used alone after 6 months of therapy (MD 0.12; 95% CI 0, 0.24).[196, 197]

**Exacerbation**

Pooled results from three RCTs showed that reduction in the risk of exacerbation was inconclusive (RR 0.82; 95% CI 0.54 ,1.23; I2=0%).[196, 198, 199] Subgroup analysis of methylxanthine plus LABD (RR 1.03; 95% CI 0.3, 2.79; I2=0%) and methylxanthine alone (RR 0.78; 95% CI 0.5, 1.22) as interventions similarly showed no significant differences in exacerbation events.

**COPD-related hospitalization**

Only the study of Xiong et al., reported the effect of methylxanthine combined with LABD on COPD related hospitalization. The reduction in the risk of hospitalization was inconclusive with the use of methylxanthine combined with LABD (RR 0.75; 95% CI 0.17, 3.25).[200]

**Mortality**

Two RCTs reported on mortality as outcome when methylxanthine was used.[199, 200] Results from the study of Rossi et al., showed inconclusive effect on mortality between methylxanthine and LABD groups (RR 0.37; 95% CI 0.02, 6.77) while there were no mortality events recorded in both treatment groups in the study by Xiong et al.[199, 200]

**Exercise Capacity**

The study by Wang et al. showed no improvement in the mean distance using 6-minute walk test when methylxanthine is used with long-acting bronchodilator after 6 months of treatment (MD -39.31; 95% CI -87.26, 8.64).[196]

**Lung Function**

Pooled analysis from 2 RCTs showed overall equivalence in the change in FEV1 after 6 months of treatment (MD 0.00; 95% CI -0.11, 0.12; I2 =0%).[196, 197] Sub-group analysis when methylxanthine is used alone, likewise, showed similar effect in FEV1 when compared to LABD group (MD 0.05; 95% CI -0.13, 0.23).

**Treatment failure**

Treatment failure was defined as the use of additional rescue salbutamol puff medication. Results from two RCTs showed a decrease in the daily use of salbutamol puff from baseline.[198, 199] One study reported a decrease from baseline in the median daily use of salbutamol puff to 1.6 per day over 12 months in the methylxanthine group. Comparing with LABD therapy, there was a significant difference in the reduction of salbutamol use favoring the LABD group.[199] Likewise, another study reported a decrease in mean daily use of salbutamol puff from baseline ($p < 0.05$), but without significant difference when compared to LABD after the 8-week study period. These studies, however, did not report IQR values and post intervention results.[196, 199]

Table 20. Summary of the Efficacy of Methylxanthine versus LABD

| Outcomes | N | Effect size | 95% CI | Interpretation | Certainty of Evidence | Importance |
|---|---|---|---|---|---|---|
| Symptom Improvement using CAT Score at 6 months | 1 RCT (n=142) | MD -0.98 points | -1.90, -0.06 | Inconclusive | Low[a,b] | Critical |
| Symptom Improvement Using UK MRC Score | 1 RCT (n=110) | MD 0.12 | 0,0.24 | Inconclusive | Very Low [b,c,d] | Critical |

| | | | | | | |
|---|---|---|---|---|---|---|
| at 6 months | | | | | | |
| Exacerbation | 3 RCT (n=837) | RR 0.82 | 0.54, 1.23 | Inconclusive | Low[a,e] | Critical |
| a.Methylxanthine with LABD vs LABD | 2 RCT (n=203) | RR 1.03 | 0.38, 2.79 | | | |
| b.Methylxanthine vs LABD | 1 RCT (n=634) | RR 0.78 | 0.5, 1.22 | | | |
| COPD related hospitalization | 1 RCT (n=170) | RR 0.75 | 0.17, 3.25 | Inconclusive | Very Low [a,b,f,g] | Critical |
| Mortality (all-cause) Methylxanthine vs LABD | 1 RCT (n=553) | RR 0.37 | 0.02, 6.77 | Inconclusive | Very Low [a,f,g] | Critical |
| Exercise Capacity measured by 6minute walk test (6MWT) | 1 RCT (n=110) | MD-39.31 meters | -87.26, 8.64 | Inconclusive | Very Low [b,d,f] | Important |
| Lung Function measured by change in FEV1 | 2 RCT (n=252) | MD 0.00 liters | -0.11, 0.12 | Equivalent | Moderate[a] | Important |
| a.Methylxanthine with LABD vs LABD | 1 RCT (n=110) | MD -0.03 | -0.18, 0.12 | | | |
| b.Methylxanthine vs LABD | 1 RCT (n-142) | MD 0.05 | -0.13, 0.23 | | | |

a. performance and detection bias (Xiong 2008)
b. publication bias suspected (single study)
c. Wang showed improvement in dyspnea score favoring LABD
d. low study population
e. study of Xiong showed greater events of exacerbations in methylxanthine group vs LABD group
f. wide confidence interval
g. few events reported. one study reported zero events both in the methylxanthine and LABD groups.

**Safety**

Results of the pooled analysis of four RCTs showed no difference in the total events of adverse effects when methylxanthine in combination or without LABD (RR 1.05; 95% CI 0.94, 1.18; I2=0%) is used.[196-199] Sub-analysis of two studies also showed no increase in adverse events when methylxanthine is used without long-acting bronchodilator (RR 1.05; CI 95% 0.93, 1.18; I2=0%).[196, 199] Combined methylxanthine with long-acting bronchodilator use did not increase risk of adverse events (RR 1.16; 95% CI 0.73, 1.8; I2=0%) [4,7]. The most commonly reported

effects were mild gastrointestinal symptoms (nausea, vomiting, dry mouth), palpitations, and insomnia.

The retrospective nested case-control study by Wilchesky et al, with adjustment to confounding variables, showed that the risk of arrhythmia among newly treated COPD patients with methylxanthine was inconclusive (n=44 out of 4,134; RR 1.28; CI 95% 0.93, 1.77).[201] The risk of arrhythmia was also inconclusive for patients with past use of methylxanthine during a 61 to 365-day period before the index date of arrhythmia (n=364 out of 4,134; RR 0.93; CI 95% 0.83, 1.05).

From twenty cross-over studies included in the Cochrane meta-analysis of Ram et al, three RCTs evaluated the risk of nausea (n=39; RR 7.67; CI 95% 1.47, 39.94; I2 0.0%); and 1 RCT for each adverse event of dyspepsia (n=33; RR 3.00; CI 95% 0.33, 27.38), insomnia (n=17; RR 0.33; CI 95% 0.01, 7.65), and headache (n=12; RR 3.00, CI 95% 0.13, 67.06).[202] There is an increased risk of nausea with use of oral theophylline compared to placebo. The risk of dyspepsia, insomnia, and headache with use of methylxanthine are all inconclusive.

Table 21. Summary of the Safety Findings of Methylxanthines versus LABD

| Outcomes | No of studies | Effect size | 95% CI | Interpretation | Certainty of Evidence | Importance |
|---|---|---|---|---|---|---|
| Any Adverse Events | 4 RCT (n=947) | RR 1.05 | 0.94, 1.18 | Inconclusive | Low | Critical |
| **a.** Methylxanthine with LABD vs LABD | 2 RCT (n=203) | RR 1.16 | 0.73, 1.84 | | | |
| **b.** Methylxanthine vs LABD | 2 RCT (n=744) | RR 1.05 | 0.93, 1.18 | | | |
| Arrhythmia | 1 cohort (n=76,661) | RR 1.28 | 0.93, 1.77 | Inconclusive | Very Low[h] | |
| Nausea | 3 RCTs (n=39) | RR 7.67 | 1.47, 39.94 | Favors Placebo | Low[i,j] | |

h. limitation on observational study design, selective reporting, and publication bias suspected
i. placebo as comparator (indirectness)
j. low sample size, low event rate, and wide confidence interval

The certainty of evidence was downgraded to very low due to inconsistencies and imprecisions of results. The use of methylxanthine with or without LABD is inconclusive in improving symptom and dyspnea score, reducing exacerbation, hospitalization, all-cause mortality, exercise capacity and does not increase the risk of adverse events of arrhythmia, dyspepsia, insomnia and headache. There is increased risk of nausea with use of methylxanthine. Methylxanthine shows same effect in change in lung function (FEV1).

## Recommendations from Other Groups

| Group | Recommendation | Strength of |
|---|---|---|

| | | Recommendation and Certainty of Evidence |
|---|---|---|
| Summary of Consensus Statements on the Diagnosis and Management of COPD in the Philippines (2021)[203] | In the primary care facility and in the absence of inhalation therapy, oral methylxanthines can be used as an alternative for short-acting (SABA or SAMA) and long-acting (LAMA or LABA) inhalers for GOLD Groups A, B, C and D. | Not Stated |
| Chronic obstructive pulmonary disease in over 16s: diagnosis and management. London: National Institute for Health and Care Excellence[204] | The use of oral theophylline should only be considered after a trial of short and long-acting bronchodilators and for patients unable to use inhaler therapy. Serum levels should be monitored especially in older patients with co-existing comorbidities to avoid drug interaction with other medications. | Noted Stated |
| Global Initiative for Chronic Obstructive Lung Disease[205] | Theophylline has minimal bronchodilator effect[1] when used in stable COPD with modest symptomatic benefit[2]. | Evidence A[1], B[2] |

## Ongoing Trials and Research Gaps

There are ongoing clinical trials evaluating efficacy of theophylline in combination with acetylcysteine, effect of theophylline in the small airways and lung function, and effect of low-dose theophylline in acute exacerbation of COPD. Results of these trials are not yet posted.

A systematic review protocol by Cochrane is available which aims to validate the combined efficacy of oral methylxanthines with inhaled long-acting bronchodilators and inhaled corticosteroid therapies. The result of this review is still not posted.[308]

## Additional Considerations for Evidence to Decision Phase

**Cost**

Theophylline SR and doxofylline are the oral methylxanthines available in the local setting. As of writing, only oral theophylline is included in the Philippine National Drug Formulary (PNDF). Price range for geographically and disadvantage areas (GIDA) is not available for both drugs.[206] Based on drug store retail price in National Capital Region, Theophylline SR is priced at Php 22.75-23.00 per 125mg/tablet and Php 17.82-18.00 per 250mg/tablet. The cost of doxofylline per preparations are at Php 15-16.50 per 200mg/tablet; Php 23.25-23.75 per 400mg/tablet; and Php 310-311.00 per 100mg bottle of 100mg/5ml suspension.

The list of included long-acting bronchodilators in mono- or combination LABA and LAMA therapies in the PNDF are tiotropium with or without olodaterol,

formoterol (with inhaled corticosteroid budesonide or fluticasone), salmeterol (with fluticasone), and indacaterol with glycopyrronium. GIDA-based price for tiotropium is Php 64.21 per 18 mcg/dose with appropriate accompanying dispenser; and glycopyrronium +indacaterol 110 mcg+50mcg dry powder capsule for inhalation is Php 66.30. For combination LABAs with inhaled corticosteroids (ICS), the GIDA-based price are as follows: fluticasone + salmeterol 125 mcg + 25mcg and 250mcg + 25mcg both with 120 actuations MDI is Php 392.00; fluticasone + salmeterol 250 mcg + 50 mcg, 60 doses dry powder inhaler (DPI) is Php 424.62; fluticasone + salmeterol 500 mcg + 50 mcg, 60 actuations in DPI is Php 491.41. The GIDA-based price for formoterol in combination with ICS are: fluticasone + formoterol 125 mcg+5 mcg, 120 actuations metered dose inhaler (MDI) is Php 957.00; budesonide + formoterol 160 mcg+4.5 mcg, 120 doses MDI is Php 792.00; budesonide + formoterol 160 mcg + 4.5 mcg, 60 doses DPI is Php 756.88; and budesonide +formoterol 80 mcg + 4.5 mcg, 60 doses DPI is Php 678.06.

The drug store retail price for tiotropium + olodaterol 2.5 mcg + 2.5 mcg in reusable Respimat inhaler is Php 2850 and Php 2565 for 4ml cartridge refill with 60 puffs (or 30 medicinal doses).

**Patient's Values and Preference, Equity, Acceptability, and Feasibility**

There are no available studies that evaluated patient's values, preference, equity, acceptability and feasibility to methylxanthine over long-acting inhaled bronchodilator.

However, a meta-analysis of Ram et al. which included 2 RCTs with combined study population of 50, showed high preference to theophylline over placebo (RR 2.27; 95% CI 1.26, 4.11).[202] The included studies were cross-over designs done in 1980 and 1993. Patient's preference to methylxanthine may have varied over the years.

## DOMAIN 3. MANAGEMENT OF COPD EXACERBATION IN THE PRIMARY CARE SETTING

**Clinical Question No. 6.** Among patients with COPD exacerbation in the primary care setting, how effective and safe are SABA+SAMA vs SABA alone in improving symptoms and preventing recurrence, hospitalization, and death?

| *Recommendation No. 6* |
| --- |
| **Among COPD patients in exacerbation, we recommend the use of SABA+SAMA (combination therapy) in the management of acute exacerbation. In situations where SABA+SAMA is not readily available, SABA may be used** *(Very low certainty of evidence, Strong recommendation)* |

### Key Findings

- Four moderate quality RCTs that were included in the evidence review comparing SABA + SAMA versus SABA monotherapy among COPD patients in acute exacerbation. Based on the pooled data, hospitalization, intubation, 7-day mortality, improvement in pulmonary function (peak expiratory flow rate and FEV1) were not statistically different between either treatment arms. There was also no difference observed on the subjective improvement of symptoms based on symptom score and Borg score.

- Length of hospital stay was improved in the SABA+SAMA group compared to SAMA. SABA+SAMA did not increase the risk of arrhythmic events in COPD patients hospitalized for an acute exacerbation while SABA was associated with an increased risk of cardiac arrhythmias among stable COPD patients. No studies were found reporting on the effect of short acting bronchodilators on preventing recurrence of COPD exacerbation.

- Overall certainty of evidence was very low due to indirectness, serious risk of bias, inconsistency and imprecision.

### Consensus Issues

The panel placed high value in an intervention that would provide relief of dyspnea and resolution of exacerbation at the shortest possible time. Both combination therapy with SABA + SAMA and monotherapy using SABA are effective based on available evidence and in clinical practice. However, combination therapy was deemed to have a greater benefit over monotherapy alone. As experienced by the patient representative and witnessed by the physicians of the consensus panel , the use of combination therapy with SABA+SAMA (i.e., salbutamol + ipratropium bromide via inhaler or nebulized form) provides significantly faster relief of dyspnea during COPD exacerbation as compared to monotherapy using SABA alone (i.e. salbutamol via inhaler or nebulized form). In addition, lesser doses of the combination therapy is usually required to achieve the desired relief of dyspnea. The use of SABA is usually associated with tremors after administration of more doses. More frequent dosing may lead to increased risk of having adverse effects such as tremors and arrhythmia.

Despite the higher cost of the use of combination therapy, it was considered to be a more cost-effective option by the panel as it relieves exacerbations faster than monotherapy, may require fewer doses and may decrease risk for adverse events, and lessens the duration of hospital stay. To ensure accessibility and equity, the panel agreed for monotherapy using SABA as an alternative in situations where combination therapy with SABA+SAMA is not available.

## Review Methods

A systematic search was done of all available published studies from inception to February 11 2023 to search for the best evidence on SABA + SAMA versus SABA for COPDIAE using Medline, Cochrane Library and Google Scholar. The following search terms were used: “chronic obstructive pulmonary disease”, “short acting bronchodilator”, “COPD [MeSH], “exacerbation”, “emergency [MeSH]”.

Studies evaluating efficacy and safety among COPDIAE were included. Subjects with stable COPD, studies focusing mainly on other obstructive pulmonary diseases including asthma, bronchiolitis and cystic fibrosis were excluded. Studies were limited to interventions comparing SABA + SAMA with SABA and additional interventions such as magnesium sulfate, inhaled corticosteroids and oral/intravenous interventions were not included. Retrieved articles were filtered to include evidence from RCTs.

Due to the limited data on safety and limited power of RCTs to detect harm, another systematic search was done for the best evidence evaluating the risk of adverse events on the use of short acting bronchodilators. Search was expanded to include obstructive lung diseases (including asthma and stable COPD) and children and adolescents. Search terms were: “adverse events [MeSH]”, “harm”, “safety” and “short acting bronchodilator”. All studies evaluating adverse events as the primary outcome were retrieved for screening.

## Evidence

**Efficacy**

Results of the pooled analysis from two RCTs showed that SABA + SAMA did not show any significant difference compared to SABA alone in reducing COPD related hospitalization (RR 1.12, 95% CI 0.63 to 1.97, p = 0.11, I2=60%), incidence of intubation (RR 0.90, 95% CI 0.39 to 2.04, p = 0.92, I2=0%) and 7-day mortality (RR 0.98, 95% CI 0.50 to 1.94, p = 0.48, I2=0%). Length of hospital stay in days was significant for SABA+SAMA compared to SABA monotherapy (MD -1.03, 95% CI -1.77 to -0.29, p = 0.81, I2=0%). In terms of mean absolute change in FEV1, one RCT showed no difference between SABA+SAMA compared to SAMA (MD 0.35, 95% CI -0.33 to 1.03, p = 0.31).[207,208]

There was also no difference observed on the subjective improvement of symptoms based on self-reporting of shortness of breath score (-1 worse; 0 same; +1 better) (MD 0.6, 95% CI -0.77 to 1.37, p > 0.05) [5] and Borg score (0 to 10, with higher scores reflecting more severe dyspnea) (MD -0.04, 95% CI 0-.9 to 1.0, p = 0.93) between the two groups. The study by Beltaiaef also evaluated dyspnea score and reported no statistically significant difference between groups after 1, 2 and 3 hours of treatment.[209, 210]

**Safety**

Data from one RCT which enumerated adverse events during treatment. A similar number of patients complaining of mild symptoms on both treatment groups were recorded. The most common included tremor in 8 patients in the SABA + SAMA group and 10 patients in the SABA group, headache that occurred in 7 patients in SABA + SAMA group and 9 patients in SABA group. No retrieved RCTs reported arrhythmias, morbidity/mortality associated with the treatment.[210]

Multiple studies published from 2012 to 2022 evaluated the safety profile of SABA with or without SAMA. Based on a 2022 meta-analysis of nested case-control studies, compared to ICS and controlling for potential confounders, stable COPD patients who are current or new users of SABA were not at an increased risk of pneumonia compared to ICS or SAMA (adjusted HR 0.81, 95% CI 0.45 – 1.44, p >0.05). However, SABA was associated with an increased all-cause mortality among COPD patients (adjusted HR 1.82, 95% CI 1.04 to 3.20, p = <0.05).[211] Increased mortality was linked to the increased use of SABA monotherapy in COPD, indicating more of its ineffectiveness rather than the association with disease severity or issues with medication safety. In another retrospective observational study evaluating the safety of SABA+SAMA among hospitalized COPD patients in acute exacerbation, shifting patients to SABA+SAMA did not increase the risk of arrhythmic events in COPD patients hospitalized with an acute exacerbation (5.5% of the SABA+SAMA, p = 0.122).[212] However, among stable COPD patients, the rate of cardiac arrhythmias, after adjustment for potential confounders, was elevated with the new use of SABA (RR 1.27, 95% CI 1.03 to 1.57) but not with SAMA (RR 1.23, 95% CI 0.95 to 1.57).[213]

A meta-analysis of RCTs showed no significant differences in the risk of adverse events between salbutamol and salbutamol with ipratropium bromide (IB) (RR 1.77, 95% CI 0.63 to 4.98, p = >0.05) in terms of dry mouth, tremor and vomiting. IB + salbutamol group showed significant reduction in the incidence of nausea compared with salbutamol alone group (RR 0.60; 95% CI 0.39, 0.93; p = 0.02; I2 = 0%).[214] Table 22 below summarizes the findings on the efficacy and safety of SABA alone and SABA and SAMA combination.

Table 22. Summary of Findings of SABA versus SABA + SAMA

| Critical OUTCOMES | BASIS (No and Type Of Studies, Total Participants) | EFFECT SIZE | 95% CI | INTERPRETATION | CERTAINTY OF EVIDENCE |
|---|---|---|---|---|---|
| COPD related hospitalizations | 2 RCTs (n = 199) | RR 1.12 | 0.63 to 1.97 | Inconclusive | Very Low[a] |
| Incidence of intubation | 2 RCTs (n = 199) | RR 0.99 | 0.39 to 2.04 | Inconclusive | Moderate[b] |
| 7-day mortality | 2 RCTs (n = 194) | RR 0.98 | 0.05 to 1.94 | Inconclusive | Very Low[c] |
| Mean absolute change in FEV1 | 1 RCT (n = 34) | MD 0.35 | -0.33 to 1.03 | Inconclusive | Low[b] |

| | | | | | |
|---|---|---|---|---|---|
| Length of hospital stay in days | 2 RCTs (n = 207) | MD -1.03 | -1.77 to -0.29 | Favors SABA+SAMA | Very Low[c] |
| Symptom improvement using self-reporting of shortness of breath score | 1 RCT (n = 62) | MD 0.6 | -0.77 to 1.37 | No difference | Moderate[d] |
| Symptom improvement using modified Borg Dyspnea score | 1 RCT (n = 67) | MD -0.04 | -0.9 to 1.0 | | |
| Adverse event: cardiac arrhythmia | 1 cohort (n = 76,661) | SABA: RR 1.27 | 1.03 to 1.58 | Increase harm with SABA | Moderate[e] |
| | | SAMA: RR 1.23 | 0.95 to 1.57 | Inconclusive | |
| Adverse event: nausea | 6 RCTs (n = 993) | RR 0.6 | 0.39 to 0.93 | Favors SABA+SAMA | Moderate[f] |

***Table 1: Summary of findings - SABA+SAMA versus SAMA for COPD in acute exacerbation***
a Downgraded due to inconsistency and imprecision (wide CI and P > 0.05)
b Downgraded due to imprecision
c Downgraded due to risk of bias and imprecision
d Downgraded due to risk of bias
e Downgraded due to risk of bias and indirectness
f Downgraded due to indirectness

Overall quality of RCTs related to efficacy were moderate due to unclear reporting of the aforementioned risks of bias. As for safety, certainty of evidence for cardiac arrhythmia was downgraded to moderate due to risk of bias and indirectness while certainty of evidence was downgraded to moderate for nausea due to indirectness.

## Recommendations from Other Groups

| Group or Agency | Recommendation | Strength of Recommendation/ Certainty/Quality of Evidence |
|---|---|---|
| Summary of Consensus Statements on the Diagnosis and Management of COPD in the Philippines (updated 2021)[215] | Recommend that the first-line medications to be used for COPDIAE in the primary care facility are:<br>• Inhaled SABA+SAMA (via nebulizer or metered dose inhaler). The use of nebulization is not recommended | Not available |

| | | |
|---|---|---|
| | when COVID-19 infection is considered.<br>● Systemic corticosteroids (oral or intravenous), for moderate to severe COPD<br>● Antibiotics (oral or intravenous), for moderate to severe COPD. | |
| Global Initiative for Chronic Obstructive Lung Disease (updated 2023)[216] | Recommend short-acting beta 2 agonists, with or without short-acting anticholinergics as the initial bronchodilators to treat an acute exacerbation | Evidence C[a] |

a There is insufficient evidence to recommend for or against the inclusion of the condition in a periodic health examination, but recommendations may be made on other grounds.

## Ongoing Trials and Research Gaps

No ongoing trials to date were retrieved through systematic search looking for the superiority of one intervention over the other looking at efficacy and safety of either medication.

## Additional Considerations for Evidence to Decision Phase

**Cost**

A study made a post hoc pharmacoeconomic evaluation comparing SABA (albuterol) alone versus SAMA (ipratropium) alone versus SABA + SAMA (albuterol + ipratropium) among stable COPD patients.[217] Outcomes, health-care resource consumption, and costs were compared for the three treatment groups over the 85-day study period with a total of 1,067 patients enrolled. Based on the study, patients receiving ipratropium and ipratropium plus albuterol experienced significantly fewer COPD exacerbations and patient-days of exacerbation compared to albuterol only treatment group with increased frequency of exacerbations observed in the albuterol group was associated with a significant increase in the number of patient hospital days and antibiotic and corticosteroid use. As a result, the total cost of treatment over the study period was significantly less for ipratropium (USD 156 per patient) and ipratropium plus albuterol ($197 per patient) than for albuterol (USD 269 per patient). Increased cost-effectiveness, defined as total estimated treatment cost per mean change in FEV1AUC0–4, was observed in both treatment arms containing ipratropium.

No studies to date have evaluated the cost of treating an exacerbation comparing SABA+SAMA versus SABA. Based on the 2023 online data, SABA+SAMA is priced at Php 33.75 to Php 40.75 while SABA is priced at Php 29.25 to Php 43.25.

Patient's Values and Preference, Equity, Acceptability, and Feasibility

There were no studies retrieved evaluating COPD patient's values and preferences on using SABA+SAMA compared to SABA monotherapy. At present both medications in nebule form are readily available in pharmacies and drugstores.

**Clinical Question No. 7.** Among COPD patients in exacerbation, how effective and safe are steroids in improving symptoms and preventing recurrence, hospitalization and death?

| *Recommendation No. 7* |
| --- |
| **Among COPD patients in exacerbation with worsening symptoms and not responding to bronchodilators, we recommend the use of short course* oral steroids in the primary care setting** *(Low certainty of evidence, Strong recommendation)* |

**The duration of short course is 5-10 days. Referral to higher level of care may be done upon discretion of the primary care physician at any time for non-responders or for those with incomplete response.*

## Key Findings

- Three RCTs were included in the final evidence review comparing steroids versus placebo among COPD patients with acute exacerbation in the primary care setting. Pooled data and analysis indicate that the use of oral steroids on COPD exacerbation improves dyspnea and lung function (FEV1) and reduces COPD-related hospitalization. Significantly higher rates of increase in appetite, weight gain and insomnia was demonstrated with the use of steroids compared with placebo.

- A systematic review and meta-analysis with eight RCTs comparing systemic steroids against placebo was adopted as direct evidence for the adverse events. Over-all adverse events were more than twice likely to develop in systemic steroid group compared to placebo. Hyperglycemia was also more likely to develop in systemic steroid group compared to placebo.

- The NICE 2019 Guidelines for the management of COPD was adopted as direct evidence for the duration and dose of systemic steroids in COPD exacerbation. The guideline committee has recommended a shorter course of systemic steroids over a longer course based on evidence from 5 RCTs.

- The overall certainty of evidence was low for the efficacy outcomes, high for safety outcomes, and very low for the duration of treatment outcome.

## Consensus Issues

The panel recognized that the use of steroids is one of the effective interventions, along with short acting inhaled bronchodilators, in the exacerbation of COPD. They also agreed that it must be given for patients with indications and for short duration to avoid overuse and risk of adverse effects.

They agreed with the available evidence that the use of oral steroids in COPD exacerbations in the primary care setting will be employed when there is sustained or worsening of symptoms despite the use or increased use of short acting inhaled bronchodilators. This was consistent with patient's as well as the primary care physicians' experience. In the outpatient or primary care setting, oral or nebulized steroids are usually used only after patients do not show improvement after providing short acting inhaled bronchodilators.

Healthcare providers should be aware of the risks (i.e., hyperglycemia, hypertension, pneumonia, gastrointestinal bleeding, dyspepsia, depression, anxiety, bacterial infections among hospitalized patients) associated with the use of steroids. International guidelines recommended using steroids for a shorter period of time in order to minimize the risks associated with the use of steroids. The panel agreed that short course duration of 5-10 days will provide primary care physicians safe and sufficient period to observe patient's response.

Oral steroids are available, accessible, and affordable in most local pharmacies. The primary care physicians are guided by the indications and recommended duration of treatment. Referral to higher level of care may be done upon discretion of the primary care physician at any time for non-responders or for those with incomplete response.

## Review Methods

PubMed (MEDLINE), Cochrane Library and Clinical Trials.gov. database and other sources were searched from inception to 05 February 2023. The search result was intersected with the intervention terms and filtered by study design. The search terms include the following: "Pulmonary Disease, Chronic Obstructive [MESH}", "Acute Exacerbation of Chronic Obstructive Pulmonary Disease", "steroid," "hydrocortisone," "prednisone," "prednisolone," "methylprednisolone," "dexamethasone," "Fluticasone," "Budesonide," "Mometasone," and "Beclomethasone." Clinical practice guidelines, systematic reviews and meta-analyses, and randomized controlled trials were included. Observational studies were also screened for the safety outcome.

Populations included were patients in acute exacerbation as defined in the studies who were managed in the primary care setting. Interventions were steroids focusing on the following types, regardless of dose and duration of therapy: hydrocortisone, prednisone, prednisolone, methylprednisolone, dexamethasone, fluticasone, budesonide, mometasone, and beclomethasone. Comparator was usual care, except steroid provision, as defined in the studies. Critical outcomes included: symptom improvement, COPD-related quality of life, COPD-related hospitalization, all-cause mortality and adverse events. Important outcomes were included such as lung function, treatment failure, exercise capacity, functional capacity, length of recovery, and COPD related mortality. The outcome of duration of steroid use was also sought. Studies were excluded from the analysis if subjects have other concomitant respiratory diseases like asthma, stable COPD, admitted, or on mechanical ventilation or non-invasive ventilation.

The risks of bias were assessed as follows: Cochrane Risk of Bias Tool v1 for RCTs, AMSTAR-2 for systematic review and meta analysis, and AGREE II tool for clinical practice guidelines.

## Evidence

**Symptom Improvement**

Results from one study showed that used the visual analogue scale (VAS) to monitor for daily change in dyspnea during the 10 day period showed that though the slope of improvement in dyspnea did not differ between the steroid group and placebo group at the end of therapy, there was a trend towards a more rapid improvement in the steroid group (3.6/d 95% CI 0.8 to 6.3) compared to placebo (2.2/d 95% CI -0.2 to 4.6) from baseline score. On the other hand, result from another study that used the traditional TDI showed a significant improvement in dyspnea after 10 days of steroid therapy compared to placebo (MD: 1.88 95% CI 0.23, 3.53 p = 0.03).[218, 219]

**COPD-related Quality of Life**

Results from one study that measured the COPD related quality of life using the CRDQ showed that though the improvement in dyspnea domain of the questionnaire was significantly higher in patients given steroids (MD: 0.72 95% CI 0.18, 1.26 p= 0.009), the overall CRQ score was not significantly higher in the steroid group compared to placebo (MD 0.38; 95% CI -0.09, 0.85 p = 0.11). Another study that used the Clinical COPD Questionnaire, did not directly compare the results between the steroid vs placebo group, however, their scores did not differ from each other (0.4 points vs 0.5 points). Both groups have improvement in quality of life that was clinically significant to the patients (MCID = 0.4).[219, 220]

**COPD-related Hospitalization**

Based on the pooled analysis of the two studies, there was a trend towards decrease in COPD related hospitalization to as good as when steroid was used as compared to placebo (RR 0.48 95% CI 0.22, 1.04 p = 0.06).[218, 219]

**All-cause Mortality**

Only one study evaluated the effect of steroids on patients' mortality.[219] The administration of steroids for COPD exacerbation did not decrease the all-cause mortality (RR 2.03; 95% CI 0.19, 21.87 p = 0.56). There was a very low number of events reported per treatment arm.

**Treatment Failure and Relapse**

Three RCTs identified treatment failure and relapse among the subjects who were randomized.[218-220] Thompson 1996 described treatment failure as hospitalization for deteriorating respiratory status or lack of improvement of subjective dyspnea requiring treatment with open label prednisone within 14 days after starting the study medication. Aaron 2003 defined relapse as an unscheduled visit to a physician's office or a return to the emergency department because of worsening dyspnea within 30 days after randomization. Though the study of Bathoorn 2008 defined treatment failure as use of systemic steroids within 2 weeks from randomization and relapse if systemic steroids were given from 2 weeks to 3 months after randomization, the study authors combined both events. Pooled analysis of the three studies showed that the risk of treatment failure or relapse was not significantly higher in patients who received steroids compared to placebo (RR 0.68; 95% CI 0.21, 2.18 p = 0.52). However, there was substantial heterogeneity noted in the results (I2:70%). In the study of Thompson there was no treatment failure or relapse in the steroid group. Two studies reported favorable outcomes for the steroid group, while one study favored the placebo group.

**Lung Function**

Three studies have measured lung function (FEV1) as an outcome.[218-220] Two studies have used the %change in FEV1 to measure the improvement in lung function, Thompson reported that there was a faster recovery of FEV1 based on the slope of change (Pred = 0.05 L/d 95% CI 0.02 to 0.09 vs Plac = 0.00 L/d 95% CI -0.01 to 0.02) and FEV1 improved after 10 days of steroid administration compared to placebo (36.6% vs 1.0% p = 0.01) and while Aaron also showed a significant increase in FEV1 in the steroid group (MD 19.00; 95% CI 7.08, 30.92 p = 0.002).[218, 219] The latest study of Bathoorn showed no significant improvement in the FEV1 after steroid administration (MD 27, p =0.71).[220]

**COPD-related mortality**

One study that reported the outcome of COPD-related mortality which was noted to be inconclusive if in favor or the placebo or the steroid (RR 1.01 95% CI 0.06, 15.90 p = 0.99).[219]

There were no studies that reported the following important outcomes: exercise capacity, functional capacity, and length of recovery. Table 23 below summarizes the efficacy outcomes

Table 23. Summary of the Efficacy Outcomes of Steroids

| Critical Outcomes | No of Studies (n) | Effect Size | 95% CI | Interpretation | Certainty of Evidence |
|---|---|---|---|---|---|
| Symptom Improvement* | 2 RCT's (n=174) | In the study of Thompson, which used the VAS to assess for dyspnea, there was a trend towards a more rapid improvement in the steroid group (3.6/d 95% CI 0.8 to 6.3) compared to placebo (2.2/d 95% CI -0.2 to 4.6) p=0.36. Aaron showed significant improvement in dyspnea, based on transitional dyspnea index (TDI), after 10 days of steroid therapy compared to placebo (MD: 1.88 95% CI 0.23, 3.53 p = 0.03). | | Benefit | Moderate |
| COPD-related Quality of Life** | 2 RCT (n=177) | In the study of Aaron, the overall CRQ score was not significantly higher in the steroid group compared to placebo (MD 0.38 95% | | Inconclusive | Moderate |

| | | | | | |
|---|---|---|---|---|---|
| | | CI -0.09, 0.85 p = 0.11). Bathoorn did not directly compare the results between the steroid vs placebo group, however their scores did not differ from each other (0.4 points vs 0.5 points, MCID: 0.4) | | | |
| COPD-related Hospitalization | 2 RCT's (n= 174) | RR 0.48 | 0.23 to 1.04 | Inconclusive (trend towards benefit to equivalent) | Moderate[a,d] |
| All-cause Mortality | 1 RCT (n=147) | RR 2.03 | 0.19 to 21.87 | Inconclusive | Moderate[a,d] |
| Important Outcomes | | | | | |
| Treatment Failure | 3 RCT's (n=204) | RR: 0.69 | 0.22 to 2.19 | Inconclusive | Low[a,c,d] |
| COPD-related mortality | 1 RCT (n=147) | RR 1.01 | 0.06 to 15.90 | Inconclusive | Moderate[d] |
| Lung Function | 3 RCT's (n=204) | Thompson reported that there was a faster recovery of FEV1 based on the slope of change (Pred = 0.05 L/d 95% CI 0.02 to 0.09 vs Plac = 0.00 L/d 95% CI -0.01 to 0.02 p= 0.006) and FEV1 improved after 10 days of steroid administration compared to placebo (36.6% vs 1.0% p = 0.01) and while Aaron also showed a significant increase in FEV1 in the steroid group (MD 19.00 95% CI 7.08, 30.92 p = 0.002). The latest study of Bathoorn showed no significant improvement in the FEV1 after steroid administration (MD: 27, p =0.71) | | Benefit | Moderate[a,e] |

a. low number of participants
b. CI of the largest study showed no effect/difference
c. Presence of substantial heterogeneity (I2>70%)
d. wide confidence interval

e. 2 studies included in the analysis showed significant improvement in FEV1 compared to placebo while in the study by Bathoorn the FEV1 did not improve significantly compared to placebo
*symptom improvement: visual analogue scale [5] and transitional dyspnea scale
**Quality of life: Chronic Respiratory Disease Questionnaire (CRQ), Clinical COPD Questionnaire

Safety
No serious adverse events were reported among the 3 studies included for the efficacy outcome.[218-220] Aaron listed the non-serious adverse events of steroids vs placebo with significantly higher rates of increase in appetite (46% vs 22% p = 0.003), weight gain (13% vs 1% p = 0.01), and insomnia (48% vs 21% p= 0.001). Though it did not reach statistical significance there was a trend towards a higher occurrence of depression (19% vs 10% p = 0.14) and anxiety (27% vs 19% p = 0.28).

The Cochrane systematic review done last 2014 comparing systemic steroids vs placebo for COPD exacerbation showed that patients given systemic steroids were more than twice more likely to develop adverse drug reactions compared to placebo in 8 studies (n = 736; OR 2.33; 95% CI 1.59 to 3.43).[221] Hyperglycemia was also more likely to develop among patients who received systemic steroids compared to placebo treatment (n=804; OR 2.79; 95% CI 1.86 to 4.19; p value = 0.25; I2 = 24%). The authors have graded these outcomes as high. Hypertension (n = 274; OR 1.20; 95% CI 0.44 to 3.25; Chi2 = 2.06; df = 1; p value = 0.15; I2 =51%) and gastrointestinal bleeding (n = 300; OR 0.93; 95% CI 0.12 to 6.91) did not differ between systemic steroids and placebo. Psychiatric adverse events were twice likely to occur in the systemic steroid group compared to placebo, though this was statistically non-significant. Table 24 below summarizes the safety outcomes.

Table 24. Summary of Safety Outcomes of Steroids

| Critical Outcomes | No of Studies (n) | Effect Size | 95% CI | Interpretation | Certainty of Evidence |
|---|---|---|---|---|---|
| Total Adverse Events (Cochrane Meta-analysis | 8 RCT (n=736) | OR 2.33 | 1.59 to 3.43 | Harm | High |
| Hyperglycemia | 6 RCT (n=804) | OR 2.79 | 1.86 to 4.19 | Harm | High |

<u>Duration of Treatment</u>
The NICE 2019 update on systemic steroids for COPD exacerbation included 5 RCTs (N = 523) for systemic steroid duration with the following outcomes: treatment failure, relapse after treatment, adverse drug effects, mortality, cardiac complications, lung function (FEV1), length of hospital stay, arterial blood gas, breathlessness, quality of life, resource use and costs.[222] Based on available evidence, the guideline committee agreed to recommend a short course of 5 days of 30 mg prednisolone.

The certainty of evidence for the efficacy outcome was downgraded to low due to a wide confidence interval and the presence of substantial heterogeneity in the treatment failure/relapse outcome. For the safety outcome, the certainty of evidence was rated as high-quality based on the meta-analysis done by Cochrane

reviews and concluded the results would unlikely be changed by future research. These effects are expected adverse effects of steroids and less likely to persist after treatment. For the duration of treatment outcome, the certainty of evidence was downgraded to very low due to a significant heterogeneity and imprecision.

## Recommendations from Other Groups

| Group | Recommendation | Strength of Recommendation and Certainty of Evidence |
|---|---|---|
| Summary of Consensus Statements on the Diagnosis and Management of COPD in the Philippines (2021)[223] | Recommend that one of the first-line medications to be used for ECOPD in the primary care facility is systemic corticosteroids (oral or intravenous), for moderate to severe COPD. | Not available |
| Global Initiative for Chronic Obstructive Lung Disease (GOLD 2023)[224] | Systemic steroids can improve lung function (FEV1), oxygenation and shorten recovery time and hospitalization duration. (Evidence mostly hospital-based) | Evidence A* |
| Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline (2017)[225] | For ambulatory patients with an exacerbation of COPD, suggested a short course (≤14 days) of oral corticosteroids | Conditional/Very Low** |
| Chronic obstructive pulmonary disease in over 16s: diagnosis and management. London: National Institute for Health and Care Excellence (NICE 2018)[222] | In the absence of significant contraindications, consider oral corticosteroids for people in the community who have an exacerbation with a significant increase in breathlessness that interferes with daily activities. | Not available |

*Evidence A: Evidence may be from endpoints of well-designed RCT's that provide consistent findings in the population for which the recommendation is made without any important limitations OR requires high quality evidence from ≥ clinical trials involving a substantial number of subjects, or a single high quality RCT involving substantial numbers of patients without any bias
**Conditional: panel was uncertain that the desirable consequences of the intervention outweighed the undesirable consequences, well-informed patients may make different choices regarding whether to have or not have the intervention
**very low certainty of evidence based on GRADE table

## Ongoing Trials and Research Gaps

There were no published reports regarding steroids vs placebo, either in admitted or outpatient settings, since 2008. There are also no ongoing trials comparing steroids vs placebo for COPD exacerbation.

## Additional Considerations for Evidence to Decision Phase

**Cost**

Based on the 2022 Department of Health drug price reference index prednisone 20 mg/tablet is P3.15* while the price range in geographically disadvantaged areas (GIDA) is P 2.86-6.50* [8]. The total cost of therapy for COPD exacerbation in the primary care setting based on the included studies will be from P28.6 to P65.00.* This is below the country's lowest the Philippines' lowest daily wage at P329.00.[226, 227]

**Prices were taken in the aforementioned reference as of 04 February 2023*

**Patient's Values and Preference, Equity, Acceptability, and Feasibility**

No studies found regarding patient's values and preference, equity, acceptability and feasibility of use of oral steroids on COPD exacerbation.

**Clinical Question No. 8.** Among COPD patients in exacerbation, how effective and safe are initiation of antibiotics in improving symptoms and preventing recurrence, hospitalization and death?

| *Recommendation No. 8* |
| --- |
| **Among outpatients with COPD, we recommend initiation of oral antibiotics in the presence of at least two of the following symptoms: increased dyspnea, increased frequency of cough, increased sputum volume or purulence** *(Low certainty of evidence, Strong recommendation)* |

## Key Findings

- Ten RCT investigated the effect of initiation of antibiotics on mortality, symptom improvement, and treatment failure, and the adverse events in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) managed in the outpatient setting.

- Initiation of antibiotics significantly decreased the risk of treatment failure. However, its effect on the quality of life, symptom severity, lung function, recovery time, and in all-cause mortality as well as adverse events were inconclusive.

- No outcomes on hospitalization, exercise capacity and functional capacity were reported.

- The overall certainty of evidence was low due to risk of bias involving selection bias, random sequence generation, allocation concealment, and blinding.

## Consensus Issues

The panel reached a consensus on the initiation of oral antibiotics for COPD exacerbations in the outpatient or primary care setting, but with the condition that specific criteria for bacterial coinfection are met. Primary care physicians will rely on Anthonisen's criteria, which include increased dyspnea, increased cough frequency, and increased sputum volume or purulence. Patients who meet at least two out of the three criteria are most likely to have bacterial co-infection. The decision to follow Anthonisen's criteria for antibiotic initiation aligns with both the evidence presented and the panelists' collective experience, including the physicians' current practices and patients' experiences. In addition, the choice of antibiotics will be based on local epidemiology and susceptibility patterns.

Oral antibiotics offer the advantage of easy accessibility, with affordable options readily available in local pharmacies. However, it's essential to consider that their use does incur additional costs for the patients. The cost of antibiotic treatment can vary significantly, ranging from Php 112.50 to Php 1,055.00, depending on the specific type of antibiotic prescribed and the duration of treatment required.

As healthcare providers, it is crucial to be mindful of the financial implications on patients when recommending antibiotic therapy. While antibiotics are essential

for treating bacterial infections, their appropriate and judicious use is paramount to prevent unnecessary expenses and reduce the risk of antibiotic resistance.

Therefore, it is prudent to weigh the potential benefits and risks of antibiotic treatment for each individual case. Considering the patient's medical condition, severity of the illness, and any available alternatives can help optimize treatment decisions while keeping the patient's financial well-being in mind. Additionally, patient education on the proper use of antibiotics and the importance of completing the prescribed course can contribute to better treatment outcomes and overall cost-effectiveness.

Despite the low certainty of evidence, the use of antibiotics for managing COPD exacerbations is considered an acceptable, beneficial, and feasible option. However, it is crucial for physicians to practice antimicrobial stewardship diligently. This involves educating patients about the importance of adhering to prescribed antibiotics and the proper duration of treatment to prevent overuse and misuse of these medications, which could lead to antimicrobial resistance.

Antibiotics play a vital role in treating bacterial infections in COPD exacerbations, but their appropriate use is paramount to maintain their effectiveness and prevent the development of resistant bacteria. Physicians must exercise caution in prescribing antibiotics only when necessary, based on the patient's clinical presentation and the likelihood of a bacterial infection. To support antimicrobial stewardship, healthcare providers should communicate clearly with patients about the rationale behind antibiotic use, potential side effects, and the importance of completing the full course of treatment. Patient education can empower individuals to take an active role in their health and contribute to better treatment outcomes.

By adopting responsible and evidence-based practices, healthcare professionals can effectively manage COPD exacerbations with antibiotics while safeguarding the long-term efficacy of these essential medications. This approach not only benefits individual patients but also helps preserve the effectiveness of antibiotics for future generations.

## Review Methods

A systematic search was done until February 4, 2023, using MEDLINE and the Cochrane Central Register of Controlled Trials. Combinations of free-text and MeSH terms including "COPD," “exacerbation,” and “antibiotic” were used. Citation searching of studies found in the database search was done to increase yield. Ongoing clinical trials were searched in ClinicalTrials.gov and the Cochrane Central Register of Controlled Trials.

Only RCTs and systematic reviews and meta-analyses that compared initiation of antibiotics versus placebo among COPD patients in acute exacerbation that were managed in the outpatient setting were included. These studies reported outcomes of interest which include all-cause mortality, COPD-related hospitalization, treatment failure, recovery time, symptom severity, lung function, quality of life, exercise capacity, functional capacity, and adverse events. No geographic restrictions were applied. Studies that were not original research, not

published in English, conference abstracts, and studies performed in vitro were excluded.

Included RCTs were appraised for risk of bias using the Cochrane Risk of Bias criteria (RoB version 1). Meta-analyses and related forest plots were generated using Review Manager 5.4. Certainty of evidence was determined using the GRADE Evidence Profile (GRADEPro).

## Evidence

**All-cause mortality**

One RCT involving use of doxycycline versus placebo reported a low proportion of deaths (10% for doxycycline vs 7% for placebo). However, it was inconclusive whether doxycycline increases or decreases the risk of all-cause mortality when compared to placebo (RR 1.26; 95% CI 0.51 - 3.10).[228]

**Recovery Time**

One study of (n = 173) reported a mean decrease of the duration of acute exacerbation of 1.40 days (95% CI 0.12-2.68) in patients taking amoxicillin, doxycycline, or TMP-SMX.[229] A second study of 88 patients reported a mean decrease of 5.18 days (95% CI 4.21-6.15) in patients taking oxytetracycline.[230] Another study (n = 62) reported a shorter mean exacerbation duration for patients taking oxytetracycline (7.5 vs.13.5 days) but did not report on statistical significance.[231] On the other hand, one study of (n = 35) reported no significant difference in the time to resolution of acute exacerbation in patients taking amoxicillin-clavulanic acid (crude HR 1.12, 95% CI 0.54-2.32).[232]

**Treatment failure**

Pooled analysis of nine RCTs suggests that antibiotics significantly decreased the risk of treatment failure compared to placebo (RR 0.69; 95% CI 0.53-0.90, I2=31%;).[229, 230, 232-238] Treatment failure was defined non-resolution of symptoms, progression of symptoms, or necessitating other interventions such as provision of other medications or hospitalization during the treatment or observation study period which varies across studies from 5 to 35 days .

Further investigating the outcome in the placebo group, more than 50% (range 52.5% - 90.5%) recovered even without antibiotics therapy in these COPD patients fulfilling the criteria for COPD exacerbation

**Lung function**

Four RCTs measured changes in lung function. One study reported a significantly faster rate of recovery of peak expiratory flow rate (PEFR) for antibiotics compared to placebo ($p < 0.02$, mean and range not stated)[229]; another study of 100 patients reports that patients treated with ciprofloxacin or amoxicillin took significantly less time to recover PEFR than patients taking placebo (antibiotic 15 ± 3 days, placebo 18 ± 5 days, $p < 0.001$).[234] One study showed no significant difference in the daily improvement of PEFR percentage predicted values between antibiotic and placebo groups (mean daily increase: amoxicillin 0.58%, 95% CI 0.27-0.89; TMP-SMX 0.78%, 95% CI 0.22-1.34; placebo 0.34%, 95% CI 0.00-0.73).[237] Another study reported no significant difference in the change in forced expiratory volume in the first second (FEV1) post-bronchodilation from days 0 to 28 between

amoxicillin-clavulanic acid and placebo groups (day 28 FEV1 0.02 vs. 0.07 L, p = 0.51; day 28 FEV1% predicted 1.6 vs. 2.4, p = 0.80).[232] One study reported no significant difference in the improvement of FEV1 (p = 0.508), forced vital capacity (FVC; p = 0.259), and FEV1/FVC ratio (p = 0.444) between antibiotic and placebo groups.[234]

**Quality of Life**

One RCT(n= 35) involving amoxicillin-clavulanic acid vs placebo, reported small change (minimal clinically important difference, MCID, of 0.5) on dyspnea and emotional domains for the two groups, and moderate change (MCID of 1) for the fatigue domain, in the chronic respiratory questionnaire (CRQ) scores measured at baseline and after 28 days.[232] However, no significant difference was observed between the mean change of the two groups (MD 0.00, 95% CI -1.79 - 1.79). Another RCT (n= 301) reported no significant difference in quality of life between patients treated with doxycycline and placebo using the SGRQ measured at baseline and after 2 years.[238]

**Symptom Severity**

Three RCTs directly compared symptom severity scores between outpatients taking antibiotics and those taking placebo. One study reported no significant difference in daily median score between amoxicillin-clavulanic acid and placebo (antibiotic 5.7, 95% CI 4.3-7.8; placebo 5.4, 95% CI 2.4-8.4; p = 0.70).[213] A second study using a symptom score based on physician assessment per clinic visit reported no significant difference between amoxicillin and placebo (p > 0.40).[235] A third study utilized a four-point symptom severity score taken at the start of exacerbation and after 14 days. It showed significant decrease in symptom severity in all three groups (mean change amoxicillin -0.05 95% CI -0.07 to -0.02; co-trimoxazole -0.06 95% CI -0.08 to -0.04; placebo -0.06 -0.08 to -0.04; (p<0.001). No direct comparisons were made between any of the three groups.[237]

**Safety**

Pooled analysis of three RCTs suggests no significant difference for the overall incidence of adverse events between antibiotics and placebo within 21 days after exacerbation (RR 1.28; 95% CI 0.79-2.07, I2 = 64%).[235-238] The antibiotics tested in these studies were amoxicillin, amoxicillin-clavulanic acid, and doxycycline. Most adverse effects were mild and sporadic, with a reported incidence range of 14.6-31.3%. One RCT reported no significant difference in the incidence of serious adverse events between doxycycline and placebo within 2 years after the first exacerbation (OR 0.98; 95% CI 0.59-1.61).[238] Table 25 below summarizes the critical outcomes for this study.

Table 25. Summary of the Critical Outcomes of Antibiotic versus No Antibiotic Use

| CRITICAL OUTCOMES | BASIS | EFFECT SIZE | 95% CI | INTERPRETATION | CERTAINTY OF EVIDENCE |
|---|---|---|---|---|---|
| All-cause mortality | 1 RCT (n=301) | RR 1.26 | 0.51, 3.10 | Inconclusive | Low |
| Recovery time (duration of exacerbatio | 4 RCTs (n=358) | Two studies (total n=235) reported a significantly shorter duration of acute | | Equivocal | Low |

| | | | | | |
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| n) | | exacerbation in the antibiotic group. One study (n=88) reported mean decrease in duration without reporting significance. One study (n=35) reported no significant difference. | | | |
| Treatment failure | 9 RCT (n=1,332) | RR 0.69 | 0.53, 0.90 | Benefit | Moderate |

Overall certainty of evidence was low. Certainty of evidence was moderate for quality of life, symptom severity, treatment failure, and serious adverse events, and low for all-cause mortality, recovery time, and overall adverse events

## Recommendations from Other Groups

| Group | Recommendation | Strength of recommendation and certainty of evidence |
|---|---|---|
| American Association of Family Physicians (January 2021)[239] | The AAFP recommends that clinicians prescribe systemic antibiotics for adults with acute exacerbations of COPD to improve clinical cure and reduce clinical failure. Choice of antibiotic should be based on local resistance patterns, affordability, and patient history and preferences because there is insufficient evidence to support a preferential recommendation. | Weak recommendation, moderate quality of evidence |
| ALAT-2014[240] | The use of antibiotics in COPD-E requiring hospitalization is justified, particularly in patients admitted to the ICU. In mild to moderate COPD-E, antibiotic treatment should be considered in patients with purulent sputum and/or high CPR levels | Severe to very severe exacerbations: strong recommendation, high quality of evidence<br>Mild to moderate exacerbations: weak recommendation, high quality of evidence |

| | | |
|---|---|---|
| COPD-X Australian Guidelines (October 2022)[241] | Exacerbations with clinical features of infection (increased volume and change in colour of sputum and/or fever) benefit from antibiotic therapy. First line antibiotics are amoxicillin or doxycycline for 5 days. | Strong recommendation, Level of Evidence I |
| European Respiratory Society/European Society for Clinical Microbiology and Infectious Diseases (May 2011)[242] | Antibiotics should be given in hospitalized patients with the following:<br>1. Patients with all three of the following symptoms: increased dyspnoea, sputum volume and sputum purulence (a type I Anthonisen exacerbation)<br>2. Patients with only two of the above three symptoms (a type II Anthonisen exacerbation) when increased purulence of sputum is one of the two cardinal symptoms<br>3. Patients with a severe exacerbation that requires invasive or non-invasive mechanical ventilation<br>4 Antibiotics are generally not recommended in Anthonisen type II without purulence and type III patients (one or less of the above symptoms). | Level of evidence: A2 |
| People's Republic of China (April 2014)[243] | There is evidence supporting the use of antibiotics in AECOPD when patients have:<br>1) three cardinal symptoms – increase in dyspnea, sputum volume, and sputum purulence | #1: Evidence B (RCTs, limited body of evidence)<br>#2: Evidence C (Non-randomized trials/observational studies)<br>#3: Evidence B (RCTs, limited body of evidence) |

| | | |
|---|---|---|
| | (Evidence B);<br>2) two of the cardinal symptoms, if increased purulence of sputum is one of symptoms (Evidence C); or<br>3) a severe AECOPD attack which requires mechanical ventilation (noninvasive or invasive) (Evidence B).<br>Antibiotics are not recommended in those with two symptoms but no sputum purulence or with one symptom alone. | |
| Global Initiative for Chronic Obstructive Lung Disease (Nov 2021)[244] | Antibiotics should be given to patients with exacerbations of COPD who have three cardinal symptoms: increase in dyspnea, sputum volume, and sputum purulence; have two of the cardinal symptoms; if increased purulence of sputum is one of the two symptoms; or require mechanical ventilation (invasive or noninvasive). The recommended length of antibiotic therapy is 5-7 days. The choice of the antibiotic should be based on the local bacterial resistance pattern. | Evidence B (RCTs, limited body of data) |
| European Respiratory Society/American Thoracic Society (2017)[244] | For ambulatory patients with an exacerbation of COPD, we suggest the administration of antibiotics. | Conditional recommendation, moderate quality of evidence |
| Indian Chest Society/National College of Chest Physicians (September 2013)[246] | 1. Antibiotics should be prescribed for all exacerbations of COPD.<br>2. The choice of antibiotics should be guided by local flora and | #1-2, 4-6: Strong recommendation, moderate quality of evidence<br>#3: Strong recommendation, high |

| | | |
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| | sensitivity pattern.<br>3. Fluoroquinolones should not be used routinely in treating AECOPD.<br>4. Patients with AECOPD being managed in the outpatient setting may be treated with first line antibiotics.<br>5. Hospitalized patients or those requiring mechanical ventilation (noninvasive/invasive) should be treated with second line drugs.<br>6. The duration of therapy should be 5-7 days. | quality of evidence |
| National Institute for Health and Care Excellence (December 2018)[247] | Consider an antibiotic for people with an acute exacerbation of COPD, but only after taking into account:<br>• the severity of symptoms, particularly sputum colour changes and increases in volume or thickness beyond the person's normal day-to-day variation<br>• whether they may need to go into hospital for treatment<br>• previous exacerbation and hospital admission history, and the risk of developing complications<br>• previous sputum culture and susceptibility results<br>• the risk of antimicrobial resistance with repeated courses of antibiotics.<br>First-choice oral antibiotics are amoxicillin 500 mg three times a day for 5 days, doxycycline 200 mg on first day then 100 mg once a day for 5-day total course, and clarithromycin 500 mg | None stated |

| | | |
|---|---|---|
| | twice a day for 5 days | |
| Philippine College of Chest Physicians (2021)[248] | Antibiotics should be given as first-line medication for moderate to severe COPD exacerbations in the outpatient setting.<br>Antibiotics should be given to ECOPD patients who have increased sputum purulence as a cardinal symptom, accompanied by either increase in sputum volume or increase in dyspnea. | Not stated |
| South African Thoracic Society (October 2019)[249] | Antibiotics should be prescribed when there is evidence of a severe exacerbation (as evidenced by the 3 cardinal symptoms of increased sputum volume, sputum purulence and increased dyspnoea) or in those who require ventilation.<br>The oral route of administration is preferred except in severe illness. The duration of treatment should be 5–7 days. | Indications for use: Evidence B (RCTs, limited body of evidence)<br><br>Route of administration: Evidence A (RCTs, rich body of evidence) |
| Spanish COPD Guidelines (May 2021)[250] | 1. Antibiotics are suggested in patients with an outpatient COPD exacerbation.<br>2. Antibiotics are suggested for patients with COPD exacerbation who require hospital admission.<br>3. Antibiotics are recommended for all patients who have COPD exacerbation and require ICU admission. | #1-2: Weak recommendation, low quality of evidence<br>#3: Strong recommendation, moderate quality of evidence |

| | | |
|---|---|---|
| Taiwanese Ministry of Health and Welfare (June 2021)[245] | When patients develop an increase of thick sputum and concomitant breathlessness or an increase in sputum, the use of antibiotics is recommended. | Strong recommendation, low quality of evidence |

## Ongoing Trials and Research Gaps

There was one ongoing clinical trial of 268 patients in Japan with an estimated completion date of June 2023.[309] Additional research is needed to further explore the efficacy of antibiotics in preventing mortality, hospitalization, and quality of life among outpatients with exacerbation, as well as to further explore adverse effects compared to placebo. More placebo-controlled studies may be done to determine whether we can properly define subgroups of COPD outpatients in which antibiotics indeed are of additional value and in whom there is no use at all.

## Additional Considerations for Evidence to Decision Phase

**Cost**

A cost-effectiveness study of an RCT (n= 887) reported that treatment with doxycycline added to prednisolone is not cost-effective compared to prednisolone plus placebo over a 2-year follow-up period.[251] The total cost and quality-adjusted life years (QALYs) were higher but not significantly different for the doxycycline group compared to the control group, and any extra QALY gained or exacerbation prevented with the antibiotic came at a high cost compared to placebo.

On the other hand, one retrospective cohort study (n = 45,375) found that the use of antibiotics for COPD exacerbations resulted in significantly lower costs and significantly fewer doctor visits, referrals, hospitalizations, prescriptions, and infections per patient over 12 months.[252]

In the 2018 National Antibiotics Guideline, oral antibiotics of choice for mild to moderate acute COPD exacerbations in the Philippines are amoxicillin 500 mg three times a day, doxycycline 100 mg twice a day, and cefuroxime 500 mg twice a day for 5-10 days.[253] Current recommended prices for a complete course of these drugs are found in Table 26 below.

Table 26. Costs for one course of antibiotics for the treatment of bacterial co-infection in COPD exacerbation in the outpatient setting

| Intervention | Cost | |
|---|---|---|
| | Philippine Drug Price Reference Index 2021[254] | Generics standard retail price (SRP) |
| Amoxicillin 500 mg TID x 5-10 days | Php 24.75-49.50 | Php 112.50-225.00 |
| Doxycycline 100 mg BID x 5-10 days | Php 43.50-87.00 | Php 450.00-900.00 |
| Cefuroxime 500 mg BID x 5-10 days | Php 108.60-217.20 | Php 527.50-1055.00 |

**Patient's Values and Preference, Equity, Acceptability, and Feasibility**

No studies were found on patient's values and preference, equity, acceptability, and feasibility.

## DOMAIN 4. REFERRAL SYSTEMS, NON PHARMACOLOGIC MANAGEMENT, AND PALLIATIVE CARE

**Clinical Question No. 9.** Among COPD patients managed by primary care physicians, what are the conditions that warrant referral to specialists to improve their symptoms and quality of life and to prevent COPD related morbidity and mortality?

*Recommendation No. 9A*

**Among COPD patients managed at the primary level, we recommend referral of any of the following conditions that are associated with higher risk of moderate to severe exacerbation to higher level of care: prior history of exacerbation, presence of comorbidities, and severe or very severe airflow limitation** *(Very low certainty of evidence, Strong recommendation)*

*Recommendation No. 9B*

**Among COPD patients managed at the primary level, we recommend referral of any of the following conditions that are associated with higher risk of mortality to higher level of care: presence of uncontrolled diabetes or cardiovascular disease, previous hospitalization for acute exacerbation within the past year, hospital readmission within 30 days, and use of long-term oxygen therapy** *(Very low certainty of evidence, Strong recommendation)*

### Key Findings

- There was no direct evidence from randomized clinical trials comparing the outcomes, in terms of improvement of symptoms and quality of life (QoL) and prevention of COPD related morbidity and mortality, of referral of certain conditions to specialist care or higher level of care versus usual care among patients with COPD. Indirect evidence was included from two systematic reviews, one on the prognostic factors for moderate to severe exacerbations, and another on the prognostic factors for mortality, among COPD patients.

- Prognostic factors for moderate to severe exacerbations were prior history of exacerbation, presence of comorbidities, severe or very severe airflow limitation, and lack of bronchodilator responsiveness.

- Prognostic factors for mortality were lower hemoglobin, presence of diabetes or cardiovascular disease, previous hospitalization for acute exacerbation, hospital readmission within 30 days, age, male sex, and use of long-term oxygen therapy.

- The overall quality of evidence was very low due to indirectness and serious risk of bias.

## Consensus Issues

The panel agreed that the higher level of care will be defined as health care provided by either an internist or specialist in a Level 2 or 3 hospital. Since direct evidence on the impact of referral to higher level care was lacking, the panel unanimously concluded that patients with a poorer prognosis, as identified in the available indirect evidence, should be prioritized for prompt referral and management.

Referral to a higher level of care is typically warranted due to multiple factors, including but not limited to the following: (1) lack of improvement on initial therapy; (2) more severe cases, such as those necessitating long-term oxygen therapy; and, (3) patients requiring advanced interventions like pulmonary rehabilitation and non-invasive or surgical treatments. The final prognostic factors, agreed upon by the panel, were derived from indirect evidence and thoroughly validated and aligned with the actual practices and experiences of primary care providers, specialists, and patient representatives within the panel.

Step-down referral from specialists or pulmonologists typically occurs when the patient's condition has shown improvement. This step-down referral is a crucial aspect of patient care as it facilitates the transition of the patient's management back to their primary care provider. Proper and clear endorsement to the primary care provider is essential, which should include detailed instructions on how to continue managing the patient's condition effectively. Moreover, the endorsement should also outline specific criteria and guidelines for when the patient might need to be referred back to a specialist in case their condition warrants specialized care again. This collaborative approach between specialists and primary care providers ensures a smooth and coordinated continuum of care for the patient, maximizing their health outcomes and well-being.

However, the implementation of the two-way referral system (i.e., step-up referral from primary care to higher levels of care and step-down referral from higher levels of care to primary care) may encounter variations. Several factors contribute to these variances, including limited local guidelines on patient referral systems, uneven availability of specialists in certain regions, lack of interconnected electronic health records, and variations in patient preferences. Referring patients to higher levels of care may also involve additional costs, including professional fees and diagnostic tests. The financial aspect of such referrals warrants careful consideration to ensure equitable access to healthcare services for all patients.

Addressing these challenges will require a collaborative effort among healthcare stakeholders, policymakers, and providers to establish clear and comprehensive guidelines for patient referrals. It is essential to prioritize patient needs and preferences while balancing the logistical and financial implications of the referral process. By working together, the healthcare community can create a more efficient and patient-centric referral system, thus improving the overall quality of care and health outcomes for all individuals.

Despite the presence of variations and the very low certainty of evidence, the panel strongly emphasizes the high potential benefits of referring patients to higher levels of care. Proper and efficient navigation of patients through the

healthcare system will play a crucial role in ensuring timely recognition of their risks and the prompt implementation of risk reduction strategies.

While acknowledging the uncertainties, referral to higher care can lead to better patient outcomes, especially for those with complex or severe conditions. The higher level of expertise and resources available in specialized care settings can offer more targeted interventions and comprehensive management tailored to each patient's unique needs. Moreover, efficient patient navigation can expedite the process of identifying potential risks and complications, allowing for timely interventions and preventive measures. This approach aims to reduce the burden of disease and enhance the overall quality of life for patients.

It is essential for healthcare providers to collaborate closely and communicate effectively to streamline the referral process and ensure that patients receive the appropriate care in a timely manner. By doing so, we can optimize patient outcomes and work towards achieving a more effective and patient-centered healthcare system.

## Review Methods

A systematic search was done from the date of the last search from inception until February 11, 2023 using Medline, Cochrane Library, Google Scholar with a combined MeSH and free text search using the terms COPD, specialist referral, and pulmonology referral.

Randomized controlled trials and/observational studies when RCTs when the former were not available were included in the review. Relevant clinical practice guidelines and systematic reviews were also included in the search.  Outcomes of interest included QOL and COPD-related morbidity and mortality.

Search for observational studies that identified risk factors associated with poor outcomes for COPD or prognostic factors for moderate or severe COPD exacerbations or for mortality as indirect evidence for a referral to a higher level of care was done in the absence of direct evidence.

## Evidence

### Prognostic factors for moderate to severe COPD exacerbations

A systematic review identified several prognostic factors for moderate to severe exacerbations in adult patients with COPD based on 76 studies (61 observational and 15 RCTs).[255]  Exacerbation history was the strongest predictor of future exacerbations based on 34 studies reporting a significant association. Two or more exacerbations in the previous year or at least one hospitalization for COPD in the previous year predicted future episodes of moderate or severe exacerbations. Even a single moderate exacerbation episode increased the risk of a future exacerbation, with a higher risk with each subsequent exacerbation. A severe exacerbation was also found to increase the risk of subsequent exacerbation and hospitalization.

Thirty-five studies examined the association of comorbidities with the COPD exacerbation. All studies except one (97.1%) reported a positive association between comorbidities and the occurrence of moderate-to-severe exacerbations.

In addition to the presence of any comorbidity, specific comorbidities which increased the risk of moderate-to-severe exacerbations included anxiety and depression, cardiovascular comorbidities, gastroesophageal reflux disease/dyspepsia, and respiratory comorbidities. Comorbidities that were significant risk factors for severe exacerbations included cardiovascular, musculoskeletal, and respiratory comorbidities, diabetes, and malignancy. Overall, the strongest association between comorbidities and COPD readmissions in the emergency department was with cardiovascular disease.

The majority of studies assessing disease severity or bronchodilator reversibility (39/41; 95.1%) showed significant association between risk of future exacerbations and greater disease severity, as assessed by greater lung function impairment (in terms of lower FEV1, FEV1/ forced vital capacity ratio, or forced expiratory flow. [25–75]/forced vital capacity ratio) or more severe Global Initiative for Chronic Obstructive Lung Disease (GOLD) class A–D, and a positive relationship between risk of future exacerbations and lack of bronchodilator reversibility.

Other significant risk factors identified included disease severity or bronchodilator reversibility (39 studies), comorbidities (34 studies), higher symptom burden (17 studies), and higher blood eosinophil count (16 studies) as shown in Table 27.

Table 27. Prognostic factors for moderate to severe exacerbations in adult patients with COPD

| Risk factor/predictor | Description |
|---|---|
| Prior history of exacerbation* | The strongest risk factor for future exacerbations is a history of exacerbations within the last 12 months |
| Comorbidities* | Underlying comorbid diseases including anxiety and depression, asthma, blindness and low vision, dyspepsia, heart failure, hypertension, lung cancer, osteoarthritis, peripheral vascular disease, and prostate disorders are associated with increased risk of exacerbations |
| COPD severity and BDR* | The risk of exacerbation is significantly higher in patients with severe or very severe airflow limitation and lack of BDR |
| Eosinophil count | Higher eosinophil count is associated with an increased risk of exacerbations |
| Quality of life | Poor quality of life at baseline or worsening quality of life over time (measured by SGRQ, CCQ, and CES-D) are associated with an increase in exacerbation risk |
| Symptomatic burden | Higher symptomatic burden of COPD (CAT≥10 and mMRC≥2) is associated with an increased risk of exacerbations |
| Smoking | Smoking (former/current) is associated with an increased risk of exacerbations |
| BMI | Underweight patients (BMI < 18.5 kg/m2) are at higher risk of exacerbations |
| Age | Older age is associated with an increased risk of exacerbations |
| Sex | Associations between sex and the risk of exacerbations are variable |
| Temperature and pollution | Colder temperature and air pollution (NO2, O3, CO, and PM10) are associated with an increased risk of exacerbations |
| Others | Low physical activity (decreased 6MWD), elevated |

| | |
|---|---|
| | inflammatory biomarkers (e.g. C-reactive protein), and certain race/ ethnicity/region factors may be associated with an increased risk of exacerbations |

*>30 studies support the risk factors or predictors. The rest are supported by < 30 studies.
6MWD six-minute walk distance, BDR bronchodilator reversibility, BMI body mass index, CAT COPD Assessment Test, CCQ Clinical COPD Questionnaire, CES-D Center for Epidemiological Studies—Depression, CO carbon monoxide, COPD chronic obstructive pulmonary disease, FEV1 forced expiratory volume in 1 s, ICS inhaled corticosteroid, mMRC modified Medical Research Council, NO2 nitrogen dioxide, O3 ozone, PM10 particulate matter≤10 μm in diameter, SGRQ St. George's Respiratory Questionnaire

**Prognostic factors for mortality**

Results from a systematic review and meta-analysis of RCTs and observational studies on the prognostic factors for mortality among patients with COPD showed that the presence of diabetes and lower hemoglobin was associated with worse survival based on fixed-effects model.[256] Significant predictors of mortality within 3–24 months in the random-effects model were: previous hospitalization for acute exacerbation, hospital readmission within 30 days, cardiovascular comorbidity, age, male sex, and long-term oxygen therapy as shown in Table 28.

Table 28. Prognostic variables for mortality among patients with COPD

| Prognostic factor | Number of studies | Hazard ratio (HR), 95% CI | Interpretation |
|---|---|---|---|
| Hospital readmission within 30 days | 6 (n=1594) | 5.0 (2.16–11.63) | Worse prognosis |
| Diabetes | 2 (n=677) | 2.69 (1.67, 4.33) | Worse prognosis |
| Previous hospitalization for acute exacerbation | 6 (n=1594) | 1.97(1.32–2.95) | Worse prognosis |
| Long-term oxygen therapy | 5 (n=1874) | 1.74 (1.10–2.73) | Worse prognosis |
| Male sex | 4 (n=1204) | 1.68 (1.38–1.59) | Worse prognosis |
| Age (per 10 year increase) | 9 (n=6613) | 1.48 (1.38–1.59) | Worse prognosis |
| Cardiovascular comorbidity | 3 (n=1019) | 1.89 (1.25–2.87) | Worse prognosis |
| Hb (g/dL) per unit increase | 2 (n=747) | 0.77 (0.64, .92) | Better prognosis |
| 6 minute walking distance (m) per unit increase | 2 (n=747) | 1.00 (0.99, 1.00) | No significant difference |
| Dyspnea, MRC scale, per unit increase | 2 (n=629) | 1.31 (0.97, 1.78) | No significant difference |
| BUN , mg/dL, per unit increase | 2 (n=183) | 1.02 (1.00, 1.04) | No significant difference |
| Charleston comorbidity risk score | 3 (n=4482) | 1.11 (0.81, 1.54) | No significant difference |

| | | | |
|---|---|---|---|
| FEV1 (% predicted) | 4 (n=1306) | 1.01 (0.89, 1.13) | No significant difference |
| BMI (per unit increase) | 4 (n=1071) | 0.85 (0.71, 1.02) | No significant difference |
| PaC02 mmHg er unit increase | 3 (n=779) | 1.02 (1.01, 03) | No significant difference |

The overall certainty of evidence is very low. Indirectness and the high to very high risk of bias of the included systematic reviews contributed to lowering the certainty of evidence to very low.

## Recommendations from Other Groups

| Group or Agency | Recommendation | Strength of Recommendation and Certainty and Quality of Evidence |
|---|---|---|
| NICE and BTS[257] | When clinically indicated*, refer people for specialist advice. Referral may be appropriate at all stages of the disease and not solely in the most severely disabled people.<br><br>People who are referred do not always have to be seen by a respiratory physician. In some cases, they may be seen by members of the COPD team who have appropriate training and expertise.<br><br>*Indications for referral: diagnostic uncertainty, suspected severe COPD, person with COPD requests for second opinion, onset of cor pulmonale, assessment for oxygen therapy, assessment for prolonged nebulization, assessment for oral corticosteroid therapy, bullous lung disease, rapid decline in FEV1, assessment for pulmonary rehab, | None |

| | | |
|---|---|---|
| | assessment for a lung volume reduction procedure, assessment for lung transplantation, dysfunctional breathing, onset of symptoms under 40 years old or a family history of alpha-1 antitrypsin deficiency, symptoms disproportionate to lung deficit, frequent infections and hemoptysis. | |
| PCCP[259] | For patients who are either more symptomatic, with increased risk of exacerbations, or both (i.e. GOLD Groups B, C and D), we suggest that these patients be referred to a pulmonary specialist, when available. | None |
| GOLD 2023[260] | There are no direct recommendations on the level of care that will manage certain conditions or facilitate certain interventions. However, the following recommendations supporting a reduction in mortality in COPD patients, imply referral to specialist or higher level of care due to the nature of the indicated intervention:<br>a. Pulmonary Rehabilitation<br>- Indicated in all patients with relevant symptoms and/or a higher risk of exacerbatio | None |

| | | |
|---|---|---|
| | n (Evidence A)<br>b. Lung Volume Reduction (LVR) Interventions<br>- upper lobe emphysema for lung volume reduction surgery (Evidence A)<br>- large bulla for surgical bullectomy (Evidence B)<br>- advanced emphysema for bronchoscopy interventions: Endobronchial valves (Evidence A), Lung coils (Evidence B), Vapor ablation (Evidence B)<br>c. Lung Transplantation<br>- very severe COPD disease (progressive disease, BODE score 7-10, not a candidate for LVR), history of hospitalization for exacerbatio | |

| | | | |
|---|---|---|---|
| | | n with acute hypercapnia (PaCO2 >50mmHg), pulmonary hypertension or cor pulmonale, despite oxygen therapy, or FEV1<20% and either DLCO <20% or homogenous distribution of emphysema (Evidence C) | |

## Ongoing Trials and Research Gaps

There are currently no ongoing studies on this research topic. More studies should be done, preferably prospective studies, on the utility of specialist referral compared with no referral among stable COPD patients.

## Additional Considerations for Evidence to Decision Phase

**Cost**

There are no cost-effectiveness studies on specialist referral among patients with COPD. The cost of consultation with a specialist is around Php 600.00 to Php 1000.00.

**Patient's Values and Preference, Equity, Acceptability, and Feasibility**

In a cross-sectional study investigating the satisfaction of COPD patients managed by specialists and primary care, there was no noted difference. Patients controlled by the pulmonologists were younger, and exhibit lower PO2 and higher PCO2 values than the remaining. Patients treated by the pneumologist had more previous COPD admissions in and presented lower FEV1/FVC values compared with those managed by primary care physicians (Aymerich et al).

**Clinical Question No. 10.** Among stable COPD patients managed in the primary care setting, how effective and safe is guided self-management utilizing a COPD action plan in improving their symptoms and quality of life, reducing exacerbations, and prevention of hospitalization and death?

| *Recommendation No. 10* |
| --- |
| **Among stable COPD patients, we recommend the use of guided self-management utilizing COPD action plan in primary care setting** *(Low certainty of evidence, Strong recommendation)* |

## Key Findings

- There were 10 RCTs that investigated the effect of guided self-management intervention utilizing COPD action plan compared to usual care among stable COPD patients.

- There was a mortality benefit favoring self-management with COPD action plan intervention over usual care. However, there were no differences in terms of COPD-related quality of life, exacerbation, hospitalization, adverse events and symptom improvement.

- Overall certainty of evidence was downgraded to very low due to serious risk of bias due to lack of blinding and attrition and imprecision.

## Consensus Issues

In the comprehensive landscape of COPD treatment, non-pharmacologic management occupies a vital role, enabling patients to actively participate in their own well-being. Consequently, it's imperative that non-pharmacologic strategies remain an integral facet of the treatment plan. Even in light of the limited certainty of evidence, the panel's resounding endorsement of the COPD action plan as a tool for guiding patient self-management is noteworthy. The patient representative supported this patient empowerment thru self management approaches and the use COPD action plan. He even shared examples of self management interventions he learned during the pulmonary rehabilitation program which helped him and his co-members in dealing with COPD symptoms. The cost of the program was manageable, but would appreciate if this is sponsored. Despite the out-of-pocket expense, he was able to finish the program, and even did some refresher courses.

Despite the current level of evidence, the utilization of a COPD action plan brings multifaceted benefits to patients. The existing data consistently showcase its efficacy in various key areas. This includes its positive impact on reducing mortality rates, mitigating the frequency of exacerbations, enhancing symptom control, and elevating overall quality of life. Notably, the successful implementation of similar approaches in the management of asthma patients underscores the potential value and adaptability of this strategy for individuals grappling with COPD.

The COPD action plan essentially serves as an empowerment tool. It equips patients with structured guidance, fostering a sense of ownership and proactive

engagement in their health management. By offering clear steps to manage worsening symptoms or exacerbations, the action plan not only bolsters patient confidence but also contributes to timelier interventions, potentially averting the escalation of symptoms.

It is crucial to recognize that evidence-based medicine rests on the careful evaluation of available data and the consistent identification of patterns or trends. While the certainty of evidence might be modest in some cases, the collective knowledge gleaned from diverse sources underscores the potential benefits of implementing certain strategies. This informed approach enables healthcare providers to make prudent decisions tailored to each patient's unique circumstances.

In conclusion, the integration of non-pharmacologic approaches, like the COPD action plan, is a cornerstone of effective COPD management. The panel's steadfast recommendation, despite the existing evidence limitations, is a testament to the potential advantages it brings to patients. Drawing parallels from its success in asthma management, the action plan holds promise in guiding COPD patients toward improved outcomes and enhanced self-efficacy in their health journey.

## Review Methods

A systematic search was done using Medline, Cochrane Library, Google Scholar with a combined MeSH and free text search using the following terms as keywords in different combinations using the operational term “OR”: COPD, stable COPD, chronic obstructive pulmonary disease, self-guided management, guided management, self-management, symptom diary, COPD action plan, action plan.

Only RCTs that compared self-guided management versus usual care among stable COPD managed in primary care from 2015 up to January 11, 2023 (date of last search) were included in this review. There were no restrictions as to the components of the “self management interventions” and “usual care” as described in the studies. Time restriction to start in the year 2015 until the date of last search was done in the attempt to limit variations and capture the more recent interventions being done in the primary care setting. Outcomes of interest included symptom improvement, COPD-related QoL, reduction of exacerbations, COPD-related hospitalization, Mortality (all-cause and COPD-related) or ER visits.

## Evidence

**Exacerbations leading to ER visits or hospitalizations**

There was no significant change in the rate of exacerbation leading to ER visit with 868 subjects from the pooled three RCTs (OR 0.33, 95% CI 0.13 to 0.84; RR 1.03, 95% CI 0.89 to 1.19; Adjusted MD -0.05, 95% CI -0.33 to -0.22).[261-263] There was a trend toward benefit in the use of self-management in terms of exacerbation leading to hospitalization with 856 subjects from three RCTs (RR 0.63, 95% CI 0.54 to 0.74).

**Symptom Improvement and Quality of life**

Self-management using COPD action plan did not show any significant difference compared to usual care in terms of SGRQ score (change in score at 12 mos 3.35 vs 4.69 with between group change of 2.21, 95% CI -2.86 to 7.28; Mean

score in 12 mos with MD -1.3, 95% CI -3.6 to 0.9;); mMRC (mMRC score at 9 mos of 2.7 from 2.4 intervention group, 2.5 to 2.4 in usual care; change in baseline score of 0.28 vs 0.08 and a change in between group difference of 0.21, 95% CI of -0.09 to 0.50); and COPD-related quality of life in terms of change in CAT score after 9 mos from 3 RCTs (mean CAT score at 9 mos of 15.5 to 15.8 at intervention group versus 14 to 14.7 usual care, MD -5.04, 95% CI -15.75 to 5.67)[261, 264-268]

Exercise Capacity

One RCT reported the 6-minute walk distance result among its 192 subjects which shows inconclusive result (adjusted Difference of 8.53; 95% CI -9.18 to 25.28).[269]

Mortality (All-cause)

Results from five RCTs noted significant difference favoring self-management (RR 0.52 95% CI, 0.27 to 0.99) over usual care.[261, 262, 263, 267]

Lung Function

There was inconclusive result from the pooled studies from three RCTs reporting FEV1 score (SMD 0.05, 95% CI -0.13, 0.23) and two RCTs reporting FEV1/FVC score (SMD 0.19, 95% CI -0.03, 0.42).[263, 265, 266]

Table 29 summarizes the critical and important outcomes of this study.

Table 29. Summary of Critical Outcomes on the Use of a Guided Self-management Utilizing a COPD Action Plan

| OUTCOMES | MEASURE | BASIS | EFFECT SIZE | 95% CI | INTERPRETATION | CERTAINTY OF EVIDENCE |
|---|---|---|---|---|---|---|
| **CRITICAL OUTCOMES** | | | | | | |
| EXACERBATIONS | ALL | 1 RCT (n =146) | AMD -48.9 | -62.5, -35.3 | Benefit | Moderate |
| | ER visits | 1 RCT (n = 155) | OR 0.33 | 0.13,0.84 | Benefit | Low |
| | | 2 RCTs (n = 555) | RR 1.03 | 0.89, 1.19 | Inconclusive | |
| | | 1 RCT (n = 158) | AMD -0.05 | -0.33, -0.22 | No difference | |
| | Hospitalization | 3 RCTs (n = 856) | RR 0.63 | 0.54,0.74 | Benefit | Moderate |
| COPD related QoL | CAT (*MCID 2 units) | 1 RCT (n = 193) | Intervention - Mean CAT score from 15.5 to 15.8 at 9 months | | No difference | Low |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | Usual care – Mean CAT score from 14 – 14.7 at 9 months | | | |
| | | 2 RCT (n=418) | MD of -5.04 | -15.75 – 5.67 | Inconclusive | |
| | SGRQ (MCID 4 units) | 1 RCT(n = 272) | Change in score at 12mos<br>Intervention 3.35 (0.57–6.14)<br>Usual Care 4.69 (1.96–7.41)<br>Between group 2.21 (−2.86 –7.28) | | Inconclusive | Low |
| | | 1 RCT (n = 528) | Mean score in 12 mos<br>Intervention 30.9 from 29.8<br>Usual care 30.9 from 29.5<br>Mean Difference -1.3 (-3.6 to 0.9) | | No difference | |
| Symptom Improvement | Level of breathlessness (mMRC) (MCID 1) | 1 RCT (n = 155) | Mean mMRC score, at 9mos<br>Intervention decreased from 2.7 to 2.4<br>Usual care decreased from 2.5 to 2.4 | | No difference | Low |
| | | 1 RCT (n = 211) | Change from baseline, 12 mos<br>Intervention 0.28<br>Usual care 0.08<br>change in between group difference 0.21 (−0.09; 0.50) | | | |
| | | 1 RCT (n = 272) | Median, % improved, at 12mos<br>Intervention 1, 21.2%<br>Control median 1, 18.2% | | | |
| Exercise Capacity | 6MWD in meters | 1 RCT (n = 192) | Adjusted Difference 8.53 | -9.18 to 25.28 | Inconclusive | Moderate |

| IMPORTANT OUTCOMES | | | | | | |
|---|---|---|---|---|---|---|
| DEATH | All-cause | 5 RCTs (n = 1459) | RR 0.52 | 0.27, 0.99 | Benefit | Low |
| LUNG FUNCTION | FEV1 | 3 RCT (n = 574) | SMD 0.05 | -0.13, 0.23 | Inconclusive | Moderate |
| | FEV1/FVC | 2 RCT (n= 302) | SMD 0.19 | -0.03, 0.42 | Inconclusive | |

Overall certainty of evidence was then downgraded to low because of serious risk of bias due to lack of blinding and attrition and imprecision across outcomes. There was also note of heterogeneity in reporting (i.e. exacerbation) and measurement (i.e. quality of life, healthcare utilization) of most of the outcomes causing inconsistency, imprecision and indirectness.

## Recommendations from Other Groups

| Group or Agency | Recommendation | Strength of Recommendation and Certainty of Evidence |
|---|---|---|
| GOLD 2023[270] | Recommends education self-management with the support of a case manager with or without the use of a written action plan | Evidence B* |
| PCCP 2021 (Summary of Consensus Statements on the Diagnosis and Management of COPD in the Philippines)[271] | Non pharmacologic management of stable COPD through educational leaflet, video or computer for instruction and education, and the use of patient exercise diary and action plan | Not available |
| NICE 2018[271] | Self-management plans improve quality of life and reduce hospital admissions | Not available |

* RCTs with important limitation, limited body of evidence

## Ongoing Trials and Research Gaps

Research on guided self-management has been started by numerous authors as early as the 1980s and is very robust not only for mild to moderate COPD but also for those with advanced disease. With the advent of web-based applications and other technology-enabled gadgets, monitoring of COPD patients with these devices as part of a guided self-management plan is currently ongoing. There are currently 2 ongoing studies on this topic.[310, 311]

## Additional Considerations for Evidence to Decision Phase

**Cost**

There are no local economic evaluation studies available at present. There are several institutions offering services similar to a self-guided management:

| | Lung Center of the Philippines | Philippine Heart Center | University of Sto Tomas |
|---|---|---|---|
| Cost | Php 1,000 x 9 sessions (service/charity)<br>Php 750/session (less senior/PWD) | Php 16,500 x 24 sessions (without CPET)<br>Php 21,000 x 24 sessions (with CPET) | Php 7,000 x 16 sessions (virtual, less senior/PWD) |

**Patient's Values and Preference, Equity, Acceptability, and Feasibility**

There were no local studies retrieved evaluating COPD patient's values and preferences on guided self-management compared to usual care.

In a systematic review conducted in Saudi Arabia, they summarized acceptability and dropout rate data of telehealth and self-management interventions. Self-management with COPD action plan across studies was integrated with telehealth monitoring with the majority of the studies (65%) done in Europe. Overall mean acceptance rate was found to be 82% (±14) with a mean dropout rate of 19% (±14). Majority of the dropout cases stated technical difficulties, a complicated system and hospital admission as reasons for not continuing the intervention.[271]

A clinical trial with the aim of providing a self-management plan integrated with community visits for GOLD B-D COPD patients from low to middle income countries (Nepal, Peru and Uganda) is ongoing. Its feasibility and cost-effectiveness data have yet to be published.[273]

**Clinical Question No. 11.** Among end-stage or advanced-stage COPD patients, how effective and safe are primary care palliative services in improving quality of life?

| *Recommendation No. 11A* |
| --- |
| **Among symptomatic COPD patients with moderate to severe breathlessness*, who are not hypoxemic, and does not fulfill criteria for long-term oxygen therapy (LTOT), we suggest using low flow oxygen therapy for relief of dyspnea with caution and close supervision of attending physician** *(Low certainty of evidence, Weak recommendation)* |

| *Recommendation No. 11B* |
| --- |
| **Among patients with advanced-stage or end-stage COPD and/or refractory dyspnea, we suggest to consider the use of opioids with close supervision to relieve dyspnea that persists despite maximized medical management** *(Very low certainty of evidence, Weak recommendation)* |

**Moderate to severe breathlessness, mMRc 3-4 (3 stops for breath after walking 100m or stops after a few minutes walking on the level; 4 Too breathless to leave the house or breathless on dressing or undressing*

## Key Findings

- There was 1 RCT that investigated the efficacy of oxygen compared to air on palliative use for advanced-stage COPD, and 1 RCT that investigated the efficacy of opioid compared to no opioid for the same indication. Several observational studies were used for the safety outcomes.

- Results of the RCT on oxygen in terms of improving dyspnea in patients who do not qualify for long-term oxygen therapy (LTOT) showed a trend towards benefit. Administration of oxygen did not show significant effect in terms of improving quality of life (QoL) based on a disease-specific questionnaire and other symptoms like fatigue, anxiety, and depression. A generic QoL questionnaire showed a trend towards harm. Based on observational studies, harms of treatment included burn injuries and tripping/falling over oxygen equipment that may occasionally lead to serious health consequences.

- Issues with risk of bias, imprecision, and indirectness (for the single observational study) led to the downgrading of the overall certainty of evidence to low.

- Results of the RCT on opioid, specifically morphine, in terms of improving QoL and dyspnea showed a trend towards benefit. As a marker of opioid-induced respiratory depression, carbon dioxide levels in the blood trended towards increased levels with morphine use. There was also a trend towards more severe constipation. Results from the observational studies generally showed harm (or a trend towards harm) in terms of

respiratory-related events like exacerbations, ER visit, and hospitalization; and cardiac events like congestive heart failure- and ischemic heart disease-related mortality with opioid use.

- Imprecision, risk of bias, and indirectness (for the 5 observational studies) led to the downgrading of the overall certainty of evidence to very low.

## Consensus Issues

Patients with end-stage COPD are severely symptomatic despite maximal management of their symptoms. The incorporation of oxygen supplementation, in conjunction with bronchodilator treatment, is often viewed as a form of rescue therapy by patients due to its capacity to offer respite and faster relief. It is considered as a more effective type of rescue therapy than other medications. However, it's important to note that instances of breathlessness might occasionally be linked to anxiety rather than solely stemming from the underlying COPD symptoms.

While oxygen therapy holds the promise of alleviating breathlessness, patients often display a reluctance to embrace it, primarily due to concerns surrounding its cost and their unfamiliarity with its usage. It is incumbent upon physicians to meticulously educate patients about the potential side effects associated with oxygen therapy, ensuring a comprehensive understanding. The relief that patients feel with oxygen is often temporary and is usually gone once they stop using their oxygen tanks.

It's worth noting that oxygen therapy typically comes with a notable financial implication. Stationary oxygen cylinders, the pricing of which is contingent on their capacity, range from approximately Php 3,800.00 (5 lbs) to Php 8,000.00 (50 lbs). Refilling oxygen incurs an additional cost of around Php 950.00. To enhance portability, patients may opt for portable cylinders, which can be conveniently transported using trolleys available at an approximate cost of PhP 2,500.00.

In order to overcome patient reservations, physicians must adopt a patient-centered approach, addressing concerns about cost, usage, and potential inconveniences. By fostering transparent communication and offering insights into the benefits of oxygen therapy, healthcare providers can enable patients to make informed decisions that prioritize their well-being.

When considering the utilization of opioids, it's crucial to bear in mind that their availability might not be universal across all local pharmacies. Additionally, physicians are mandated to possess an S2 license for prescribing them. Ensuring comprehensive patient monitoring is of paramount importance to ensure both safety and treatment efficacy.

Turning to the financial aspect, the cost of opioids spans from Php 16.00 to Php 108.69. The ultimate expense incurred is intricately linked to the dosage frequency required daily by the patient. This underscores the significance of tailoring treatment plans to individual patient needs, thereby optimizing both therapeutic benefits and cost-effectiveness.

Any intervention that exhibits a discernible trend of benefit for patients grappling with end-stage COPD merits consideration for implementation. The primary objective is to alleviate their suffering and enhance their quality of life. However, a cautious approach is indispensable in such cases, and rigorous oversight must be maintained throughout the process.

The decision to introduce relief measures hinges on a thorough evaluation of the available evidence. The potential advantages, weighed against potential risks and drawbacks, should guide this decision-making process. The ultimate goal is to provide patients with the best possible care while minimizing any adverse effects. Close supervision plays a pivotal role in ensuring the safety and effectiveness of any implemented intervention. Regular monitoring, prompt assessment of patient response, and timely adjustments are imperative. This proactive approach not only safeguards patient well-being but also contributes to a more accurate understanding of the intervention's impact.

In conclusion, while the pursuit of relief for patients with end-stage COPD is essential, it must be approached thoughtfully. The evidence-based implementation of relief measures, coupled with meticulous supervision, underscores the commitment to enhancing patient and their caregivers comfort and quality of life in the face of challenging circumstances.

## Review Methods

A systematic search was done from inception to January 29, 2023 using PubMed, Herdin Plus, ClinicalTrials.Gov, and Cochrane databases with combined MeSH and free text search. Search terms used were chronic obstructive pulmonary disease, oxygen, opioid, morphine, and palliative care. Additional relevant publications that were found in reference lists or cited in local and international guidelines on the topic were also screened for eligibility. The search focused on studies that were published in the English language.

Only RCTs that recruited patients with advanced-stage COPD and studied in an outpatient setting were included. Advanced-stage COPD was operationally defined as having grade 3 or 4 dyspnea on the mMRC scale. Given the palliative context of the research question, we focused on studies that assessed the effect of intervention in the daily life setting.

Studies that compared oxygen against placebo or standard care, and opioid against placebo or standard care were included. For oxygen, the search focused on low-flow oxygen with no limits on the mode of delivery. Studies that used medical/cylinder/compressed air as comparators were included. For opioid, codeine was excluded (applicability issue); no other limits were placed on dosing and route of delivery. Outcomes of interest were QoL, symptom improvement, and adverse events. Symptoms were not specific to respiratory.

Because of anticipated recruitment challenges (low willingness of patients) and potential ethical issues that may arise when inviting end-of-life patients to participate in a clinical trial, we still opted to include studies for which patients with limited life expectancy or use of intervention for palliation were systematically excluded, in spite of the research question.

## Evidence

**Efficacy**

*Oxygen*

Follow-up (post-treatment) scores were used to compare between the treatment and control arms.

With the CRDQ, the mean score was 1.40 points higher in the oxygen group compared to the air group, ranging from 5.70-point reduction to 8.50-point increase in score (scale 20 to 140; a higher score indicates improvement in QoL).[274] Thus, QoL as measured by a disease-specific tool was equivalent between the two groups. With the AQoL tool, the mean score was 0.05 points lower in the oxygen group compared to the air group, ranging from 0.14-point reduction to 0.04-point increase in score (scale -0.04 to 1; a lower score indicates worsening in QoL).[274] QoL trended towards harm when generic measures were used.

For the outcome of dyspnea, the mean score of the dyspnea domain of the CRDQ was 1.10 point higher in the oxygen group compared to the air group, ranging from 0.85-point reduction to 3.05-point increase in score (scale 5 to 35; a higher score indicates improvement in dyspnea).[274] A trend towards benefit was noted.

For the other efficacy outcomes (fatigue, anxiety, and depression), there was no significant difference between the treatment arms.

*Opioid*

The treatment difference over time, or the change in score from baseline to follow-up, was used to compare between the treatment and control arms. Unless otherwise specified, data was taken from the subgroup analysis of COPD patients with mMRC 3-4.

The mean difference in CAT score was 1.17 points lower in the morphine group compared to the placebo group, ranging from 4.17-point reduction to 1.84-point increase (scale 0 to 40; a lower score indicates improvement in QoL). Thus, morphine demonstrated a trend towards improved QoL.

For the outcome of breathlessness, subcategorized as mean and worst breathlessness in the previous 24 hours and measured by the NRS, it showed a trend towards benefit with morphine use (MD −1.31; 95% CI −2.80 to 0.17 for mean breathlessness and MD −1.33; 95% CI −2.50 to −0.16 for worst breathlessness; scale 0 to 10; a lower score indicates improvement in breathlessness).[275] For the total study population, the percentage of participants reporting at least 1.0-point improvement on NRS mean breathlessness was 48% (21/44) in the morphine group and 35% (18/51) in the placebo group, with a trend towards more responders in the morphine group (RR 1.35, 95% CI 0.83 to 2.19). The NRS cutoff was set by the study authors to qualify response.

At the end of the study (4 weeks), the average number of capsules taken per day by participants was 2.55 (SD 0.50) for the morphine group, and 2.73 (SD 0.45) for the placebo group (p=0.07). There were 24 participants (55%) and 37 participants

(73%) in the morphine group and placebo group, respectively, using 3 capsules per day (p=0.07). Data was taken from the total study population.

## Safety

*Oxygen*
For oxygen, the search focused on adverse effects of home low-flow oxygen in COPD, with no limits on the prescription (e.g., LTOT, short-burst/intermittent, palliative), mode of delivery, and indication (e.g., hypoxemia at rest/exercise, breathlessness). Out of 403 citations screened for eligibility, five studies were included (1 comparative cohort, 1 single-arm cohort, 3 case series). Most adverse effects found were related to the handling of the equipment rather than clinical adverse events.

A retrospective cohort study showed that burn injury was significantly associated with home oxygen use in COPD patients (HR 1.68; 95% CI 1.42 to 2.00).[276] As described in several case series, burn injuries of varying severity have resulted from the use of oxygen while smoking.[277-278] At times, the fire risk may come from cohabitants of the patient who smoke or from cooking.[278, 280]

In the treatment cohort of an RCT, adverse events reported to be possibly, probably or definitely related to use of supplemental oxygen were also described. There were 42 reports of expected, related events (1.64 reports per 100 person-years), with tripping/falling over oxygen equipment being the most common (n = 23), followed by nosebleed (n = 9), and burn from liquid oxygen frost (n = 4). Tripping/falling over oxygen equipment resulted in hospitalization in two cases: overnight hospitalization with humerus fracture, and six-day hospitalization with rib fractures. There were 9 reports of unexpected, related events (0.35 reports per 100 person-years), with blisters and ear pain being most common (n = 3), followed closely by headache (n = 2). Out of 490 total number of patients ever using supplemental oxygen during follow-up, 42 (8.6%) reported at least one related adverse event [19].[281]

It is well-recognized that some COPD patients are prone to develop worsening respiratory acidosis and hypercapnia in response to uncontrolled oxygen administration during acute exacerbations [20].[282] However, the search failed to retrieve evidence on this in stable COPD. The RCT used for the efficacy outcomes screened for increasing PaCO2 after a trial of oxygen (6 liters per minute, at rest, for 30 minutes) in patients with baseline hypercapnia but it was unclear how many patients were excluded because of this.

*Opioid*
For opioid, the search focused on adverse effects of outpatient opioids in COPD, with no limits on the type of opioid, route of delivery, dosing, and indication (e.g., breathlessness, pain, cough). Out of 342 citations screened for eligibility, six studies were included (1 RCT, 2 comparative cohorts, 1 case-control, 2 case-crossovers).

The RCT used for the efficacy outcomes also reported on adverse effects and was included. Results of subgroup analysis of COPD patients with mMRC 3-4 showed an increase in PaCO2 of 1.84 mmHg in the morphine group compared to the

placebo group, ranging from 4.95 mmHg reduction to 8.64 mmHg increase. There was a trend towards increased PaCO2 with morphine use. For the rest of respiratory outcomes examined, the results were mostly equivalent (for arterial oxygen saturation, respiratory rate, transcutaneous CO2, pulse oxygen saturation (SpO2), mean overnight SpO2); while PaO2 showed a trend towards decrease with morphine use (MD -5.92; 95% CI -15.73 to 3.90) and the percentage of time that the overnight SpO2 was below 90% showed inconclusive results.

Morphine-related adverse effects of interest were nausea, vomiting/retching, drowsiness, constipation, and sleeplessness. Based on the number of participants who had 1 or more adverse effects of interest in the total study population, there was a trend towards experiencing adverse events in the morphine group compared to the placebo group (43/53 [81%] vs 40/57 [70%]; RR 1.16, 95% 0.93 to 1.43). There was a trend towards more severe constipation with morphine use (MD 1.53; 95% CI 0.44 to 2.62), while for nausea and sleeplessness, there was a trend towards less intense symptoms (MD -0.61, 95% CI -1.57 to 0.35 and MD -0.44, 95% CI -1.67 to 0.80, respectively) (scale 0 to 10; a higher score indicates more intense symptoms). For vomiting/retching and drowsiness, the intensity of symptoms was equivalent between both arms (MD -0.27, 95% CI -0.69 to 0.14 and MD -0.11, 95% CI -0.124 to 1.01, respectively). Other spontaneously reported adverse effects did not differ between the treatment groups but specifics were not provided. Eighteen of 111 participants (16%) experienced a moderate to severe COPD exacerbation: 7 (13%) in the morphine group and 11 (19%) in the placebo group (RR 0.67, 95% CI 0.28 to 1.61). Three hospital admissions (all for COPD exacerbation) occurred, with 1 of 54 (2%) in the morphine group and 2 of 57 (4%) in the placebo group (RR 0.53; 95% CI 0.05 to 5.65). Both results were inconclusive. No morphine-related deaths occurred.

In a comparative cohort study, incident (new) opioid use was associated with a trend towards increased risk of ER visits for COPD or pneumonia (HR 1.14; 95% CI 1.00 to 1.29), and a significant increase in COPD- or pneumonia-related mortality (HR 2.16, 95% CI 1.61 to 2.88) and all-cause mortality (HR 1.76; 95% 1.57 to 1.98) in the community-dwelling cohort of older adults within 30 days of exposure to any opioid, alone or in combination with other non-opioid agents. According to the study authors, opioid-only agents generally contain more potent opioids like hydromorphone, fentanyl, and levorphanol unlike combination agents, most of which contain less-potent codeine. In the subgroup analysis of patients using opioid only, there were significantly increased associations with ER visits (HR 1.64; 95% CI 1.35 to 1.98) and hospitalizations (HR 1.54; 95% CI 1.31 to 1.81) for COPD or pneumonia, COPD- or pneumonia-related mortality (HR 4.76; 95% CI 3.40 to 6.66), and all-cause mortality (HR 4.01; 95% CI 3.53 to 4.56). There was a trend towards significance between new opioid-only use and outpatient respiratory exacerbations (HR 1.27; 95% CI 1.14 to 1.41), as well as ICU admissions during hospitalizations for COPD or pneumonia (HR 1.27; 95% CI 0.82 to 1.96) [21].[283]

Incident use of any opioid was associated with a trend towards reduction in ER visit or hospitalization for congestive heart failure (CHF) within 30 days of opioid exposure among community-dwelling older adults (HR 0.84; 95% CI 0.73 to 0.97), but with a trend towards harm for ER visit or hospitalization for ischemic heart disease (IHD) (HR 1.76; 95% CI 1.00 to 3.09) and significantly increased rates of IHD-related mortality among long-term care residents (HR 2.15; 95% CI 1.50 to 3.09). The results were inconclusive for the rest of the outcomes examined (for

community-dwelling cohort, ER visit or hospitalization for IHD, IHD-related mortality, CHF-related mortality; for long-term care resident cohort, ER visit or hospitalization for CHF, CHF-related mortality). When subgroup analysis was done on the community-dwelling group, it was the users of combination opioid/non-opioid agents that showed a trend towards decreased rates of ER visit or hospitalization for CHF (HR 0.81, 95% CI 0.71 to 0.94) and IHD-related mortality (HR 0.84; 95% CI 0.63 to 1.10) while those using opioid-only agents trended towards increased rates of ER visits or hospitalizations for IHD (HR 1.38; 95% CI 1.08 to 1.77) and showed a significant increase in IHD-related mortality (HR 1.83; 95% 1.32 to 2.53), similar to the negative effects seen in long-term care residents. Again, this was hypothesized by the same study authors as due to the lower opioid potency and dose that generally characterize combination agents and that may have facilitated cardioprotective ischemic preconditioning.[284]

A case-control study showed that the odds of hospitalization was higher in those with opioid use in the preceding 30 days compared to none and was strongly significant (adjusted odds ratio [aOR] 1.73; 95% CI 1.52 to 1.97). The odds were even higher with concurrent use of benzodiazepine (aOR 2.32; 95% 1.94 to 2.77). There was decreasing odds as the exposure moved farther away from the date of hospitalization (i.e., 60-day and 90-day exposure windows), both for opioid only and concomitant opioid and benzodiazepine use (aOR 1.58; 95% CI 1.40 to 1.78 and aOR 2.21; 95% CI 1.88 to 2.59, respectively, with 90-day exposure.[285] The authors of a broadly similar study hypothesized that the decreasing strength of association with longer exposure times may have been due to the development of tolerance.[286]

Similar findings were seen in two case-crossover studies where the odds of COPD exacerbation was increased by approximately 80% with opioid exposure compared to none in the preceding seven days.[287, 288] Data could not be aggregated into a meta-analysis because of missing data for input. Based on the sensitivity analysis conducted in one of the studies, opioid exposure in the prior 5 days had increased odds of exacerbation (aOR 2.00; 95% 1.73 to 2.30) compared to the 8-day exposure window (aOR 1.74; 95% CI 1.54 to 1.97). This was attributed by the study authors to a very short-term onset of respiratory depression associated with opioids.[287]

As with all observational studies, despite adjustment for several covariates, we cannot reliably conclude whether events were because of opioid receipt per se or simply reflected sicker status of patients (i.e., more symptoms/more severe COPD, more underlying illnesses) that both predisposed to the events we examined and provided the indication for use of the intervention.

### Recommendations from Other Groups

| Group or Agency | Recommendation | Strength of Recommendation and Certainty of Evidence |
|---|---|---|
| Global Initiative for Chronic Obstructive Lung Disease, 2023[289] | Palliative Care, End of Life, and Hospice Care in COPD:<br><br>Opiates, neuromuscular | Evidence C<br><br>Evidence B |

| | | |
|---|---|---|
| | electrical stimulation (NMEs), oxygen, and fans blowing air on to the face can relieve breathlessness<br><br>In malnourished patients, nutritional supplementation may improve respiratory muscle strength and overall health status<br><br>Fatigue can be improved by self-management education, pulmonary rehabilitation, nutritional support, and mind-body interventions | Evidence B |
| Summary of Consensus Statements on the Diagnosis and Management of COPD in the Philippines, 2021[290] | Monitoring and Non-Pharmacologic Management of Stable COPD:<br><br>For Group D, discuss with their healthcare providers palliative strategies and advance care directives | Not available |
| European Respiratory Society (ERS)/American Thoracic Society (ATS), 2020 [291] | In individuals with COPD who experience advanced refractory dyspnea despite otherwise optimal therapy, we suggest that opioid-based therapy be considered for dyspnea management, within a personalized shared decision-making approach | Conditional recommendation; very low certainty evidence |
| National Institute for Health and Care Excellence (NICE), 2018[292] | Palliative Care:<br><br>When appropriate, use opioids to relieve breathlessness in people with end-stage COPD that is unresponsive to other medical therapy | Not available |

| | | |
|---|---|---|
| | When appropriate, use benzodiazepines, tricyclic antidepressants, major tranquilizers, and oxygen for breathlessness in people with end-stage COPD that is unresponsive to other medical therapy<br><br>People with end-stage COPD and their family members or carers (as appropriate) should have access to the full range of services offered by multidisciplinary palliative care teams, including admission to hospices | |

## Ongoing Trials and Research Gaps

As of time of search, there were two (2) ongoing studies on the topic in ClinicalTrials.gov (study identifiers: NCT03834363 [morphine or fentanyl] and NCT01783808 [oxygen]) that can potentially have an impact on the conclusion of this evidence summary.

Particularly for oxygen, most studies evaluated its acute effects during exercise test or pulmonary rehabilitation, while evidence of its efficacy in daily life is limited. The latter is especially important when considering the palliative context of the research question, hence, focusing more on symptom relief and improving QoL and less on cure or restoration of function.

Notably, patients with advanced-stage COPD in whom the impact of the disease is felt the greatest, tend to be underrepresented in RCTs of interventions with actual or potential application to palliative care. Their inclusion in studies is particularly challenging because of the low willingness to participate, among other proposed reasons. As such, conclusions derived from these studies may not be easily applied to their population.[312]

## Additional Considerations for Evidence to Decision Phase

**Cost**

*Oxygen*

Stationary oxygen cylinders have a bigger capacity and are higher-priced at PhP 8,000 (50 lbs) while smaller-capacity but portable cylinders are priced at Php 3,800 (5 lbs), inclusive of the regulator.[293] The nasal cannula costs Php 35.00.[294] At a typical flow rate of 2 lpm when given continuously, a 50-lb tank is estimated to last two days.[295] Refill for a 50-lb cylinder costs Php 950. For ease of transport, portable cylinders may be carried in trolleys that cost approximately Php 2,500.00.[293]

Oxygen concentrators have higher upfront costs but may be less costly in the long-term, especially when used for several hours during the day. The price may range from PhP 40,000 to PhP 350,000 depending on features that include flow rate output, low-noise, portability, internal battery, and option for continuous use.[293]

*Opioids*
As mandated by the government, the maximum retail price (MRP) for morphine is Php 16.00 for the 10-mg modified-release (sustained-release) tablet, Php 41.58 for the 30-mg modified release tablet, and PhP 108.69 for the 60-mg modified-release tablet.[296] At a dose of 10 mg 2x a day, the daily cost of morphine is Php 32.00.

There are no economic evaluation studies on either intervention available locally.

**Patient's Values and Preference, Equity, Acceptability, and Feasibility**
*Oxygen*
In the RCT cited for efficacy data, a survey of participants at study completion (12 weeks) found that almost half of the participants in the oxygen group and medical air group each would have preferred to cease using cylinders altogether. Approximately half of the total study population (62 participants) reported difficulties with the apparatus, citing poor portability and difficulty changing the regulator. Other reported barriers to use included fear of dependence and embarrassment.[274] Another RCT on the effect of ambulatory oxygen on health-related QoL included assessment of clinical preference of patients for oxygen. At study completion (12 weeks), 14 patients (41%) who had either an acute or short-term response to oxygen, did not wish to be considered for continued oxygen therapy. Poor acceptability or tolerability were cited as barriers to use.[297]

For safety reasons, patients who smoke cigarettes and e-cigarettes must stop when prescribed oxygen therapy. Studies have shown that the percentage of active smokers among COPD patients on home oxygen therapy may be between 22% and 51%.[298, 299] Even in the setting of a clinical trial and with strong advice to quit, 44% of patients assigned to the oxygen group continued to smoke at the end of the study.[300]

*Opioid*
A qualitative study on patients' and caregivers' experiences with regular, low-dose, sustained-release morphine for chronic breathlessness associated with COPD revealed that the following factors drive patients' decisions to continue taking morphine in the long-term: degree of symptom reduction, improved function, side effects' severity, and caregivers' availability to help cope with the side effects of therapy, e.g., constipation. The authors recommended that, in clinical practice, discussion of the role of morphine in reducing chronic breathlessness and emphasizing the small doses required to achieve this may increase patients' acceptance of the treatment. When available, caregivers should be informed and prepared for the adverse effects of treatment to alleviate their anxiety and help them to better respond to such situations.[301]

On the experiences of healthcare providers in the treatment of advanced COPD in primary care settings, a study done in Canada revealed that there was discomfort

among family physicians in prescribing opioids.[302] Barriers to use included insufficient knowledge, lack of education and guidelines, and fear of censure when prescribing opioids for dyspnea in advanced COPD in the absence of guidelines. Providers with experience in palliative care tended to be more comfortable prescribing opioids but generally limit its use to palliative or terminal stages of COPD. A similar conclusion was drawn in a study of general practitioners in Australia. Most respondents desired education and support to overcome these common barriers.[303]

A local survey on the knowledge and preference of Filipino COPD patients on advance-care planning revealed that most of the 90 patients recruited (66.67%) felt anxious in particular about the financial situation of their family.[304] Because of the cost entailed by either intervention, this is likely to have an impact on acceptability and feasibility, especially with long-term prescription. The study also found that patients with a higher symptom burden (i.e., CAT score >10), not unlike our population of interest, were more likely to relegate health decision-making to their doctors. It was not clear from the study if this also meant less desire for shared decision-making which is an approach that physicians treating patients at end-of-life are encouraged to take. The small sample size of the study limited the generalizability of findings.

No local studies are available that specifically evaluated patient's values and preferences regarding the use of oxygen or opioid for COPD, as well as those that explored its equity, acceptability, and feasibility.

# Applicability Issues

### Organizational Considerations to Implementation

The final CPG manuscript was equipped with 3 management algorithms (Appendix F): (1) prevention, screening and diagnosis, (2) management of stable COPD, and (3) management of COPD exacerbations. The algorithms were designed to address inequities (i.e. lack of spirometry in some settings → may label as COPD probable and may initiate treatment). These shall guide end-users in the implementation of this CPG in the primary care setting. Monitoring tools and indications for referrals were incorporated in the algorithm to guide proper navigation of patients.

In order to facilitate implementation, proper dissemination of the CPG and the management algorithms should be done. The algorithms are designed to capture the actual practice and the present limitations of the rural health units as discussed during panel meetings by the primary care physicians in the panel.

However, the task force was made aware of the barriers to implementation of recommendations derived during the consensus discussions. The identified barriers were the variabilities in the availability of resources such as facility based spirometry, medications such as inhalers - LABA/LAMA/ICS, LABA/LAMA, and trained primary care providers especially in areas such as pulmonary rehabilitation, palliative care, and smoking cessation and control of air pollution. Addressing the resource and research implications discussed in the next sections would cover for these variabilities and further strengthen the implementation of this CPG.

### Resource Implications

This CPG shall facilitate the following community and individual based programs that would require corresponding resource allocation (i.e. national or local government unit funding, UHC or Philhealth benefit package development): (1) Prevention of COPD: need for cleaner fuel alternatives and smoking cessation; (2) Screening and Diagnosis of COPD: access to facility based spirometer, provision of hand held spirometer; (3) Pharmacologic Management: availability of affordable inhaled bronchodilators +/- ICS in local pharmacies, provision of resources to primary care facility to manage exacerbations of COPD; (4) Nonpharmacologic Management: training programs on self management and COPD action plan, access to palliative care services or training of primary care providers in administering palliative care; and (5) Referrals to higher of care: to cover healthcare provider network navigation costs.

# Monitoring and Evaluation

### Dissemination

The final manuscript for the CPG shall be submitted to the DOH NPG Clearinghouse for quality appraisal. Once the quality standards are met and the CPG is approved for adoption as a national practice guideline, the dissemination of the CPG will take place. The launch of the CPG will occur during an official DOH-initiated event and will be followed by dissemination at conferences

initiated by specialty societies. Relevant factors and issues captured by the domains, guideline questions, and management algorithms shall be emphasized for each launching activity to ensure understanding and guidance in their adoption and implementation. The DOH will be responsible for producing the official online copy and mass reprinting of the manuscript for distribution to stakeholders.

### Implementation

The steering committee recommends DOH-led monitoring of short term outcomes (adherence to recommendations as reflected in the algorithms as indicators or measures) and long term outcomes (improved respiratory health outcomes in terms of the following measures or indicators: quality of life, symptoms of breathlessness, exercise capacity, exacerbations, hospitalizations, mortality, and lung function). Interval and frequency of monitoring will be dependent on the outcome being measured (i.e. short term outcomes such as adherence to recommendations may be monitored quarterly while long term outcomes such as mortality may be monitored annually). Quality of care studies and program evaluation research may aid and facilitate the monitoring and evaluation of the implementation of this CPG. May refer to the research implications section for the specific research studies.

### Updating

The PCCP Council on COPD shall assist DOH in evaluating for the need to update the CPG every 3 years or earlier as deemed necessary. Factors that may trigger update of the guideline include: (1) novel drugs, interventions, and technology that warranted investigation for inclusion in the standard of care of COPD patients, (2) noted practice variations that needs to be resolved, or (3) new evidences or global or local events that could affect the direction and strength of recommendations of the specific recommendation statement/s in the CPG. A formal letter of request for update shall be sent by the PCCP Council on COPD to DOH (Disease Prevention and Control Bureau, Evidence Generation Department) stating the rationale for the requested update. The DOH shall evaluate the request, provide corresponding response, and allocate funding if the update request was deemed valid.

## Research Implications/Gaps

Addressing the swiftly evolving landscape of COPD research requires comprehensive efforts to bridge existing gaps in disease management, treatment, prevention, and control. These gaps were unearthed during thorough evidence reviews, stand as focal points demanding attention and resolution.

Among the critical imperatives that emerged from these discussions is the pressing requirement for comprehensive evaluation studies pertaining to COPD management and the quality of care dispensed. Simultaneously, the meticulous assessment of intervention cost-effectiveness and the viability of its integration into primary care settings emerges as an equal imperative.

A meticulous examination of short-term outcomes, including augmented enrollment in prevention programs, enhanced case identification, increased criterion/evidence based inhaler utilization, and swift referrals to advanced care, assumes paramount significance. The availability of data in this sphere is crucial for a judicious evaluation of the efficacy of such initiatives. Additionally, local data concerning enhancements in QoL and the alleviation of COPD-related burdens, encompassing prevalence, exacerbations, hospitalizations, and mortality rates, emerges as an invaluable asset.

Efforts directed at enhancing diagnostic accuracy also demand meticulous attention. The precise utility of a composite approach, incorporating clinical scoring systems, peak flow meters, handheld spirometers, and facility-based spirometry, warrants comprehensive scrutiny to ascertain the most effective diagnostic modality.

Integral to the refinement of the current CPG is the development and validation of clinical questionnaires tailored specifically for COPD diagnosis and screening. Moreover, gaining insights into the values and preferences of Filipino COPD patients and their caregivers, especially in the rural areas, alongside an appraisal of the efficacy of self-management strategies and COPD action plans, emerges as a vital cornerstone for further advancements.

In summation, navigating the intricate realm of COPD research necessitates an unwavering commitment to bridging research gaps, culminating in the advancement of knowledge and improved care paradigms for those affected by this debilitating condition.

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