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# Efficacy Tiotropium Combine Olodaterol In Chronic Obstructive Pulmonary Disease : A Review

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***Abstract***
*Chronic obstructive pulmonary disease (COPD), a respiratory disease characterized by a progressive decline in lung function, is considered to be a leading cause of morbidity and mortality. Long-acting inhaled bronchodilators, such as long-acting β2 agonists (LABAs) or long-acting muscarinic antagonists (LAMAs), are the cornerstone of maintenance therapy for patients with moderate-to-very-severe COPD.Tiotropium, a once-daily dosing LAMA, demonstrated sustained improvements in lung function as well as improved health-related quality of life, reduced exacerbations, and increased survival without altering the rate of decline in the mean forced expiratory volume in 1 second (FEV1) with fairly tolerable side effects. Olodaterol is a once-daily dosing LABA that has proven to be effective in improving lung function, reducing rescue medication use, and improving dyspnea and health-related quality of life, as well as improving exercise endurance with an acceptable safety profile. The combination of olodaterol and tiotropium provided additional improvements in lung function greater than monotherapy with each drug alone.*
***Keywords:*** *chronic obstructive pulmonary disease, bronchodilators, long-acting β2 agonists, long-acting muscarinic antagonist, olodaterol, tiotropium*

## I. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by airflow limitation that is not fully reversible(1). Chronic obstructive pulmonary disease (COPD) is triggered by an inflammatory response to several noxious stimuli, mainly cigarette smoke (2). The chronic inflammatory response may eventually stimulate the development of parenchymal tissue destruction (emphysema) and chronic bronchitis, which in turn contribute to most of the symptoms of the disease, mainly dyspnea and chronic cough (3). COPD is a leading cause of morbidity and mortality, with data supporting future predictions of it becoming the third leading cause of death, resulting in a substantial and increasing worldwide economic and social burden mainly driven by disease exacerbations and hospitalizations (1,2). As a result, management of COPD is primarily aimed at relieving and reducing symptoms as well as reducing the risk of future exacerbations (1,2).

## II. COPD

COPD is a preventable and treatable disease characterized by persistent airflow limitation caused by smoking and/or exposure to noxious gases. This disease is characterized by chronic and progressive breathlessness, cough, sputum production, and reduced exercise tolerance, punctuated by episodes of acute worsening of symptoms needing additional treatment and possibly emergency or hospital care. This all eventually leads to reduced activities of daily living and poor quality of life. COPD is not curable, and represents a major cause of morbidity and mortality with a considerable economic and social impact (4).

COPD results from persistent pathologic abnormalities in the small airways, most often associated with parenchymal destruction, which are both progressive in nature and lead to an annual decline in forced expiratory volume in 1 second (FEV1) that is faster than normal(5–9). The management of COPD consists essentially of smoking cessation, reduction of occupational risk factors, influenza vaccination, promotion of physical activity, pulmonary rehabilitation, and treatment with bronchodilating and anti-inflammatory medicines (4). COPD is a heterogeneous disease (10).

Previous COPD guidelines attempted to describe COPD mainly by using general statements about symptoms and more specific thresholds of FEV1 (11,13). However, such an approach does not fully capture the complexity of COPD, leading to the development of multicomponent indices, such as the Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity (BODE), Age, Dyspnea, and airflow Obstruction (ADO), and Dyspnea, Obstruction, Smoking, and Exacerbation (DOSE) indices (14-16), which have largely focused on the prediction of mortality and/or exacerbations. However, until ECLIPSE, no more comprehensive assessment of the degree of heterogeneity in stable COPD had been conducted in a large patient cohort.

The very extensive and detailed assessment of COPD at baseline in the ECLIPSE study enables such analyses that confirmed that symptoms, health status, and exercise capacity varied substantially between patients and these outcomes were often poorly related with FEV1. Thus, to base a diagnosis and the clinical assessment of COPD on spirometry alone provides a very incomplete picture of the illness. Importantly, heterogeneity was present at all levels, regardless of severity of airflow limitation studied (12). Comorbidities are common in COPD (17,19). In ECLIPSE, patients with COPD had a higher prevalence of osteoporosis, anxiety/panic attacks, heart trouble, heart attack, and heart failure than smokers or nonsmokers. Heart failure, ischemic heart disease, any heart disease, and diabetes all increased odds of mortality significantly when coexistent with COPD. Coexistence of COPD and cardiovascular disease was associated with more dyspnea and poor quality of life (20).

Depression is a particularly common comorbidity in COPD (18), and is associated with clinical outcomes and prognosis (21,22). ECLIPSE used the Center for Epidemiologic Studies of Depression Scale and found that 26% of patients with COPD had symptoms compatible with depression, twice the rate seen in healthy smokers and three times the rate of never-smokers (23). Increased fatigue, higher St. George's Respiratory Questionnaire for COPD score, younger age, female sex, history of cardiovascular disease, and current smoking were all significantly associated with depression, whereas physiologic and biologic measures were only weakly associated (23).

Inflammatory mechanisms in COPD. Cigarette smoke activates macrophages and epithelial cells to release chemotactic factors that recruit neutrophils and CD8 cells from the circulation. These cells release factors that activate fibroblasts, resulting in abnormal repair processes and bronchiolar fibrosis. An imbalance between proteases released from neutrophils and macrophages and antiproteases leads to alveolar wall destruction (emphysema). Proteases also cause the release of mucous. An increased oxidant burden, resulting from smoke inhalation or release of oxidants from inflammatory leucocytes, causes epithelial and other cells to release chemotactic factors, inactivate antiproteases, and directly injure alveolar walls and cause mucous secretion (1).

## III. TREATMENT IN COPD

Inhaled bronchodilators are the mainstay of the current management of chronic obstructive pulmonary disease (COPD) (2). Three classes of broncholytic agents are currently available: b2-adrenoceptor (AR) agonists, antimuscarinic agents and methylxanthines. These can be used individually or in combination(11). The use of short-acting bronchodilators is advocated for the rescue of symptoms, whereas inhaled long-acting bronchodilators are recommended as the treatment of choice for maintenance therapy(11). Because of the central role of bronchodilators in the treatment of respiratory diseases, there is still considerable interest in finding novel classes of broncholytic drugs. To date, finding new classes of bronchodilators has proved difficult, and thus many research groups have sought to improve the existing classes of bronchodilator (24,25).

Patients with complex medication regimens or a frequent change of schedule can have episodes of erratic nonadherence (26). It has been documented that COPD patients who initiated treatment with once-daily dosing had significantly higher adherence than other daily dosing frequencies (26). Therefore, criteria for a new bronchodilator should include longer duration of action compared with existing agents, with a true 24-h sustained bronchodilator effect allowing once-daily dosing, a fast onset of action at least similar to that of salbutamol and, obviously, a favorable safety and tolerability profile (24,25). Several novel bronchodilators and their combination with another bronchodilator class or an inhaled corticosteroid are in development (24,25).

### *i. b2-Adrenoceptor agonists*

A variety of b2-AR agonists with long half-lives are currently under development with the aim of achieving oncedaily dosing. To differentiate them from the currently used long-acting b2-AR agonists (LABAs, such as formoterol and salmeterol, which induce a bronchodilator that is limited to 12 h), these compounds are now called ultra-LABAs. The development of carmoterol, which has been under investigation from many years (24,25), has probably been stopped, most likely because it is not a real 24-h bronchodilator.

### *ii. Olodaterol*

Olodaterol shows a potent, nearly full agonist response at the human b2-AR in vitro and, unlike formoterol and salmeterol (which exerted either a full-agonist or a partial- agonist profile for all b-ARs), olodaterol showed an improved selectivity profile (27). Interestingly, olodaterol has a biphasic dissociation profile from the human b2-ARs, with the slow component (approx. 30–40% of the total b2- AR pool) showing a half-life of dissociation of more than 12 h, providing a rationale for its long duration of action (28). On isolated human bronchi, olodaterol concentration- dependently reversed the constriction induced by different stimuli, such as histamine, acetylcholine and electrical field-stimulated (EFS), with an efficacy not significantly different from the full agonist formoterol under all conditions(28). Furthermore, formoterol induced significant b2-AR desensitization in vitro, whereas olodaterol preserved the b2-AR signaling capacity even after long term preincubation(29). An initial proof-of-

concept study demonstrated 24 h bronchodilation following 4 weeks of once-daily administration of olodaterol in COPD patients(30).

***iii. Combination therapy in COPD***

Current guidelines for the treatment of COPD recommend the combination of bronchodilators that work through different mechanisms in patients with continuous symptoms (2). They also recommend a LABA plus an inhaled corticosteroid (ICS) for symptomatic patients with a FEV1 of less than 50% of predicted value, particularly if there have been frequent exacerbations (11). It is clear, therefore, that there is considerable interest in developing inhalers containing a combination of several classes of long-acting bronchodilator drugs and also a once-daily combination therapy with a LABA plus an ICS, again in an attempt to simplify the treatment(24,25).

## IV. CONCLUSION

Bronchodilators are still central to the symptomatic treatment of COPD. Because it has been documented that COPD patients who initiated treatment with once-daily dosing had significantly higher adherence than other daily dosing frequencies (26), there is a real interest within the pharmaceutical industry in developing novel inhaled bronchodilators with an improved duration of action compared to drugs currently on the market (24,25). However, it has proven difficult to discover novel classes of bronchodilatory agents, although potential new targets are emerging. Consequently, the logical approach has been to improve the existing bronchodilators.

Unfortunately, several new broncholytic agents are not capable of inducing a true 24-h sustained bronchodilation, at least at doses that provide a safety and tolerability profile. Nonetheless, considering that there is a progressive attempt to shift attention towards controlling nocturnal symptoms and those present on awakening, that epidemiological studies indicate as the most troublesome for COPD patients (31), the twice-daily dosing of bronchodilators will still be considered a useful approach to the symptomatic treatment of COPD. The current opinion is that it will be advantageous to develop inhalers containing combinations of several classes of long-acting bronchodilator drugs in an attempt to simplify treatment regimes as much as possible. It is probable that the development of once-daily dual-action ultra-LABA + LAMA combination products can serve as a basis for improved 'triple therapy' combinations through coformulation with novel anti-inflammatory compounds such as inhaled PDE4 inhibitors, that could deliver three complementary therapeutic effects for patients with COPD. In any case, the development of once-daily dualaction ultra-LABA + LAMA combination products can also serve as a basis for improved 'triple therapy' combinations through coformulation with novel ICS. The potential for these therapeutic strategies to be administered once-daily simplifies patient treatment regimens and therefore increases the likelihood of compliance with therapy.

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