# Bronchodilators: Current and Future

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**KEYWORDS**

• Chronic obstructive pulmonary disease • $\beta_2$-Agonists • Antimuscarinic agents • Methylxanthines • Choice of bronchodilators • Emerging bronchodilators

**KEY POINTS**

- Bronchodilators are central in the symptomatic treatment of chronic obstructive pulmonary disease (COPD), although there is often limited reversibility of airflow obstruction.
- Three classes of bronchodilators ($\beta_2$-agonists, antimuscarinic agents, and methylxanthines) are currently available, which can be used individually, or in combination with each other or inhaled corticosteroids.
- It is still not known whether long-acting bronchodilators should be started in obstructed patients also in the absence of symptoms, whether it is better to start with a β-agonist or an antimuscarinic agent in patients with mild/moderate stable COPD, and whether once-daily or twice-daily dosing is preferable.
- Novel classes of bronchodilators have proved difficult to develop.
- It is likely that an approach using muscarinic antagonist $\beta_2$-agonist (MABA) molecules will provide the best opportunity to develop combinations that combine corticosteroids with 2 bronchodilator activities, and thus potentially achieve better efficacy than is apparent with the current combination products that dominate the treatment of COPD.

## THE IMPORTANCE OF BRONCHODILATION IN COPD

The use of bronchodilators is one of the key elements in the treatment of chronic obstructive pulmonary disease (COPD), although there is often limited reversibility of airflow obstruction.[1] Bronchodilation aims at alleviating bronchial obstruction and airflow limitation, reducing hyperinflation, and improving emptying of the lung and exercise performance. Bronchodilators work by relaxing airway smooth muscle tone, leading to reduced respiratory muscle activity and improvements in ventilatory mechanics.[1] In particular, they reduce airway resistance and elastic loading of the inspiratory muscles during exercise at constant work rate.[2] Bronchodilators acting on peripheral airways diminish air trapping, thereby reducing lung volumes. The lower operating lung volume allows patients to achieve the required alveolar ventilation during rest and exercise at a lower oxygen cost of breathing, improving symptoms and exercise capacity.[3]

The importance of bronchodilation explains why all guidelines highlight that inhaled bronchodilators are still the mainstay of the current management of COPD at all stages of the disease,[4–6] although the recent American College of Physicians (ACP)/American College of Chest Physicians (ACCP)/American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines conclude that no sufficient evidence exists to support bronchodilator treatment in asymptomatic COPD patients.[5]

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## CLASSES OF BRONCHODILATORS

Three classes of bronchodilators, namely $\beta_2$-agonists, antimuscarinic agents, and methylxanthines, are currently available; these can be used individually, or in combination with each other or inhaled corticosteroids (ICSs). For both $\beta_2$-agonists and antimuscarinic agents, long-acting formulations are preferred over short-acting formulations.[6] Inhaled bronchodilators are preferred over oral bronchodilators and, in any case, because of relatively low efficacy and more side effects, treatment with theophylline is not recommended unless other long-term treatment bronchodilators are unavailable or unaffordable.[6] For patients whose COPD is not sufficiently controlled by monotherapy, guidelines recommend combining medications of different classes, in particular an inhaled antimuscarinic agent and a $\beta_2$-agonist, as a convenient way of delivering treatment and obtaining better lung function and improved symptoms.[6]

### *$\beta_2$-Agonists*

$\beta_2$-Agonists act by mimicking some of the effects of epinephrine at several levels: (1) inhibitory action on airway smooth muscle; (2) stimulation of the heart, leading to increased heart rate, contraction, and conduction; (3) inhibition of the release of mediators from mast cells; (4) metabolic actions (eg, glycogenolysis in liver and skeletal muscle, resulting in an increase in glucose); (5) endocrine actions (increasing insulin and glucagon release); and (6) prejunctional action on parasympathetic ganglia, increasing or decreasing acetylcholine release.[1,7,8] In addition to their main bronchodilator effect, this class of drugs also protects against the actions of bronchoconstrictor stimuli.

Short-acting $\beta_2$-agonists (SABAs), such as salbutamol and terbutaline, have long been used as rescue medications for COPD. Their short half-life, however, limits their efficacy as maintenance medications. A volume of published evidence supports the role of long-acting $\beta_2$-agonists (LABAs) in the treatment of stable COPD.[1,7,8] There are currently 3 LABAs: formoterol and salmeterol, which are twice-daily LABAs, and indacaterol, a once-daily LABA. Physiologic studies have shown that $\beta_2$-agonists dilate the airways and reduce air trapping, leading to reduced dyspnea, improved lung function, and improved exercise tolerance for patients.[9] Moreover, they reduce the frequency of COPD exacerbations[10] and offer a potential survival advantage.[11] Of note, LABAs, rather than SABAs, also have the potential to improve the mucociliary component of COPD.[12]

All $\beta_2$-agonists can induce increased heart rate, palpitations, vasodilation, and reflex tachycardia.[1,7,8] These agents can also produce a transient decrease in the partial pressure of arterial oxygen despite concomitant bronchodilation, an effect that is of doubtful clinical significance.[1,7,8] $\beta_2$-Agonists induce glycogenolysis and raise blood sugar levels. In addition, they can cause hypokalemia because of stimulation in the skeletal muscle of the $Na^+$,$K^+$-ATPase–driven pump coupled to $\beta_2$-adrenoceptors.[1,7,8] Dose-related tremor is one of the most characteristic adverse effects after administration of $\beta_2$-agonists, as they can directly stimulate $\beta_2$-adrenoceptors on skeletal muscle.[13] Although prolonged or repeated use of $\beta_2$-agonists may lead to tolerance to rescue SABA, in patients with COPD the long-term use of $\beta_2$-agonists results in sustained improvements in bronchodilatory activity, with no indication of development of tolerance.[14]

### *Antimuscarinic Agents*

Cholinergic parasympathetic nerves contribute to the elevated tone of airway smooth muscle in COPD, and this primary reversible component of airway limitation is sensitive to muscarinic receptor antagonists.[1,15] Acetylcholine (ACh) and other bronchoconstrictor mediators can also be released from nonneuronal cells to act on airway smooth muscle cells and other cells involved in the chronic inflammatory response in COPD and airway remodeling.[1,15] The effects of ACh are mediated by a family of 5 G-protein–coupled receptors ($M_1$–$M_5$). These receptors have distinct anatomic distribution and functions. Only subtypes $M_1$ to $M_3$ are expressed in airways.[15] The contraction of airway smooth muscle cells in response to ACh is predominantly mediated via $M_3$ receptors.[1,15]

There are currently 2 short-acting antimuscarinic agents (SAMAs) (ipratropium bromide and oxitropium bromide), 1 twice-daily long-acting antimuscarinic agent (LAMA) (aclidinium bromide), and 2 once-daily LAMAs (tiotropium bromide and glycopyrronium bromide) that have been licensed for use in the treatment of COPD.

Aclidinium bromide, 400 μg twice daily, shows clinically meaningful effects in lung function and other important supportive outcomes, such as health-related quality of life, dyspnea, and nighttime/early-morning symptoms, and is safe.[16] Tiotropium bromide is a once-daily treatment for COPD that provides 24-hour bronchodilation, and improves symptoms and health-related quality of life.[1,15] LAMAs offer distinct advantages over SAMAs in terms of maintaining 24-hour bronchodilation.[1,15] However, although tiotropium bromide provides 24-hour bronchodilation, it takes