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**Chronic Obstructive Pulmonary Disease** WINTER 2021-2022 Volume 7 Number 1



DIGEST

**Benefit/risk profile of single-inhaler triple therapy in COPD**

*International Journal of Chronic Obstructive Pulmonary Disease*  
**2021; 16:499-517**

Chronic obstructive pulmonary disease (COPD) is associated with major healthcare and socioeconomic burdens. International consortia recommend a personalized approach to treatment and management that aims to reduce both symptom burden and the risk of exacerbations. Recent clinical trials have investigated single-inhaler triple therapy (SITT) with a long-acting muscarinic antagonist (LAMA), long-acting  $\beta$ 2-agonist (LABA), and inhaled corticosteroid (ICS) for patients with symptomatic COPD. Here, evidence from randomized controlled trials showing the benefits of SITT is reviewed, weighed against the reported risk of pneumonia with ICS use. The challenges associated with cross-trial comparisons of benefit/risk, discuss blood eosinophils as a marker of ICS responsiveness are highlighted, and current treatment recommendations and the position of SITT in the management of COPD, including potential advantages in terms of improving patient adherence is summarized.

Evidence from trials of SITT versus dual therapies in symptomatic patients with moderate to very severe airflow limitation and increased risk of exacerbations shows benefits in lung function and patient-reported outcomes. Moreover, the key benefits reported with SITT are significant reductions in exacerbations and hospitalizations, with data also suggesting reduced all-cause mortality. These benefits outweigh the ICS-class effect of higher incidence of study-reported pneumonia compared with LAMA/LABA. Important differences in trial design, baseline population characteristics, such as exacerbation history, and assessment of outcomes, have significant implications for interpreting data from cross-trial comparisons. Current understanding interprets the blood eosinophil count as a continuum that can help predict response to ICS and has utility alongside other clinical factors to aid treatment decision-making. The researchers concluded that treatment decisions in COPD should be guided by an approach that considers benefit versus risk, with early optimization of treatment essential for maximizing long-term benefits and patient outcomes.

The COPD Digest is published by Chronicle Information Resources Ltd. for COPD Canada. Each issue reviews recently published (PubMed) clinical abstracts (Digests) with reviews (Dialogues) written by:

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**Sources:** Jean Bourbeau, Mona Bafadhel, Neil C. Barnes, Chris Compton, Valentina Di Boscio, David A. Lipson, Paul W. Jones, Neil Martin, Gudrun Weiss, David M.G. Halpin

PMID: 33688176 [PubMed - Free PMC article]



**Acute Exacerbations of COPD (AECOPD)** continues to be, outside of child-birth, the number one cause for hospitalizations in Canada and is associated with poor patient-related outcomes. Prevention of an AECOPD is a primary goal in the chronic management of this disease. Inhaled therapies, including LAMA, LABA, LAMA/LABA, ICS/LABA either alone or in combination have been shown to improve quality of life and reduce exacerbations. The most recent addition to inhaled treatment options is single inhaler triple therapy (SITT) which combines LAMA, LABA and ICS into one inhaler. In this extensive review of recent landmark pharmacological studies in a population of symptomatic COPD patients, with moderate to severe lung function impairment and who are at high risk of future exacerbations, Bourbeau, et al, summarize the evidence of SITT when compared to dual therapy (ICS/LABA or LAMA/LABA) in reducing exacerbations, improving lung function and quality of life. Although there are strengths and weaknesses in the design of all the studies, the authors conclude that, with the evidence to date, SITT confers improved outcomes in patients uncontrolled on dual therapy including a reduction in exacerbation frequency and importantly, a signal for reduced all-cause mortality. Although the small risk of pneumonia in patients on an ICS was once again reported, the studies show that there are no differences in the pneumonia risk between ICS formulations and overall, the risk/benefit supports the use of the ICS in the appropriate patient population. The studies continue to show that the blood eosinophil level can be useful in assessing whether a patient may benefit from the use of an ICS. These studies highlight the benefit of LAMA/LABA/ICS combinations in appropriate COPD patients. The SITT delivery systems may provide opportunities to simplify treatment in patients whose management is challenged by inhaler compliance and technique. It is, however, important to remember that all treatments for COPD should be personalized and appropriate to the patient's symptoms and exacerbation history. **MB**



DIGEST

## A systematic literature review of the humanistic burden of COPD

*International Journal of Chronic Obstructive Pulmonary Disease* 2021; 16:1303-1314

**Background:** Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide, causing substantial economic and social burden.

**Objective:** This review assessed the patient-reported humanistic burden associated with moderate to very severe COPD, specifically the impact on health-related quality of life (HRQoL), symptoms, limitations in daily life, and emotional implications, through the use of HRQoL instruments.

**Methods:** A systematic review was conducted to retrieve relevant clinical data from published literature using a representative sample of countries where healthcare systems provide wide availability of COPD medications and/or universal coverage includes respiratory medicines (Australia, Canada, China, France, Germany, Italy, Spain, the UK, and the USA). The primary inclusion criteria were patients with moderate to very severe COPD. HRQoL was quantified with non-disease-specific and disease-specific questionnaires.

**Results:** In total, 82 studies from 95 publications presented HRQoL data from patients with moderate to very severe COPD. Patient-reported HRQoL declined with worsening airflow limitation, advancing GOLD group, and increasing exacerbation frequency. Both increasing frequency of hospitalization for COPD exacerbations and recurrent hospitalization adversely impacted HRQoL. Comorbidity incidence was higher in patients with increased airflow limitation. It was associated with a further decline in HRQoL and increased depression and anxiety, particularly as disease-associated pain worsened. Physical activity improved HRQoL over time.

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**Conclusion:** This review highlighted the impact of exacerbations and associated hospitalizations on the humanistic burden of COPD. These findings underline the importance of managing COPD actively, including prompt and appropriate use of pharmacological and non-pharmacological therapies that can improve symptoms and reduce the risk of exacerbations, thereby lessening the humanistic burden. Future reviews could consider a broader range of countries and publications to further assess the humanistic impact of COPD in low- and middle-income economies.

**Source:** *John R. Hurst, Mohd Kashif Siddiqui, Barinder Singh, Precil Varghese, Ulf Holmgren, Enrico de Nigris*

**PMID: 34007170 [PubMed - Free PMC article]**



**The burden of COPD is enormous** and is influenced by many factors that can be measured at a population or societal level. These measures include overall prevalence and the prevalence of known risk factors, mortality, disability including premature life years lost and productivity loss, and healthcare related costs associated with exacerbations and hospitalizations. COPD is the third leading cause of death worldwide and the leading cause of hospital admissions and readmissions. At an individual level, burden is measured and reported through clinical and patient-reported outcomes, including quality of life (QoL). This review of the literature by Hurst and colleagues gathered studies that assessed the impact of symptoms, lung function and exacerbations, comorbidities and physical activity on health-related quality of life (HRQOL) among patients with moderate to very severe COPD. The studies reviewed showed HRQOL deteriorated with more severe airflow limitation and among those with high COPD symptom burden and history of exacerbations. Increased comorbidities were associated with lower quality of life, with mental health conditions being more prevalent among those with more severe airflow obstruction and associated with lower HRQOL. Physical activity strongly correlated with increased quality of life among COPD patients. This review demonstrated that moderate to very severe COPD has a significant impact on HRQOL resulting in a considerable humanistic burden. This review highlights the importance of comprehensive yet personalized management for patients with COPD, including pharmacologic and non-pharmacologic treatments that reduce the risk of exacerbations, improve symptoms, and slow the rate of decline in lung function. Pulmonary rehabilitation and interventions aimed at promoting active lifestyle are critical to improving physical activity and reducing the burden of disease experienced by COPD patients. **EP**



### **Association between initiation of pulmonary rehabilitation and rehospitalizations in patients hospitalized with COPD**

**Am J Respir Crit Care Med 2021 Nov 1; 204(9):1015-1023. doi: 10.1164/rccm.202012-4389OC.**

**Rationale:** Although clinical trials have found that pulmonary rehabilitation (PR) can reduce the risk of readmissions after hospitalization for a chronic obstructive pulmonary disease (COPD) exacerbation, less is known about PR's impact in routine clinical practice.

**Objectives:** To evaluate the association between initiation of PR within 90 days of discharge and rehospitalization(s).

**Methods:** The researchers analyzed a retrospective cohort of Medicare beneficiaries (66 years of age or older) hospitalized for COPD in 2014 who survived at least 30 days after discharge.

**Measurements and main results:** They used propensity score matching and estimated the risk of recurrent all-cause rehospitalizations at one year using a multistate model to account for the competing risk of death. Of 197,376 total patients hospitalized in 4,446 hospitals, 2,721 patients (1.5%) initiated PR within 90 days of discharge. Overall, 1,534 (56.4%) patients who initiated PR and 125,720 (64.6%) who did not were rehospitalized one or more times within one year of discharge. In the propensity-score-matched analysis, PR initiation was associated with a lower risk of readmission in the year after PR initiation (hazard ratio, 0.83; 95% confidence interval, 0.77-0.90). The mean cumulative number of rehospitalizations at 1 year was 0.95 for those who initiated PR within 90 days and 1.15 for those who did not (p<0.001).

**Conclusions:** After hospitalization for COPD, Medicare beneficiaries who initiated PR within 90

days of discharge experienced fewer rehospitalizations over one year. These results support findings from randomized controlled clinical trials and highlight the need to identify effective strategies to increase PR participation.

**Source:** Mihaela S. Stefan, Penelope S. Pekow, Aruna Priya, Richard ZuWallack, Kerry A. Spitzer, Tara C. Lagu, Quinn R. Pack, Victor M. Pinto-Plata, Kathleen M. Mazor, Peter K. Lindenauer

PMID: 34283694 [PubMed - DOI: 10.1164/rccm.202012-4389OC



DIALOGUE

**Patients discharged from hospital** following an acute exacerbation of COPD (AECOPD) have high 30 day and one year all cause and COPD-related readmission rates. There are many factors that contribute to this including severity of disease, comorbid conditions and socio-economic factors. Pulmonary rehabilitation (PR) is an important cornerstone therapy for patients with COPD. To date, multiple studies have shown that patients who enter into a PR program within three to four weeks following a hospitalization for an AECOPD, are less likely to be re-hospitalized in the following year. However, significant challenges exist to fulfill this goal of early PR, as access to PR programs across Canada is limited. The last Canadian survey showed that only 0.4% of COPD patients have access to PR! Access has undoubtedly been further impacted by the pandemic, as many of the PR programs were suspended at different time points during the pandemic and have only recently been restarted. In this study by Stefan, et al, they retrospectively looked at a large group of PR eligible patients who started PR within 90 days of the hospitalization and compared them to patients starting PR after 90 days or for those who never completed PR at all. They show that patients starting PR within 90 days had a 17% reduction in all-cause hospitalizations in the year following PR when compared to the other two groups. In another publication, the authors showed that there was also a mortality benefit in the same patient cohort who started PR within 90 days. The results of this study are important as this more practical time frame of PR initiation (within 90 days vs. three to four weeks) after discharge from hospital demonstrates the continued benefit of early PR, that has been shown in other studies. This study further adds to the urgent need for a call to action by patients and clinicians to improve access to PR, especially for patients with COPD who are hospitalized. **MB**



DIGEST

### Treatable traits in an English cohort: Prevalence and predictors of future decline in lung function and quality of life in COPD

*European Respiratory Journal Open Res 2021; 7: 00934-2020*

**Background:** “Treatable traits” (TTs) is a precision medicine approach for facilitating multidimensional assessment of every patient with chronic airway disease, in order to determine the core traits associated with disease outcomes where targeted treatments may be applied.

**Objectives:** To determine the prevalence of TTs in chronic obstructive pulmonary disease (COPD) and which traits predict future decline in lung function and quality of life (QoL).

**Methods:** A four-year longitudinal evaluation was conducted using data from 3,726 participants in the English Longitudinal Study of Ageing (ELSA). TTs were identified based on published recommendations. Traits that predicted decline in lung function and QoL were analysed using generalized estimating equations.

**Results:** Overall, 21 TTs, including pulmonary (n=5), extra-pulmonary (n=13) and behavioural/lifestyle risk-factors (n=3) were identified. In multivariate analyses, the traits of chronic bronchitis ( $\beta$  -0.186, 95% CI -0.290 to -0.082), breathlessness ( $\beta$  -0.093, 95% CI -0.164 to -0.022), underweight ( $\beta$  -0.216, 95% CI -0.373 to -0.058), sarcopenia ( $\beta$  -0.162, 95% CI -0.262 to -0.061) and current smoking ( $\beta$  -0.228, 95% CI -0.304 to -0.153) predicted decline in forced expiratory volume in 1 s (FEV1). Of the seven traits that predicted decline in QoL, depression ( $\beta$  -7.19, 95% CI -8.81 to -5.57) and poor family and social support ( $\beta$  -5.12, 95% CI -6.65 to -3.59) were the strongest.

**Conclusion:** The core TTs of COPD associated with a decline in lung function and QoL were identified. Targeting these impactful traits with individualized treatment using a precision medicine approach may improve outcomes in people with COPD.

**Sources:** Muhammad Rehan Sarwar, Vanessa Marie McDonald, Michael John Abramson, Eldho Paul, Johnson George

PMID: 34084787 DOI: 10.1183/23120541.00934-2020 [PubMed - Free PMC article]



**Chronic obstructive pulmonary disease (COPD)** is a heterogeneous disease complicated by comorbidities and exacerbations. To date, management has focused on improving symptoms and reducing exacerbations; however, the individual response to treatments remains varied. Despite the use of evidence-based approaches to management, the burden from COPD exacerbations and symptoms continue. “Treatable traits” (TTs) is a precision medicine strategy for chronic airway diseases that involves a multidimensional assessment of every patient to identify characteristics that relate to genetic factors (genotyping), clinical and inflammatory phenotypes, and psychosocial factors in that individual. Based on individual traits, therapy can be tailored to address these traits with the goal of improving outcomes. Traits can be classified as pulmonary, extrapulmonary and behavioural/lifestyle. This study by Sarwar and colleagues sought to determine the prevalence of TTs among participants in a population-based cohort study, the English Longitudinal Study of Ageing (ELSA) and to determine which traits predict decline in lung function (forced expiratory volume (FEV1)) and quality of life (QoL) over time. The authors found that five TTs were associated with a significant decline in lung function, including chronic bronchitis, breathlessness, underweight, sarcopenia and current smoking. They found that seven TTs were significantly associated with a decline in QoL including chronic bronchitis, cardiovascular disease, arthritis, depression, anaemia, disability, and poor family and social support. The study found that different TTs were associated with different outcomes, in this case, lung function decline and QoL; therefore requiring a comprehensive yet personalized approach to management that should be influenced by patient preferences. Future studies designed to assess more holistic interventions with multi-disciplinary teams would be useful to assess the impact on important patient outcomes. **EP**



DIGEST

## Dyspnea and symptom burden in mild–moderate COPD: the Canadian Cohort Obstructive Lung Disease Study

**ERJ Open Research 2021; DOI: 10.1183/2312054.00960-2020**

Studies assessing dyspnea and health-related quality of life (HRQoL) in chronic obstructive pulmonary disease (COPD) have focused on patients in clinical settings, not the general population. The aim of this analysis was to compare the prevalence and severity of dyspnea and impaired HRQoL in individuals with and without COPD from the general population, focusing on mild–moderate COPD. Analysis of the three-year Canadian Cohort Obstructive Lung Disease (CanCOLD) study included four subgroups: mild COPD (Global Initiative for Chronic Obstructive Lung Disease (GOLD) 1); moderate COPD (GOLD 2); non-COPD smokers; and non-COPD never-smokers. The primary outcome was dyspnoea (Medical Research Council (MRC) scale), and the secondary outcome was HRQoL (COPD Assessment Test (CAT) score; Saint George’s Respiratory Questionnaire (SGRQ) score). Subgroups were analysed by sex, physician-diagnosed COPD status and exacerbations. The study included 1,443 participants (mild COPD (n=397); moderate COPD (n=262); smokers (n=449) and never-smokers (n=335)). People with mild COPD were more likely to report more severe dyspnoea (MRC 2 vs. 1) than those without COPD (OR (95% CI) 1.42 (1.05–1.91)), and non-COPD never-smokers (OR (95%CI) 1.64 (1.07–2.52)). Among people with mild COPD, more severe dyspnea was reported in women versus men (MRC2 vs. 1; OR (95% CI) 3.70 (2.23–6.14)); people with, vs. without, physician-diagnosed COPD (MRC2 vs. 1; OR (95% CI) 3.27 (1.71–6.23)), and people with vs. without recent exacerbations (MRC2 vs. 1;  $\geq 2$  vs. 0 exacerbations: OR (95% CI) 3.62 (1.02–12.86); MRC  $\geq 3$  vs. 1; 1 vs. 0 exacerbation: OR (95% CI): 9.24 (2.01–42.42)). Similar between-group differences were obtained for CAT and SGRQ scores. Careful assessment of dyspnoea and HRQoL could help identify individuals for earlier diagnosis and treatment.

**Sources:** Mathew Cherian, Dennis Jensen, Wan C. Tan, Sara Mursleen, Emma C. Goodall, Gilbert A. Nadeau, Amnah M. Awan, Darcy D. Marciniuk, Brandie L. Walker, Shawn D. Aaron, Denis E. O’Donnell, Kenneth R. Chapman, François Maltais, Paul Hernandez, Don D. Sin, Andrea Benedetti, Jean Bourbeau

PMID: 33898621 [PubMed - Free PMC article]



DIALOGUE

**Patients living with COPD** are often diagnosed at an advanced stage of the disease. Although they may experience symptoms of COPD for many years prior to the diagnosis, such as shortness of breath, they often discount the symptoms as they think it is due to their ongoing smoking, aging or being deconditioned and not in good shape. Although most of the research has reported on patients with advanced disease, the severity of symptoms and quality of life in patients with mild to moderate COPD is relatively unknown. In this study by Cherian, et al, they used data from the Canadian Cohort Obstructive Lung Disease (CanCOLD) study to report on the symptom burden and quality of life of patients with mild to moderate COPD. They found that these patients were significantly more short of breath and have a worse quality of life when compared to patients who did not have COPD. They had more shortness of breath even when compared to active smokers but who did not have COPD. Interestingly, they found that women in this cohort of mild to moderate disease, had a higher symptom burden and worse quality of life when compared to men. This difference has been reported before but in more advanced COPD. Although there are theories as to why this gender difference exists, the exact mechanisms have not been clearly understood and more research is needed. COPD is the third leading cause of death worldwide and is a leading cause of hospitalization in Canada. In order to change these trends, studies like this highlight the need for clinicians to “Think COPD” in people who have risk factors for and symptoms of this disease and for patients to report any chronic respiratory symptoms to their health care providers and not ignore them. The earlier a diagnosis of COPD is made, the more impactful preventative and disease specific treatment strategies will be. **MB**



DIGEST

## Employment status, readmission and mortality after acute exacerbation of COPD

*International Journal of Chronic Obstructive Pulmonary Disease* 2021 Aug 5;16:2257-2265.

**Introduction:** The understanding of whether and to what extent employment status affects readmission and mortality is limited in patients with COPD.

**Aim:** To explore how employment status affects readmission and mortality after first admission to the hospital with acute exacerbation of COPD (AECOPD).

**Methods:** This study used Danish national registry-based data. All patients admitted for the first time to the hospital between 1999 and 2014 with a diagnosis of AECOPD, age 35 to 59 years, without a previous asthma diagnosis were included in the study. Employment status effect on 30-, 90-, and 365-day readmission and mortality was examined using logistic regression, adjusting for relevant confounders.

**Results:** A total of 11,850 COPD patients were included in the study of which 3,563 (30%) were working, 1,368 (12%) unemployed, 840 (7%) on sick leave, and 6,079 (51%) receiving early retirement. Patients receiving early retirement had, compared to patients working, an adjusted increased likelihood of readmission at 30, 90, and 365 days (odds ratio (OR) 1.26 (CI95% (1.06–1.49)), 1.33 (CI95% (1.16–1.53)), and 1.48 (CI95% (1.33–1.66)), respectively). An increased likelihood was also seen in unemployed at 365 days follow-up (OR 1.44 (CI95% (1.22–1.68))). Early retirement was associated with an increased mortality at 30, 90, and 365 days (OR 1.39 (CI95% (1.07–1.80)) 1.37 (CI95% (1.09–1.79)) and 1.48 (CI95% (1.25–1.75)), respectively). An increased likelihood was also seen in patients receiving sick leave (OR 1.57 (CI95% (1.21–2.04))).

**Conclusion:** Patients with COPD who are not working at the time of first admission have a higher likelihood of readmission and mortality.

**Source:** Peter Ascanius Jacobsen, Kristian Hay Kragholm, Christian Torp-Pedersen, Daisy J.A. Janssen, Martijn A. Spruit, Ulla Møller Weinreich

PMID: 34385815 DOI: 10.2147/COPD.S319840 [PubMed - Free PMC article]



**COPD is the leading cause of readmissions to hospital**, ranging between almost 10 to 25% at one month and between 18 to 39% at three months post discharge from an acute exacerbation of COPD (AECOPD). AECOPD is associated with a higher risk of death, particularly when it is associated with admission and readmission to hospital. Decreased physical activity has also been linked with increased risk of death among patients with COPD. Patients with COPD also have reduced workforce participation, which has been associated with increased sedentary behaviour and reduced physical activity. The impact of reduced workforce participation (via disability pensions and unemployment) on AECOPD rates, admissions to hospital and death have been studied previously with variable results and have not focussed solely on a working age population. This study by Jacobsen and colleagues explored how employment status is associated with short- (30 days), medium- (90 days) and long- (365 days) term readmission and mortality following severe AECOPD in patients with COPD between the ages of 35 and 59 years using a Danish national registry database from 1999 to 2014. Employment status was categorized as either i) working, ii) unemployment benefit, iii) sick leave or iv) early retirement. They found that early retirement was associated with a significantly higher likelihood for readmission to hospital with AECOPD and death at 30-, 90-, and 365-days of follow-up in patients compared with those still working. Significantly higher likelihood of readmission was seen at one year of follow-up for patients receiving unemployment benefit compared to patients working and significantly higher likelihood for death at one year was seen in patients receiving sick leave compared to patients working. This study raises interesting questions which cannot be answered by the study's design. Specifically, does COPD lead to workforce detachment or does workforce detachment increase the risk of negative outcomes from COPD? The role of other important factors affecting readmission to hospital such as COPD disease severity, smoking status, level of physical activity and underlying comorbidities were not directly captured in this study, however would certainly influence the overall effect of employment status on readmission and mortality. Having said that, this study highlights the fact that workforce activity may be an important variable in a patient's COPD disease trajectory and potential predictor of health outcomes and warrants consideration in future studies. **EP**

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The COPD Digest is supported in part by an educational grant from **AstraZeneca Canada**

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