

Adverse effects

Stimulation of beta₂-adrenergic receptors can produce resting sinus tachycardia and has the potential to precipitate cardiac rhythm disturbances in susceptible patients. Exaggerated somatic tremor is troublesome in some older patients treated with higher doses of beta₂-agonists, regardless of route of administration. Although hypokalemia can occur, especially when treatment is combined with thiazide diuretics,⁽⁹¹¹⁾ and oxygen consumption can be increased under resting conditions in patients with chronic heart failure,⁽⁹¹²⁾ these metabolic effects decrease over time (i.e., show tachyphylaxis). Mild falls in partial pressure of oxygen (PaO₂) can occur after administration of both SABAs and LABAs⁽⁹¹³⁾ but the clinical significance of these changes is uncertain. Despite prior concerns related to the use of beta₂-agonists in the management of asthma, no association between beta₂-agonist use and loss of lung function or increased mortality has been reported in COPD.^(906,914,915)

Antimuscarinic drugs

Antimuscarinic drugs block the bronchoconstrictor effects of acetylcholine on M3 muscarinic receptors expressed in airway smooth muscle.⁽⁹¹⁶⁾ Short-acting antimuscarinics (SAMAs), namely ipratropium and oxitropium, also block the inhibitory neuronal receptor M2, which potentially can cause vagally induced bronchoconstriction.⁽⁹¹⁷⁾ Long-acting muscarinic antagonists (LAMAs), such as tiotropium, aclidinium, glycopyrronium bromide (also known as glycopyrrolate), umeclidinium and revefenacin have prolonged binding to M3 muscarinic receptors, with faster dissociation from M2 muscarinic receptors, thus prolonging the duration of bronchodilator effect.⁽⁹¹⁶⁾

A systematic review of RCTs concluded that ipratropium, a short acting muscarinic antagonist, alone provided small benefits over short-acting beta₂-agonist in terms of lung function, health status and requirement for oral steroids.⁽⁹¹⁸⁾ Among LAMAs, some are administered once a day (tiotropium, umeclidinium, revefenacin), others twice a day (aclidinium), and some are approved for once daily dosing in some countries and twice daily dosing in others (glycopyrrolate).^(916,919) LAMA treatments improve symptoms, including cough and sputum and health status.^(916,920,921) They also improve the effectiveness of pulmonary rehabilitation^(922,923) and reduce exacerbations and related hospitalizations.⁽⁹²⁰⁾ Clinical trials have shown a greater effect on exacerbation rates for LAMA treatment (tiotropium) versus LABA treatment.^(924,925)

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Inhaled anticholinergic drugs are poorly absorbed which limits the troublesome systemic effects observed with atropine.^(916,926) Extensive use of this class of agents in a wide range of doses and clinical settings has shown them to be very safe. The main side effect is dryness of mouth.^(917,927) Although occasional urinary symptoms have been reported, there are no data to prove a true causal relationship.⁽⁹²⁸⁾ Some patients using ipratropium report a bitter, metallic taste. An unexpected small increase in cardiovascular events in COPD patients regularly treated with ipratropium bromide has been reported.^(929,930) In a large, long-term clinical trial in COPD patients, tiotropium added to other standard therapies had no effect on cardiovascular risk.⁽⁸⁸⁹⁾ Although there were some initial concerns regarding the safety of tiotropium delivery via the Respimat®⁽⁹³¹⁾ inhaler, the findings of a large trial observed no difference in mortality or exacerbation rates when comparing tiotropium in a dry-powder inhaler and the Respimat® inhaler.⁽⁹³²⁾ There are less safety data available for the other LAMAs, but the rate of anti-cholinergic side effects for drugs in this class appears to be low and generally similar. Use of solutions with a facemask can precipitate acute glaucoma, probably as a direct result of the contact between the solution and the eye.⁽⁹³³⁻⁹³⁵⁾

Methylxanthines

Controversy remains about the exact effects of xanthine derivatives. They may act as non-selective phosphodiesterase inhibitors, but have also been reported to have a range of non-bronchodilator actions, the significance of which is disputed.⁽⁹³⁶⁻⁹³⁸⁾ Data on duration of action for conventional, or even slow-release, xanthine preparations are lacking in COPD.