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Anticholinergics/Antimuscarinic Drugs in Asthma

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Abstract Anticholinergic alkaloids have been used for thousands of years for the relief of bronchoconstriction and other respiratory symptoms, and their use in the treatment of chronic obstructive pulmonary disease is well established. Acetylcholine, acting through muscarinic receptor (M) receptor, modulates multiple physiologic functions pertinent to asthma including airway muscle tone, mucus gland secretion, and various parameters of inflammation and remodeling. In addition, activation of M receptors may inhibit beta2 adrenoreceptor. These observations offer the rationale for the use of M receptors antagonists in the treatment of asthma. Short-acting antimuscarinic agents may be effective alone or in combination with short-acting beta agonists for the relief of acute symptoms. Long-acting antimuscarinic agents have emerged as potentially useful in the long-term treatment of difficult-to-control asthma. This review will analyze the mechanisms of action and therapeutic role of antimuscarinic agents on asthma including current guidelines regarding antimuscarinic drugs, recent studies in asthma, special populations to consider, and possible predictors of response.

Keywords Asthma · Anticholinergics · Muscarinic agents · COPD · Bronchitis · Lung · Bronchodilator · Chronic obstructive pulmonary disease · Emphysema · Ipratropium · Tiotropium · Aclinidium · Umeclinidium

This article is part of the Topical Collection on *Asthma*

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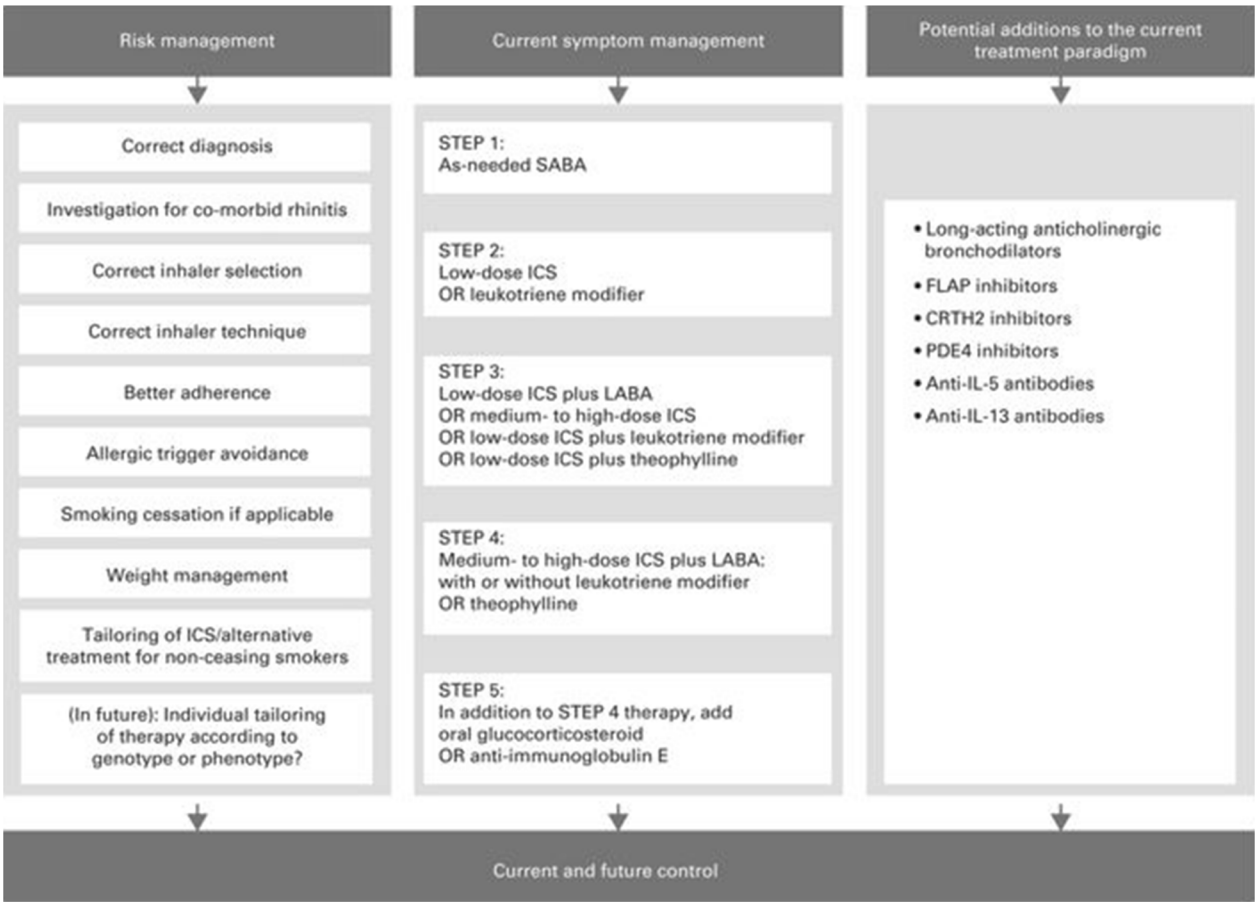
Introduction

Asthma is an important, potentially lethal, chronic respiratory disease that affects ~10 % of children and ~5 % of adults in developed countries and significantly impacts morbidity and quality of life [1–3]. Most patients with asthma can be well controlled using a short-acting beta-agonist (SABA) for rescue during acute symptoms and inhaled corticosteroids (ICS) for chronic management as recommended by asthma treatment guidelines [1, 2]. In patients not well controlled with ICS/SABA regimen, these guidelines suggest the addition of a long-acting beta-agonist (LABA), a leukotriene modifier, or an increased dose of an inhaled glucocorticoid [1, 2]. Despite these guidelines and the range of available treatments, over a half of patients with asthma continue to suffer from poor asthma control with substantial impact on quality of life and healthcare costs [1, 4••, 5]. The safety of LABA therapy is under question and general recommendations to minimize the use of these drugs have been issued [6, 7]. Leukotriene modifiers are not universally effective and ICS have been noted to have a relatively flat dose-response curve [8–10]. In light of this, alternative add-on medications would be a welcome addition in the treatment of asthma (see Table 1).

There is emerging evidence that the use of anticholinergic/antimuscarinic agents may play a significant role as add-on therapy in asthma. Anticholinergic compounds such as atropine or scopolamine have been used for hundreds of years for the relief of bronchoconstriction and other respiratory symptoms [11]. Smoke or fumes of medicinal plants containing naturally occurring anticholinergic alkaloids were widely used until past century, when safer and more effective synthetic analogs of atropine including ipratropium, oxitropium, and tiotropium were introduced [12•]. This review examines the proposed mechanisms and rationale for the clinical use of anticholinergic medications as add-on therapy in asthma.

Table 1 Combined approaches for the management of control in asthma. *FLAP* 5-lipoxygenase-activating protein, *ICS* inhaled corticosteroids, *IL* interleukin, *LABA* long-acting β_2-agonist, *PDE4* phosphodiesterase-4, *SABA* short-acting β_2-agonist. (From Price et al. [44] with permission[3])



Mechanisms

The parasympathetic nervous system is the primary regulator of bronchial tone in normal airways and regulates mucus secretion [13–15]. Acetylcholine (Ach), the main neurotransmitter in the cholinergic neuronal system, is synthesized by pre-ganglionic fibers in the sympathetic nervous system and pre- and post-ganglionic fibers in the parasympathetic autonomic nervous system [16]. Acetylcholine is also expressed in nonneuronal cells and may contribute to a pro-inflammatory state [17•].

Acetylcholine acts by stimulating muscarinic acetylcholine receptors (M receptors) in lung tissue, and the immediate, direct actions of the vagally mediated Ach release on M receptors on airway smooth muscle contraction and mucus secretion are widely recognized [18]. Activation of M receptors results in a rise in cyclic GMP and signal amplitude peaks resulting in the final physiologic outcomes (e.g., increased bronchomotor tone) [19]. Three types of M receptors are present in the lung: M1, M2, and M3 [18, 20, 21]. Stimulation of M1 and M3 receptors mediates the parasympathetic bronchoconstriction while M2 receptors protect against bronchoconstriction by inhibiting Ach release in the post-ganglionic parasympathetic nerves [20]. Beyond their physiologic role, M receptors play a direct role in both immediate and delayed airway hyperreactivity. Interactions between M2 receptors and eosinophils in the allergic airway offer a good example of the interplay between the nervous system and inflammation. Eosinophil degranulation is associated with a loss of M2 receptor effectiveness, and specific adhesion molecules on parasympathetic nerves are recognized by eosinophils and facilitate degranulation [22]. This phenomenon has been demonstrated in studies using the mouse model of allergic asthma and in the context of respiratory tract viral infection [23]. Cholinergic stimulation in response to inhaled allergens in this model activates TRPA1 channels thereby initiating a central reflex event leading to bronchoconstriction associated with the late bronchospastic response, and this response can be blocked by the cholinergic antagonist tiotropium [24]. Studies using this model have also demonstrated that along with blocking the immediate methacholine-stimulated lung resistance, the cholinergic antagonist aclidinium blocks the accompanying airway eosinophilia [25].

Parasympathetic signaling also modulates nonneuronal resident cell types such as fibroblasts and smooth muscle contributing to chronic allergic inflammation and tissue remodeling [26, 27•, 28]. Tiotropium has also been shown to impact multiple aspects of remodeling including decreasing M3-mediated smooth muscle thickening and peribronchial collagen deposition, preventing allergen-induced mucous gland hypertrophy and reducing the increase in MUC5AC-positive goblet cell numbers, eosinophilic infiltration, and Th2 cytokine production resulting in reduced chronic airway inflammation [29–32]. In human cell cultures, M2 receptor stimulation in the context of prolonged exposure to TGF-β_1 enhances airway smooth muscle cell proliferation mediated by extracellular matrix-integrin interactions [33] and aclidinium inhibits the transformation of human lung fibroblast to myofibrobast, another important theoretical step in remodeling [34]. Finally, in addition to direct pro-inflammatory/remodeling effects, mechanical changes caused by M agonist-induced bronchoconstriction may also stimulate airway remodeling [35].

Muscarinic receptors impact asthma in other ways. Mediators of inflammation have been shown to enhance the release of Ach from vagal nerve endings, and this may be a factor in virus-induced asthma exacerbations [36]. Infections with parainfluenza viruses trigger Ach release and potentiate vagally mediated bronchoconstriction by blocking inhibitory M2 receptors on parasympathetic neurons in a Guinea pig model [36]. The same investigators demonstrated that human cell cultures exposed to influenza infection develop virus-induced M2 receptor dysfunction that is enhanced by the release of tumor necrosis factor-alpha (TNF-α) suggesting that TNF-α is a key mediator of virus-induced M2 receptor dysfunction and airway hyperresponsiveness [37]. Finally, M receptors may have an additional regulatory role (Fig. 1) in beta2 adrenoreceptor function, and interactions between M receptors and beta2 adrenoreceptor (Fig. 2) on airway smooth muscle may lead to a reduced bronchodilator response to beta2 agonists suggesting that M receptor antagonists may have an additional benefit in the treatment of asthma [12•, 38•, 39].

Therefore, current research suggests that Ach acting through M receptors plays a critical role in many of the key mechanisms of asthma. If this accurately reflects in vivo mechanisms, then M receptor antagonists could be beneficial in preventing chronic airway hyperresponsiveness and decline in lung function in asthma. As a result, muscarinic antagonists are experiencing a rebirth of interest for the treatment of asthma [40].

Anticholinergic/Antimuscarinic Medications

Currently available anticholinergic medications target M receptors, hence their alternative name of antimuscarinics [13]. Anticholinergic alkaloids (e.g., atropine) exist in nature in the roots, seeds, and leaves of a variety of belladonna plants. Extracts have been used for hundreds of years in India for treating respiratory symptoms. It was incorporated in Western medicine by British colonists in the early nineteenth century and was isolated in a pure form in 1831. The first successful asthma attack treated with atropine was reported in 1859 [15]. Nonetheless, the role of antimuscarinic drugs in chronic asthma management has been underestimated in the modern era [12•].

The rational for using antimuscarinic agents in asthma follows from the critical role of the M receptor in the cardinal features of asthma, bronchospasm, mucus secretion, and inflammation/airway remodeling. An ideal antimuscarinic drug would inhibit the M1 and M3 receptors, sparing the M2 receptor [14]. The primary bronchodilator effect of antimuscarinic drugs is assumed to be the interruption of this vagally mediated airway tone with subsequent bronchodilation [41]. It is likely not that straightforward in the presence of chronic inflammation where the interaction of chronic inflammation and muscarinic receptors in the lung is complex.

The short-acting muscarinic antagonist (SAMA), ipratropium bromide, and long-acting muscarinic antagonists (LAMAs) such tiotropium bromide, aclinidium bromide, umeclidinium bromide, and glycopyrronium are currently available or under development in Europe and USA [42]. They are quaternary ammonium synthetic derivatives of naturally occurring tertiary ammonium compounds, such atropine. Tertiary ammonium compounds have substantial systemic effects such tachycardia, blurred vision, dry mouth, and gastrointestinal upset. The quaternary compounds are insoluble in lipids and therefore have fewer side effects due to negligible passage through biological barriers [14]. Side effects include dry mouth (6–16 %), urinary retention, nausea (~3 %), constipation (<10 %), and headache (~3 %) [15]. Tachycardia and atrial fibrillation have been reported and should be used with caution especially among patients with COPD as those patients are older with often-associated comorbidities. However, a recent meta-analysis does not confirm an increased risk of cardiovascular events [43].

A detailed review of ongoing trials on the effects of LAMAs in asthma is published elsewhere [44]. In summary, two phase II trials of umeclidinium bromide have been completed (NCT01641692; NCT01573624), and phase II and III trials with tiotropium, as add-on therapy, have demonstrated improvements in lung function and a reduction in exacerbation risk but not real change in asthma controller quality of life [45••, 46•]. Glycopyrronium bromide and other LAMAs are also being evaluated as combination treatments with LABAs or/and ICS in a double or triple therapy as potential option for patients who require augmentation therapy to achieve optimal therapeutic response, and several are under investigation for difficult-to-control asthma [42, 44].

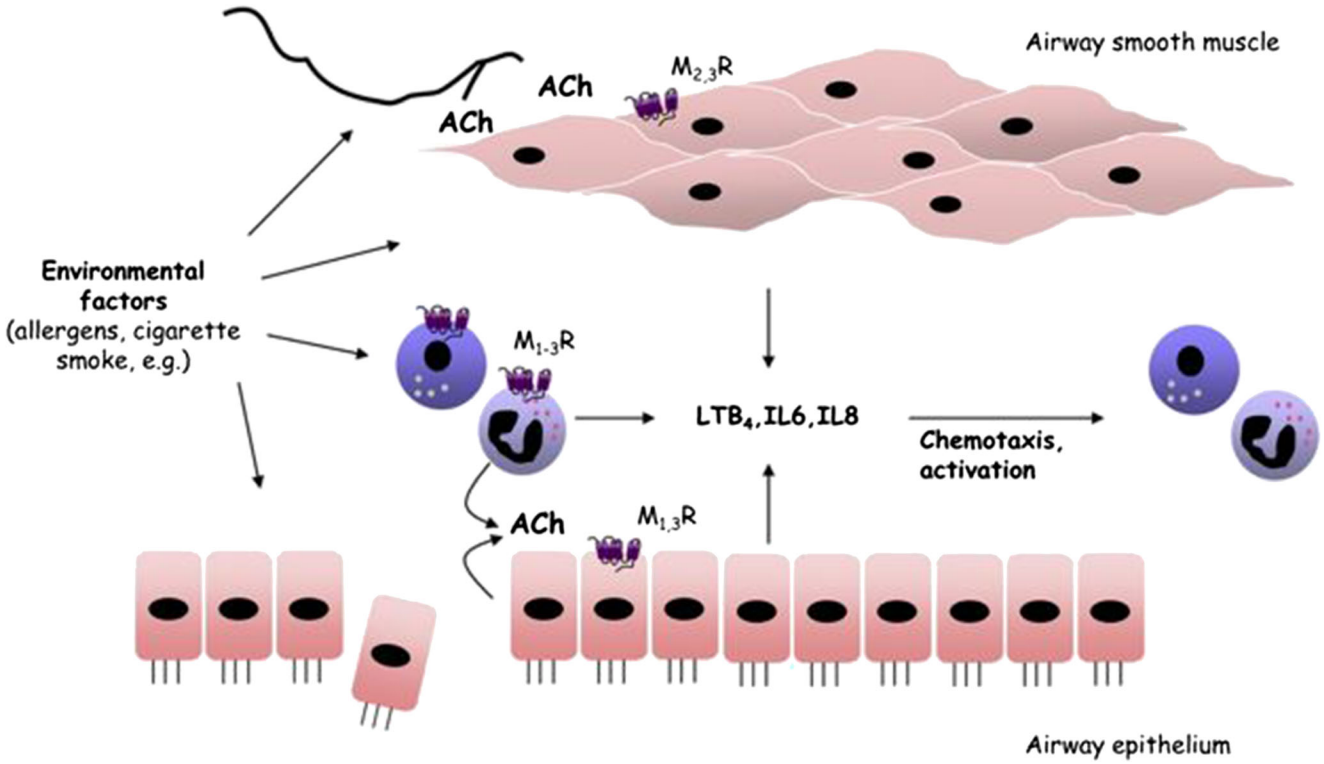


Fig. 1 Proposed regulatory role of acetylcholine in inflammatory cell chemotaxis and activation. The release of Ach may be enhanced in response to environmental factors leading to increased pro-inflammatory cytokines and inflammatory cell activation. M3 receptors (M_3R) expressed on airway smooth muscle and M1-3 receptors ($M_{1-3}R$) expressed by airway epithelial cells mediate the release of these factors (From Kistemaker et al. [38], with permission; caption modified.)[1]

Clinical Use

Current National Asthma Education and Prevention Program (NAEPP) and Global Initiative for Asthma treatment guidelines (available from free download at http://www.nhlbi.nih.gov/about/org/naepp/naep_pd.htm and www.ginasthma.org respectively) do not address the role of antimuscarinic agents [1, 2]. However, a recently updated ATS-ERS guidelines for severe asthma discussed the use of ipratropium in severe asthma for patients trying to reduce SABA use or were intolerant of SABA side effects and the use of LAMA for chronic management in severe difficult-to-control asthma [4••]. Ipratropium may be used to prevent exercise-induced asthma, but its effect varies among individuals [47]. Emerging evidence also supports the utility of the LAMA, tiotropium, as maintenance of therapy in some patients with moderate to severe asthma who are uncontrolled on combination ICS/LABA therapy [48].

- Acute Symptom Control

  Ipratropium has a quick onset of action, a safe profile, and short duration of action. In the acute setting, ipratropium has been used with great benefit and was equipotent in the asthmatic subject and chronic bronchitis patients for improving forced expiratory volume in one second (FEV_1) and airways' conductance [49]. This is particularly true for patients with poor initial response to SABAs [50].
- Severe Exacerbations

  Ipratropium is not recommended as first-line treatment for intermittent and mild asthma [1, 2]. It is, however, effective when added to a SABA in the context of severe exacerbations [4••, 51–53]. Treatment with inhaled ipratropium combined with albuterol in the emergency room reduced hospital admissions and improved lung function, particularly in patients with FEV_1 <30 %, and symptoms for more than 1 day [54, 55]. Although other studies have concluded that did not reduce the length of hospitalization or admission to intensive care unit [56], a Cochrane Review concluded that nebulized ipratropium combination with a SABA significantly reduces the risk of hospital admission and other had other clinically important outcomes [57]. The National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 guidelines advise the addition of ipratropium to SABA therapy for the treatment of patients with severe acute asthma exacerbation [2].
- Maintenance Therapy

  Ipratropium is not a useful first-stage maintenance drug, and a Cochrane Review of ipratropium concluded that there was no justification for its routinely use in

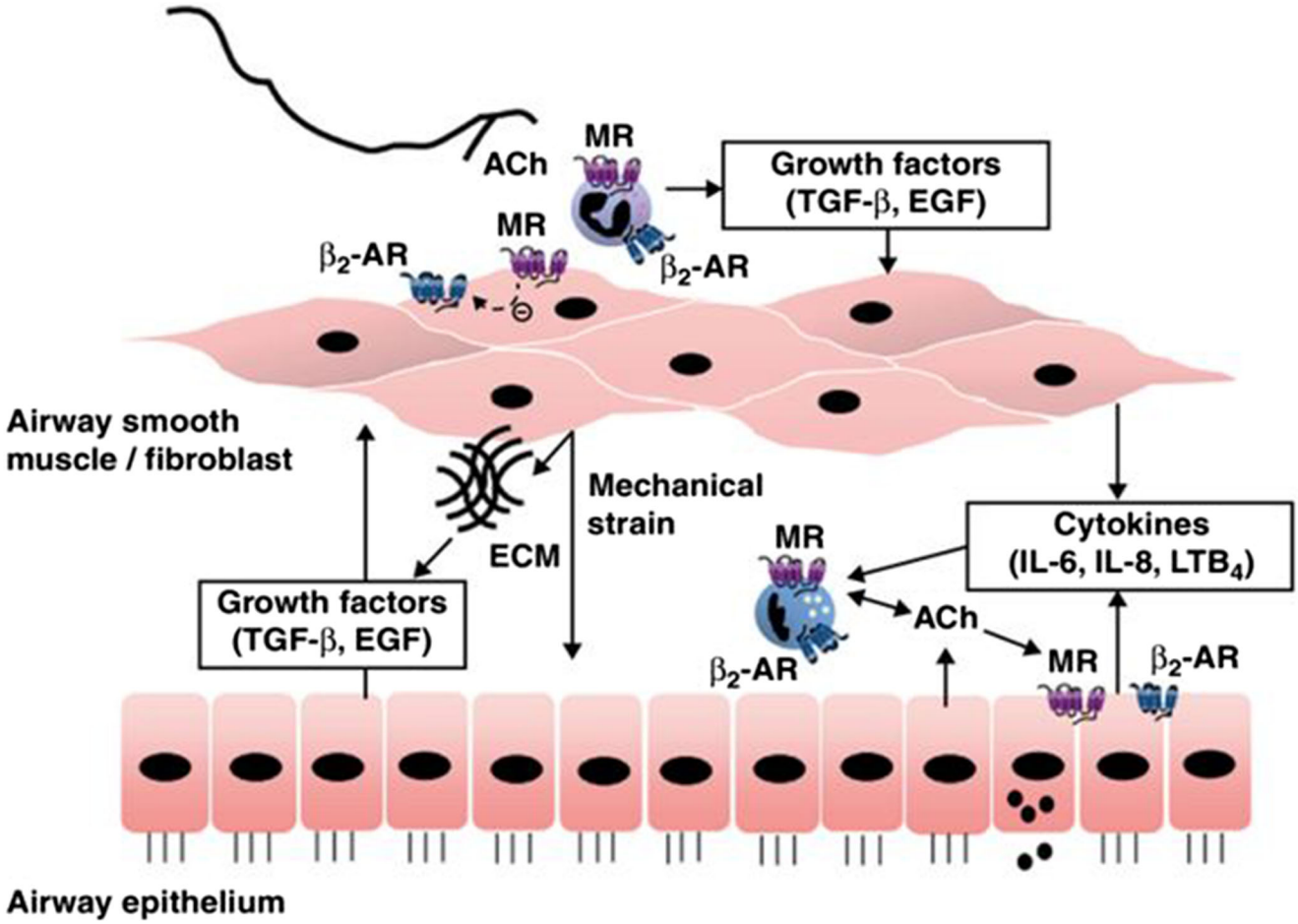


Fig. 2 Interactions between M (MR) and beta2-agonists receptors ($ß_2$-AR); MR stimulations reduces β2-AR responsiveness. Crosstalk between these receptors could attenuate anti-inflammatory and anti-fibrotic effects of β2 agonists. MR activation on epithelial and mesenchymal cells promotes the secretion of cytokines and promotes tissue remodeling via mesenchymal cells and extracellular matrix induction. Mechanical forces induced by activation of muscarinic receptors on airway smooth muscle and fibroblasts also promote airway remodeling. *Ach* acetylcholine, *β2-AR* β2-adrenoceptor, *ECM* extracellular matrix, *EGF* epidermal growth factor, *IL* interleukin, *LTB4* leukotriene B4, *MR* muscarinic receptor, *TGF-β* transforming growth factor (From Meurs et al. [12], with permission; caption modified[2])

asthma maintenance therapy [15, 58]. As a result, ipratropium is not currently recommended as first-line treatment for chronic maintenance therapy in intermittent and mild asthma [1, 50, 53]. In contrast to monotherapy, there is evidence that regular use of ipratropium combined with albuterol provides a greater improvement in FEV_1 and a longer duration of action than the use of albuterol alone in patients with moderate to severe persistent asthma [59].

LAMAs are much more efficacious, and there is increasing evidence for the use of LAMA therapy in difficult-to-control asthma. The addition of tiotropium to standard therapy in patients whose symptoms are poorly controlled results in significant improvements in symptoms and lung function [45••, 46•]. A recent three-way, double-blind, triple-dummy crossover trial of patients with poorly controlled asthma on standard therapy (i.e., SABA rescue medication and ICS maintenance) reported that the addition of tiotropium to this regimen resulted in a superior primary outcomes (morning peak flow or asthma-control days among others), as compared with doubling the dose of ICS [45••]. The addition of once-daily tiotropium to standard asthma treatment, including a high-dose inhaled corticosteroid plus a LABA, significantly improved lung function over 24 h in patients with inadequately controlled, severe, persistent asthma [44, 45••, 60, 61•, 62].

- Predictors of Response

There are clinical predictors, which may be helpful in prospectively identifying patients who will respond to antimuscarinic agents. In addition to 16 Arg/Arg or 16 Arg/Gly polymorphism of the ADRB2 gene (see below), patients with high sputum neutrophil levels or an acute response to a short-acting bronchodilator (especially albuterol) were more likely to demonstrate a beneficial effect of added tiotropium, but ethnicity, sex, atopy, IgE level,

sputum eosinophil count, fraction of exhaled nitric oxide, asthma duration, and body mass index did not predict a beneficial response [61•]. This finding is consistent with evidence that patients with non-eosinophilic sputum profiles or neutrophilic inflammation do not gain the same benefit from ICS as those with eosinophilic inflammation and may be good candidates for antimuscarinic therapy [44, 63]. Of course, inhaled antimuscarinic treatment should also be considered in those patients who are intolerant to SABA treatment [15].

- Special Populations

  There are special populations in whom antimuscarinic therapy may be particularly effective [64].

  Smoking asthmatics—antimuscarinic agents may be particularly useful add-on therapy for smoking asthmatics. M receptor-linked signaling pathways regulating the release of calcium and subsequent contraction of airway smooth muscle are enhanced by cigarette smoking in rat bronchial smooth muscle models [65]. Furthermore, the expression of the predominate mucin gene in human airways, MUC5AC, is augmented in asthmatics, patients with COPD, and normal smokers [66]. This overexpression can be blocked by aclidinium [67]. Acetylcholine has also been implicated in cell signaling that leads to fibrosis and airway remodeling in smokers [68]. Finally, increased cholinergic tone and downregulation of adrenergic receptors may be particularly important in bronchospasm associated with smoking [69]. These clinical and mechanistic observations provide a sound rationale for the use of antimuscarinic as add-on therapy for smoking asthmatics whose symptoms are not well controlled.

  Genetic subsets—patients who have an arginine/arginine homozygosity of the β2-adrenergic receptor (B16-Arg/Arg) may have a compromised responsiveness to SABA medications [70]. Tiotropium has been shown to be as efficacious as salmeterol as a chronic control medication in maintaining lung function [71•, 72, 73]. Antimuscarinic agents also provide significant bronchoprotective effect in these patients, and ipratropium was shown to be a safe alternative to SABAs as a rescue medication in these patients [1, 64, 71•, 72, 73].

  Chronic viral infection—antimuscarinic agents have also been demonstrated to enhance effectiveness in asthma associated with chronic viral infection such as hepatitis C and perhaps prevent airway remodeling [1, 64].

  COPD/asthma overlap—antimuscarinics may be particularly useful in the COPD/asthma overlap syndrome. An open-label crossover study found that FEV_1 in patients with asthma and emphysema increases by 12.6 % compared to placebo whereas in asthmatics with no emphysema increase of 5.4 % [62]. A larger, randomized clinical trial demonstrated improvements in lung function and symptom relief and reduces the use of SABA rescue medication when tiotropium was added to the therapy of patients with COPD/asthma overlap syndrome [74].

  Exercise-induced bronchospasm—finally, the use of a SAMA prior to exercise has been recognized to be effective in exercise-induced bronchospasm [1]. Interestingly, this effect appears to be subject to diagonal variation [47].

- Age

  The safety and usefulness of antimuscarinic agents in the elderly and children has not been well studied. There is little evidence that a muscarinic therapy improves lung function in the elderly asthmatic population, but this is an area of active investigation [75]. There is evidence that antimuscarinic agents may be useful in childhood exercise-induced asthma [76] and in children with moderate to severe asthma exacerbations where the addition of inhaled ipratropium to SABA therapy reduced hospital admissions and improved lung function although other studies have concluded that it did not reduce the length of hospitalization or admission to intensive care unit [51, 52, 77]. A Cochrane Review concluded that ipratropium as a single agent was less efficacious than SABA alone and that their use was not appropriate as a single agent in children acute asthma exacerbations [78]. It is yet to be determined whether LAMA drugs offer benefits in children similar to those demonstrated in adults, although several phase III trials are underway with tiotropium in these populations (NCT01316380; NCT01634139; NCT01634152; NCT01277523) [44].

Conclusions

Difficult-to-control asthma is a prevalent problem with significant healthcare costs and quality-of-life burden. The cholinergic parasympathetic tone contributes to contraction of bronchial smooth muscle, increased mucus secretion, increased airways inflammation, and remodeling leading to narrowing of the airways. This provides a rationale for the use of long-acting antimuscarinic bronchodilators in asthma, which can result in recently clinical benefits and lung function improvements [45••, 46•]. Based on current knowledge, antimuscarinic bronchodilators may be a useful add-on therapy for patients with difficult-to-control asthma, or at risk for exacerbation, and special populations such as smokers in patients with genetic mutations to their beta receptor gene.

Compliance with Ethics Guidelines

Conflict of Interest Xavier Soler and Joe Ramsdell have nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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- •• Of major importance

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