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CTS GUIDELINES AND POSITION PAPERS

CTS position statement: Pharmacotherapy in patients with COPD—An update

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ABSTRACT

RATIONALE: Since the last published Canadian Thoracic Society (CTS) COPD guideline in 2007 and the 2008 update – highlights for primary care, many new clinical trials have challenged COPD treatment practices. The current Canadian position statement provides the reader with an update on pharmacotherapy of patients with COPD as reviewed by the CTS.

OBJECTIVES: The objectives of this position statement are: 1) to summarize the literature on topics relevant to the pharmacological therapy of patients with stable COPD; and 2) to provide clinical guidance with evidence-based recommendations and expert-informed key messages for the pharmacological therapy for patients with stable COPD.

METHODS: The authors systematically reviewed the relevant literature focusing on randomized controlled trials and when available, systematic reviews of randomized controlled trials. The proposed key messages, based on scientific evidence and expert-informed opinion, were agreed upon by a majority consensus.

MAIN RESULTS: There is typically a significant delay in seeking medical care by patients with dyspnea, often waiting until symptoms affect the performance of activities of daily living. The diagnosis of COPD requires spirometry to confirm the presence of airflow obstruction in any patient presenting with symptoms and/or risk factors of COPD. An effective management plan for individuals with COPD should include: smoking cessation, vaccination and education. A number of non-pharmacological treatments are available for COPD patients with symptoms to improve outcomes such as self-management with coaching from a health care professional; pulmonary rehabilitation; supplemental oxygen in selected patients; and surgery.

Current pharmacotherapy for COPD has been shown to alleviate symptoms and prevent exacerbations and related complications such as hospital admissions. In symptomatic patients with stable COPD not having or having infrequent exacerbation, treatment should be started with inhaled LAMA or LABA monotherapy, and if experiencing persistent or increased dyspnea, exercise intolerance, and/or reduced health status despite use of monotherapy, patients should be considered for treatment *"step up"* with an inhaled LAMA plus LABA dual therapy. In this situation, the use of a single inhaler would be preferred to simplify the treatment regimen and minimize the cost. In patients with stable COPD experiencing exacerbations despite the use of LAMA or LABA monotherapy, treatment *"step up"* with inhaled LAMA plus LABA dual therapy should be considered unless a patient has concomitant asthma (Asthma/COPD overlap (ACO)). There has been recent interest in using biomarkers to identify patients who are more likely to respond to ICS. Most of the studies have demonstrated that high blood eosinophils could be valuable to predict an increase response in terms of reduction of exacerbation rate when treated with combination ICS/LABA; there is still uncertainty about the exact cut-off level of blood eosinophils having potential therapeutic value. If a patient is still experiencing exacerbations despite the use of LAMA and LABA dual therapy, treatment *"step up"* with LAMA plus ICS/LABA triple therapy can be considered. Because the superiority of inhaled triple or dual therapy may not be achieved in every patient, the notion of treatment *"step down"* may be a consideration in some patients. These patients would be those not demonstrating expected benefits or having side effects exceeding benefits. In any circumstance, when a physician decides using a treatment *"step down"*, this approach should be undertaken under close medical supervision.

Individuals with ACO are a population of medical interest, however, the paucity of original studies precluded evidence-based recommendations. The position statement, therefore, presents key messages from a survey which at best reflects the practice in our Canadian community and academic respirologists on assessment, diagnosis, and pharmacotherapy of ACO patients.

KEYWORDS
Position statement; COPD; ACO; ACOS; pharmacotherapy

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CONCLUSIONS: This position statement is an evolution towards personalized treatment, compared to the previous published CTS COPD guideline. It promotes approaches to match treatment decisions based on symptom burden and risk of future exacerbations. Personalized medicine becomes increasingly possible, but to make future progress, we will need clinical research to be more specific, including greater focus on or defining better subsets of patients that are characterized by specific biomarkers and disease severity.

RÉSUMÉ

JUSTIFICATION: Depuis les dernières lignes directrices publiées par la Société canadienne de thoracologie (SCT) en 2007 et actualisées pour le médecin de famille en 2008, de nombreux essais cliniques ont remis en question les pratiques relatives au traitement de la MPOC. Cet énoncé de position canadien présente au lecteur les plus récentes informations concernant la pharmacothérapie destinée aux patients souffrant de MPOC, telle que revue par la SCT.

OBJECTIFS: Les objectifs de cet énoncé de position sont : 1) résumer la littérature sur les sujets pertinents au traitement pharmacologique des patients souffrant d'une MPOC stable; et 2) présenter des directives comprenant des recommandations fondées sur les données probantes et des messages-clés fondés sur l'avis d'experts pour le traitement pharmacologique des patients souffrant d'une MPOC stable.

MÉTHODES: Les auteurs ont revu la littérature pertinente de manière systématique en privilégiant les essais contrôlés randomisés et, lorsque disponibles, les revues systématiques d'essais randomisés. Les messages-clés proposés, qui se fondent sur les données probantes et sur l'opinion d'experts, ont été approuvés par consensus obtenu à la majorité.

PRINCIPAUX RÉSULTATS: Les patients souffrant de dyspnée retardent généralement leur quête de soins médicaux jusqu'au moment où les symptômes commencent à affecter leurs activités quotidiennes. Le diagnostic de MPOC nécessite une spirométrie pour confirmer la présence d'une obstruction des voies respiratoires chez un patient qui présente des symptômes ou des facteurs de risque de MPOC. Un plan de prise en charge efficace pour les individus souffrant de MPOC devrait comprendre : la cessation du tabagisme, la vaccination et l'éducation. Un certain nombre de traitements non pharmacologiques sont disponibles pour les patients atteints de MPOC symptomatique afin d'optimiser les résultats, dont l'auto-prise en charge accompagnée des conseils d'un professionnel de la santé; la réadaptation pulmonaire; l'oxygène d'appoint chez certains patients; et la chirurgie.

Il a été démontré que la pharmacothérapie actuelle pour la MPOC soulage les symptômes et prévient les exacerbations ainsi que les complications qui en découlent, comme les hospitalisations. Chez les patients atteints de MPOC symptomatique stable avec ou sans exacerbations occasionnelles, le traitement devrait commencer par l'inhalation d'un anticholinergique à longue durée d'action (ACLA) ou d'un $Beta_2$ agoniste à longue durée d'action (BALA) en monothérapie, et dans les cas où la dyspnée, l'intolérance à l'exercice et la détérioration de l'état de santé persistent ou augmentent, une intensification du traitement devrait être envisagée pour ces patients en combinant l'inhalation d'un ACLA à celle d'un BALA en double thérapie. Dans une telle situation, l'usage d'un seul inhalateur devrait être privilégié afin de simplifier le régime de traitement et minimiser les coûts. Chez les patients atteints de MPOC stable qui ont des exacerbations malgré l'utilisation d'un ACLA ou d'un BALA en monothérapie, l'intensification du traitement par l'inhalation d'un ACLA associé au BALA en double thérapie devrait être envisagée, sauf dans les cas où le patient souffre d'asthme concomitant (chevauchement asthme/MPOC). Récemment, on assiste à un accroissement de l'intérêt pour l'utilisation de biomarqueurs afin de déterminer les patients qui sont les plus susceptibles de répondre aux CSI. La plupart des études ont démontré qu'un nombre élevé d'éosinophiles dans le sang pourrait être utile pour prédire une meilleure réponse en ce qui a trait à la réduction du taux d'exacerbation lorsque traité par une combinaison de CSI et de BALA; toutefois, l'incertitude demeure quant au seuil d'éosinophiles dans le sang pouvant avoir une valeur thérapeutique. Si le patient connaît encore des exacerbations malgré un double traitement par ACLA et BALA, l'intensification du traitement par l'ajout d'un ACLA au traitement CSI/BALA en trithérapie peut être envisagé. Puisque la supériorité du traitement par inhalation double ou triple pourrait ne pas être réalisable pour chaque patient, la notion de « diminution graduelle » du traitement pourrait être envisagée pour certains patients. Ces patients seraient ceux qui ne démontrent pas les bénéfices attendus ou qui ont des effets secondaires qui dépassent les bénéfices. Dans toute circonstance, lorsqu'un médecin décide d'avoir recours à une « diminution graduelle » du traitement, cette approche devrait être entreprise sous supervision médicale étroite.

Les personnes souffrants de chevauchement asthme/MPOC sont une population de grand intéretê médical. Toutefois, le nombre limité d'études originales empêche la formulation de recommandations fondées sur des données probantes. Cet énoncé de position présente donc des messages-clés issus d'une enquête qui, au mieux, reflète la pratique dans notre communauté canadienne et chez les pneumologues universitaires en ce qui concerne l'evaluation, le diagnostic et la pharmacothérapie dans le cas des patients souffrant de chevauchement asthma/MPOC.

CONCLUSION: Cet énoncé de position constitue une évolution vers le traitement personnalisé, comparativement aux lignes directrices de la SCT relatives à la MPOC publiées précédemment. Il favorise les approches qui visent à établir une correspondance entre les décisions thérapeutiques fondées sur le fardeau des symptômes et le risque d'exacerbations futures. La médecine personnalisée devient de plus en plus possible, mais pour progresser, la recherche clinique doit être plus spécifique, notamment en ciblant ou en définissant plus clairement des sous-ensembles de patients caractérisés par des biomarqueurs précis et par le degré de gravité de leur maladie.

Introduction

Since the last published Canadian Thoracic Society (CTS) COPD guideline in 2007[1] and the 2008 update – highlights for primary care,[2] many new clinical trials have challenged COPD treatment practices. Identifying important new evidence and assessing whether these findings warrant change in current practice is needed. Furthermore, a new Canadian statement and position on the pharmacotherapy of COPD is timely considering the recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) Report 2017.[3] In the GOLD Report 2017, as in the previous CTS COPD guideline, severity of airflow limitation is no longer considered in the treatment algorithm. Rather, pharmacotherapy is modified according to symptom burden and risk of COPD exacerbations. The current Canadian position paper provides the reader with an update on pharmacotherapy of patients with COPD as reviewed by the CTS.

Epidemiology and burden of COPD

From the Global Burden of Disease Study 2015,[4] the Chronic Respiratory Disease Collaborators concluded: « COPD and asthma are important contributors to the burden of non-communicable disease. Although much of the burden is either preventable or treatable with affordable interventions, these diseases have received less attention than other prominent non-communicable diseases like cardiovascular disease, cancer, or diabetes. » Although we may have made progress in the adoption of some evidence-based practice in the last decades, there remains a degree of nihilism about COPD and its treatment.

COPD is the fourth leading cause of death worldwide, and twice as many individuals die from COPD than from lung cancer.[5] Although historically, more men than women died from COPD, the gender gap in mortality has virtually disappeared.[6] While 4% of Canadians aged 35 to 79 self-reported with a doctor diagnosis of COPD, direct measurements of lung function from the Canadian Health Measures Survey (CHMS) indicate that 13% of Canadians demonstrated airflow limitation consistent with the diagnosis of COPD.[7] In the recent Canadian Cohort Obstructive Lung Disease (CanCOLD), a population-based study among randomly chosen adult Canadians 40 years of age and older, the prevalence of COPD, defined spirometrically, was 2.5 times higher than the rate of self-reported diagnosis and four-fold higher than self-reported rates from annual community surveys.[8] Smoking is the largest contributor to the COPD burden in countries at the higher end of the sociodemographic index (SDI) such as Canada (69.4% of COPD burden in high-SDI quintile countries) although a considerable proportion of COPD still remains unexplained.[4] COPD can have a devastating impact on patient wellbeing, family members, health care system, and society. It accounts for the highest rate of hospital admissions among major chronic illnesses in Canada.[9] The Conference Board of Canada has estimated that with the population aging, the combined direct and indirect costs of COPD will increase from $4 billion in 2010 to $9.5 billion by 2030—an increase of 140 percent.[10] This is an average compounding annual growth in the economic burden associated with COPD of 4.5 percent over the 2010–2030 period, a significant social and economic toll on Canadians.

Key messages from the last CTS COPD guideline that remain relevant

Since the last published CTS COPD Guidelines in 2007 and 2008,[1,2] key messages regarding disease management remain at the forefront:

1) Use spirometry in targeted populations for case finding of "early" and undiagnosed COPD for prompt intervention (including enhancing effectiveness of smoking cessation interventions);
2) Improve the treatment algorithms by incorporating accurate assessment of dyspnea and activity limitation and;
3) Use strategies to prevent and manage acute exacerbations, particularly in moderate to severe disease.

Spirometry measurements in targeted populations for case finding

The presence of symptoms is not a reliable indicator to make the diagnosis; spirometry is a prerequisite for the diagnosis of COPD. Spirometry testing should focus on patients at risk, particularly from smoking, and those having respiratory-relevant symptoms (i.e. dyspnea). However, patients with potential chronic respiratory disease may not raise respiratory symptoms with their general practitioner; they may attribute their symptoms to ageing and/or multi-causal explanations that lessen the importance of obtaining a diagnosis. Fifty percent or more of patients with COPD are still undiagnosed in Canadian family medicine practices.[11,12] Early diagnosis is a contentious issue, but it optimizes the opportunities to prevent worsening of disease and prevention of exacerbations. The population-based cohort study CanCOLD has shed light on the question of undiagnosed COPD. The study has shown for the first time that despite experiencing fewer overall exacerbations, the rate of moderate to severe exacerbations (i.e. those requiring health care utilization including emergency department (ED) visits and/or hospital admissions) among undiagnosed COPD patients is similar to that among diagnosed individuals.[12] These findings further support the need to diagnose COPD using objective measures when symptoms are present, in order to prevent this morbidity by providing proper therapy.

Spirometry is a safe, practical and reproducible breathing test that can be used in primary care to objectively determine lung function. However, it is important to appreciate that the clinical value of spirometry is critically dependent on the correct operation and accuracy of the spirometer, performance of the correct maximal breathing maneuver, selection of the best test results to use and correct interpretation. A recent systematic scoping review found that misdiagnosis of COPD most commonly occurred due to an incorrect spirometric threshold used for defining COPD; errors linked to the spirometry test itself; errors in differentiating COPD from other diseases; and finally, patient-related factors affecting spirometry interpretation (e.g. obesity).[13] Most of these errors were noted to take place predominantly in the primary care setting. These findings

support early diagnosis of COPD using objective measures with spirometry testing.

Improving symptom burden and preventing exacerbations in COPD patients

With the right treatment and support, people diagnosed with COPD can improve their health and reduce hospital admissions.[3] Current therapies are effective in reducing dyspnea and activity limitation, two of the most burdensome manifestations of COPD. Exacerbations can also be prevented with appropriate management. Management of COPD typically involves multiple interventions, including non-pharmacological and pharmacological therapies. Figure 1 presents an update from the last published CTS COPD Guideline 2007 and 2008[1,2] with an organized approach that includes COPD diagnosis with spirometry, evaluation of symptom burden and exacerbations with ongoing monitoring, assessment for concomitant asthma, and comprehensive management, i.e., pharmacological and non-pharmacological therapies.

Non-pharmacological management of COPD includes smoking cessation strategies, vaccination, self-management education, pulmonary rehabilitation and supplemental oxygen. Smoking cessation and supplemental oxygen in those with persistent resting hypoxemia, remain the only interventions with a proven mortality benefit in COPD. Non-pharmacological treatment for a smaller number of patients may also include ventilatory support, in particular non-invasive positive pressure ventilation, various forms of lung volume reduction (bronchoscopic and surgical interventions) and lung transplantation. Palliative care in patients with advanced COPD is another area that requires special attention. It encompasses approaches to symptom control to management of patients with refractory dyspnea and also patients with terminal disease approaching death. Managing dyspnea in patients with advanced COPD has been addressed in a separate CTS clinical practice guideline.[14]

Non-pharmacological management is an often neglected area of chronic respiratory care.

It is well known that emphasis should be given in practice to education and training in inhaler device technique. According to a systematic review on errors in inhaler use,[15] incorrect inhaler use remains unacceptably high outside of clinical trials. This may be a major obstacle to achieving good COPD control. As recommended in the GOLD report 2017,[3] instruction should be provided on inhalation technique and patient technique should be re-checked at each visit. Furthermore, the choice of inhalers should be individually tailored and will depend on access, cost, prescriber and most importantly, patient ability and preference. Another example of non-pharmacological management being neglected is access and referral to pulmonary rehabilitation (PR). According to a 2015 survey of PR in Canada,[16] despite an increase in the number of programs and patients enrolled since the previous survey in 2005, PR capacity has not kept pace with demand, with only 0.4% of eligible Canadians with COPD having access.[16] When asked, physicians who are regularly seeing COPD patients say that only 16% of their patients are referred to PR.[17] This is in contrast with the 34% of high-risk cardiac patients who have been referred to cardiac rehabilitation programs in Ontario.[18] Finally, an often forgotten non-pharmacological management principle in patients with advanced COPD is referral for end-of-life care services (e.g. palliative care, opiates for dyspnea relief, etc.).

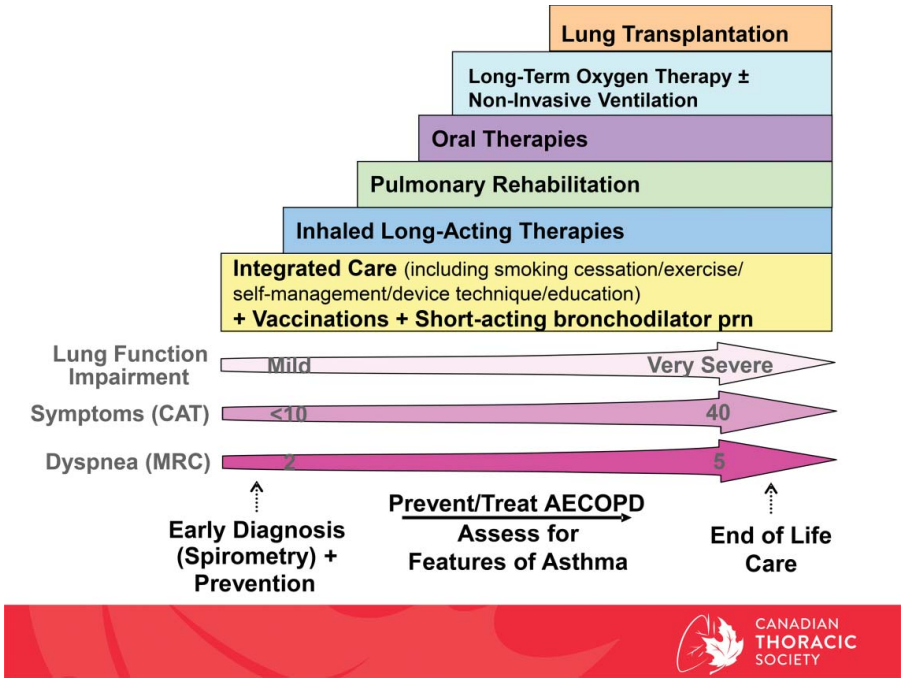

Figure 1. Comprehensive Management of COPD. Integrated approach of care that includes COPD diagnosis with spirometry, evaluation of symptom burden and risk for future exacerbations with on-going monitoring, assessment for features of asthma, and comprehensive management, both non pharmacologic and pharmacologic. CAT = COPD assessment test; MRC = Medical Research Council; SABD PRN = short-acting bronchodilator as needed; AECOPD = acute exacerbation of COPD; Inhaled Long-Acting Therapies = long-acting muscarinic antagonist and/or long-acting B2-agonist and/or inhaled corticosteroid; LTOT = long-term oxygen therapy.

New review and CTS COPD position statement

We did not review non-pharmacological therapies in this position statement, as recommendations have been promulgated through recent national and international guidelines.[3,19] For example, pulmonary rehabilitation has been addressed in the CTS clinical practice guideline: "Optimizing pulmonary rehabilitation in chronic obstructive pulmonary disease – practical issues".[20] We did not review, COPD related to α1-antitrypsin deficiency, as recommendations on testing and treatment have been addressed in a separate CTS clinical practice guideline.[21]

This position statement focuses on the pharmacological therapy of COPD. This position paper will be updated in accordance with the CTS Living Guideline Model www.cts-sct.ca/guidelines which includes a process for guideline review at least every 3 years to determine whether guideline updates are required. However, based on new evidence post March 2017 (literature search cut-off date), an update will be provided in 2018 and in following years.

The **overall goal** of the CTS COPD position statement is to help clinicians to appropriately match therapeutic decision to the clinical status of each individual patient. This is a first step towards personalizing therapy based on increasing individual characterization, i.e., COPD patient phenotypes.

The **specific objectives** are: **1)** to summarize the literature on topics relevant to the pharmacological therapy of patients with stable COPD; and **2)** to provide clinical guidance with evidence-based recommendations and expert-informed key messages for the pharmacological therapy for patients with stable COPD.

Target patient population

Patients with stable COPD, including those who have concomitant asthma (Asthma/COPD overlap).

Target users

The recommendations provided herein are intended for use primarily by respirologists, internists, primary care physicians, pharmacists, nurse practitioners, respiratory educators and certified respiratory educators (CRE). This document should also be useful to patients and patient advocates. Finally, health care decision makers may also use this in policy processes to inform coverage decisions.

Methodology

The position statement was developed in accordance with CTS requirements for a position statement (www.cts-sct.ca/guidelines), which is derived from the CTS guideline production methodology.[22] A working group was created within the CTS COPD Clinical Assembly. The lead authors utilized the AGREE II checklist to guide the development of this position statement. The COPD working group identified two relevant questions pertaining to the pharmacotherapy of COPD and one question to the specific diagnosis and pharmacotherapy of ACO (see subsection "Selection and Formulation of Key Questions"). These questions were selected based on the needs to assess new evidence and whether these findings warrant change in current practice. Each section provides a literature summary, recommendations from a systematic review that informs key messages for each question vetted by the working group members. The recommendations were classified using the GRADE system, as adapted for use by the American College of Chest Physicians for the level of evidence and were agreed upon by a majority consensus. The key messages provide a summary of the most important recommendations and include a step-by-step approach that will be useful in guiding practical choices by clinicians.

In accordance with the CTS guideline production methodology, this position statement underwent both internal and external review. The external review was conducted by two international COPD experts who were not part of the CTS. The internal review was conducted by three Certified Respiratory Educators (members of the Canadian Respiratory Health Professionals Assembly); one respirologist from another CTS Clinical Assembly who completed an AGREE II score sheet; and three Executive Members of the Canadian Respiratory Guidelines Committee. Original reviews and responses to reviews are posted along with the position statement and all authors' conflicts of interest at www.cts-sct.ca/guidelines. The CTS Executive approved the final document for publication.

Representation on the COPD position statement committee

The COPD working group was constituted of ten respirologists, two primary care physicians appointed by the College of Family Physicians of Canada, one pharmacist and one patient with COPD. These healthcare professionals are all directly involved in the clinical management of COPD patients in different health care settings. They had expressed interest in being part of the working group or were actively invited based on their expertise. Members of the working group were assigned to 1 of 3 writing groups that addressed each question. All members reviewed and agreed on the overall content of this position statement.

Selection and formulation of key questions

The COPD working group developed key clinical questions using the Problem/population Intervention/prognostic factor/exposure, Comparison, Outcome (PICO) format, which were then reviewed, revised and agreed upon by members from each writing group (details in Table 1). The PICO questions were selected to address the concept that personalized treatment of COPD in clinical practice should be guided by recognized treatable and/or preventable clinical features such as symptom burden, health status, and risk of exacerbations.

The members also agreed that dyspnea/exercise tolerance/health status (but not disease progression and/or mortality) would serve as the most relevant outcomes for PICO 1 and exacerbations would serve as the most relevant outcome for PICO 2.

Literature searches

Systematic reviews in Medline OVID were conducted for interventions identified in each PICO question starting with a search

for guidelines and systematic reviews (Tables 1 and 2). The search for the ACO PICO question yielded primarily opinion papers and, for this reason, data were collected and expert-informed key messages formulated using features of a Delphi technique.[23] The review was limited to publications between January 2008 to March 6, 2017 for PICO questions 1 and 3 (starting from the review date of the prior CTS guideline) and between February 2014 and March 6, 2017 for PICO question 2 (starting from the review date of the "Prevention of Acute Exacerbation of Chronic Obstructive Pulmonary Disease: American College of Chest Physicians and Canadian Thoracic Society Guideline"). Literature search results informing recommendations for each question are presented in Table 2.

Study selection and data extraction

Studies were excluded if not related to COPD. Only randomized clinical trials (RCTs) were kept for further review and inclusion into the evidence review. The inclusion/exclusion exercise and the review of full text articles for data extraction were completed by pairs of reviewers to ensure the selection criteria were met and agreed upon. The evidence tables are posted along with the position statement at www.cts-sct.ca/guidelines.

Recommendations

All of the studies included in the evidence review informed the recommendations and their associated grades. The recommendations were devised using recognized document evaluation tools to assess and choose the most appropriate studies and evidence to extract meaningful data in a balanced and unbiased fashion. All recommendations were classified using the GRADE system, as adapted for use by the American College of Chest Physicians (CHEST).[24] In instances where there was insufficient evidence, but a recommendation was still warranted, a weak suggestion was developed and consensus-based (CB) replaced the grade. Completed recommendations and supporting text were reviewed by each writing group and revised before they were shared with the entire working group. Recommendations and supporting text were sent out to all the members of the working group asking them to identify any recommendations deemed controversial based on their wording and/or

Table 1. CTS COPD Position Statement PICO questions.

PICO 1: How does a clinician choose appropriate maintenance pharmacotherapies in patients with stable COPD to improve dyspnea, exercise tolerance, physical activity and health status?			
PICO elements			
Population	Intervention(s)	Comparator	Outcomes
Adults with stable COPD*, chronic bronchitis, emphysema	Maintenance inhaled therapy, alone or in combination: short-acting anticholinergic, short-acting beta-agonists, long-acting bronchodilators, long-acting beta-agonists, long-acting anticholinergic, long-acting muscarinic antagonists, inhaled corticosteroids, dual long-acting bronchodilators, combination ICS/LABA, triple therapy; oral therapy, alone or in combination (s): methylxanthines, theophylline, antibiotics, n-acetylcysteine, PDE-4 inhibitors, roflumilast.	Placebo, combination therapies compared to single modality, head to head comparison	Dyspnea, exercise, exercise tolerance, exercise capacity, health-related quality of life
PICO 2: How does a clinician choose appropriate maintenance pharmacotherapies in patients with stable COPD to reduce the risk of frequent exacerbations?			
Adults with stable COPD*, chronic bronchitis, emphysema	Maintenance inhaled therapy, alone or in combination: short-acting anticholinergic, short-acting beta-agonists, long-acting bronchodilators, long-acting beta-agonists, long-acting anticholinergic, long-acting muscarinic antagonists, inhaled corticosteroids, dual long-acting bronchodilators, combination ICS/LABA, triple therapy; oral therapy, alone or in combination (s): methylxanthines, theophylline, antibiotics, n-acetylcysteine, PDE-4 inhibitors, roflumilast.	Placebo, combination therapies compared to single modality, head to head comparison	Exacerbations requiring change in medication (antibiotic and/or prednisone), ER and hospital admissions/readmissions, time to first exacerbation, exacerbation rate
PICO 3: How does a clinician approach the treatment of patients who have both Asthma and COPD (including the definition of ACO, assessment and management differences)?			
Adults with asthma-COPD symptoms —greater than 40 years of age; Asthma-COPD Overlap Syndrome (ACOS); Asthma-COPD Overlap (ACO); eosinophils and COPD assessment and/or management; eosinophils and ACO/ACOS	Maintenance inhaled therapy: long acting anticholinergic; short acting anticholinergic alone and in combination with short-acting beta-agonists; inhaled corticosteroids; long-acting beta-agonists; combination of long-acting anticholinergic, inhaled corticosteroids, and long-acting beta-agonists; should not include short acting reliever medications (short-acting beta agonists alone)	Placebo, combination therapies compared to single modality, head to head comparison	Any outcome

*Stable COPD meaning not currently having an exacerbation

Table 2. Literature search results informing recommendations.

Section	Topic	Abstracts reviewed, n	Abstracts accepted for full review, n	Publications informing recommendations for practice, n (references)
PICO 1	How does a clinician choose appropriate maintenance pharmacotherapies in patients with COPD to improve dyspnea, exercise tolerance, physical activity and health status?	689	156	111
PICO 2	How does a clinician choose appropriate maintenance pharmacotherapies in COPD to reduce the risk of frequent exacerbations?	237	88	88
PICO 3	How does a clinician approach the treatment of patients who have both Asthma and COPD (including the definition of ACO, assessment and management differences)?	269	54	2

grade. Members of the working group were then sent revised statements and were asked to vote on the recommendations. Any recommendations that were not agreed upon by a majority were revised based on feedback and included in the second round of voting. For the purposes of this document, when the comparison treatment arm refers to "placebo therapy," it applies to the use of a prn short-acting beta-2-agonist only.

Summary of evidence

Section 1 – Improving symptom, exercise tolerance and health status in stable COPD

PICO 1: How does a clinician choose appropriate maintenance pharmacotherapies in patients with stable COPD to improve dyspnea, exercise tolerance, physical activity and health status?

Alleviation of symptom burden (e.g. dyspnea), improving exercise tolerance, physical activity and health status are key goals of COPD management.[1,3] This section of the COPD position statement specifically addresses the use of pharmacological maintenance therapies and their impact on patient-related outcomes (PRO) in patients with stable COPD. The importance of effective non-pharmacological therapies that target these PRO in COPD have been discussed previously and reviewed elsewhere.[1,3]

Dyspnea, a subjective experience of unpleasant, discomfort with breathing, is a cardinal symptom of COPD.[1,3] Dyspnea is associated with decreased exercise intolerance, reduced health status and poor prognosis in COPD. Pathophysiological mechanisms for dyspnea and exercise intolerance in COPD have been well described elsewhere.[25] Dyspnea measurement in clinical practice using a validated tool such as the Medical Research Council (MRC) dyspnea scale is important in determining COPD disease severity; moderate to severe COPD is associated with MRC scores 3–5.[1] Overall symptom burden and health status can be assessed clinically with a validated and simple to use measurement tool such as the COPD Assessment Test (CAT); a CAT score of $\geq$10 (out of possible maximum score of 40) suggests significant symptom burden and impairment in health status.[3,26]

Bronchodilators are the mainstay of maintenance pharmacotherapy in stable COPD. Bronchodilators reduced dyspnea that is a consequence of improving lung function (FEV_1), reducing resting hyperinflation and gas trapping, and reducing dynamic hyperinflation during exercise. Due to better efficacy and safety profiles, inhaled bronchodilators are preferred over oral bronchodilators (e.g. theophyllines). The two main classes of inhaled bronchodilator drugs are beta-2-agonists and antimuscarinics (or anticholinergics). Both classes of inhaled medications are available in short-acting (taken on a prn basis or 4 times or more daily) beta-2-agonists (SABA) and antimuscarinics (SAMA) and long-acting (taken once or twice daily) beta-2-agonists (LABA) and antimuscarinics (LAMA). Inhaled long-acting bronchodilators are preferred over short-acting bronchodilators (SABD) for regular maintenance use except in less symptomatic individuals (e.g. MRC score 1–2, CAT score $<$ 10) or for those with intermittent symptoms.

Conclusions from the systematic literature review (for Key Messages, see Box 1)

For maintenance therapy in patients with stable COPD, and with the intention of alleviating symptom burden (e.g. dyspnea), improving exercise tolerance, physical activity, and health status:

1. We *recommend* the use of an inhaled long-acting bronchodilator, either LAMA or LABA monotherapy, to reduce dyspnea, improve exercise tolerance, and improve health status in stable COPD patients[27–48,32,33,37,38,40,44,49–60] (Grade 1A).
2. We *suggest* that in stable COPD patients who experience persistent dyspnea, exercise intolerance, and/or poor health status despite use of inhaled LAMA or LABA monotherapy that they be considered for treatment "*step up*" with LAMA plus LABA dual therapy[32,61–71, 70,72–76] (Grade 2A).
3. We *suggest* the use of a treatment with an inhaled long-acting bronchodilator(s), i.e. LAMA, LABA, or LAMA plus LABA dual therapy, to improve physical activity levels in stable COPD patients[30,43,77–80] (Grade 2A).
4. We *suggest* in stable COPD patients without ACO who have persistently poor health status despite the regular use of a LABA, to "*step up*" therapy to an inhaled LAMA plus LABA dual therapy rather than to inhaled ICS/LABA combination[81,82] (Grade 2B).
5. There is *insufficient evidence* in stable COPD patients to determine whether inhaled LAMA plus ICS/LABA triple therapy confers additional benefit to inhaled LAMA plus LABA dual therapy in reducing dyspnea, improving exercise tolerance and activity levels, or improving health status.[83,84] However, in stable COPD patients with high symptom burden and poor health status despite the use of inhaled LAMA plus LABA dual therapy, "*step up*" of treatment to LAMA plus ICS/LABA triple therapy may be considered (CB).
6. There is *insufficient evidence* in stable COPD patients to determine whether treatment "*step down*", i.e.,

inhaled triple therapy to inhaled LAMA plus LABA dual therapy or inhaled LAMA plus LABA dual therapy to LAMA or LABA monotherapy can be safe and/or without reducing patient benefits (i.e., dyspnea, exercise tolerance and health status). However, in stable COPD patients with no improvement of dyspnea, exercise tolerance or health status despite the use of triple inhaled therapy or inhaled LAMA plus LABA dual therapy, treatment *"step down"* may be considered (CB).

7. There is *insufficient or equivocal evidence* in stable COPD patients to determine whether the addition of an oral therapy, such as theophyllines,[85,86] phosphodiesterase-4-inhibitors,[87–89] mucolytics,[90] statins,[91–93] anabolic steroids,[94,95] oral Chinese herbal medicines,[65,96–98] or phosphodiesterase-5-inhibitors,[99–102] confers additional benefit to inhaled LAMA or LABA monotherapy, or LAMA plus LABA dual therapy in reducing dyspnea, improving exercise tolerance and activity levels, or improving health status (Grade 2C).
8. We *recommend* against treatment with ICS monotherapy in stable COPD patients (CB).

Box 1. Improving symptom burden, exercise tolerance and health status in stable COPD

PICO 1: How does a clinician choose appropriate maintenance pharmacotherapies in patients with stable COPD to improve dyspnea, exercise tolerance, physical activity and health status?

Key Messages:

1) In symptomatic patients with stable COPD, treatment should be started with inhaled LAMA or LABA monotherapy, and if experiencing persistent or increased dyspnea, exercise intolerance, and/or poor health status despite use of monotherapy, patients should be considered for treatment *"step up"* with an inhaled LAMA plus LABA dual therapy. In this situation, the use of a single inhaler would be preferred to simplify the treatment regimen and minimize the cost. Recommendations #1, 2, 3, 4
2) In stable COPD patients with increasing symptom burden, exercise intolerance, and/or reduced health status despite the use of an inhaled LAMA plus LABA dual therapy, treatment *"step up"* to LAMA plus ICS/LABA triple therapy may be considered (the main indication is exacerbation prevention). Recommendation #5
3) In stable COPD patients with no improvement of dyspnea, exercise tolerance, physical activity or health status despite the use of inhaled triple therapy or inhaled LAMA plus LABA dual therapy, treatment *"step down"* may be considered, but patients will require careful follow up for any evidence of clinical deterioration. Recommendation #6
4) ICS monotherapy should not be used in stable COPD patients. Recommendation #8

The summary of the most important evidence-based recommendations on the pharmacotherapy treatment and a step-by-step approach to guide practical choices is shown in Figure 2.

Section 2 – Preventing acute exacerbation in stable COPD

PICO 2: How does a clinician choose appropriate maintenance pharmacotherapies in patients with stable COPD to reduce the risk of frequent exacerbations?

Preventing acute exacerbations of COPD (AECOPD) is a key goal of COPD management.[1,3] An AECOPD is defined as an acute worsening of respiratory symptoms that results in a requirement for additional therapy.[3] This section of the position statement specifically addresses the use of inhaled and oral pharmacologic maintenance therapies demonstrated to be effective in preventing AECOPD in patients with stable COPD. These current recommendations have been revised and updated from the 2015 Prevention of Acute Exacerbations of COPD – American College of Chest Physicians and Canadian Thoracic Society Guideline document,[19] i.e. to include new publications from February 2014 to March 6, 2017. Some recommendations have been revised to account for additional research findings or have had their strength updated to reflect more recently published literature. The number of recommendations for the specific purpose of preventing AECOPD in patients with stable COPD has been reduced to focus on recommendations with the highest clinical impact. The importance of effective non-pharmacological therapies that target preventing exacerbations, and complications such as ED visits and hospital admissions in COPD have been discussed previously and reviewed elsewhere.[1,3]

Exacerbations are to COPD what myocardial infarctions are to coronary artery disease: they are acute, trajectory changing and often deadly manifestations of a chronic disease.[19] Exacerbations cause frequent hospital admissions, relapses, and readmissions; contribute to death during hospitalization or shortly thereafter; dramatically reduce quality of life, and hasten a progressive decline in pulmonary function, a cardinal feature of COPD. Admission to hospital due to AECOPD is the most frequent cause for acute hospitalization in adult in Canada.[9]

The best way to identify COPD patients susceptible to exacerbations is through their exacerbation history, where frequent exacerbations predict risk of future events.[103] An exacerbation-like respiratory event is a trigger for patients to come to the attention of the health care system and for a physician to consider the diagnosis of COPD. The severity of AECOPD is stratified as mild – when the changes in clinical symptoms require an increased use of as-needed bronchodilators but no changes in maintenance treatment; moderate – when changes in medication such as the use of antibiotics and/or systemic corticosteroids are required; and severe – when ED visit or hospitalization is necessary.[19] In the CanCOLD study, individuals with diagnosed COPD reported 0.63 exacerbations per person-year.[12] Overall, exacerbations of any severity were reported by 40%, and moderate to severe exacerbations by 32% of individuals with diagnosed COPD. An important and achievable goal of therapy in the management of stable COPD is to decrease the frequency and reduce the severity of AECOPD. Furthermore, providing proper

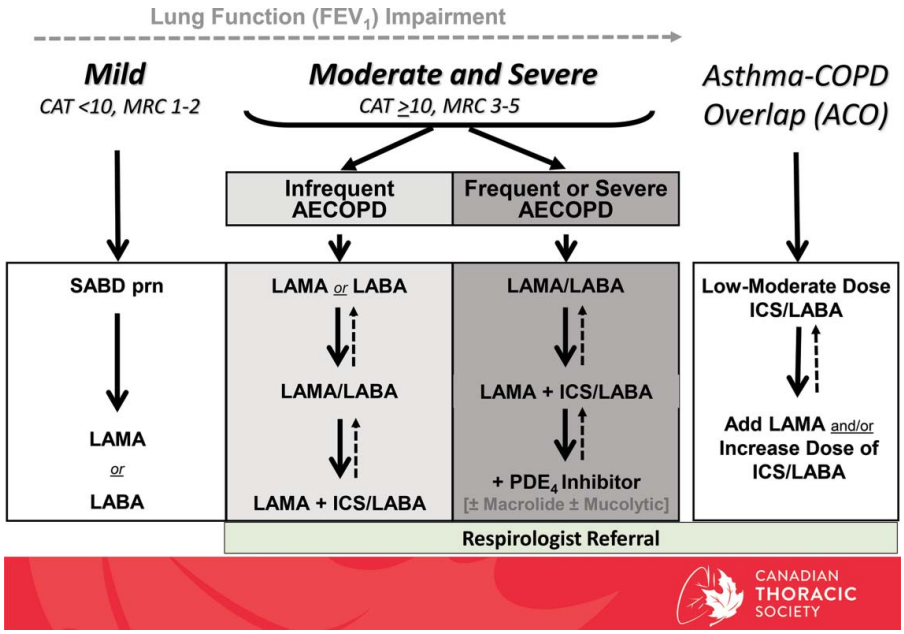

Figure 2. COPD Pharmacotherapy. Suggested COPD pharmacotherapy promoting an approach that matches treatment decisions with symptom burden and risk of future exacerbations. Solid arrows indicate step up therapy to optimally manage symptoms of dyspnea and/or activity limitation, as well as the prevention of AECOPD where appropriate. Dashed arrows indicate potential step down of therapy, with caution, and with close monitoring of the patient symptoms, exacerbations and lung function. Frequent AECOPD is ≥2 events requiring antibiotics ± systemic corticosteroids over 2 years; *or* ≥1 Severe AECOPD requiring hospitalization. As-needed (prn) use of short-acting bronchodilator should accompany all recommended therapies. CAT = COPD assessment test; MRC = Medical Research Council; SABD prn = short-acting bronchodilator as needed; AECOPD = acute exacerbation of COPD; LAMA = long-acting muscarinic antagonist; LABA = long-acting B2-agonists; ICS = inhaled corticosteroid; PDE_4 = phosphodiesterase-4.

preventive therapy in patients at increased risk of exacerbation will reduce and prevent ED visits and hospital admissions.

Conclusions from the systematic literature review (for Key Messages, see Box 2)

For maintenance therapy in patients with moderate to very-severe COPD, and with the intention of preventing moderate to severe AECOPD:

1. We *recommend* the use of an inhaled LAMA (Grade 1A) or an inhaled LABA (Grade 1B) compared with placebo (i.e. SABD prn) to prevent AECOPD.[19,59,104–109]
2. We *recommend* the use of an inhaled LAMA as a preferred choice compared with an inhaled LABA to prevent AECOPD (Grade 1B).[19,110]
3. We *recommend* an inhaled LAMA (Grade 1A) or *suggest* an inhaled LABA (Grade 2C) compared with an inhaled short-acting muscarinic antagonist to prevent AECOPD.[19,51,108]
4. We *recommend* inhaled LAMA plus LABA dual therapy for patients experiencing AECOPD despite the use of inhaled LAMA or LABA monotherapy (Grade 1C).[19,74,111–118]
5. We *recommend* combination ICS/LABA compared to placebo (Grade 1B) or an inhaled LABA (Grade 1C) to prevent AECOPD.[19,119–125]
6. We *recommend* inhaled LAMA plus LABA dual therapy as a preferred choice compared with ICS/LABA combination therapy to prevent AECOPD (Grade 1C).[19,116,117,126–131]
7. We *recommend* LAMA plus LABA/ICS triple therapy to prevent AECOPD for patients experiencing AECOPD despite the use of inhaled LAMA (Grade 1B) or ICS/LABA (Grade 1C).[19,106,132–135]
8. We *recommend* the use of oral roflumilast to prevent AECOPD for patients with chronic bronchitis and a history of at least one exacerbation in the previous year despite long-acting inhaled therapy (Grade 1B).[19,136–141]
9. We *suggest* treatment with oral N-acetylcysteine (600 mg po BID) to prevent AECOPD for patients with chronic bronchitis, a history of at least one exacerbation in the previous year, and on long-acting inhaled therapy (Grade 2B).[19,142–147]
10. We *suggest* a macrolide as maintenance therapy to prevent AECOPD for patients with a history of recurrent moderate or severe COPD exacerbations in the previous year despite long-acting inhaled therapy (Grade 2A).[19,126,148–151]
11. We *suggest* treatment with oral slow-release theophylline* to prevent AECOPD for patients on long-acting inhaled therapy (Grade 2B).[19]

Although recent evidence supports the benefit of inhaled LAMA plus LABA dual therapy in preventing AECOPD[130] compared to a combination of ICS/LABA, further prospective comparisons are necessary, particularly in patient subgroups with 2 or more exacerbations per year or those with very severe airflow obstruction. These new data would suggest that for COPD patients who don't have concomitant asthma, step up from LAMA or LABA monotherapy to a LAMA plus LABA dual therapy is preferred over step up to combination ICS/LABA. Regardless, it is important to emphasize that ICS should not be used as monotherapy in COPD to prevent exacerbations and when used should only be combined with an inhaled LABA

i.e. ICS/LABA. This has been highlighted in previous CTS[1] and joint CHEST/CTS guidelines.[19] Furthermore, when a combination of ICS/LABA is used, high doses of ICS[1] are typically not needed to achieve optimum benefit in COPD, as recently shown by a relatively flat dose-response curve.[152] More recently, considering the potential for ICS side effects (pneumonia, cataract, osteoporosis, etc.) that have been demonstrated in many RCTs[152,153] and administrative database studies,[154] step down ICS or stepwise ICS withdrawal has been proposed in COPD patients on ICS treatment. In one recent large trial, patients with COPD receiving combined inhaled treatment with a LAMA plus ICS/LABA who underwent stepwise ICS withdrawal did not experience significantly increased exacerbation rates.[128] The overall exacerbation rate in both groups was quite low (about 0·5 exacerbations per patient per year) and 1/3 of participants were not on ICS at screening (before the study). Finally, there was a statistically significant reduction in FEV_1 of 43 ml after ICS withdrawal at the end of the study and the number of deaths was numerically higher in the ICS withdrawal group (n = 40) compared to the ICS continuation group (n = 34).

If inappropriate therapy was previously initiated, step down should be undertaken. However, if appropriate therapy was initiated and treatment was shown to be effective, step down may not be appropriate. Given the significantly negative consequences of AECOPD, including hospitalization and death, the panel felt this could only be considered in patients at low risk of morbidity and mortality, and after a period of considerable stability. Moreover, while awaiting further objective proof supporting the safety of this approach, close supervision would be mandatory if the decision is made to step down, including monitoring of lung function and the re-occurrence of AECOPD.

There has been recent interest in using biomarkers to identify patients who are more likely to respond to ICS, and it has been suggested that blood eosinophils could predict benefit with ICS therapy in COPD. Most of the studies[155–157] except one[158] have demonstrated that high blood eosinophils could be valuable to predict an increase response in terms of reduction of exacerbation rate when treated with combination ICS/LABA. However, all these studies were secondary analyses or post hoc subgroup analyses. Furthermore, there is still uncertainty about the exact cut-off level of blood eosinophils having potential therapeutic value. Some studies[155,157] have shown a better response in patients with blood eosinophils ≥2% while in other studies[159] a cut-off of 4% or eosinophil count >300 cells/μL has been suggested. Data suggests that in COPD, blood eosinophil levels >340 cells/μL is associated with a 1.76 fold increased risk of severe exacerbations[160]; however using the 2% cut-off in this study did not predict increased risk of exacerbations. Finally, blood eosinophils demonstrated reasonable repeatability over 1 year in a population-based cohort of COPD patients in primary care.[161]

Box 2. Preventing acute exacerbation in stable COPD

PICO 2: How does a clinician choose appropriate maintenance pharmacotherapies in patients with stable COPD to reduce the risk of frequent exacerbations?

Key messages:

1) In stable COPD patients susceptible to exacerbations, LAMA or LABA inhaled monotherapy can be used to prevent moderate to severe exacerbations
   - 1.1) LABA or LAMA are superior to SABD; Recommendation #1
   - 1.2) LAMA is superior to LABA. Recommendation #2
2) In patients with stable COPD experiencing exacerbations despite the use of LAMA or LABA monotherapy, treatment *"step up"* with inhaled LAMA plus LABA dual therapy should be considered
   - 2.1) LAMA plus LABA dual therapy is superior to LAMA or LABA monotherapy; Recommendation #4
   - 2.2) LAMA plus LABA dual therapy is preferred to combination ICS/LABA to prevent AECOPD in COPD patients with infrequent (1 or less mild or moderate AECOPD/year) (except in COPD patients with features of asthma) Recommendation #6
3) In patients with stable COPD experiencing exacerbations despite the use of LAMA and LABA dual therapy, treatment *"step up"* with LAMA plus ICS/LABA triple therapy can be considered (unknown if triple therapy superior to LAMA plus LABA dual therapy: ongoing trials).
4) In stable COPD without exacerbation (none or exacerbation that has been both infrequent and exclusively mild), treatment *"step down"*, i.e., stepwise ICS withdrawal may be cautiously considered, but careful monitoring and close clinical follow-up for recurrent AECOPD and any deterioration is mandatory.
5) In stable COPD susceptible to exacerbations despite being on optimal inhaled therapy, oral therapies that include
   - 5.1) PDE_4-inhibitors and mucolytics may be considered in patients who still have exacerbations. Recommendations #8, 9, 11
   - 5.2) macrolides may be considered in patients who have recurrent exacerbations. Recommendations #10
6) Systemic corticosteroids should not be used for maintenance therapy.

The summary of the most important evidence-based recommendations on the pharmacotherapy treatment and a step-by-step approach to guide practical choices is shown in Figure 2.

[1] Low to moderate dose ICS <500 ugs fluticasone propionate or <1000 ugs budesonide; high dose ICS >=500 ugs fluticasone propionate or >=1000 ugs budesonide.

*Clinical remark: Theophylline has a relatively narrow therapeutic window, and the lowest effective dose should be used in prescribing theophylline to avoid adverse effects. Theophylline use requires close vigilance to avoid serious drug interactions which could lead to significant changes in serum theophylline levels and serious toxicity.

Section 3 –Asthma/COPD overlap (ACO)

PICO 3: How does a clinician approach the treatment of patients who have COPD and features of asthma?

Most of the evidence we have on the pharmacotherapy of COPD comes from RCTs that have excluded patients who have features of asthma. There is a growing recognition that many COPD patients may also present with features of asthma, thus making an accurate and singular diagnosis challenging. These patients are often labeled as having ACO. This section of the position statement specifically addresses diagnosis and pharmacotherapy in patients with ACO. The current recommendations could not be based on reviewed publications because only 2 articles were selected for data extraction, as most of the studies published are opinion papers. For this reason, key messages in our position statement were determined using a survey with features of a Delphi technique.[23]

Although the terminology and discussion surrounding ACO is relatively new, the concept of asthma and COPD overlapping is not. Fletcher coined the term "the Dutch Hypothesis" in the 1960's and ever since, there has been ongoing debate regarding the validity of this explanation for the pathophysiology of obstructive lung disease.[162–164] In recent years, there has been a greater push to further our understanding of ACO and assessing its impact on clinical practice, largely driven by the evolution of the inhaled medications available for both asthma and COPD, and more specifically the role of ICS in COPD. Clinicians now more than ever need clarity on the definition and diagnosis of ACO as the approach to the inhaled medication treatment for an ACO patient may differ from that of a patient with asthma or COPD alone. Unfortunately, despite this need and the plethora of articles published on this topic, many significant gaps in knowledge around ACO currently exist.

This knowledge gap presented several challenges in the preparation of this section regarding the diagnosis and pharmacotherapy of ACO. First, there is no universally accepted definition or diagnostic criteria for ACO. The Spanish consensus paper[165] agreed upon a combination of six major and minor criteria, which included both clinical and physiologic components. These major and minor criteria differ slightly from the ones proposed by Sin et al.[166] Both of those reports differ from the approach recommended in the 2015 Global Initiative for Asthma (GINA) and GOLD recommendations. Several other articles have been written on diagnostic criteria,[165–167] all with differing opinions. This lack of consensus affects our understanding of the impact, management and outcomes of ACO. To highlight the challenges faced as it pertains to ACO, its prevalence has been reported to vary from 15–45% depending on the definition used.[168,169] Although both a recent systematic review and a meta-analysis report higher health care utilization and worse outcomes for ACO patients when compared to asthma or COPD alone, both articles highlight that without a consensus definition or diagnostic criteria, there are significant limitations to the reliability of the data.[170,171]

Secondly, there are no consistent recommendations regarding the evaluation of patients with suspected ACO. There remains no consistent agreement among experts as to which historical factors are required (e.g. patient-reported vs physician diagnosis of previous asthma); physiologic criteria on spirometry (e.g. the degree of reversibility, i.e., 12% and 200 ml or 15% and 400 ml, or frequency of demonstrating reversibility); the role of biomarkers (blood and/or sputum eosinophil levels, IgE, FeNO and allergy skin tests are all debated without consensus on cut-off levels or their significance if present).[172–174]

Lastly, there are no randomized controlled pharmacotherapy studies in this patient population. The majority of asthma RCTs exclude smokers and the majority of COPD trials exclude patients with a history of asthma or who demonstrate significant bronchial reversibility. Sin et al[166] reviewed the inclusion and exclusion criteria of recent large phase 3 COPD and asthma clinical trials and found that the likely ACO population was systematically excluded from all of the trials. Thus, the majority of the pharmacotherapy recommendations for patients with ACO are consensus based.[166,167,175] The CTS COPD Clinical Assembly highlights the urgent need for well-designed RCTs to support clinical decision making for these patients.

As a result of the limitations in the literature regarding the definition, assessment, diagnosis and treatment of patients with ACO, the authors of this position statement sought this opportunity to provide readers of this statement with a Canadian perspective on the evaluation, diagnosis and treatment of patients with ACO. The position statement process included two e-surveys with features of a Delphi technique, and after each round, results were discussed and finalized within the ACO author group. The key messages were approved by all authors of this position statement.

In order to achieve a broader Canadian perspective, a decision was made by the authors to include CTS respirologist members from across Canada (both academic and community) to participate in this two-part survey, to gain insights on ACO. In total, 93 respirologists from across Canada were invited to participate in the survey. In the first round, we received 34 responses, and we were able to gain consensus (>80% agreement) on the components of the assessment and treatment of patients with ACO. However, there was disagreement on the specific diagnostic criteria and definition of reversibility on spirometry that would be consistent with ACO. Thus, a second survey with features of a Delphi technique was conducted, focusing on these two topics. We received 23 responses and an agreement was achieved on a revised diagnostic criteria but a consensus was not achieved on the definition of reversibility. The full summary of the questions and results of the full survey is available separately online at www.cts-sct.ca/guidelines.

Based on information from this survey and further input by the authors of the position statement, we submit the

Table 3. Proposed assessment and diagnostic criteria of patients suspected of having ACO.

Assessment of a Patient with suspected ACO	1. Risk factors for COPD
Must be asked	2. Symptoms compatible with COPD (ex. cough, sputum, dyspnea and/or exercise limitation, exacerbations)
	3. History of Allergy and/or Atopy, Asthma (defined as a. history of asthma in childhood, physician diagnosed asthma, wheeze, exacerbations, previously documented physiology)
	4. Pre and post bronchodilator spirometry
Diagnostic criteria of ACO	1. Diagnosis of COPD (includes risk factors, symptoms and spirometry)
*The following **are required***:	2. History of Asthma (ex. previous diagnosis, current or previous symptoms in keeping with asthma, physiologic confirmation)
	3. On Spirometry, the presence of persistent post bronchodilator fixed airflow obstruction ($FEV_1/FVC < 0.7$)
*The following **are supportive but are not required***:	1. Documentation (either current or previous) of an acute bronchodilator improvement in the FEV_1 of 12% and >200 ml
	2. Sputum eosinophils >3%
	3. Blood eosinophils (current or previously documented) >300 cells/μL

following as the Canadian perspective and recommendations on ACO. The **proposed definition of ACO** is the following: *"ACO is characterized by post bronchodilator airflow limitation that is not fully reversible, in symptomatic patients with risk factors for COPD and who have clinical features of both asthma and COPD."* The **proposed assessment** of patients suspected of having ACO and the **diagnostic criteria for ACO** are presented in Table 3. There was strong agreement amongst all participants that there is no high quality RCTs in this patient population and no evidence-based recommendations can be formulated. A majority of respondents (more than 80%) indicated that they would initiate **maintenance therapy for patients with ACO** with a low/moderate dose ICS/LABA (i.e. maximum fluticasone propionate 500 mcg/day or equivalent). If a patient reaches maximal inhaled therapy (high dose ICS/LABA and LAMA), and after insuring that related factors such as patient adherence and inhaler technique were addressed, clinicians might consider the addition of biologics that are currently indicated for asthma, if specific indication criteria are met (e.g. significant blood eosinophils). This would particularly be a consideration in patients experiencing recurrent exacerbations and/or requiring repeated use of systemic corticosteroids. Although studies examining the use of these biologics in COPD are ongoing, there was strong agreement that the use of these medications would be considered if the patient met the criteria from the individual product monographs. However, the group agreed that such patients would require referral to a respirologist. Furthermore, it is also important to evaluate if the patient would be a candidate for a third line pharmacotherapy such as a prescription of a PDE_4 antagonist (roflumilast) and/or macrolide prophylaxis.

Despite our endeavors to add further perspective to the questions that surround ACO, we recognize that limitations and gaps from the definition to treatment continue to exist. We further recognize that the concepts put forward in this position paper on ACO require further validation and may change depending on research and further understanding of this disease entity. We make a strong call to action to all partners in the respiratory field to engage in collaborative efforts to further our knowledge and understanding of ACO in order to provide optimal care to our patients.

Box 3. Asthma/COPD Overlap (ACO)

PICO 3: How does a clinician approach the treatment of patients who have COPD and features of Asthma (ACO)?

Key messages:

1) ACO represents a significant challenge both in terms of diagnosis and treatment. For ACO, scientific consensus regarding diagnostic criteria and management is currently lacking.
2) Based on a survey among Canadian respirologists and the authors, we propose 3 diagnostic criteria that are required to support ACO (this will require future validation and may change, depending on research and progress in this area):
   i. Diagnosis of COPD (includes risk factors, symptoms and spirometry)
   ii. History of Asthma (i.e. a previous diagnosis based on spirometry testing, current or previous symptoms in keeping with asthma, physiologic confirmation)
   iii. Spirometry: post bronchodilator fixed airflow obstruction ($FEV_1/FVC < 0.7$)
3) Treatment for COPD patients who have ACO:
   3.1) Initiate maintenance therapy with a ICS/LABA (low/moderate dose), and consider step up treatment to high dose ICS/LABA (high dose), addition of a LAMA, or both based on symptoms and exacerbation frequency;
   3.2) Refer patient to a respirologist after insuring that related factors such as patient's compliance and inhaler technique were addressed; consider addition of biologics that are currently indicated for asthma when indication criteria are met (particularly in patients experiencing recurrent exacerbations and requiring repeated or long-term use of systemic corticosteroids).

The summary of the recommendations on the pharmacotherapy treatment of ACO and a step-by-step approach to guide practical choices is shown in Figure 2.

Discussion

This position statement is an evolution towards personalized treatment, compared to the last published CTS COPD guideline in 2007[1] and the 2008 update – highlights for primary care.[2] Although the position statement emphasizes the importance of patient characteristics in treatment choice, most of the evidence coming from large clinical trials investigating COPD pharmacological treatments have not clearly identified predictors of response to treatment or patients at increased risk of side-effects.

This position statement promotes approaches that are intended to reduce both symptom burden and the risk of future exacerbations. This is an important step forward acknowledging the importance of making decisions on treatment options based not only on the degree of airflow obstruction and/or the FEV_1, but also on the clinical assessment of symptom burden (MRC or CAT) and risk of exacerbations. Other groups have proposed conceptually similar approaches,[176,177] including GOLD in 2013.[178] GOLD proposed treatment objectives to be matched not only on the degree of airflow obstruction (FEV_1) but to be reorganized into a four-quadrant assessment system (GOLD ABCD) characterizing patients on symptom burden and risk of exacerbations. In 2017, GOLD[3] adopted an approach even more conceptually similar to the CTS COPD 2007 guideline,[1] matching treatment decisions exclusively on symptom burden and risk of COPD exacerbations and not taking into account airflow obstruction. GOLD 2017 maintains spirometry as a requirement for the diagnosis of COPD and for classifying the degree of airflow obstruction (GOLD1–4).

This position statement identifies new data and proposes new evidence-based recommendations on pharmacotherapy (PICO 1 and 2) using the CHEST grading system.[24] However, this position statement is different from a guideline. Where there was a lack of data and/or insufficient evidence, but a recommendation was still warranted for guiding clinical practice, a suggestion was developed and designated as "consensus-based" instead of with a conventional "grade." Furthermore, for each PICO question, key messages are presented to better assist physician practice in managing COPD patients with different phenotypes. Some treatment propositions from this new CTS position statement, in particular the *"step up"* and *"step down"* treatment approaches could be criticized for not being evidence-based, as no therapeutic trial strictly assessed such therapeutic approaches. The notion to add or to stop a drug according to the evaluation of the prescribing physician has always been around, in any medical field, and it is considered as a good clinical practice. Treatment *"step up"* in COPD comes from the evidence that inhaled combined therapy is superior to monotherapy. Based on more limited data, the evidence of treatment *"step up"* to triple therapy (the combination of LAMA, ICS and LABA) is also suggested. The data are even more scattered to support the notion of treatment *"step down,"* except for some ICS withdrawal trials in COPD.[128] Because the superiority of inhaled triple or dual therapy may not be achieved in every patient, the notion of treatment *"step down"* may be a consideration in some patients. However, this is a challenge to assess in an individual patient since medication may have limited benefit in some patients and the disease may continue to progress in others. Patients in whom to consider treatment *"step down"* would be those not demonstrating expected benefits or having side effects exceeding benefits. In any circumstance, when a physician decides using a treatment *"step down"* for a given patient, this approach should be undertaken under close medical supervision.

Any decision physicians are taking should be in consideration of the known risk – benefit rather than an approach solely based on effectiveness. For example, for COPD patients not having concomitant asthma (ACO), we should favor the combination of inhaled long-acting bronchodilators instead of ICS and LABA. There are growing concerns that ICS are associated with an increased risk of pneumonia and systemic side effects, especially when high doses are used[154,179] Yet, these risks should be balanced with an apparent reduction of a composite outcome of death and admissions to hospital for COPD, as described in patients who received LABA and inhaled corticosteroids compared with those given LABA alone.[180–182] More studies are needed to support a risk-benefit approach based on the specific therapy and patient phenotypes.

More recently, there have been studies pointing to blood biomarkers that might be clinically useful to individualize the treatment regimen. Biomarker-directed pharmacotherapy approaches are starting to gain interest in practice and research. For example, it has been suggested that blood eosinophils could be useful clinically to predict COPD phenotype more likely to respond to ICS.[155–159] Another example is the bacterial colonization in some COPD patients that could contribute to the biological mechanisms of recurrent acute exacerbations. Under these circumstances, macrolides may reduce the risk for AECOPD although patients should be selected carefully considering the risk of bacterial resistance and side effects.[183–185] Whether this benefit is due to the antibacterial effect or more from direct anti- inflammatory effects is uncertain, but biomarkers of bacterial colonization in COPD could be valuable to target azithromycin or other emerging antibacterial approaches. However, we need studies to support or challenge these new pharmacotherapy approaches and to weigh the benefits and risks. There is currently a paucity of data and/or well-designed trials to inform evidence based recommendations.

This position statement also focuses on the phenotype ACO (PICO 3), a subgroup of patients which has been given much attention. Several national and international societies have suggested diagnostic criteria for the diagnosis of ACO.[119,176,182,186] Recently, the joint consensus GOLD-GINA proposed some characteristics of asthma and COPD to help to identify ACO individuals,[119] although the same weight was given for each particular characteristic and no further specifications were provided to reach the diagnosis. The paucity of original studies on ACO versus patients with only COPD made any evidence-based recommendations impossible. All the drug trials have excluded patients with features of asthma in COPD studies and COPD patients in studies on asthma. For this reason, the position taken in this position statement on ACO comes from a pan Canadian survey with features of Delphi technique and, at best, reflects the practice of Canadian community and academic respirologists on the assessment, diagnosis and pharmacotherapy of ACO patients.

Knowledge transfer and tools for practice

- The present document is available for download at www.cts-sct.ca/guidelines and in the new CTS Journal, Respiratory, Critical Care, and Sleep Medicine www.tandfonline.com
- A slide deck for teaching and self-learning as well as a handout for health care professionals and students is available at www.cts-sct.ca/guidelines
- The CTS COPD Clinical Assembly welcomes the opportunity to partner with other organizations and stakeholders in the development of educational tools and resources that support the implementation of the key messages described herein, with various targeted groups.

Future research directions

In order to generate evidence supporting, complementing or challenging current treatment recommendations, future studies are required in which patients are assigned specific pharmacotherapy based on symptom burden and exacerbation risk. *A priori* sub groups of patients defined by specific features rather than the current practice of *a posteriori* extensive subgroup analyses. Important questions remain such as to in whom and when to use combination therapies – inhaled LABA plus LAMA, ICS plus LABA, and LAMA plus ICS plus LABA triple therapy. It remains uncertain whether inhaled therapy should be initiated early with the hope of preserving lung function or only in the presence of COPD-related symptoms. Future studies should also encourage pragmatic trial designs that strike a good balance between internal and external validity, including analyses which highlight both numbers needed to treat and to harm among populations that are representative of COPD patients not typically included RCTs.

Personalized medicine becomes increasingly possible as clinical research becomes more specific, including greater focus on or defining better subsets of patients that are characterized by specific biomarkers and disease severity. Existing longitudinal COPD cohorts in which detailed phenotype data are available through biologic specimen and a data repository, should be supported as these cohorts offer opportunities to evaluate new scientific hypotheses that translate bench research to disease prevention and treatment. They also provide insight into the complex interaction of environment, behaviors, and genetics on chronic obstructive pulmonary diseases. This is a very promising way for the clinical and research communities to improve the evaluation of personal risk, identify mechanisms of disease and direct potential targets for medical interventions.

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