GOALS OF COPD TREATEMENT FOCUS ON SYMPTOMS AND EXACERBATIONS

[1]Rahul rajendra Mahajan, [2]Nikita ravindra morankar

Department of pharmacy
Shastry Institute of pharmacy
Erandol.

Abstract- **Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide. While COPD is a mainly chronic disease, a substantial number of patients suffer from exacerbations. Severe exacerbations are related to a significantly worse survival outcome. This review summarises the current knowledge on the different aspects of COPD exacerbations. The impact of risk factors and triggers such as smoking, severe airflow limitation, bronchiectasis, bacterial and viral infections and comorbidities is discussed. More severe exacerbations should be treated with β-agonists and anticholinergics as well as systemic corticosteroids. Antibiotic therapy should only be given to patients with presumed bacterial infection. Noninvasive ventilation is indicated in patients with respiratory failure. Smoking cessation is key to prevent further COPD exacerbations. Other aspects include choice of pharmacotherapy, including bronchodilators, inhaled corticosteroids, phosphodiesterase-4 inhibitors, longterm antibiotics and mucolytics. Better education and self-management as well as increased physical activity are important. Influenza and pneumococcal vaccination is recommended. Treatment of hypoxaemia and hypercapnia reduce the rate of COPD exacerbations, while most interventional bronchoscopic therapies increase exacerbation risk within the first months after the procedure.**

Keywords: **COPD; Exacerbations; GOLD; Management goals; symptoms.**

1. Introduction

Healthcare systems [ductions in spirometry measures such as forced expiratory volume in 1 s 1]. COPD can be progressive, as indicated by repected to increase further in the coming years due to an aging populaapproximately 300 million in 2017 [States in 2017 [treatable disease marked by persistent respiratory symptoms and airflow limitation [wide in 2016 [tion and continued exposure to COPD risk factors, including tobacco smoke, occupational dusts and chemicals, biomass fuel and air pollution [1]. However, COPD can be prevented by reducing exposure to these risk Chronic obstructive pulmonary disease (COPD) is a preventable and 1]. It was ranked as the third leading cause of death world2], and the fourth leading cause of death in the United 3]. The prevalence of COPD was reported to be 4], with the burden of COPD ex--- (to improve long-term outcomes and quality of life. Recommendations discusses the challenges that many healthcare professionals face in for monitoring treatment outcomes and adjusting management strateChronic Obstructive Lung Disease (GOLD) strategy report [gies are also discussed. gies for the management of symptoms and prevention of exacerbations consider both pharmacologic and nonpharmacologic treatment stratetrying to meet these goals. In the context of the 2020 Global Initiative for FEVThis review examines the current goals of COPD management and [1]) over time, though patients may progress at different rates 1][, we 1,6]--. factors, including avoidance or early cessation of smoking [most common respiratory symptoms associated with COPD include 1,5].

2.Challenges in management of COPD dyspnea, cough and/or sputum production [symptom burden, COPD may be punctuated by periods of acute worsening of respiratory symptoms (often referred to as ‘exacerbations1]. In addition to the daily’)-, genetic and environmental factors [COPD is a heterogeneous, multifaceted disease that is influenced by 7]. The heterogeneity of COPD has

Abbreviations

CAPTURE COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease & Exacerbation Risk CAT COPD Assessment Test
CCQ Clinical COPD Questionnaire
COPD chronic obstructive pulmonary disease
FEV_1 forced expiratory volume in 1 s
GOLD Global Initiative for Chronic Obstructive Lung Disease
ICS inhaled corticosteroids
LABA long-acting β_2-agonist
LAMA long-acting muscarinic antagonist
MIRROR Medical Investigation of Respiratory COPD Perception mMRC modified Medical Research Council
SGRQ St. George's Respiratory Questionnaire

led to much interest in defining different phenotypes based on clinical characteristics [8]. For example, the GOLD ABCD classification defines four groups (phenotypes) of patients based on symptom severity and exacerbation history [1]. The concept of COPD endotypes refers to the definition of patient subgroups based on underlying biologic differences, for example bacterial colonization, and more controversially, eosinophilic inflammation [8–10]. Precision medicine refers to the use of both clinical (phenotype) and biologic (endotype) information on an individual basis in order to tailor treatment strategies accordingly [11]. Currently, our level of understanding of COPD subtypes is limited, and improvements are needed to better develop novel targeted therapeutic approaches, rather than adopting a 'one-size-fits-all' approach to COPD treatment [8]. Healthcare professionals need to work with their patients to find the best combination of pharmacologic and nonpharmacologic treatment strategies (including lifestyle changes) to manage the condition [1].

Due to environmental and genetic factors, abnormal lung function growth trajectories, beginning at birth, may occur [12]. These trajectories have recently been implicated in clinical outcomes, such as the propensity to develop respiratory disease [12]. Studies have demonstrated that some patients never reach peak lung function but then experience 'normal' rates of decline [12]. For others, the period of fastest decline in lung function may occur much earlier than originally thought [12], hence early detection and treatment of COPD may be beneficial to reduce associated morbidity and mortality [13]. Despite these findings, these concepts are not currently routinely considered, and COPD is often perceived as a progressive disease that responds poorly to treatment.

Evidence suggests that COPD is underdiagnosed, with most cases identified during an exacerbation or after significant loss of lung function [14]. The US Preventive Services Task Force continues to recommend against screening for COPD with spirometry due to a lack of data to indicate that this impacts long-term outcomes [15], but unfortunately this has been interpreted by some as meaning that identifying and treating COPD is not beneficial. A good option for diagnosing COPD is to use systematic and targeted case-finding approaches. For example, a case-finding methodology was reported [14] which entailed a brief five-item questionnaire (COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease & Exacerbation Risk; CAPTURE) as an initial screen. Peak expiratory flow was then performed on a subset of patients with positive questionnaire results, to increase the accuracy of case identification [14]. This method is currently being further evaluated in a large primary care patient population [14]. Another potential approach involves the use of microspirometers such as the PiKo-6® device (nSpire Health, Inc.) [16,17]. Following a postal questionnaire, patients reporting respiratory symptoms can be invited for spirometric assessment to confirm the diagnosis of COPD [18]. When full spirometry is not available or practical, for instance during a primary care consultation, then hand-held microspirometers have been shown to reliably and quickly measure pre-bronchodilator FEV_1/FEV_6, and to therefore identify patients for further spirometric assessment [16,17]. Both of these approaches may have a future role in reducing the underdiagnosis of COPD whilst also increasing the efficiency of full diagnostic spirometry use in primary care.

Currently, management of COPD focuses on the alleviation of symptoms and prevention of the future risk of exacerbations [1]. Challenges relating specifically to the management of symptoms and exacerbations are described in the relevant sections below.

3. Goals of COPD treatment: focus on symptoms

COPD symptoms have a considerable influence on patients' activities, health status and quality of life [19–30], and it is this impact that motivates some patients to seek a diagnosis [31]. In particular, dyspnea is responsible for much of the anxiety and disability associated with COPD [22], as it affects patients with all severities of the disease [23,29, 31]. The negative impact of COPD symptoms on physical activity promotes muscle deconditioning, which can lead to further dyspnea, thereby promoting a cycle of decline that results in deterioration of health status [32–35]. Symptoms

such as dyspnea affect family life and the patient's ability to perform everyday activities, for instance household chores and walking up stairs [36]. In addition to pulmonary symptoms, COPD can be associated with systemic features such as fatigue, weight loss and sleep disturbance, as well as psychiatric symptoms including depression and anxiety, significantly impacting quality of life [37,38].

3.1. Challenges of symptom recognition and management

Despite the significant impact of COPD symptoms on patients' lives, there is evidence that the most common respiratory symptoms, such as dyspnea, cough and sputum production, are under-reported [1]. In particular, night-time symptoms and sleep disturbance are often under-recognized [19,24]. Even in those with severe airflow limitation, many patients with COPD do not report symptoms [39], and are often slow to discuss them with their physician [40] or attribute them to factors such as aging, workplace exposure to pollution or smoking [41, 42]. Some patients with COPD may adapt their lifestyle to compensate for symptoms, and often only present to physicians when their condition has deteriorated significantly [37]. A report describing the burden and impact of COPD in North America and Europe highlighted that even patients with severe dyspnea and significant compromise of daily physical activities requiring exertion tended to underestimate their disease burden, ranking it as mild or moderate [30]. In addition, the Medical Investigation of Respiratory COPD Perception (MIRROR) survey recently confirmed that there were differences between the perceptions that patients with COPD have of their disease and those of their physicians [40]. For instance, patients with severe or very severe COPD perceived their disease to have a greater impact than that perceived by their pulmonologists, particularly in terms of the impact on their quality of life (e.g. daily activities and work) [40].

FEV_1 is a very important parameter at the population level, for predicting clinical outcomes such as mortality and hospitalizations, or prompting consideration for non-pharmacologic procedures such as lung volume reduction or lung transplantation [1,43]. However, it is important to note that, at the individual patient level, FEV_1 loses precision and thus cannot be used to determine the most appropriate therapeutic option, as it does not necessarily correlate with all symptoms experienced by patients and their impact on quality of life or exacerbation frequency [1,37]. In addition, some individuals with chronic respiratory symptoms and/or structural evidence of lung disease may have normal spirometry [1,44]; therefore, healthcare professionals must consider both spirometry and symptoms when assessing patients, to avoid disease progression and the development of acute respiratory events [1,37]. Evidence regarding the impact of COPD symptoms on younger patients (e.g. data on absenteeism, presenteeism and socioeconomic status) is sparse; however, it has been reported that COPD likely represents a significant burden for patients of working age [45]. Lastly, although the benefits of COPD treatments are well established in terms of pulmonary symptoms, their impact on psychologic symptoms such as confidence, social interaction and sleep quality is less clear [46]. However, it has recently been shown that behavioral modifications that motivate patients to increase their daily physical activity can also improve anxiety, cognitive function and depression in patients with COPD [47]. *3.2. Symptom assessment*

Given the under-reporting and under-recognition of symptoms, there is a need for appropriate tools in clinical practice to identify symptoms and adjust treatment accordingly. The most efficient and accurate way for physicians to assess symptom severity, activity limitation and health- related quality of life is to use a standardized measure, such as a short patient-centered questionnaire [37]. A number of questionnaires are available for assessing symptoms, yet uptake is often limited in clinical practice, most likely due to a combination of lack of awareness, difficulty in incorporating questionnaires into practice flow, or lack of electronic medical record support for questionnaires.

The COPD Assessment Test (CAT) is a useful and practical questionnaire for clinical practice [37]. CAT aims to quickly measure the impact of COPD on health-related quality of life and to facilitate patient–physician communication [37]. Items covered include physical symptoms such as cough, phlegm, chest tightness, breathlessness when going up hills and stairs, activity limitation at home, and energy, as well as related factors that affect patients' quality of life, including confidence leaving home and sleep quality [37]. CAT has also been shown to be responsive to pulmonary rehabilitation and in assessing recovery from an exacerbation [37].

Other questionnaires include the modified Medical Research Council (mMRC) dyspnea scale,
Clinical COPD Questionnaire (CCQ) and St. George's Respiratory Questionnaire (SGRQ) [37,48–50].
Simple to administer, the mMRC dyspnea scale (0– 4) is easily used to indicate the extent to which dyspnea impacts on daily activities alone; however, drawbacks include its insensitivity to change (e.g. in response to treatment), and it does not take into account the fact that patients often modify their behavior and the amount of effort exerted due to dyspnea [37]. The CCQ enables a more complete understanding of the impact of COPD on patients, including a more comprehensive assessment of activity limitation and emotional dysfunction, and is a useful tool in the everyday clinical setting to assess COPD [37]. Areas of assessment include symptoms (e.g. dyspnea, cough and phlegm), functional state and mental state. CCQ has also been shown to be sensitive to clinical improvement after smoking cessation, and during and after exacerbations [37].

Lastly, while frequently used in clinical trials, the SGRQ includes numerous questions and is not suitable for use in daily clinical practice [37].

4. Goals of COPD treatment: focus on exacerbations

An exacerbation in COPD is defined as an acute worsening of respiratory symptoms that results in additional therapy [1], and is mainly triggered by respiratory infections (mostly viral, such as rhinovirus, as well as bacterial infections), and environmental factors such as air pollution. Exacerbations associated with viral infections tend to be more severe, last longer, and require more hospitalizations (e.g. during winter) [1]. Current treatment goals for exacerbations are to minimize the negative impact of the current exacerbation and reduce the risk of any future exacerbations [1]. The majority of patients that experience exacerbations can be managed on an outpatient basis with pharmacologic therapies; however, some patients may require hospitalization for a number of reasons, including severity of symptoms, failure to respond to initial treatment, poor or limited home-based care, and presence of comorbidities [1]. As the clinical presentation of exacerbations is heterogeneous, the GOLD report recommends that the determination of severity in hospitalized patients should be based on clinical signs [1].

4.1. Challenges of exacerbation management

The long-term prognosis following hospitalization for exacerbations is poor, especially in patients with additional risk factors such as older age, comorbidities, lower body mass index and poorer quality of life [1]. Some patients with COPD are particularly susceptible to frequent exacerbations, and these patients have been shown to have worse health status, morbidity and mortality than those with less frequent exacerbations [1,51]. Despite this, many patients do not report their exacerbations to healthcare professionals [1]. Patient education on when to seek medical attention for exacerbations is of vital importance. A recent Cochrane review reported that COPD self-management interventions, which include written negotiated action plans for worsening symptoms, lead to a lower probability of respiratory-related hospitalization and all-cause hospitalizations [52]. However, there have been concerns that health benefits from self-management programs in COPD could be counterbalanced by increased mortality [53,54], although this should be interpreted with caution, as not all studies have been able to replicate the data [52,55]. Self-management programs are not intended to replace other components of patient care; however, the authors suggest that inappropriate use of self-managed therapies by patients may delay acute healthcare, with the potential of ultimately increasing the use of inhospital healthcare.

COPD exacerbations are usually identified based on an increase in a variety of symptoms, including increased breathlessness and/or increased sputum production [56]. However, there are no objective criteria for measuring exacerbations, and this increase in symptoms may be an extension of regular COPD symptoms [57]. It may also be difficult to distinguish true increased symptoms versus the patient's perception of symptoms. It has been reported that the sensation of dyspnoea is enhanced in patients with COPD who experience frequent acute exacerbations and is blunted in those who suffer from exacerbations infrequently [58].

Identifying exacerbation triggers in COPD patients is often difficult in practice. Pulmonary inflammation varies greatly between individuals, and this has proven challenging in terms of biomarker evaluation or inflammation-targeted therapeutic intervention [56]. Unlike COPD exacerbations [57], other acute presentations of chronic diseases (e.g. myocardial infarction) have specific and sensitive diagnostic toolkits, such as biomarkers and imaging techniques, that are used in routine management of patients [56].

Exacerbations can also be difficult to recognize, and many patients presenting with a COPD exacerbation have comorbid conditions, which complicates evaluation and management. Indeed, it may be that events recorded as exacerbations are actually a presentation of a comorbidity [59]. Some studies suggest that clinicians are less likely to diagnose comorbidities (e.g. heart failure and myocardial infarction) if there is an existing diagnosis of COPD [60,61]. Additionally, the presence of a comorbidity has been shown to increase the duration of an exacerbation and lead to longer hospital stays [62,63], while there is evidence to suggest that comorbidities (e.g. asthma) may contribute to more frequent severe exacerbations
[64].

Many novel treatments have failed to prevent exacerbations. This may be due to the use of inappropriate or ineffective molecules, or because the concept of a single medicine treating a heterogeneous disease such as COPD is unrealistic [65]. However, personalized medicine may have a role in preventing exacerbations in some COPD patients [9, 11,66–68]. Blood eosinophil counts can help healthcare professionals to predict the probability of clinical benefit with the addition of inhaled corticosteroids (ICS) to maintenance bronchodilators [1]. Treatment with macrolides may also have a role in COPD therapy. Low-dose erythromycin therapy for 12 months reduced the frequency and severity of exacerbations in patients with moderate-to-severe COPD, with an acceptable tolerability [69]. Daily azithromycin therapy has also been shown to reduce COPD exacerbations, and has been recommended for use in patients who are at risk of recurrent exacerbations [69,70]. However, besides the potential to generate resistant microbes, azithromycin has been associated with a small increased risk of hearing decrements, as well as cardiovascular events relating to QT-interval prolongation in some patients with concurrent risk factors [70,71]. Additional subgroup analyses suggest that chronic azithromycin therapy may not benefit current smokers [72]. Furthermore, data on macrolide treatment for longer than 12 months, and the use of other antibiotics for the treatment of COPD, are currently lacking.

5. Recommendations for COPD treatment

5.1. Control of risk factors and non-pharmacologic management

It is important to identify and reduce COPD risk factors in the prevention and treatment of COPD [1]. For instance, smoking cessation is a key intervention, and healthcare professionals are therefore encouraged to deliver smoking cessation messages and interventions to patients, such as using counselling, financial incentive programs and patient education [1,73]. Therapies for tobacco dependence, including varenicline, sustainedrelease bupropion, nortriptyline, nicotine gum, nicotine inhaler, nicotine nasal spray, and nicotine patches, can be effective as quitting aids and are recommended in the absence of contraindications [1,74]. In addition, reducing exposure to indoor and outdoor pollution, including biomass fuel and occupational inhalants, may require public policy changes, as well as protective steps taken by individuals [1].

Pulmonary rehabilitation should be considered an important component of integrated patient management [73] in combination with pharmacologic therapies. A Cochrane meta-analysis of 65 randomized controlled trials involving 3822 patients has reported that pulmonary rehabilitation can relieve dyspnea and fatigue, improve emotional function and enhance the sense of control that patients have over their condition [75]. The effect with pulmonary rehabilitation was larger for quality of life domains (Chronic Respiratory Questionnaire) than the minimal clinically important difference of 0.5 units [75]. In addition, statistically significant improvements were noted in all domains of the SGRQ, and both functional and maximal exercise showed statistically significant improvements [75]. Similarly, another Cochrane review including 1477 patients suggested that pulmonary rehabilitation after an exacerbation can improve health-related quality of life and exercise capacity [76].

It has been reported that patients who undertake regular physical activity have a lower risk of exacerbations, COPD hospital admissions and allcause mortality [77,78]. Health education can also help patients cope with their illness, and it may be effective in influencing behavioural changes (e.g. smoking cessation) and attainment of certain treatment goals [5]. Lastly, influenza and pneumococcal (PCV13 and PPSV23) vaccinations are recommended for patients with COPD, in particular older patients [1]. Vaccination can reduce serious illness, and some studies have shown reductions in the total number of exacerbations [79–81].

5.2. Pharmacologic treatment

Pharmacologic therapy for COPD is used to treat symptoms, reduce the frequency and severity of exacerbations, and improve exercise tolerance and health status [1]. The classes of medications commonly used to treat COPD include long-acting β_2-agonists (LABAs), long-acting muscarinic antagonists (LAMAs) and ICS [73]. The choice within each class depends on the availability of medication and patients' responses and preferences [1].

Once the clinical and spirometry diagnosis of COPD is confirmed, clinical guidance from the GOLD strategy report can be applied for initial pharmacologic treatment using the best available evidence, emphasizing the importance of selecting the correct treatment from the start [1]. The model, involving the individualized assessment of symptoms and exacerbation risk using the ABCD assessment scheme, is shown in Fig. 1 [1]. Rescue medication with short-acting bronchodilators should be prescribed for immediate symptom relief, but use of these is not generally recommended on a regular basis [1]. A long-acting bronchodilator is then usually offered. In some patients, a
combination treatment such as LAMA/LABA (e.g. for patients with severe breathlessness) or LABA/ICS (for patients with a high risk of exacerbations and higher blood eosinophil counts) may be offered as initial treatment [1]. *5.3. The management cycle*

Following initiation of therapy, patients should be followed up for achievement of treatment goals, and adjustments made where necessary (Fig. 2) [1]. If response to initial treatment is not appropriate, it is important to consider whether symptoms or exacerbations are the predominant characteristic, and follow the most appropriate pharmacologic path, as per Fig. 3 [1]. The addition of a long-acting bronchodilator is used for dyspnoea; for exacerbations, either a long-acting bronchodilator or an ICS is added. Factors that favour adding an ICS include more frequent exacerbations, higher eosinophil counts, or the coexistence of bronchial asthma [1].

As most COPD pharmacotherapies are inhaled, proper inhaler technique is key [1]. A recommendation in the GOLD report is that the choice of inhaler device needs to be individually tailored based on access, as well as the patient's ability and preference [1]. Good instructions and demonstrations are critical, and technique should be assessed at each visit [1,82]. A significant relationship has been identified between poor inhaler use and symptom control in patients with COPD [82], although education can improve inhalation techniques in some patients [82,83]. Errors in delivery device use include low inhalation flow, multiple breaths, and exhalation into the inhaler [84]. Thus, inhaler technique and adherence should be assessed before concluding that the current therapy requires modification.

6. Summary and conclusions

Although COPD imposes a significant burden in terms of mortality and morbidity, it is both preventable (by reduction of exposure to risk factors) and treatable (by reducing COPD symptoms and exacerbations). The goals of COPD treatment include recognizing the significance of both symptoms and exacerbations when considering optimal

management. The authors recommend using the best tools available to diagnose and assess COPD (including comorbidities), and combining both pharmacologic and non-pharmacologic measures for effective COPD management.

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Declaration of competing interest

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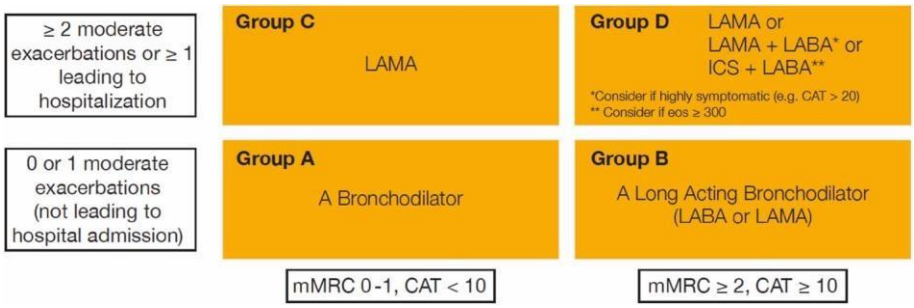

Fig. 1. Initial pharmacologic treatment of COPD. © 2020, Global

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CAT, COPD Assessment Test; ICS, inhaled corticosteroid; LABA, longacting β_2-agonist; LAMA, long- acting muscarinic antagonist; mMRC, modified Medical Research Council dyspnea scale.

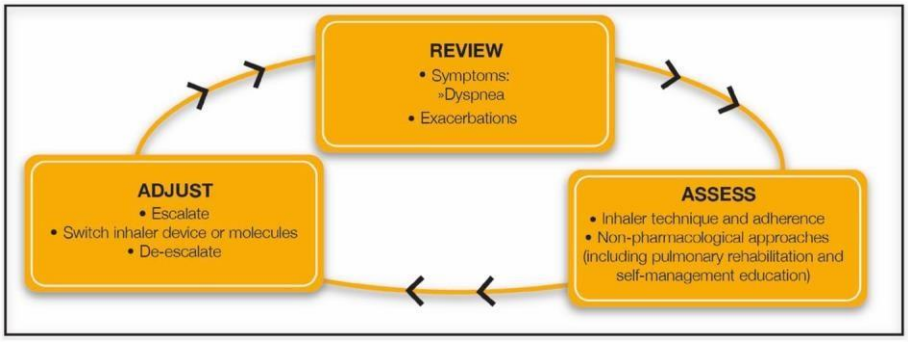

Fig. 2. The management cycle of patients with COPD.

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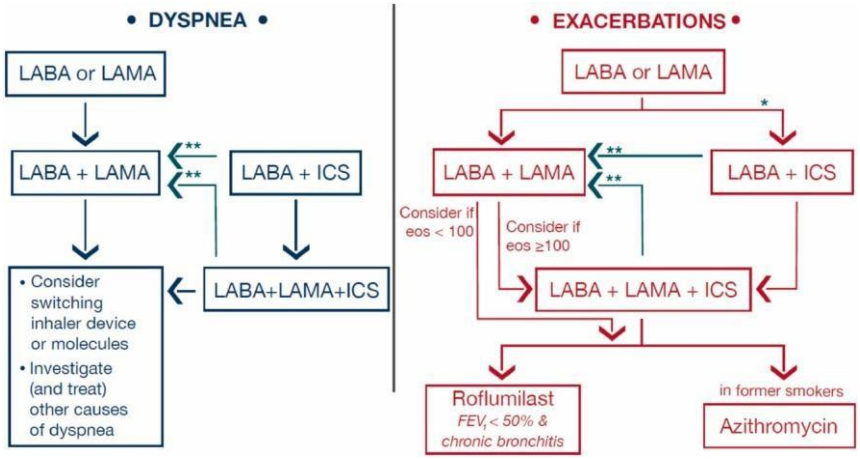

Fig. 3. Follow-up of pharmacologic management in patients with COPD in whom dyspnea or exacerbations predominate. © 2020, Global Initiative for Chronic Obstructive Lung Disease, reproduced with permission.

Consider if eos 300 or 100 AND 2 moderate exacerbations or 1 hospitalization; ** Consider deescalation of ICS or switch if pneumonia, inappropriate original indication or lack of response to ICS.
eos, eosinophils; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; LABA, long-acting $\beta_2$agonist; LAMA, long-acting muscarinic antagonist.
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REFERENCES:

[1] Global Initiative for Chronic Obstructive Lung Disease, Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (2020 report), accessed 6 December 2019, https://goldcopd.org/wp-conte nt/uploads/2019/11/GOLD-2020-REPORTver1.0wms.pdf, 2019.
[2] World Health Organization, The top 10 causes of death, accessed 7 November 2019, https://www.who.int/en/news-room/factsheets/detail/the-top-10-causes -of-death, 2018.
[3] M. Heron, Deaths: leading causes for 2017, Natl. Vital Stat. Rep. 68 (6) (2019) 1–77.
[4] GBD Disease Injury Incidence Prevalence Collaborators, Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017, Lancet 392 (10159) (2018) 1789–1858, https://doi.org/10.1016/S01406736(18)32279-7.
[5] World Health Organization, COPD management, accessed 16 December 2019, htt ps://www.who.int/respiratory/copd/managem ent/en/, 2016.
[6] P. Lange, B. Celli, A. Agusti, G. Boje Jensen, M. Divo, R. Faner, S. Guerra, J. L. Marott, F.D. Martinez, P. Martinez-Camblor, P. Meek, C.A. Owen, H. Petersen, V. Pinto-Plata, P. Schnohr, A. Sood, J.B. Soriano, Y. Tesfaigzi, J. Vestbo, Lung- function trajectories leading to chronic obstructive pulmonary disease, N. Engl. J. Med. 373 (2) (2015) 111–122, https://doi.org/10.1056/NEJMoa1411532.
[7] C. Seifart, A. Plagens, Genetics of chronic obstructive pulmonary disease, Int. J. Chronic Obstr. Pulm. Dis. 2 (4) (2007) 541–550.
[8] S. Garudadri, P.G. Woodruff, Targeting chronic obstructive pulmonary disease phenotypes, endotypes, and biomarkers, Ann Am Thorac Soc 15 (2018) S234–S238, https://doi.org/10.1513/AnnalsATS.201808533MG.
[9] V.K. Sidhaye, K. Nishida, F.J. Martinez, Precision medicine in COPD: where are we and where do we need to go? Eur. Respir. Rev. 27 (149) (2018), 180004 https:// doi.org/10.1183/16000617.0022-2018.
[10] B.R. Celli, G.J. Criner, Using the peripheral blood eosinophil count to manage patients with chronic obstructive pulmonary disease, Ann Am Thorac Soc 16 (3) (2019) 301–303, https://doi.org/10.1513/AnnalsATS.201810729PS.
[11] A. Agusti, E. Bel, M. Thomas, C. Vogelmeier, G. Brusselle, S. Holgate, M. Humbert, P. Jones, P.G. Gibson, J. Vestbo, R. Beasley, I.D. Pavord, Treatable traits: toward precision medicine of chronic airway diseases, Eur. Respir. J. 47 (2) (2016) 410–419, https://doi.org/10.1183/13993003.01359-2015.
[12] A. Agusti, R. Faner, Lung function trajectories in health and disease, Lancet Respir. Med. 7 (4) (2019) 358–364, https://doi.org/10.1016/S2213-2600(18)30529-0.
[13] N.G. Csikesz, E.J. Gartman, New developments in the assessment of COPD: early diagnosis is key, Int. J. Chronic Obstr. Pulm. Dis. 9 (2014) 277–286, https://doi. org/10.2147/COPD.S46198.
[14] F.J. Martinez, D. Mannino, N.K. Leidy, K.G. Malley, E.D. Bacci, R.G. Barr, R. P. Bowler, M.K. Han, J.F. Houfek, B. Make, C.A. Meldrum, S. Rennard, B. Thomashow, J. Walsh, B.P. Yawn, High-RiskCOPD Screening Study Group, A new approach for identifying patients with undiagnosed chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 195 (6) (2017) 748–756, https://doi.org/10.1164/rccm.201603-0622OC. [15] J.M. Guirguis-Blake, C.A. Senger, E.M. Webber, R.A. Mularski, E.P. Whitlock, Screening for chronic obstructive pulmonary disease: evidence report and systematic review for the US Preventive Services Task Force, J. Am. Med. Assoc. 315 (13) (2016) 1378–1393, https://doi.org/10.1001/jama.2016.2654.

[16] L. van den Bemt, B.C.W. Wouters, J. Grootens, J. Denis, P.J. Poels, T.R. Schermer, Diagnostic accuracy of pre-bronchodilator FEV1/FEV6 from microspirometry to detect airflow obstruction in primary care: a randomised cross-sectional study, NPJ Prim Care Respir Med 24 (2014) 14033, https://doi.org/10.1038/ npjpcrm.2014.33.
[17] P. Frith, A. Crockett, J. Beilby, D. Marshall, R. Attewell, A. Ratnanesan, G. Gavagna, Simplified COPD screening: validation of the PiKo-6® in primary care, Prim. Care Respir. J. 20 (2) (2011) 190–198, https://doi.org/10.4104/ pcrj.2011.00040.
[18] R.E. Jordan, K.-b.H. Lam, K.K. Cheng, M.R.
Miller, J.L. Marsh, J.G. Ayres, D. Fitzmaurice, P. Adab, Case finding for chronic obstructive pulmonary disease: a model for optimising a targeted approach, Thorax 65 (6) (2010) 492–
498, https:// doi.org/10.1136/thx.2009.129395.
[19] A. Agusti, J. Hedner, J.M. Marin, F. Barbe, M. Cazzola, S. Rennard, Night-time symptoms: a forgotten dimension of COPD, Eur. Respir. Rev.
20 (121) (2011) 183–194, https://doi.org/10.1183/09059180.00004311.
[20] N. Roche, N.H. Chavannes, M. Miravitlles, COPD symptoms in the morning: impact, evaluation and management, Respir. Res. 14 (2013) 112, https://doi.org/ 10.1186/1465-9921-14-112.
[21] I. Tsiligianni, E. Metting, T. van der Molen, N. Chavannes, J. Kocks, Morning and night symptoms in primary care COPD patients: a cross-sectional and longitudinal study. An
UNLOCK study from the IPCRG, NPJ Prim Care Respir Med 26 (2016) 16040, https://doi.org/10.1038/npjpcrm.2016.40.
[22] T. Doyle, S. Palmer, J. Johnson, M.A. Babyak, P.
Smith, S. Mabe, K. Welty-Wolf, T. Martinu, J.A. Blumenthal, Association of anxiety and depression with pulmonary-specific symptoms in chronic obstructive pulmonary disease, Int. J. Psychiatr. Med. 45 (2) (2013) 189–202, https://doi.org/10.2190/PM.45.2.g.
[23] M. Miravitlles, H. Worth, J.J. Soler Cataluna, D.
Price, F. De Benedetto, N. Roche, N.S. Godtfredsen, d.M. van, C.-G. Lofdahl, L. Padull€ es, A. Ribera, Observational study to characterise 24-hour COPD symptoms and their relationship with patient- reported outcomes: results from the ASSESS study, Respir. Res. 15 (1) (2014) 122, https://doi.org/10.1186/s12931014-0122-1.
[24] P. Lange, J.L. Marott, J. Vestbo, B.G. Nordestgaard, Prevalence of night-time dyspnoea in COPD and its implications for prognosis, Eur. Respir. J. 43 (6) (2014) 1590–
1598, https://doi.org/10.1183/09031936.00196713.
[25] M. Miravitlles, A. Anzueto, D. Legnani, L. Forstmeier, M. Fargel, Patient's perception of exacerbations of COPD – the PERCEIVE study, Respir. Med. 101 (3) (2007) 453–460, https://doi.org/10.1016/j.rmed.2006.07.010
[pii].
[26] M. Monteagudo, T. Rodriguez-Blanco, M.
Llagostera, C. Valero, X. Bayona, M. Ferrer, M. Miravitlles, Factors associated with changes in quality of life of COPD patients: a prospective study in primary care, Respir. Med. 107 (10)
(2013) 1589–1597, https://doi.org/10.1016/j.rmed.2013.05.009.
[27] D. Price, M. Small, G. Milligan, V. Higgins, E.G. Gil, J. Estruch, Impact of night- time symptoms in COPD: a real-world study in five European countries, Int. J.
Chronic Obstr. Pulm. Dis. 8 (2013) 595–603, https://doi.org/10.2147/COPD. S48570.
[28] I. Tsiligianni, J. Kocks, N. Tzanakis, N. Siafakas, T. van der Molen, Factors that influence diseasespecific quality of life or health status in patients with COPD: a review and meta-analysis of Pearson correlations, Prim. Care Respir. J. 20
(3) (2011) 257–268, https://doi.org/10.4104/pcrj.2011.00029.
[29] J.J. Stephenson, D. Wertz, T. Gu, J. Patel, A.A. Dalal, Clinical and economic burden of dyspnea and other COPD symptoms in a managed care
setting, Int. J. Chronic Obstr. Pulm. Dis. 12
(2017) 1947–1959, https://doi.org/10.2147/COPD.S134618.
[30] S. Rennard, M. Decramer, P.M. Calverley, N.B. Pride, J.B. Soriano, P.A. Vermeire, J. Vestbo, Impact of COPD in North America and Europe in 2000: subjects' perspective of confronting COPD international survey, Eur. Respir. J. 20 (4) (2002) 799–805, https://doi.org/10.1183/09031936.02.03242002.
[31] M. Miravitlles, A. Ribera, Understanding the impact of symptoms on the burden of COPD, Respir. Res. 18 (1) (2017) 67, https://doi.org/10.1186/s12931-017-0548- 3.
[32] D.E. Donnell, Impacting patient-centred outcomes in COPD: breathlessness and exercise tolerance, Eur. Respir. Rev. 15 (99) (2006) 37, https://doi.org/10.1183/ 09059180.00009903.
[33] R. Casaburi, Activity promotion: a paradigm shift for chronic obstructive pulmonary disease therapeutics, Proc. Am. Thorac. Soc. 8 (4) (2011) 334–337, https://doi.org/10.1513/pats.201101-001RM.

[34] J. Gea, S. Pascual, C. Casadevall, M. Orozco-Levi, E. Barreiro, Muscle dysfunction in chronic obstructive pulmonary disease: update on causes and biological findings, J. Thorac. Dis. 7 (10) (2015) E418–E438, https://doi.org/10.3978/j. issn.20721439.2015.08.04.

[35] ERS Task Force, P. Palange, S.A. Ward, K.H. Carlsen, R. Casaburi, C.G. Gallagher, R. Gosselink, D.E. O'Donnell, L. Puente-Maestu, A.M. Schols, S. Singh, B.J. Whipp, Recommendations on the use of exercise testing in clinical practice, Eur. Respir. J. 29 (1) (2007) 185–209, https://doi.org/10.1183/09031936.00046906.

[36] P. Vermeire, The burden of chronic obstructive pulmonary disease, Respir. Med. 96 (2002) S3– S10, https://doi.org/10.1016/S09546111(02)80028-2 [pii].

[37] T. van der Molen, M. Miravitlles, J.W. Kocks, COPD management: role of symptom assessment in routine clinical practice, Int. J. Chronic Obstr. Pulm. Dis. 8 (2013) 461–471, https://doi.org/10.2147/COPD.S49392.

[38] K.B. Stage, T. Middelboe, T.B. Stage, C.H. Sorensen, Depression in COPD – management and quality of life considerations, Int. J. Chronic Obstr. Pulm. Dis. 1 (3) (2006) 315–320, https://doi.org/10.2147/copd.2006.1.3.315.

[39] A. Agusti, P.M. Calverley, B. Celli, H.O. Coxson, L.D. Edwards, D.A. Lomas, W. MacNee, B.E. Miller, S. Rennard, E.K. Silverman, R. Tal-Singer, E. Wouters, J. C. Yates, J. Vestbo, ECLIPSE investigators, Characterisation of COPD heterogeneity in the ECLIPSE cohort, Respir. Res. 11 (2010) 122, https://doi.org/10.1186/1465- 9921-11-122.

[40] B. Celli, F. Blasi, M. Gaga, D. Singh, C. Vogelmeier, V. Pegoraro, N. Caputo, A. Agusti, Perception of symptoms and quality of life – comparison of patients' and physicians' views in the COPD MIRROR study, Int. J. Chronic Obstr. Pulm. Dis. 12 (2017) 2189–2196, https://doi.org/10.2147/COPD.S136711.

[41] E.C. Hansen, J. Walters, R.W. Baker, Explaining chronic obstructive pulmonary disease (COPD): perceptions of the role played by smoking, Sociol. Health Illn. 29 (5) (2007) 730–749, https://doi.org/10.1111/j.14679566.2007.01013.x.

[42] M.A. Tageldin, S. Nafti, J.A. Khan, C. Nejjari, M. Beji, B. Mahboub, N.M. Obeidat, E. Uzaslan, A. Sayiner, S. Wali, N. Rashid, A. El Hasnaoui, Distribution of COPD- related symptoms in the Middle East and North Africa: results of the BREATHE study, Respir. Med. 106 (2012) S25– S32, https://doi.org/10.1016/S0954-6111 (12)70012-4.

[43] M. Duong, S. Islam, S. Rangarajan, D. Leong, O. Kurmi, K. Teo, K. Killian, G. Dagenais, S. Lear, A. Wielgosz, S. Nair, V. Mohan, P. Mony, R. Gupta, R. Kumar, O. Rahman, K. Yusoff, J.L. du Plessis, E.U. Igumbor, J. Chifamba, W. Li, Y. Lu, F. Zhi, R. Yan, R. Iqbal, N. Ismail, K. Zatonska, K. Karsidag, A. Rosengren, A. Bahonar, A. Yusufali, P.M. Lamelas, A. Avezum, P. Lopez-Jaramillo, F. Lanas, P. M. O'Byrne, S. Yusuf, Mortality and cardiovascular and respiratory morbidity in individuals with impaired FEV_1 (PURE): an international, community-based cohort study, Lancet Glob. Health 7 (5) (2019) e613–e623, https://doi.org/10.1016/ S2214-109X(19)30070-1.

[44] R. Rodriguez-Roisin, M.K. Han, J. Vestbo, J.A. Wedzicha, P.G. Woodruff, F. J. Martinez, Chronic respiratory symptoms with normal spirometry: a reliable clinical entity? Am. J. Respir. Crit. Care Med. 195 (1) (2016) 17–22, https://doi. org/10.1164/rccm.2016071376PP.

[45] M.J. Fletcher, J. Upton, J. Taylor-Fishwick, S.A. Buist, C. Jenkins, J. Hutton, N. Barnes, T. Van Der Molen, J.W. Walsh, P. Jones, S. Walker, COPD uncovered: an international survey on the impact of chronic obstructive pulmonary disease [COPD] on a working age population, BMC Publ. Health 11 (2011) 612, https:// doi.org/10.1186/1471-2458-11-612.

[46] R. Garrod, M. Malerba, E. Crisafulli, Determinants of success, Eur. Respir. J. 38 (5) (2011) 1215, https://doi.org/10.1183/09031936.00088611.

[47] K.L. Lavoie, M. Sedeno, A. Hamilton, P.-Z. Li, D. De Sousa, T. Troosters, F. Maltais, J. Bourbeau, Behavioural interventions targeting physical activity improve psychocognitive outcomes in COPD, ERJ Open Res. 5 (4) (2019), https://doi.org/ 10.1183/23120541.000132019, 00013-2019.

[48] T. Glaab, C. Vogelmeier, R. Buhl, Outcome measures in chronic obstructive pulmonary disease (COPD): strengths and limitations, Respir. Res. 11 (2010) 79, https://doi.org/10.1186/1465-9921-11-79.

[49] M. Cazzola, W. MacNee, F.J. Martinez, K.F. Rabe, L.G. Franciosi, P.J. Barnes, V. Brusasco, P.S. Burge, P.M. Calverley, B.R. Celli, P.W. Jones, D.A. Mahler, B. Make, M. Miravitlles, C.P. Page, P. Palange, D. Parr, M. Pistolesi, S.I. Rennard, M.P. Rutten-van Molken, R. Stockley, S.D. Sullivan, J.A. Wedzicha, E.F. Wouters, American thoracic society, European respiratory society Task Force on outcomes of COPD, outcomes for COPD pharmacological trials: from lung function to biomarkers, Eur. Respir. J. 31 (2) (2008) 416–469, https://doi.org/10.1183/ 09031936.00099306.

[50] M. Cazzola, N.A. Hanania, W. MacNee, K. Rudell, C. Hackford, N. Tamimi, A review of the most common patient-reported outcomes in COPD – revisiting current knowledge and estimating future challenges, Int. J. Chronic Obstr. Pulm. Dis. 10 (2015) 725–738, https://doi.org/10.2147/COPD.S77368.

[51] J.J. Soler-Cataluna, M.A. Martinez-Garcia, P. Roman Sanchez, E. Salcedo, M. Navarro, R. Ochando, Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease, Thorax 60 (11) (2005) 925–931, https:// doi.org/10.1136/thx.2005.040527.
[52] A. Lenferink, M. Brusse-Keizer, P.D. van der Valk, P.A. Frith, M. Zwerink, E. M. Monninkhof, J. van der Palen, T.W. Effing, Self-management interventions including action plans for exacerbations versus usual care in patients with chronic obstructive pulmonary disease, Cochrane Database Syst. Rev. 8 (2017), CD011682, https://doi.org/10.1002/14651858.CD011682.p ub2.
[53] V.S. Fan, J.M. Gaziano, R. Lew, J. Bourbeau, S.G. Adams, S. Leatherman, S. S. Thwin, G.D. Huang, R. Robbins, P.S. Sriram, A. Sharafkhaneh, M.J. Mador, G. Sarosi, R.J. Panos, P. Rastogi, T.H. Wagner, S.A. Mazzuca, C. Shannon, C. Colling, M.H. Liang, J.K. Stoller, L. Fiore, D.E. Niewoehner, A comprehensive care management program to prevent chronic obstructive pulmonary disease hospitalizations: a randomized, controlled trial, Ann. Intern. Med. 156 (10) (2012) 673–683, https://doi.org/10.7326/0003-4819-156-10201205150-00003.
[54] I. Peytremann-Bridevaux, P. Taffe, B. Burnand, P.O. Bridevaux, M.A. Puhan, Mortality of patients with COPD participating in chronic disease management programmes: a happy end? Thorax 69 (9) (2014) 865–866, https://doi.org/ 10.1136/thoraxjnl-2013204983.
[55] M. Zwerink, M. Brusse-Keizer, P.D. van der Valk, G.A. Zielhuis, E.M. Monninkhof, J. van der Palen, P.A. Frith, T. Effing, Self management for patients with chronic obstructive pulmonary disease, Cochrane Database Syst. Rev. 3 (2014), CD002990, https://doi.org/10.1002/14651858.CD002990.p ub3.
[56] E. Sapey, M. Bafadhel, C.E. Bolton, T. Wilkinson, J.R. Hurst, J.K. Quint, Building toolkits for COPD exacerbations: lessons from the past and present, Thorax 74 (2019) 898–905, https://doi.org/10.1136/thoraxjnl-2018213035.
[57] A. Agusti, R. Faner, B. Celli, R. Rodriguez-Roisin, Precision medicine in COPD exacerbations, Lancet Respir. Med. 6 (9) (2018) 657–659, https://doi.org/ 10.1016/S22132600(18)30296-0.
[58] G. Scioscia, I. Blanco, E. Arismendi, F. Burgos, C. Gistau, M.P. Foschino Barbaro, B. Celli, D.E. O'Donnell, A. Agusti, Different dyspnoea perception in COPD patients with frequent and infrequent exacerbations, Thorax 72 (2) (2017) 117–121, https://doi.org/10.1136/thoraxjnl2016-208332.
[59] V. Kim, S.D. Aaron, What is a COPD exacerbation? Current definitions, pitfalls, challenges and opportunities for improvement, Eur. Respir. J. 52 (5) (2018), 1801261, https://doi.org/10.1183/13993003.01261-2018.
[60] K.J. Rothnie, J.K. Quint, Chronic obstructive pulmonary disease and acute myocardial infarction: effects on presentation, management, and outcomes, Eur. Heart J. Qual. Care Clin. Outcomes 2 (2) (2016) 81–90, https://doi.org/10.1093/ ehjqcco/qcw005.
[61] J. de Miguel Diez, J. Chancafe Morgan, R. Jimenez Garcia, The association between COPD and heart failure risk: a review, Int. J. Chronic Obstr. Pulm. Dis. 8 (2013) 305–312, https://doi.org/10.2147/COPD.S31236 [doi].
[62] A.R.C. Patel, G.C. Donaldson, A.J. Mackay, J.A. Wedzicha, J.R. Hurst, The impact of ischemic heart disease on symptoms, health status, and exacerbations in patients with COPD, Chest 141 (4) (2012) 851–857, https://doi.org/10.1378/chest.11- 0853.
[63] E.H. Baker, C.H. Janaway, B.J. Philips, A.L. Brennan, D.L. Baines, D.M. Wood, P. W. Jones, Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease, Thorax 61 (4) (2006) 284– 289, https://doi.org/10.1136/thx.2005.051029.
[64] S.H. Jeong, H. Lee, K.C. Carriere, S.H. Shin, S.M. Moon, B.-H. Jeong, W.-J. Koh, H. Y. Park, Comorbidity as a contributor to frequent severe acute exacerbation in COPD patients, Int. J. Chronic Obstr. Pulm. Dis. 11 (2016) 1857–1865, https://doi. org/10.2147/COPD.S103063.
[65] D. Singh, U. Martin, Biologics for chronic obstructive pulmonary disease: present and future, Barcelona Respir. Netw. 4 (2018) 34–52, https://doi.org/10.23866/ BRNRev:2017-0032.
[66] J.M. Leung, M. Obeidat, M. Sadatsafavi, D.D. Sin, Introduction to precision medicine in COPD, Eur. Respir. J. 53 (4) (2019), 1802460, https://doi.org/ 10.1183/13993003.024602018.
[67] M. Cazzola, L. Calzetta, P. Rogliani, M.G. Matera, The challenges of precision medicine in COPD, Mol. Diagn. Ther. 21 (4) (2017) 345–355, https://doi.org/ 10.1007/s40291-017-0266-z.
[68] A. Agusti, M. Bafadhel, R. Beasley, E.H. Bel, R. Faner, P.G. Gibson, R. Louis, V. M. McDonald, P.J. Sterk, M. Thomas, C. Vogelmeier, I.D. Pavord, s. on behalf of all participants in the, Precision medicine in airway diseases: moving to clinical practice, Eur. Respir. J. 50 (4) (2017), https://doi.org/10.1183/13993003.01655- 2017 pii: 1701655.
[69] T.A. Seemungal, T.M. Wilkinson, J.R. Hurst, W.R. Perera, R.J. Sapsford, J. A. Wedzicha, Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations, Am. J. Respir. Crit. Care Med. 178 (11) (2008) 1139–1147, https://doi.org/10.1164/rccm.200801-145OC.
[70] R.K. Albert, J. Connett, W.C. Bailey, R. Casaburi, J.A.D. Cooper, G.J. Criner, J. L. Curtis, M.T. Dransfield, M.K. Han, S.C. Lazarus, B. Make, N. Marchetti, F. J. Martinez, N.E. Madinger, C. McEvoy, D.E. Niewoehner, J. Porsasz, C.S. Price, J. Reilly, P.D. Scanlon, F.C. Sciurba, S.M. Scharf, G.R. Washko, P.G. Woodruff, N. R.

Anthonisen, Azithromycin for prevention of exacerbations of COPD, N. Engl. J. Med. 365 (8) (2011) 689–698, https://doi.org/10.1056/NEJMoa1104623.

[71] S.P. Taylor, E. Sellers, B.T. Taylor, Azithromycin for the prevention of COPD exacerbations: the good, bad, and ugly, Am. J. Med. 128 (12) (2015), https://doi. org/10.1016/j.amjmed.2015.07.032, 1362.e1-1362.e6.

[72] M.K. Han, N. Tayob, S. Murray, M.T. Dransfield, G. Washko, P.D. Scanlon, G. J. Criner, R. Casaburi, J. Connett, S.C. Lazarus, R. Albert, P. Woodruff, F. J. Martinez, Predictors of chronic obstructive pulmonary disease exacerbation reduction in response to daily azithromycin therapy, Am. J. Respir. Crit. Care Med. 189 (12) (2014) 1503–1508, https://doi.org/10.1164/rccm.201402-0207OC.

[73] B.R. Celli, J.A. Wedzicha, Update on clinical aspects of chronic obstructive pulmonary disease, N. Engl. J. Med. 381 (13) (2019) 1257–1266, https://doi.org/ 10.1056/NEJMra1900500.

[74] K. Cahill, S. Stevens, R. Perera, T. Lancaster, Pharmacological interventions for smoking cessation: an overview and network metaanalysis, Cochrane Database Syst. Rev. (5) (2013), CD009329, https://doi.org/10.1002/14651858.CD009329. pub2.

[75] B. McCarthy, D. Casey, D. Devane, K. Murphy, E. Murphy, Y. Lacasse, Pulmonary rehabilitation for chronic obstructive pulmonary disease, Cochrane Database Syst. Rev. (2) (2015), CD003793, https://doi.org/10.1002/14651858.CD003793.p ub3.

[76] M.A. Puhan, E. Gimeno-Santos, C.J. Cates, T. Troosters, Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease, Cochrane Database Syst. Rev. 12 (2016), CD005305, https://doi.org/10.1002/14651858. CD005305.pub4.

[77] E. Gimeno-Santos, A. Frei, C. Steurer-Stey, J. de Batlle, R.A. Rabinovich, Y. Raste, N.S. Hopkinson, M.I. Polkey, H. van Remoortel, T. Troosters, K. Kulich, N. Karlsson, M.A. Puhan, J. Garcia-Aymerich, P.R. consortium, Determinants and outcomes of physical activity in patients with COPD: a systematic review, Thorax 69 (8) (2014) 731–739, https://doi.org/10.1136/thoraxjnl-2013204763.

[78] J. Garcia-Aymerich, P. Lange, M. Benet, P. Schnohr, J.M. Anto, Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study, Thorax 61 (9) (2006) 772–778, https:// doi.org/10.1136/thx.2006.060145.

[79] P. Wongsurakiat, K.N. Maranetra, C. Wasi, U. Kositanont, W. Dejsomritrutai, S. Charoenratanakul, Acute respiratory illness in patients with COPD and the effectiveness of influenza vaccination: a randomized controlled study, Chest 125 (6) (2004) 2011–2020, https://doi.org/10.1378/chest.125.6.2011.

[80] J.A.E. Walters, J.N.Q. Tang, P. Poole, R. WoodBaker, Pneumococcal vaccines for preventing pneumonia in chronic obstructive pulmonary disease, Cochrane Database Syst. Rev. 1 (2017), https://doi.org/10.1002/14651858.CD001390. pub4.

[81] P. Poole, E.E. Chacko, R. Wood-Baker, C.J. Cates, Influenza vaccine for patients with chronic obstructive pulmonary disease, Cochrane Database Syst. Rev. 1 (2006), https://doi.org/10.1002/14651858.CD002733.p ub2.

[82] A.S. Melani, M. Bonavia, V. Cilenti, C. Cinti, M. Lodi, P. Martucci, M. Serra, N. Scichilone, P. Sestini, M. Aliani, M. Neri, Gruppo Educazionale Associazione Italiana Pneumologi Ospedalieri, Inhaler mishandling remains common in real life and is associated with reduced disease control, Respir. Med. 105 (6) (2011) 930–938, https://doi.org/10.1016/j.rmed.2011.01.005.

[83] G.N. Rootmensen, A.R. van Keimpema, H.M. Jansen, R.J. de Haan, Predictors of incorrect inhalation technique in patients with asthma or COPD: a study using a validated videotaped scoring method, J. Aerosol Med. Pulm. Drug Deliv. 23 (5) (2010) 323–328, https://doi.org/10.1089/jamp.2009.0785.

[84] I. Sulaiman, B. Cushen, G. Greene, J. Seheult, D. Seow, F. Rawat, E. MacHale, M. Mokoka, C.N. Moran, A. Sartini Bhreathnach, P. MacHale, S. Tappuni, B. Deering, M. Jackson, H. McCarthy, L. Mellon, F. Doyle, F. Boland, R.B. Reilly, R. W. Costello, Objective assessment of adherence to inhalers by patients with chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 195 (10) (2017) 1333–1343, https://doi.org/10.1164/rccm.201604-0733OC.