Original Research

Change in Inhaler Use, Lung Function, and Oxygenation in Association with Symptoms in COPD

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Abstract

Despite clinical guidelines for chronic obstructive pulmonary disease (COPD) patients to self-treat worsening respiratory symptoms with supplemental inhaler/nebulizer use, few studies have investigated if symptom changes are associated with differences in oxygenation, lung function, or self-treatment. A total of 26 former smokers (mean age 72.7 ±7.5 years; 57.7% female) with COPD (≥ Global Initiative for Chronic Obstructive Lung Disease Stage 2) were followed for up to 4 months, during which they recorded daily oxygenation, lung function, and inhaler/nebulizer use. Differences in these health measures were assessed in association with self-reported worsening symptoms and COPD exacerbations, as defined by validated questionnaire. We collected 2451 observations with spirometry and questionnaire data and identified 253 symptom days (10.3%) and 47 (1.92%) exacerbation days. In linear mixed effects models adjusted for age, sex, race, height, weight, and season, each respiratory symptom reported worse than baseline was associated with a 0.19 percentage point (95% CI -0.31 to -0.07) lower daily oxygen saturation (*p*=0.002). On major symptom days (defined as worse-than-baseline dyspnea, sputum purulence or sputum amount), oxygen saturation was 0.56 percentage points lower (95% CI -0.89 to -0.23, *p*=0.001) than days without increased major symptoms. We found no association of symptom days or exacerbations with forced expiratory volume in 1 second. There were 8 reports of increased inhaler/nebulizer use from baseline on symptom days (1.5% of 253). In this moderate-to-severe COPD population, worsening respiratory symptoms were common and associated with lower oxygenation. However, participants did not self-treat symptoms with increased inhaler/nebulizer use, which may suggest poor perceived clinical benefit from short-acting bronchodilators and a potential target for patient education.

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Introduction

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States[1] and became the third leading cause of death in the world in 2016.[2] Numerous studies have established that exacerbations, defined by acute periods of worsened symptoms, are a major driver of the morbidity and mortality of this disease.[3-6] As a result, there is growing interest in the role of self-management in COPD to prompt early initiation of pharmacological treatment of exacerbation symptoms.[7]

A number of COPD self-management action plans have been evaluated.[8-11] While rescue treatment via short-acting inhalers has been extensively evaluated as the initial step for self-treatment of day-to-day fluctuations of asthma symptoms and is a key component of any asthma action plan,[12-18] the focus of self-treatment action plans for COPD has been on the use of oral corticosteroids and antibiotics to self-treat moderate-to-severe exacerbations. Nonetheless, the 2019 Global initiative for chronic Obstructive Lung Disease (GOLD) document recommends the use of short-acting beta2-agonists as the initial step for immediate symptom relief and treatment of an acute exacerbation of COPD.[19] This recommendation is based on a limited number of studies that have found that short-acting bronchodilators can relieve COPD symptoms in most patients.[20,21]

Short-acting inhalers and nebulizers are commonly prescribed for COPD in accordance with the GOLD document.[22] However, it is not well understood how COPD patients use or integrate as-needed bronchodilators in the management of their daily symptoms and milder exacerbations. The aim of this study was to evaluate self-treatment of COPD symptoms and exacerbations with short-acting inhaler/nebulizer medication in the outpatient setting in a cohort of 26 participants with moderate-to-severe COPD, from whom we collected daily data on symptoms, oxygenation, lung function, and medication use for up to 4 months each. We investigated if changes in self-reported COPD symptoms and exacerbations by validated daily questionnaire were associated with daily differences in as-needed inhaler/nebulizer use or objective measures of COPD disease activity, including oxygenation and lung function.

Materials and Methods

Study Population

The study population consisted of 26 former smokers with COPD who were recruited as part of the Study of Air Pollution and COPD Exacerbation at Beth Israel Deaconess Medical Center in Boston, Massachusetts. To be eligible, study participants were required to be former smokers with a ≥10 pack-year smoking history, and to have a clinical diagnosis of COPD with at least moderate GOLD Stage 2 airflow obstruction on spirometry (defined as forced expiratory volume in 1 second [FEV_1]/forced vital capacity [FVC]<70% and FEV_1<80% predicted). Participants with a history of lung cancer, interstitial lung disease, or bronchiectasis were ineligible to take part in the study. The study was approved by the authorized institutional review board of the Beth Israel Deaconess Medical Center (Protocol # 2015P000336/03). Written informed consent was obtained from all study participants.

Data Collection

Participants entered the study between February 24, 2017 and January 17, 2019. At study entry, demographic information, height, weight, past medical history, medication history, and baseline measures of lung function and oxygen saturation were obtained. Study participants were instructed on how to use a portable spirometer and oximeter and were shown how to complete a daily electronic questionnaire (see the online supplement to view the full questionnaire). Participants were instructed to measure their oxygen saturation at a consistent time in the morning. Those on supplemental oxygen at rest were instructed to use their usual supplemental oxygen when measuring their oxygen saturation.

Study participants were then observed for up to 4 non-consecutive 30-day periods in different seasons over 12 months, up until February 20, 2019. During observation periods, participants recorded daily changes in respiratory symptoms and treatment by daily questionnaire, accessed electronically through Research Electronic Data Capture (REDCap), a

secure web application developed by Vanderbilt University.[23] This questionnaire was developed and validated for the purpose of identifying COPD exacerbations from self-reported worsening respiratory symptoms.[10,24-27] The questionnaire consisted of the 2 questions below:

(1) Please record any worsening of symptoms above your usual daily level in the previous 24 hours. Any symptom that is at your "normal" level should be left blank. [*Response options*: No change; increased breathlessness; increased sputum color; increased sputum amount; a cold (such as a runny or blocked nose); increased wheeze or chest tightness; sore throat; increased cough; fever]

(2) Please record any change to your usual treatment in the previous 24 hours for as many days as it applies. [*Response options*: No change; I am taking: more than my usual inhaler, more than my usual nebulizer, steroid (prednisone) tablets, and/or an antibiotic]

In addition, participants recorded and submitted their daily oxygen saturation (SpO$_2$) via the REDCap questionnaire, measured using a Nonin GO2 LED Achieve 9571 Finger Pulse Oximeter (Plymouth, Minnesota). The Nonin GO2 device uses the same PureSAT® SoO2 technology as the medical grade oximeters and has a declared oxygen saturation accuracy range of 70%-100% SpO$_2$+2 digits. Participants also performed spirometry every morning before taking their morning medication, with a portable EasyOne^{TM} Plus Diagnostic Spirometer (ndd, Switzerland). This device meets American Thoracic Society guidelines and has built-in quality assurance and incentive software.[28,29]

Statistical Analysis

Respiratory symptom days and COPD exacerbations were defined per the survey tool.[10,24-27] Dyspnea, sputum purulence, and sputum amount were classified as major symptoms. Nasal discharge/congestion, wheeze, sore throat, cough, and fever were classified as minor symptoms.

Observation-days were classified as follows, in accordance with the survey tool:

(1) <u>Mild-to-moderate:</u> increase in at least 1 minor symptom, but no major symptoms, in the previous 24 hours compared to baseline.

(2) <u>Moderate-to-severe:</u> increase in at least 1 major symptom in the previous 24 hours compared to baseline.

(3) <u>Exacerbation:</u> increase in 2 or more symptoms (at least 1 major symptom) in the previous 24 hours compared to baseline on 2 or more consecutive days.

We constructed multi-level linear mixed effects models to assess for associations between the presence of self-reported respiratory symptoms, using the 3 classifications of "symptom day" as described above, and oxygenation and FEV$_1$:

$$Y_{imt}=b_0 + b1\ symp_{imt} + b_2\ c_{imt} + w_i + e_{imt}$$

where Y$_{imt}$ is any continuous outcome (oxygenation or FEV$_1$) for participant i at observation month m on day t; symp$_{imt}$ indicates "symptom day," the main predictor of interest, and c$_{imt}$ represents a vector of potential confounders (age, sex, race, height, weight, and season). The term w_i denotes a participant-specific random effect and was used to account for intra-individual correlations between repeated measurements among the same person. The residuals e$_{imt}$ are normally distributed errors, assumed to follow a first order autoregressive process modeling the serial correlation among the daily time series within the same person's observation month.

Season was categorized as winter, spring, summer, and fall, based on the calendar start dates of each observation month. We excluded 25 outlier observations with oxygen saturation values >100% or <80% that were likely entered erroneously by the study participant. We also performed a sensitivity analysis examining differences in oxygen saturation on symptoms days in which we excluded all participants who reported use of supplemental oxygen at rest (N=4). In addition, we evaluated the frequency of as-needed inhaler and nebulizer use on symptom days for each of the 3 classifications of "symptom day." Finally, we examined the association between the total number of reported symptoms per day (minor or major) and differences in oxygenation and lung function. In this analysis, we used the same mixed model structure as in our primary analyses.

Table 1. Baseline Characteristics of Study Participants

	Mean (SD) or N (%)
Age, years	72.7 (7.5)
FEV$_1$, L	1.3 (0.5)
FEV$_1$, % predicted	53.1 (14.4)
FVC, L	2.5 (0.7)
FVC, % predicted	79.3 (16.5)
FEV$_1$/FVC, %	50.8 (12.1)
Body Mass Index	32.2 (7.7)
Pack-years Smoking History	57.8 (29.9)
Oxygen Saturation	93.4 (4.2)
Supplemental Oxygen at Rest	4 (15%)
Sex: Male	11 (42%)
Race: Black	5 (19%)
Race: White	21 (81%)

N=26
FEV$_1$=forced expiratory volume in 1 second;
FVC=forced vital capacity

Table 2. Frequency of the Number of Reported Symptoms Worse Than Baseline

Number of Symptoms/Day[a]	n (%)
0	2198 (89.7)
1	162 (6.6)
2	48 (2.0)
3	21 (0.9)
4	12 (0.5)
5	5 (0.2)
6	4 (0.2)
7	0 (0.0)
8	1 (0.0)

[a]Includes the total number of symptoms (nasal discharge/congestion, wheeze, sore throat, cough, fever, dyspnea, sputum purulence, or sputum amount) that were worse than baseline.

Results

Baseline measures of the 26 study participants that were collected at the time of their respective study entry visit are presented in Table 1. There was a total of 2451 observations (days) with complete records of both spirometry and questionnaire data, with a mean of 94.3 observations per study participant. The distribution of the number of symptoms per day is displayed in Table 2. On 89.7% of observation days, there were no changes in baseline symptoms. On 6.6% of days, participants reported 1 respiratory symptom (nasal discharge/congestion, wheeze, sore throat, cough, fever, dyspnea, sputum purulence, or sputum amount) that was worse than baseline. On 2.0% of observation days, participants reported 2 of these symptoms were worse than baseline.

Associations between symptom days and oxygenation and lung function are shown in Table 3. There were 130 mild-to-moderate symptom days (5.3% of 2451), and 123 moderate-to-severe symptom days (5.0% of 2451). There was a total of 47 COPD exacerbation days (1.9% of 2451).

Of the 26 total participants, 9 reported any use of supplemental oxygen, and of these 9, a total of 4 used oxygen at rest. In fully adjusted linear mixed models using all participant data, mild-to-moderate symptom days were associated with a 0.28 percentage point lower oxygen saturation (95% CI -0.63 to 0.07, p=0.012) compared to non-symptom days. Moderate-to-severe symptom days were associated with a 0.56 percentage point lower oxygen saturation (95% CI -0.89 to -0.23, p=0.001) compared to non-symptom days. Exacerbation days were associated with a 0.54 percentage point lower oxygen saturation (95% CI -1.13 to 0.05, p=0.07) compared to days without a COPD exacerbation (Table 3). In the sensitivity analysis excluding the 4 participants on supplemental oxygen at rest, associations between symptoms and oxygenation were similar and slightly greater in magnitude than in the full cohort: oxygen saturation was 0.68 percentage points lower (95% CI -1.03 to -0.34) on moderate-to-severe symptom days compared to baseline (p=0.0001), and each respiratory symptom reported worse than baseline was associated with a 0.22 percentage point (95% CI -0.22 to -0.10) lower daily oxygen saturation (p=0.0003).

We found no associations between self-reported worsening symptoms and FEV$_1$ for all 3 classifications of symptom days (Table 3). In our analysis examining the association between the number of symptoms per day and differences in oxygenation and lung function, each additional respiratory symptom reported to be worse than baseline was associated with a 0.19 percentage point lower oxygen saturation (95% CI -0.31 to -0.07, p=0.002) per additional symptom. There was no association between the number of symptoms per day and lung function.

Table 4 displays the use of additional inhaler

Table 3. Difference in Oxygen Saturation and Forced Expiratory Volume in 1 Second on Symptom/Exacerbation Days Versus Non-Symptom/Exacerbation Days[a]

	# Observation Days n (%)	Difference in O_2 Saturation % Point (95% CI)	P Value	Difference in FEV_1 mL (95% CI)	P Value
Symptom Days					
No Change	2198 (89.7%)	ref.	ref.	ref.	ref.
Mild-to-Moderate	130 (5.3%)	-0.28 (-0.63, 0.07)	.12	17.35 (-8.31, 43.00)	.19
Moderate-to-Severe	123 (5.0%)	-0.56 (-0.89, -0.23)	.001	0.52 (-23.79, 24.82)	.97
Exacerbation Days					
No Exacerbation	2404 (98.1%)	ref.	ref.	ref.	ref.
Exacerbation	47 (1.9%)	-0.54 (-1.13, 0.05)	.07	29.61 (-15.22, 74.45)	.20

[a]Mild-to-moderate: reported increase in at least 1 minor symptom (i.e., nasal discharge/congestion, wheeze, sore throat, cough, fever), but no major symptoms (i.e., dyspnea, sputum purulence, sputum amount), in the previous 24 hours compared to baseline.

Moderate-to-severe: reported increase in at least 1 major symptom (i.e., dyspnea, sputum purulence, sputum amount) in the previous 24 hours compared to baseline.

Exacerbation: reported increase in 2 or more symptoms that includes at least 1 major symptom (i.e., dyspnea, sputum purulence, sputum amount) in the previous 24 hours compared to baseline on 2 or more consecutive days.

Table 4. Inhaler and Nebulizer Use on Symptom/Exacerbation Days[a]

Symptom Day Categories	# Observation Days, n (%)	Days of Inhaler Use, n (%)	Days of Nebulizer Use, n (%)
No Change	2198 (89.7%)	1 (0.0%)	0 (0.0%)
Mild-to-Moderate	130 (5.3%)	2 (1.5%)	0 (0.0%)
Moderate-to-Severe	123 (5.0%)	3 (2.4%)	3 (2.4%)
Exacerbation	47 (1.9%)	1 (2.1%)	1 (2.1%)

[a]Mild-to-moderate: reported increase in at least 1 minor symptom (i.e., nasal discharge/congestion, wheeze, sore throat, cough, fever), but no major symptoms (i.e., dyspnea, sputum purulence, sputum amount), in the previous 24 hours compared to baseline.

Moderate-to-severe: reported increase in at least 1 major symptom (i.e., dyspnea, sputum purulence, sputum amount) in the previous 24 hours compared to baseline.

Exacerbation: reported increase in 2 or more symptoms that includes at least 1 major symptom (i.e., dyspnea, sputum purulence, sputum amount) in the previous 24 hours compared to baseline on 2 or more consecutive days.

and/or nebulizer medication on self-reported symptom days. Despite the fact that all 26 (100%) of the study participants held an active prescription for rescue medication (i.e., short-acting beta agonist and/or short-acting muscarinic antagonist, via inhaler or nebulizer) at the time of enrollment, there were very few reports of increased inhaler or nebulizer use, with only 6 reports of increased inhaler use and 3 reports of increased nebulizer use out of 2451 observation-days. Eight of these 9 reported increases in inhaler or nebulizer use fell on symptom days. There were also few reports of oral prednisone and antibiotic use to treat symptom changes, with only 3 reports of each across the study period.

Discussion

This is one of few studies to examine daily changes in respiratory symptoms, oxygenation, lung function, and rescue inhaler/nebulizer use in moderate-to-severe COPD participants. We found that increases in self-reported respiratory symptoms were common and aligned with an objective measure of COPD disease activity (i.e., oxygenation). However, there was an extremely low (< 4%) utilization rate of rescue inhaler and nebulizer medication to self-treat these worsening symptoms.

To our knowledge, no previous studies have evaluated the relationship between worsening daily

symptoms and changes in oxygenation in COPD patients. We found that each additional symptom was associated with a 0.19 percentage point lower oxygen saturation. Self-report of at least 1 moderate-to-severe symptom (defined as worsening dyspnea, sputum purulence or amount) was associated with a 0.56 percentage point lower average oxygen saturation, compared to days without any symptom increases. We observed a similar difference in oxygenation on exacerbation days compared to non-exacerbation days; however, this relationship had a wider confidence interval, likely due to limited power (there were only 47 observations meeting the questionnaire definition of a COPD exacerbation). We found a statistically robust relationship of lower average oxygen saturation and days with increased respiratory symptoms. The magnitude of this association (0.6% lower pulse oximetry on major symptom days, and 0.2% lower pulse oximetry per self-reported symptom) is modest, and unlikely to be clinically meaningful as it falls within the normal variation of oximeter. Rather, our findings provide evidence that subjective worsening of patient-reported respiratory symptoms are associated with an objective measure of worsened gas exchange and COPD disease activity. Our findings are consistent with other studies that have also found patient-reported COPD symptoms to be associated with objective health measures, such as FEV_1% predicted, peak expiratory flow, and increased risk of clinically confirmed exacerbation.[30-33]

We found no association between worsening self-reported symptoms and lung function measured by FEV_1. In contrast, previous studies using the same symptom survey tool observed declines in lung function as measured by peak expiratory flow rate, FEV_1, and FVC after onset of COPD exacerbation (defined by consecutive days of minor and major symptoms), but did not evaluate associations with milder respiratory symptoms.[25,27] Although there is evidence linking exacerbation frequency and moderate-to-severe exacerbation episodes to the rate of long-term decline in lung function in COPD,[26,34,35] the literature on acute changes in lung function in association with COPD symptoms or exacerbations is limited.[36-38]

Perhaps the most striking finding of our study is that despite the common occurrence of worsening COPD symptoms, and the association of these symptoms with worsened oxygenation, study participants rarely increased their use of inhalers or nebulizers on symptom days. There is only limited evidence supporting the use of short-acting bronchodilators to improve lung function and symptoms (e.g., breathlessness) for COPD,[21] and these results have informed recommendations for initial pharmacological treatment in the GOLD document.[19] While all of our study participants had access to short-acting bronchodilators for relief of acute respiratory symptoms, our results suggest that adherence to these recommendations in the outpatient setting is poor.

One possible explanation for this poor adherence issue could be a perception of little to no therapeutic benefit. It has been reported that COPD patients do not often feel their medication alleviates symptoms.[39] Another possibility is that these short-acting inhalers are being overused at baseline and not as a step-up therapy to alleviate worsening symptoms. This has been observed in other studies. For example, a 2016 study of 32 participants with moderate-to-severe COPD found that almost half of participants overused short-acting beta2-agonists during clinically stable days.[22] It is also possible that participants did not accurately report incremental inhaler or nebulizer use, or that they under-reported rescue treatment because the quantitative threshold for reporting increased use of rescue medication "above your usual treatment" was not well-defined. For example, a patient who usually reaches for her rescue inhaler 2 days per week may not report the days that she used her rescue inhaler as "above your usual treatment" because twice weekly use still falls within her usual pattern. Future work is needed to explore factors associated with over- and under-use of rescue medications in patients with COPD.

Our study has a number of limitations. Our findings are based on a small sample size of only 26 former smokers with COPD living in the Boston area who are followed at a tertiary academic institution and adherent to a complex study protocol involving daily lung function and electronic surveys. Therefore, our findings may not be generalizable to other COPD populations, including current smokers, followed in the community. Additionally, we relied on self-reported daily respiratory symptoms and treatment changes through an electronic questionnaire, and there is potential for reporting error by these elderly

participants. Our work did not assess the effectiveness of rescue inhaler/nebulizer medication on treating daily COPD symptoms, reducing risk of exacerbation, or improving overall health outcomes. There are also some important strengths of our study. Our study is one of few to collect months of daily health measures in former smokers with moderate-to-severe COPD. Our repeated measures study design allowed us to uniquely evaluate day-to-day changes in respiratory symptoms, oxygenation, lung function, and self-treatment over many months among clinically stable COPD participants.

In conclusion, this study confirms that self-reported COPD symptoms are associated with worsening oxygenation, but also finds that symptoms do not prompt increased utilization of as-needed inhaler or nebulizer medication for symptom relief. Future research evaluating patient utilization, clinical effectiveness, and patient perception of rescue short-acting bronchodilators may identify the reasons for the apparent low utilization of rescue inhaler/nebulizer among patients with COPD.

Acknowledgements

Declaration of Interest

References

1. Heron M. Death: leading causes for 2017. *Nat Vital Stat Rep.* 2019;68(6):1-77. Accessed September 2020. https://www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_06-508.pdf .

2. World Health Organization (WHO). The top 10 causes of death. WHO website. Published May 24, 2018. Accessed September 2020. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

3. Anzueto A. Impact of exacerbations on COPD. *Eur Respir Rev.* 2010;19(116):113-118. doi: https://doi.org/10.1183/09059180.00002610

4. Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax.* 2005;60(11):925-931. doi: https://doi.org/10.1136/thx.2005.040527

5. López-Campos JL, Tan W, Soriano JB. Global burden of COPD. *Respirology.* 2016;21(1):14-23. doi: https://doi.org/10.1111/resp.12660

6. Quaderi SA, Hurst JR. The unmet global burden of COPD. *Glob Health Epidemiol Genom.* 2018;3:e4. doi: https://doi.org/10.1017/gheg.2018.1

7. Snider GL. Exacerbations of chronic obstructive pulmonary disease: should self-management be used? *Am J Respir Crit Care Med.* 2004;170(8):920. doi: https://doi.org/10.1164/ajrccm.170.8.950

8. Lenferink A, Brusse-Keizer M, van der Valk PD, et al. Self-management interventions including action plans for exacerbations versus usual care in patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2017;8:CD011682. doi: https://doi.org/10.1002/14651858.CD011682.pub2

9. Rice KL, Dewan N, Bloomfield HE, et al. Disease management program for chronic obstructive pulmonary disease: a randomized controlled trial. *Am J Respir Crit Care Med.* 2010;182(7):890-896. doi: https://doi.org/10.1164/rccm.200910-1579OC

10. Wilkinson TM, Donaldson GC, Hurst JR, Seemungal TA, Wedzicha JA. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2004;169(12):1298-1303. doi: https://doi.org/10.1164/rccm.200310-1443OC

11. Bourbeau J, Julien M, Maltais F, et al. Reduction of hospital utilization in patients with chronic obstructive pulmonary disease: a disease-specific self-management intervention. *Arch Intern Med.* 2003;163(5):585-591. doi: https://doi.org/10.1001/archinte.163.5.585

12. Janson SL, McGrath KW, Covington JK, Cheng SC, Boushey HA. Individualized asthma self-management improves medication adherence and markers of asthma control. *J Allergy Clin Immunol.* 2009;123(4):840-846. doi: https://doi.org/10.1016/j.jaci.2009.01.053

13. Cowie RL, Revitt SG, Underwood MF, Field SK. The effect of a peak flow-based action plan in the prevention of exacerbations of asthma. *Chest.* 1997;112(6):1534-1538. doi: https://doi.org/10.1378/chest.112.6.1534

14. Liu WT, Huang CD, Wang CH, Lee KY, Lin SM, Kuo HP. A mobile telephone-based interactive self-care system improves asthma control. *Eur Respir J.* 2011;37(2):310-317. doi: https://doi.org/10.1183/09031936.00000810

15. Rasmussen LM, Phanareth K, Nolte H, Backer V. Internet-based monitoring of asthma: a long-term, randomized clinical study of 300 asthmatic subjects. *J Allergy Clin Immunol.* 2005;115(6):1137-1142. doi: https://doi.org/10.1016/j.jaci.2005.03.030

16. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. 2018 Report. GINA website. Published 2018. Accessed 2020. https://ginasthma.org/wp-content/uploads/2018/04/wms-GINA-2018-report-tracked_v1.3.pdf

17. Gibson PG, Powell H, Coughlan J, et al. Self-management education and regular practitioner review for adults with asthma. *Cochrane Database Syst Rev.* 2003(1):CD001117.

18. Rank MA, Volcheck GW, Li JT, Patel AM, Lim KG. Formulating an effective and efficient written asthma action plan. *Mayo Clin Proc.* 2008;83(11):1263-1270. doi: https://doi.org/10.4065/83.11.1263

19. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of COPD, 2019 Report. GOLD website. Published 2019. Accessed 2020. https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf

20. Cazzola M, Rogliani P, Ruggeri P, et al. Chronic treatment with indacaterol and airway response to salbutamol in stable COPD. *Respir Med.* 2013;107(6):848-853. doi: https://doi.org/10.1016/j.rmed.2013.02.008

21. Sestini P, Renzoni E, Robinson S, Poole P, Ram FS. Short-acting beta 2 agonists for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2002(4):CD001495. doi: https://doi.org/10.1002/14651858.CD001495

22. Fan VS, Gylys-Colwell I, Locke E, et al. Overuse of short-acting beta-agonist bronchodilators in COPD during periods of clinical stability. *Respir Med.* 2016;116:100-106. doi: https://doi.org/10.1016/j.rmed.2016.05.011

23. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2):377-381. doi: https://doi.org/10.1016/j.jbi.2008.08.010

24. Aaron SD, Donaldson GC, Whitmore GA, Hurst JR, Ramsay T, Wedzicha JA. Time course and pattern of COPD exacerbation onset. *Thorax*. 2012;67(3):238-243.
doi: https://doi.org/10.1136/thoraxjnl-2011-200768

25. Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2000;161(5):1608-1613.
doi: https://doi.org/10.1164/ajrccm.161.5.9908022

26. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. *Thorax*. 2002;57(10):847-852.
doi: https://doi.org/10.1136/thorax.57.10.847

27. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1998;157(5 Pt 1):1418-1422.
doi: https://doi.org/10.1164/ajrccm.157.5.9709032

28. Barr RG, Stemple KJ, Mesia-Vela S, et al. Reproducibility and validity of a handheld spirometer. *Respir Care*. 2008;53(4):433-441.

29. Enright P, Vollmer WM, Lamprecht B, et al. Quality of spirometry tests performed by 9893 adults in 14 countries: the BOLD Study. *Respir Med*. 2011;105(10):1507-1515.
doi: https://doi.org/10.1016/j.rmed.2011.04.008

30. Leidy NK, Murray LT, Monz BU, et al. Measuring respiratory symptoms of COPD: performance of the EXACT- Respiratory Symptoms Tool (E-RS) in three clinical trials. *Respir Res*. 2014;15:124. doi: https://doi.org/10.1186/s12931-014-0124-z

31. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD Assessment Test. *Eur Respir J*. 2009;34(3):648-654.
doi: https://doi.org/10.1183/09031936.00102509

32. DeVries R, Kriebel D, Sama S. Validation of the breathlessness, cough and sputum scale to predict COPD exacerbation. *NPJ Prim Care Respir Med*. 2016;26:16083.
doi: https://doi.org/10.1038/npjpcrm.2016.83

33. Leidy NK, Schmier JK, Jones MK, Lloyd J, Rocchiccioli K. Evaluating symptoms in chronic obstructive pulmonary disease: validation of the Breathlessness, Cough and Sputum Scale. *Respir Med*. 2003;97 Suppl A:S59-70.
doi: https://doi.org/10.1016/S0954-6111(03)80016-1

34. Halpin DMG, Decramer M, Celli BR, Mueller A, Metzdorf N, Tashkin DP. Effect of a single exacerbation on decline in lung function in COPD. *Respir Med*. 2017;128:85-91.
doi: https://doi.org/10.1016/j.rmed.2017.04.013

35. Dransfield MT, Kunisaki KM, Strand MJ, et al. Acute exacerbations and lung function loss in smokers with and without chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2017;195(3):324-330.

36. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med*. 1987;106(2):196-204. doi: https://doi.org/10.7326/0003-4819-106-2-196

37. Davies L, Angus RM, Calverley PM. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. *Lancet*. 1999;354(9177):456-460.
doi: https://doi.org/10.1016/S0140-6736(98)11326-0

38. Sachs AP, Koëter GH, Groenier KH, van der Waaij D, Schiphuis J, Meyboom-de Jong B. Changes in symptoms, peak expiratory flow, and sputum flora during treatment with antibiotics of exacerbations in patients with chronic obstructive pulmonary disease in general practice. *Thorax*. 1995;50(7):758-763.
doi: https://doi.org/10.1136/thx.50.7.758

39. Lareau SC, Yawn BP. Improving adherence with inhaler therapy in COPD. *Int J Chron Obstruct Pulmon Dis*. 2010;5:401-406.
doi: https://doi.org/10.2147/COPD.S14715