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Review article

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

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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.

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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

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