Respiratory Medicine 125 (2017) 49–56

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Review article

Symptom variability and control in COPD: Advantages of dual bronchodilation therapy

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ARTICLE INFO

Article history:
Received 4 October 2016
Received in revised form
23 December 2016
Accepted 1 March 2017
Available online 2 March 2017

Keywords:
Aclidinium
Formoterol
Chronic obstructive pulmonary disease
Lung function
Dual bronchodilator therapy
Symptom variability

ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) is a heterogeneous disorder characterized by usually progressive development of airflow obstruction that is not fully reversible. While most patients will experience symptoms throughout the day or in the morning upon awakening, many patients do not experience their symptoms as constant but report variability in symptoms during the course of the day or over time. Symptom variability adversely affects patients' health status and increases the risk of COPD exacerbations.

Methods: We examined data from the literature on symptom variability and control in patients with COPD, with focus on the use of inhaled bronchodilator therapy with long-acting muscarinic antagonist agents (LAMA) plus long-acting β_2-agonists (LABA); in particular twice-daily fixed-dose combination LAMA/LABA therapy with aclidinium/formoterol.

Results: Correct diagnosis and assessment of COPD requires comprehensive clinical and functional evaluation and consideration of individual needs to support the clinical decisions necessary for effective long-term management. Combining bronchodilators from different and complementary pharmacological classes with distinct mechanisms of action can increase the magnitude of bronchodilation as opposed to increasing the dose of a single bronchodilator.

Conclusions: The use of inhaled bronchodilator therapy with LAMA/LABA fixed-dose combinations in patients with stable COPD is supported by current evidence. This treatment approach provides robust effects on lung function and symptom control and may improve patients' adherence to treatment. Administration of the long-acting bronchodilators aclidinium and formoterol as twice daily fixed-dose aclidinium/formoterol 400/12 μg has the potential to control symptoms throughout the 24 h in patients with stable moderate-to-severe COPD.

Contents

1. Introduction 50
2. Variability and symptom control in COPD 50

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http://dx.doi.org/10.1016/j.rmed.2017.03.001

3. Use of combination bronchodilators in COPD 51
4. Potential advantages of twice-daily fixed-dose LAMA/LABA combinations 52
5. Discussion 53
6. Conclusions 54
Funding 54
Authorship 54
Declarations of interest 54
Acknowledgments 54
References 54

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by progressive development of airflow obstruction that is not fully reversible and is associated with an abnormal inflammatory response in the airways and lung to noxious particles or gases [1–3]. COPD is a heterogeneous disorder. It is increasingly recognized that, though spirometry is essential to establish the presence of airflow limitation and to diagnose COPD, it is not adequate to fully assess the impact and severity of the disease. Indeed, the assessment of COPD requires a comprehensive clinical and functional evaluation including assessment of comorbid conditions affecting the patient to support the proper clinical decision for effective long-term patient management [2].

The reduced capacity to generate expiratory flows is the principal functional characteristic of COPD. It is the outcome of a complex interaction of abnormal respiratory mechanics, including peripheral airway obstruction and reduced lung elastic recoil. Expiratory flow limitation during tidal breathing is a key pathophysiological characteristic of COPD resulting from the inability to further increase expiratory flow rate at a given lung volume despite increasing expiratory effort [4–9]. In the presence of expiratory flow limitation, the available expiratory time is not sufficient to allow full emptying of the lung, leading to gas trapping and lung hyperinflation, which reduces inspiratory capacity with a corresponding increase in functional residual capacity (dynamic hyperinflation), in particular during exercise, thus increasing dyspnea and limiting exercise capacity. Initially presenting only in the supine position, when the patient's ventilation is constrained, expiratory flow limitation further develops and worsens with the progression of the disease, occurring more commonly during physical exertion and even at rest in more severe cases, when the patient is sitting or standing [8].

Both resting and dynamic lung hyperinflation better reflect improvements in symptoms and exercise performance after bronchodilator treatment than do spirometric assessments of reduced maximal expiratory flow rates [10]. Hyperinflation imposes major clinical consequences on patients with COPD, and reducing lung hyperinflation has been shown to be a key mechanism by which patients with COPD derive benefit, regardless of disease severity [11,12]. Importantly, in the presence of expiratory flow limitation, in the majority of patients pulmonary dynamic hyperinflation is promoted, which leads to worsening dyspnea, reduced exercise capacity, altered cardiac function and gas exchange, and ultimately results in negative consequences that have a major impact on health-related quality of life (HR-QoL) and mortality in patients with COPD [1,6,8,13]. During exercise, hyperinflation may cause functional respiratory muscle weakness, increasing breathing effort and impairing cardio-circulatory function, which collectively impairs performance. The negative consequences arising from hyperinflation have a major impact on HR-QoL and mortality for patients with COPD [1,6], and are the main contributors to reduced participation in everyday activities. Daily physical activity has been shown to be mainly associated with dynamic hyperinflation, regardless of COPD severity [14], and dynamic hyperinflation is present even in patients with only mild functional impairment [7,15]. Furthermore, impairments of respiratory mechanisms imposed by pathophysiological processes such as hyperinflation and expiratory flow limitation increase levels of proinflammatory cytokines and contribute to systemic inflammation and structural remodeling of the airways of patients with COPD [1,16].

Forced expiratory volume in 1 s (FEV_1) is an independent predictor of morbidity and mortality in patients with COPD [1,2,17,18]. However, lung function is now recognized as only one of a number of independent factors predictive of clinical outcomes [2], and there is increasing awareness of the importance of COPD features such as dyspnea (especially during exercise), exercise capacity, COPD exacerbations, and hyperinflation, which are in fact more effective predictors of mortality than FEV_1 alone [13,19–21].

The use of inhaled medication, mainly bronchodilators, is central to the management of COPD [1,2]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends treatments based on LAMAs alone or in combination with LABAs for the long-term management of COPD; in stable COPD, inhaled corticosteroids (ICS), always in combination with long-acting β_2-agonists (LABA), are limited to specific indications, i.e. patients with severe and very severe COPD at high risk of exacerbations [1]. Inhaled bronchodilator therapy with long-acting muscarinic antagonist anticholinergic agents (LAMA) and long-acting β_2-agonists (LABA) not only improve breathlessness by direct action on bronchial smooth muscle, but also by reducing dynamic hyperinflation; thus clinical benefits may be apparent even without clear changes in FEV_1 [2].

This review examines symptom variability and control in patients with COPD, with particular focus on the use of twice-daily fixed-dose combination (FDC) LAMA/LABA therapy with aclidinium/formoterol. For this purpose, we conducted a literature search of the PubMed database using the following MESH descriptors: pulmonary disease, chronic obstructive, COPD, sign and symptoms (respiratory), bronchodilator agents, adrenergic beta-2 receptor agonists, and muscarinic antagonists.

2. Variability and symptom control in COPD

There is increasing awareness that, although most patients experience symptoms throughout the day or in the morning upon awakening, many patients do not experience their symptoms as constant but report variability in one or more of their symptoms during the course of the day or over time (Fig. 1) [22–25]. It is estimated that over 75% of patients with COPD experience nocturnal symptoms, which are likely to be under-reported and insufficiently considered in the clinical management of COPD, despite their negative impact on sleep quality and health status and increased risk of cardiovascular morbidity and mortality [24,26]. Patients reporting both or either night-time and/or early morning

symptoms have significantly poorer health status than those without symptom variability. Finally, there is a greater risk of COPD exacerbations in patients with both night-time and early morning symptoms [24].

Miravitlles et al. showed that more than 60% of patients reported one or more symptomatic episodes nightly, and the presence of symptoms throughout the whole of the day (during the night, in the morning upon waking or during the day) was associated with worse HR-QoL, dyspnea and sleep quality [25], as well as higher levels of anxiety and depression [25,27]. Symptoms related to breathlessness were the most common, occurring in over 70% of patients, with coughing, bringing up phlegm or mucus, wheezing, and chest tightness and congestion also reported. However, the frequency and pattern of individual symptoms varied over the 24 h day. There were also significant relationships between when patients experienced symptoms during the day and physical activity levels [25].

Similarly, morning symptoms can also be a burden, with many patients reporting troublesome symptoms upon waking or in the early morning; in particular, phlegm, cough, dyspnea, wheezing and chest tightness [28]. Indeed, for many patients with COPD, the morning is the worst time of the day, as morning symptoms significantly limit the ability of patients to perform normal morning activities. Furthermore, increased symptom variability is correlated with symptom severity, suggesting that this feature is indicative of respiratory impairment and its impact on exercise limitation [28]. Notably, despite the perceptions by patients with severe COPD of daily and weekly variability of their symptoms, only a minority of patients in the study of Kessler et al. adapted their treatment in response to worsening of symptoms, and many were taking their medications too late in the day to obtain full benefit [28], suggesting that improved disease management may improve health status in patients with COPD and symptom variability.

During sleep, changes in central respiratory control, lung mechanics, and muscle contractility which in healthy individuals produce a modest reduction in functional residual capacity without causing any adverse effects, may create problems for patients with COPD [29]. The combination of airway obstruction, hyperinflation, respiratory muscle hypotonia, cephalad displacement of the diaphragm, decreased dynamic lung compliance, and other COPD-related abnormalities intensify sleep-related alterations in gas exchange [30]. COPD-related sleep disturbances, in turn, contribute to the persistence of troublesome symptoms the next morning, more frequent exacerbations and impaired health status for many patients with COPD [25]. In addition, patients with COPD may develop greater oxygen desaturation during sleep than during maximal exercise, with a consequent increased risk of cardiovascular morbidity and mortality [8,29].

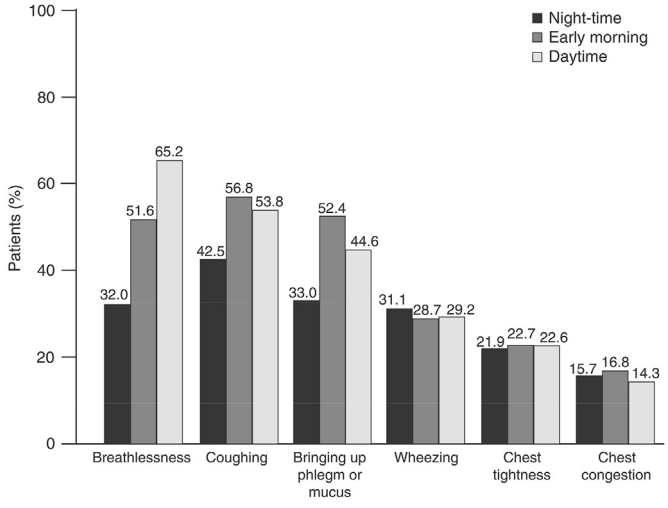

Fig. 1. Prevalence of individual COPD symptoms throughout the 24 h day despite ongoing treatment for COPD.
Reproduced with acknowledgment from Ref. [25], Miravitlles et al. Respir Res (BioMed Central) 2014, 15:122 (Fig. 2) under the Creative Commons Public Domain Dedication waiver according to the terms of the Creative Commons license: https://creativecommons.org/licenses/by/4.0/.

It has been shown that there are significant circadian variations in FEV_1, FEV_1/forced vital capacity (FVC), which can be associated with changes in the cortisol levels as well as a higher cholinergic tone during the sleeping hours, leading to airflow limitation in patients with COPD [31,32].

The supine position predisposes to expiratory airflow limitation (EFL) owing to the fact that tidal breathing occurs at lower lung volumes where maximal expiratory flow rates are reduced [8]. EFL is linked to the presence of airflow reduction in obstructive lung diseases such as COPD, and can be augmented by increased airway resistance, augmented cholinergic bronchial tone, airway-parenchyma uncoupling, and airways collapsibility. EFL is associated and/or promotes dynamic pulmonary hyperinflation, which in turn fosters neuromechanical dissociation, with impairment of the function of the inspiratory muscles, adverse effects on hemodynamics and, ultimately, may contribute to the dyspnea sensation [8].

Long-acting bronchodilators increase inspiratory capacity and reduce breathlessness even in the absence of marked improvement in FEV_1 in patients with EFL [5]. There is additional evidence that fast-acting bronchodilators (both LABAs and LAMAs) may have an additional role in controlling morning symptoms and improving HR-QoL in patients experiencing an increase of disease-related symptoms in the morning and/or night-time [22]. Moreover, it has been shown that administering the LAMA tiotropium in the evening, rather than in the morning, does not substantially improve lung function parameters during the night [31]. The LAMA aclidinium, which is rapidly and extensively hydrolyzed in the plasma, has a low absolute systemic bioavailability (<5%) that allows twice-daily administration without an increase in the risk of side effects [33–35].

In a study that compared administration of aclidinium twice daily with tiotropium once daily in the morning, aclidinium provided significant improvement in lung function that was maintained throughout the entire 24 h, and aclidinium, but not tiotropium, significantly reduced the severity of early-morning cough, wheeze, shortness of breath, and phlegm, and of night-time symptoms, compared with placebo ($p < 0.05$) [36].

3. Use of combination bronchodilators in COPD

The majority of COPD patients across all FEV_1 severities report that their symptoms persist when on therapy with a LABA or LAMA [37]. Combining bronchodilators from different and complementary pharmacological classes with distinct mechanisms can increase the degree of bronchodilation compared to increasing the dose of a single bronchodilator in patients with stable COPD [38,39]. This is now recognized in current international management guidelines for COPD, such as the Global Initiative for Chronic Obstructive Lung Disease (GOLD) document [1] and the Spanish guidelines (GesEPOC) [40], which recommend using two long-acting bronchodilators with different mechanisms of action (LABA plus LAMA) as second-line treatment in patients without frequent exacerbations. For patients with severe breathlessness, the 2016 revised version of the GOLD document [1] suggests the initial therapy with two bronchodilators, as previously proposed by Singh

[38]. Furthermore, the safety profile of dual long acting bronchodilator therapy in COPD is favorable [38,39], as confirmed by a network meta-analysis which found the same level of safety of LABA/LAMA combinations compared with monotherapies [41]. The rationale for combining a β_2-agonist and an antimuscarinic agent is supported by evidence from biological models of airway smooth muscle [42] and in patients with COPD in a number of preliminary studies. Among them the elegant study by Calverley et al. on acute bronchodilator reversibility testing, showing that using a second drug, whether ipratropium or salbutamol, increased the mean FEV_1 and changed the number of patients classified as reversible [43].

The use of combined LABA plus LAMA as an appropriate treatment option is supported by the results of various studies, among which the ILLUMINATE study, where the fixed dose combination indacaterol/glycopyrronium administered using the same device (Breezhaler®) once daily was shown to be superior to salmeterol/fluticasone in terms of the main outcome, the area under the 0–12 h FEV_1 curve at week 26 (difference of 138 mL, 95% C.I., 100–176 mL; $p < 0.0001$), without any increase in the frequency of adverse effects, including a worsening in COPD, amongst patients treated with bronchodilators but no ICS [44].

These results support the recommendation of treatment with bronchodilators without anti-inflammatories in patients who do not have frequent exacerbations, and suggest that there is no significant negative effect on the risk of exacerbations due to ICS discontinuation in this specific population. However, the recent big trial FLAME demonstrated that LAMA/LABA FDC can be more effective than ICS/LABA, not only in terms of symptoms and function, but also for prevention of exacerbations; these novel findings will reasonably lead to a revision of national and international guidelines with the indication of LAMA/LABA FDC also in patients with at least one exacerbation per year [45].

According to the "*Documento italiano sulla Gestione clinica integrata della BPCO*" [Italian document on integrated COPD management], resulting from the partnership between "*Agenzia Nazionale per i Servizi Sanitari Regionali* (AGE.NA.S.)" (National Regional Health Services Agency), the three Italian societies for respiratory diseases (AIMAR, AIPO and SIMeR) and the Italian Society of General Medicine (SIMG), the main aim of COPD maintenance medication is bronchodilation [46]. Long-acting inhaled bronchodilators are the first-line treatment in patients with stable COPD. If the patient and/or the general practitioner are not satisfied with the results of monotherapy with a long-acting bronchodilator, the following alternatives should be considered:

- An increase in the dose of bronchodilator in accordance with its pharmacological characteristics [1,2,47–50].
- The addition of a second long-acting bronchodilator with a different mechanism of action [1,2,44,51–59].
- The addition of ICS, in patients with frequent exacerbations [1,2,55,60–62].

In summary, for patients whose symptoms are not controlled with a single long-acting bronchodilator, a combination of bronchodilator drugs with different mechanisms of action (LABA plus LAMA) has benefits over the increase in dose of a single bronchodilator.

4. Potential advantages of twice-daily fixed-dose LAMA/LABA combinations

In the management of symptomatic COPD, FDCs of LAMAs and LABAs have the potential to improve convenience and patient compliance compared with the use of separate inhalers. As part of the development process for FDCs, optimization of the dose of each component can be undertaken, while balancing the risk of increased adverse events compared with monotherapy. In addition, careful consideration of the most appropriate delivery device is important to aid with effective inhaler technique and ensure optimal disease management. The three main classes of device for combination inhaled LAMA/LABA therapy are pressurized metered dose inhalers (pMDIs), dry powder inhalers (DPIs) and the propellant-free Soft Mist™ inhaler (SMI) [56]. LAMA/LABA combinations currently available include glycopyrronium/indacaterol, umeclidinium/vilanterol, tiotropium/olodateroland aclidinium/formoterol; there are other combinations in development. These fixed-dose combinations have variously been shown to provide greater improvements in FEV_1, higher morning pre-trough and peak inspiratory capacity, greater improvements in dyspnea symptoms, improved HR-QoL, and lower use of rescue medication than monotherapy with either of the component agents, with similar or better adverse events and cardiac safety profiles [56].

As already discussed, early morning symptoms can be a burden to patients with COPD, and the morning is reported to be the worst time of the day for many patients [28]. Therefore, it can be hypothesized that fast-acting bronchodilators could be more effective in providing rapid relief of symptoms after morning dosing than bronchodilators with a slower onset of action. LABAs such as formoterol, indacaterol, olodaterol, and vilanterol have a more rapid onset of action than LABAs such as salmeterol, and the LAMAs aclidinium, umeclidinium or glycopyrronium are faster-acting than tiotropium. Similarly, with the increasing awareness of the importance of symptom variability in COPD, twice-daily dosing of bronchodilators may be more effective than once-daily administration in controlling troublesome night-time symptoms and those present on awakening.

For example, it has been shown that, for the same total daily dose, the trough FEV_1 response to twice-daily administration of the LAMA aclidinium is higher than that with once-daily administration [63]. Therefore, twice-daily dosing of FDC bronchodilators should be considered a useful strategy for the treatment of symptomatic COPD, although conclusive evidence from large controlled trials for the long-term superiority of twice-daily administration of bronchodilators over once-daily administration is lacking.

There is evidence for a synergistic, as distinct from additive, interaction for aclidinium and formoterol administered at therapeutic doses [42]. Aclidinium and formoterol induced significant and time-dependent bronchodilatory activity after inhalation, with a synergistic interaction for FEV_1 5 min after inhalation and from 120 to 240 min post-inhalation, whereas the drug interaction was additive from 30 to 60 min post-administration [42]. The combination of aclidinium and formoterol also induced a moderate-to-strong synergistic interaction in a human isolated bronchi model. These data support the rationale for combining bronchodilators with different mechanisms of action.

Aclidinium/formoterol 400/12 μg fixed dose combination (FDC) (Duaklir®; AstraZeneca) consists of aclidinium 400 μg, a long-acting muscarinic antagonist anticholinergic agent, and formoterol 12 μg, a long-acting β_2 adrenoceptor agonist bronchodilator. Aclidinium/formoterol 400/12 μg FDC is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD [59], and is administrated via a multidose breath-actuated dry powder inhaler (DPI; Genuair®).

The efficacy and safety of aclidinium/formoterol was established in two large 24-week double blind phase III pivotal studies, AUGMENT-COPD and ACLIFORM-COPD, which randomized a total of 3421 patients with stable moderate-to-severe COPD to twice daily treatment with aclidinium/formoterol 400/12 μg, FDC aclidinium/formoterol 400/6 μg, aclidinium 400 μg, formoterol 12 μg, or placebo, administered by DPI [64,65]. In the studies, aclidinium/

formoterol FDC produced rapid and sustained improvements in lung function over the 24 h, providing significantly improved bronchodilation compared with placebo and the two monotherapies ($p < 0.05$), without evidence of adverse events (Fig. 2). In fact, the safety profile of aclidinium/formoterol were similar to that of placebo [64,65]. Aclidinium/formoterol FDC met the co-primary endpoints of change from baseline at week 24 in 1-h morning post-dose FEV_1 compared with the monotherapies (aclidinium 400 μg and morning pre-dose formoterol 12 μg), indicating that the FDC provides bronchodilation that is faster in onset of action than aclidinium alone and with a greater magnitude across the dosing interval than formoterol alone.

A pre-specified pooled analysis of data from the two studies, powered to provide more reliable estimates of treatment effects of the aclidinium/formoterol FDC on COPD symptoms and exacerbations was conducted [66]. The analysis showed that aclidinium/formoterol 400/12 μg FDC significantly improved Transitional Dyspnea Index (TDI) focal score and EXAcerbations of Chronic pulmonary disease Tool (EXACT) Respiratory Symptoms (E-RS) total score at week 24 compared with placebo ($p < 0.01$) and both monotherapies ($p < 0.05$). Of particular interest in the light of symptom variability in COPD, aclidinium/formoterol 400/12 μg FDC also significantly improved overall early-morning and night-time symptom severity and limitation of early morning activities (Fig. 3) [66]. The FDC also significantly reduced the rate of moderate or severe exacerbations ($p < 0.05$), as assessed by the Healthcare Resource Utilization (HCRU) definition, compared with placebo but not the monotherapies, except for the rate of EXACT exacerbations, which were significantly lower with aclidinium/formoterol 400/12 μg than with aclidinium 400 μg ($p < 0.05$). Overall, the findings of the two studies indicated that twice-daily aclidinium/formoterol 400/12 μg provides rapid and sustained bronchodilation day and night in patients with stable moderate-to-severe COPD more effectively than monotherapy with either drug, with significant improvements in symptoms and health status, without additional safety concerns [66].

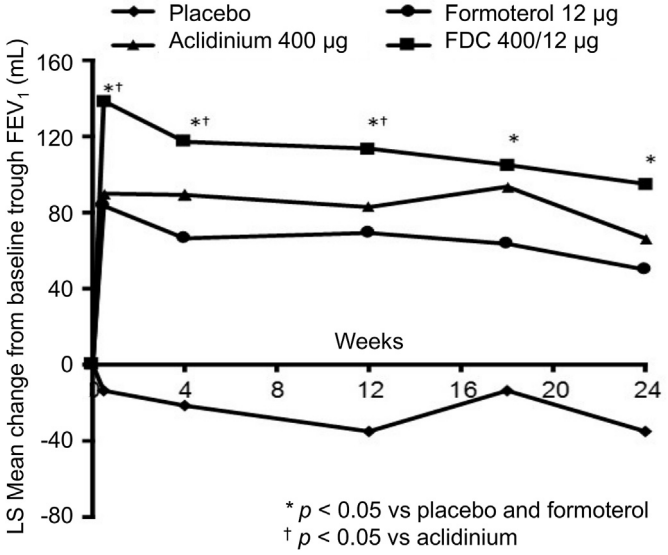

Fig. 2. Aclidinium/formoterol 400/12 μg FDC significantly improves trough FEV_1 versus placebo and formoterol monotherapy at every measured time point.
FDC, fixed-dose combination; FEV_1, forced expiratory volume in 1 s; LS, least squares. Modified with acknowledgment from Ref. [64], D'Urzo et al. Respir Res (BioMed Central) 2014; 15:123 (Figure 4B) under the Creative Commons Public Domain Dedication waiver according to the terms of the Creative Commons license: https://creativecommons.org/licenses/by/4.0/.

In summary, aclidinium/formoterol 400/12 μg FDC significantly improved early morning, day, and night symptom control compared with placebo and the single components (aclidinium and formoterol) in patients with moderate-to-severe COPD.

5. Discussion

COPD is a heterogeneous disorder characterized by the usually progressive development of airflow obstruction that is not fully reversible. While improving FEV_1 is a key aim of pharmacological therapy, other clinical features of COPD should be considered in the management of patients with COPD. It is increasingly recognized that effective diagnosis and management of COPD requires consideration of individual clinical features rather than reliance on spirometric variables. Expiratory flow limitation and lung hyperinflation are related and key physiological manifestations of COPD that have major consequences for health status and patient quality of life, and reducing expiratory flow limitation and hyperinflation

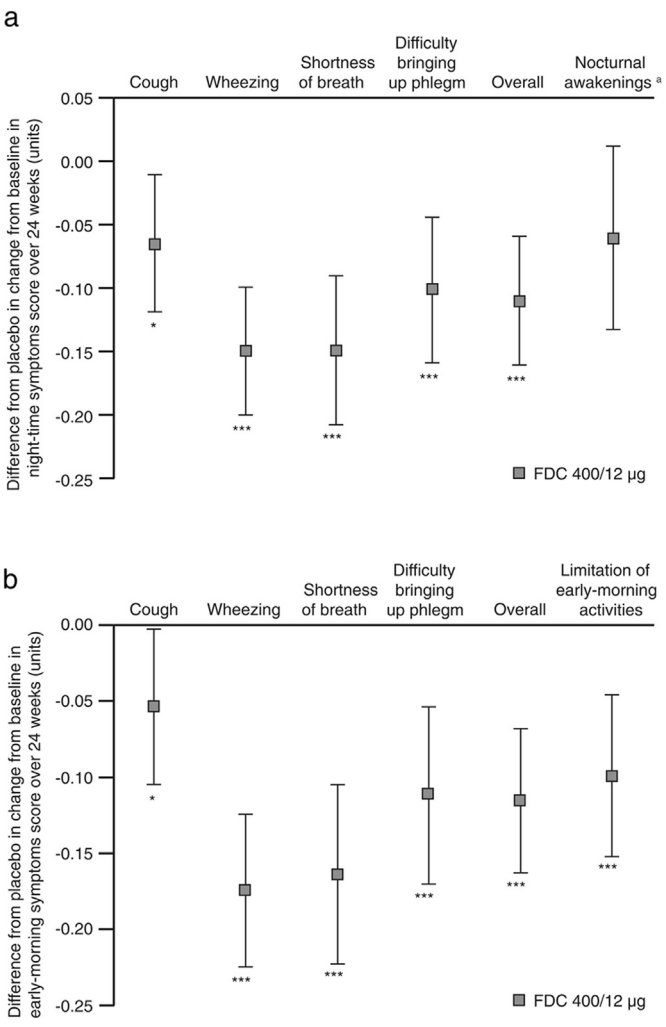

Fig. 3. Difference from placebo in change from baseline in symptom severity over 24 weeks. **a** Night-time symptoms; **b** early-morning symptoms. Data are LS means differences from placebo ±95% CIs; $^{*}p < 0.05$, $^{***}p < 0.001$ vs placebo.
[a]Nocturnal awakenings were the average number of awakenings per night. CI, confidence interval; FDC, aclidinium/formoterol fixed-dose combination; LS, least squares. Reproduced with acknowledgment from Ref. [66], Bateman et al. Respir Res (BioMed Central) 2015 16(1):92 (Fig. 3) under the Creative Commons Public Domain Dedication waiver according to the terms of the Creative Commons license: https://creativecommons.org/licenses/by/4.0/.

can provide significant benefits to patients, even in the absence of marked improvements in spirometry values. The supine position predisposes to expiratory flow limitation [8], and approximately three-quarters of patients with COPD report troublesome symptoms during the night, which are likely to be under-reported and/or insufficiently considered by clinicians managing patients with COPD, despite their negative impact on sleep quality and HR-QoL and increased risk of cardiovascular morbidity and mortality [24,26]. Because symptoms during the night-time and/or early morning have a marked negative effect on the health status of patients, clinicians and patients alike need to be aware of their importance, and evaluation and monitoring of symptom variability should be an essential part of developing a treatment plan. Providing inhaled bronchodilator therapy that maintains efficacy throughout the entire 24 h should be a goal of therapy.

Long-acting inhaled bronchodilators (LABAs and LAMAs) are the mainstay of therapy for patients with moderate-to-severe COPD, and treatments based on LAMAs alone or in combination with LABAs are recommended for the long-term management of COPD [1,2]. Inhaled bronchodilator therapy with LAMAs and LABAs is effective in improving lung function by direct action on bronchial smooth muscle, and they also reduce dynamic hyperinflation.

The use of combinations of bronchodilators from different and complementary pharmacological classes that have distinct mechanisms and durations of action is growing, with recognition from international treatment guidelines [1,2,40]. In patients for whom symptoms are not controlled with a single long-acting bronchodilator, LAMA/LABA combinations have been shown to be more effective in improving lung function and improving HR-QoL than either of the medication components as monotherapy or by increasing the dose of a single bronchodilator, without additional safety concerns [56].

Aclidinium and formoterol have particular characteristics that make them suitable as an FDC for maintenance therapy in patients with moderate-to-severe COPD. Twice-daily fast-acting muscarinic antagonists such as aclidinium are especially successful in controlling nocturnal symptoms, with a relevant impact on HR-QoL and long-term outcomes, and the aclidinium/formoterol FDC has synergistic activity, compared with aclidinium and formoterol administered as monotherapies [36,42]. Furthermore, the safety and efficacy of aclidinium/formoterol FDC has been established in large, well-designed phase III clinical trials [64,65], with additional support from pooled analysis [66].

6. Conclusions

In conclusion, administration of the long-acting bronchodilators aclidinium and formoterol as twice daily fixed-dose aclidinium/formoterol 400/12 μg offers the potential for symptoms control throughout the 24 h, including night-time and early mornings, in patients with stable moderate-to-severe COPD, providing significant improvements in lung function and HR-QoL. Further confirmation of the benefits of this FDC bronchodilator therapy in terms of reducing the risk of exacerbations and improving patient-reported outcomes and HR-QoL will need to be established by appropriate long-term trials.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Authorship

FDM and AGC conceived the review and its content, including the interpretation of the studies described, and drafted the manuscript. All Authors revised and commented on the manuscript critically for important intellectual content on the first draft and approved the final version.

Declarations of interest

FDM has received honoraria for lectures at national and international meetings from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Dompé, Guidotti/Malesci, GSK, Menarini, Novartis, Zambon. He has served as a consultant for Astra Zeneca, Chiesi Farmaceutici, Novartis, and Zambon and has received financial support for research from Novartis. PAS has received financial support for research from Pfizer, Almirall, Chiesi Farmaceutici, and AirLiquide. He has received honoraria for lectures at national meetings from Chiesi Farmaceutici, Novartis, Zambon Italia, AstraZeneca, Almirall, GlaxoSmithKline, Boehringer Ingelheim, Menarini, and Malesci Guidotti and has served as a consultant for Zambon Italia, AstraZeneca, Novartis, Chiesi Farmaceutici, and Boehringer Ingelheim. NS has received financial support for research from Astra Zeneca, Chiesi Farmaceutici, and Novartis, and has been a member of the scientific board for Astra Zeneca, Boehringer Ingheleim, Chiesi Farmaceutici, Novartis, and Roche. PS has received honoraria for lectures and advisory board membership from Almirall Spa, AstraZeneca Spa, Boehringer Ingelheim Spa, Chiesi Farmaceutici Spa, Dompé Spa, Guidotti/Malesci Spa, Glaxo Smith Kline Spa, Menarini Spa, Novartis Spa, Biofutura Pharma Spa ABC Farmaceutici Spa, Biotest. MC reports grants for research from Chiesi and AstraZeneca, personal fees from Chiesi, AstraZeneca, Boehringer Ingelheim, Novartis, Menarini, Mundipharma, Almirall, and Zambon. FB has received personal fees from AstraZeneca, Biofutura, Boehringer Ingelheim, Chiesi Farmaceutici, Dompè, GlaxoSmithKline, Guidotti, Malesci Menarini, MSD, Mundipharma, Novartis, Takeda, Zambon. AGC has received payments for board membership, income for lectures, or support for research in respiratory disease from the following organizations: Astra Zeneca SPA, Boehringer Ingelheim Italia SPA, GlaxoSmithKline S.p.A., Grifols Italia S.P.A., Meda Pharma, Novartis Farma S.p.A., Stallergenes Italia S.r.l, CSL Behring SpA, A. Menarini Industrie Farmaceutiche Riunite Srl.

Acknowledgments

The authors thank Ray Hill, an independent medical writer, who provided medical writing support and journal styling on behalf of Health Publishing & Services Srl.

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