



Role of anticholinergics in asthma management: recent evidence and future needs

Linda Rogers^a and Nicola A. Hanania^b

Purpose of review

Anticholinergic antimuscarinic bronchodilators play a major role in the treatment of chronic obstructive pulmonary disease, but their role in asthma has long been limited to acute management. More recently, the role of long-acting antimuscarinic bronchodilators (LAMAs) in chronic asthma management has been explored. This review will examine the pharmacological rationale for use of inhaled anticholinergics in the treatment of asthma, and provide an overview of the current literature supporting this use, as well as describe future research needs in this area.

Recent findings

Short-acting anticholinergic bronchodilators have a role as add-on agents in the treatment of acute asthma. Preliminary clinical studies suggest that inhaled LAMAs may be comparable to long-acting beta2-agonists (LABAs) as an add-on therapy in patients not controlled by inhaled corticosteroids (ICS) alone, and may also have added benefit in patients not controlled on combined ICS–LABA. Mechanistic studies suggest that apart from their bronchodilator activity, LAMAs may have anti-inflammatory and antiremodeling influences on the airways. Further research is needed to clarify the clinical relevance of these experimental observations.

Summary

Accumulating evidence supports the use of inhaled LAMAs as an add-on therapy in patients with asthma, who remain symptomatic despite guideline-based therapy with ICS with or without LABAs. Further studies are warranted to help define mechanisms of action of LAMAs, apart from their role as bronchodilators, and determine how these other actions impact asthma outcomes over time. Furthermore, future studies need to examine the long-term efficacy and safety of LAMAs in asthma and identify a subgroup of patients who would benefit from such therapies to facilitate early, personalized therapy.

Keywords

anticholinergics, asthma, bronchodilators, ipratropium bromide, tiotropium bromide

INTRODUCTION

Bronchodilators play a pivotal role in the acute and maintenance management of asthma. Among the available groups of bronchodilators, beta2-agonists have been considered by asthma guidelines as first-line agents [1]. Short-acting beta2-agonists (SABAs) such as albuterol sulfate are recommended to treat acute symptoms of asthma in both outpatient and inpatient settings. Inhaled long-acting beta2-agonists (LABAs) such as salmeterol and formoterol are effective only when added to inhaled corticosteroids (ICS) in patients whose asthma remains uncontrolled despite adequate ICS therapy. Their routine use in this situation has demonstrated improvement in lung function and symptoms, reduction in exacerbations, and has allowed the reduction of ICS dose needed to achieve asthma control. However, the long-term safety of LABAs

in asthma has been questioned, and the US Food and Drug Administration (FDA) recommends withdrawal of these agents from asthma regimens of patients whose asthma symptoms become controlled [2]. Furthermore, many patients with asthma remain symptomatic despite the use of moderate doses of ICS and LABAs [3].

^aSection of Pulmonary and Critical Care Medicine, Icahn School of Medicine at Mount Sinai, New York and ^bSection of Pulmonary and Critical Care Medicine, Baylor College of Medicine, Houston, Texas, USA

Correspondence to Linda Rogers, MD, FCCP, Icahn School of Medicine at Mount Sinai, 1468 Madison Avenue 5-20 D, New York, NY 10029, USA. Tel: +1 212 241 2779; fax: +1 212 876 5519; e-mail: linda.rogers@mssm.edu

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KEY POINTS

- Cholinergic activity is a major driver of bronchial smooth muscle contraction, and asthma patients have increased bronchial smooth muscle contraction that is the major contributor for respiratory symptoms in asthma
- Inhaled anticholinergics, also known as inhaled muscarinic antagonists, target these receptors and have been used in the treatment of airway disease for many years.
- Preliminary clinical studies suggest that inhaled anticholinergics may be comparable to long-acting beta agonists as an add-on therapy in patients not controlled by ICS alone, and may reduce exacerbations in patients not controlled on combined ICS–long-acting beta agonists.
- It is not currently clear who among patients with asthma might benefit from addition of a LAMA, but ongoing clinical trials may clarify this issue in addition to documenting their long-term efficacy and safety in asthma

Inhaled anticholinergics constitute another group of bronchodilators that have been predominantly used in the management of chronic obstructive pulmonary disease (COPD). The use of short-acting anticholinergic agents (SAMAs) such as ipratropium bromide in asthma has been limited to treatment of acute asthma symptoms, especially when it is added to inhaled SABAs in both adults and children [4–7]. More recently, some studies have examined the role of long-acting antimuscarinic bronchodilators (LAMAs) such as tiotropium bromide in the treatment of chronic asthma as an add-on to other maintenance medications [8–19,20^{***},21].

RATIONALE FOR USE OF ANTICHOLINERGICS IN ASTHMA

Parasympathetic nerves control airway caliber and airway inflammation in allergic airway diseases including asthma by signaling through peripheral muscarinic receptors [22,23]. Effector tissues in this situation include airway smooth muscles and mucous glands. Cholinergic activity is a major driver of bronchial smooth muscle contraction, and asthma patients have increased bronchial smooth muscle contraction that is the major contributor for respiratory symptoms in asthma [24]. Furthermore, increased cholinergic and smooth muscle tone may contribute to airway hyper-responsiveness present in the majority of patients with asthma [25,26^{***}]. In

addition, parasympathetic signaling may modulate inflammatory cells and other non-neuronal airway cells including fibroblasts, which contribute to airway inflammation, and remodeling [25,26^{***}].

Animal as well as human studies clearly demonstrate beneficial effects of blocking cholinergic activity in the lungs by improving lung function through the modulation of airway narrowing [14], but also through nonbronchodilatory effects including reduction of mucus secretion and airway hyper-responsiveness [14,25,27–31].

PHARMACOLOGY OF ANTICHOLINERGICS

Five muscarinic receptor subtypes – M1, M2, M3, M4, and M5 – are expressed in the human lung, but a functional role has been identified only for M1, M2, and M3 receptors [14]. Muscarinic receptor density is highest in the parasympathetic ganglia, followed by mucous glands, smooth muscle, and nerve fibers [14]. Inhaled anticholinergics, also known as inhaled muscarinic antagonists, target these receptors and have been used in the treatment of airway disease for many years [32,33]. In the early 17th Century, smoking plant alkaloids containing anticholinergics such as *Atropa belladonna* and *Datura stramonium* was routinely recommended by Ayurvedic medicine to treat bronchospasm in different diseases including asthma. Early in the 19th Century, anticholinergic alkaloids were first introduced in Europe and then in the USA, and were used to treat acute asthma, in the form of atropine and stramonium cigarettes and cigars [34,35]. However, a major concern with the use of such agents was their safety, especially since atropine, a tertiary ammonium compound, is well absorbed across the blood–brain barrier. This safety concern led to the development of synthetic quaternary ammonium agents that are very poorly absorbed when given by inhalation.

Ipratropium bromide has a relatively short duration of action, ranging from 4 to 8 h [32]. It is delivered by either a metered dose inhaler (MDI) or nebulized solution. In addition, it has been used in combination with albuterol delivered in one device for the maintenance treatment of COPD. Its use in asthma has been limited to treat acute symptoms. Tiotropium bromide was introduced in the early 2000, has a duration of action of at least 24 h, and thus has been recommended for once-daily maintenance treatment of COPD. It is delivered by either a dry powder inhaler (DPI), but more recently, through a soft mist inhaler (SMI). Several new inhaled LAMAs have been recently approved (aclidinium, glycopyrronium, and umeclidinium) for either twice-daily or once-daily use as stand-alone

agents or in combination with inhaled LABAs in COPD [36[¶]].

CLINICAL ROLE OF SHORT-ACTING ANTICHOLINERGICS IN ACUTE ASTHMA AND CHRONIC ASTHMA MANAGEMENT

Short-acting anticholinergic bronchodilators are commonly used for acute asthma treatment in children and adults. Systematic reviews of the addition of ipratropium to SABAs in acute asthma show modestly greater improvements in lung function, but significantly reduced risk of hospital admission [5,7]. Benefits in both adults and children are mostly limited to those experiencing moderate to severe exacerbations [7,37]. In children, the benefit of use is limited to emergency department care, and dual bronchodilator use after admission does not appear to reduce length of stay or improve other outcomes, and thus is not recommended [38[¶]].

Use of SAMAs in the management of chronic asthma in adults is often limited to those with intolerance to SABA or in lieu of SABAs in patients with underlying cardiovascular disease. Studies in adult asthma reveal that SAMAs are associated with statistically significant albeit small improvements in dyspnea scores and peak expiratory flow (PEF) that are of unlikely clinical significance [39]. SAMAs are traditionally thought to have slower onset of action and purported weaker bronchodilator effect than SABAs, but both bronchodilators showed similar mean forced expiratory volume in 1 s (FEV₁) responses during bronchodilator testing in patients with asthma in a recent study, challenging this idea [11,12]. There are conflicting data regarding cardiovascular safety of SAMAs, and prospective safety comparisons to SABAs have not been performed in vulnerable populations [40,41]. There has not been published evidence suggesting increased cardiovascular effects when adding SAMA to SABA. Use of combination SABA and SAMA produces statistically greater bronchodilation of unclear clinical significance [42]. Pooled analysis of studies, albeit ones with significant limitations, found little benefit in regards to most physiologic and clinical measures arguing against routine use of combination SAMA and SABA in asthma [39].

CLINICAL ROLE OF LONG-ACTING ANTICHOLINERGICS IN PATIENTS NOT CONTROLLED ON ICS ALONE

Despite maximal-dose ICS and LABA treatment, 25–38% of patients have asthma that remains uncontrolled [43]. Existing add-on treatments in this Global Initiative for Asthma step 4/5 patients such as leukotriene modifiers, theophylline,

anti-Immunoglobulin E (IgE) monoclonal antibodies, oral corticosteroids, and bronchial thermoplasty are burdened with problems of limited efficacy, expense, lack of availability, inconvenience, or significant adverse effects. Recent guidelines have not included LAMAs in recommended asthma step therapy as neither the US FDA nor the European Medications Agency have currently approved them for asthma treatment. Nevertheless, initial reports suggested possible benefit of LAMAs in severe asthma and asthma–COPD overlap syndrome [8,9,19,44].

Long-acting antimuscarinic bronchodilators have now been studied in patients with asthma not controlled with ICS alone, and those with severe asthma not controlled on ICS–LABA therapy (Table 1) [11,45]. Tiotropium Bromide Step-Up Therapy for Adults with Uncontrolled Asthma (TALC) was a three-way, double-blind, triple-dummy crossover trial comparing addition of tiotropium to either doubling of ICS (primary superiority comparison) or the addition of salmeterol (secondary noninferiority comparison) in patients with uncontrolled symptoms and an FEV₁ less than 70%, despite moderate-dose ICS. The primary outcome, AM PEF, and secondary outcomes (FEV₁, symptoms scores and proportion of asthma control days) were superior for tiotropium compared to doubling ICS. AM PEF was noninferior and other outcomes were comparable for tiotropium and salmeterol.

A randomized, double-blind, crossover study looking at the safety and efficacy of adding tiotropium or placebo in patients with uncontrolled severe asthma, despite high-dose ICS–LABA, found that peak FEV₁, the primary endpoint, was higher in both active treatments than placebo [45]. Interestingly, no significant differences in symptoms or health status, and only small and nonsignificant differences in SABA use were observed. Out of concern for possible adverse effects of LABAs in asthma patients with a specific β 2-receptor genotype, Bateman *et al.* [12] looked at the role of LAMAs instead of LABAs in genotype stratified patients not controlled with ICS alone. In this study, the primary endpoint, mean weekly AM predose PEF, was maintained when patients treated with ICS–LABA were either kept on LABA or switched to LAMA. Other endpoints were similar between tiotropium and LABA, suggesting similar performance of these two agents in patients not controlled by ICS alone.

CLINICAL ROLE OF LAMAS AS ADD-ON ‘TRIPLE THERAPY’ IN PATIENTS NOT CONTROLLED ON ICS–LABA

Two replicate randomized controlled trials including over 800 patients examined the effect of LAMA

Table 1. Summary table of major clinical trials of long-acting muscarinic bronchodilators in asthma

Study	Inclusion criteria	Design	Primary outcome	Size	Duration (weeks)	Intervention	Results
Fardon <i>et al.</i> [44]	Severe persistent FEV ₁ <65% predicted on high-dose ICS	Placebo crossover	FEV ₁	18	4	Run-in fluticasone 1000 µg then 4-week crossover periods; Fluticasone 500 µg for all + salmeterol and placebo vs. salmeterol and tiotropium	Addition of tiotropium/salmeterol allowed 1/2 dose of ICS w/ stable/small improvement in PEF and FEV ₁ w/o improved symptoms or QOL
Peters <i>et al.</i> [11]	Severe persistent; FEV ₁ <70% on ICS alone	Double-blind, placebo crossover	AM PEF	210	14	Run-in 160 µg beclomethasone then 14-week crossovers of tiotropium (18 µg vs. salmeterol vs. double-dose ICS (320 µg)	Tiotropium noninferior to salmeterol and superior to doubled dose of ICS
Bateman <i>et al.</i> [12]	Moderate persistent; B16-Arg/Arg+ on FEV ₁ <90% on ICS/LABA or <80% on ICS	Three-way double-blind triple dummy crossover	AM PEF	388	16	Run-in high dose ICS/LABA then 16 weeks tiotropium (5 µg) vs. salmeterol vs. placebo	Tiotropium superior to placebo and noninferior to salmeterol in B16-Arg/Arg patients
Kersijens <i>et al.</i> [45]	Severe persistent FEV ₁ <80% on high-dose ICS/LABA	Double-blind, double dummy, placebo, parallel group	Peak FEV ₁ determined at the end of each 8-week treatment period	107	8	2 weeks usual ICS/LABA then 8-week crossover: tiotropium 5 or 10 µg in AM or placebo	Addition of tiotropium to ICS/LABA improved lung function
Kersijens <i>et al.</i> [13]	Severe persistent; FEV ₁ <80%; high-dose ICS-LABA, at least 1 course OCS in prior year	Double-blind, placebo crossover	2 co-primary endpoints – change in peak FEV ₁ response at 3 weeks and the trough FEV ₁ response at week 24	912	48	Run-in 4 weeks usual ICS (>800 µg) + LABA then 48 weeks tiotropium (5 µg) vs. placebo	Addition of tiotropium to ICS-LABA improved lung function and reduced exacerbations by 21%

All patients had uncontrolled asthma on baseline regimen listed in the inclusion criteria and all studies were randomized. B16-Arg/Arg, polymorphism at the 16th amino acid of the beta adrenergic receptor gene; FEV₁, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; LABA, long-acting beta2-agonists; OCS, oral corticosteroids; PEF, peak expiratory flow.

vs. placebo in patients with severe asthma defined by postbronchodilator FEV₁ below 80% on at least moderate-dose ICS–LABA and with at least one asthma exacerbation in the year prior to enrollment [13]. A significant increase in the primary endpoints of FEV₁ and time to first severe asthma exacerbation (as defined by American Thoracic Society/European Respiratory Society) was observed with addition of tiotropium to ICS–LABA [46]. The rate of exacerbations requiring oral corticosteroids was reduced by 21% with treatment of 15 patients needed to prevent one severe exacerbation during the 48-week treatment period. Interestingly, there was no difference in symptom-free days or SABA use, nor was a minimal clinically important difference in symptoms scores such as the Asthma Control Questionnaire (ACQ) or Asthma Quality of Life Questionnaire (AQLQ) observed. An editorial accompanying the publication of this study raised concerns about the cardiovascular safety of tiotropium delivered via Respimat, but these concerns have abated somewhat following the publication of the Tiospir study in which an increased rate of adverse cardiovascular outcomes was not observed [47,48]. A recently published systematic review of anticholinergics in asthma identified five randomized controlled trials and two open-labeled uncontrolled trials, but statistical pooling and analysis of the data were precluded by the small number of studies and heterogeneity of study design [49]. To date, the relative merits of LAMA as add-on to patients with ICS–LABA have not been compared directly to leukotriene modifiers, omalizumab, or theophylline.

It is not currently clear how to identify specific groups of patients with asthma who might benefit from addition of a LAMA. Most studies to date have included patients with persistent airflow limitation, despite at least moderate-dose ICS. An initial study suggested that the single-nucleotide polymorphism Arg16Gly in the β -2 adrenergic receptor was associated with a lung function response to tiotropium [10]. In a follow-up publication, the authors of the TALC study assessed the prespecified hypotheses that response to individual SAMA or SABA, both of which were tested at baseline, would predict response to the respective long-acting agents of that class [50]. Somewhat surprisingly, an acute response to a SABA, but not SAMA, and higher cholinergic tone (as determined by lower resting heart rate) predicted a positive lung function response to tiotropium. Other demographic factors (ethnicity, sex, BMI) and asthma characteristics (atopy, total serum IgE sputum eosinophil count, FeNO, asthma duration) did not predict a significant response. In most studies published to date, LAMAs do not reduce frequency of SABA use or significantly

improve patient-reported outcomes such as ACQ and the Asthma Control Test (ACT) despite relatively consistent lung function improvement across studies. This suggests that either the lung function effects were not of sufficient clinical significance to correlate with an impact on symptoms or that our current patient-centric outcomes scores are insensitive to change in patients with the level of disease severity in these trials [51].

CONCLUSION

In conclusion, tiotropium improves lung function when added to ICS alone or to ICS–LABA combination. Tiotropium may also maintain lung function with step-down of ICS dose or if LABA is discontinued during treatment with ICS–LABA combination therapy. Till the date of publication of this review, no large randomized controlled trial has been published examining the efficacy of LAMAs other than tiotropium in asthma. However, a broader role for anticholinergics in asthma is actively under investigation, and a review of clinicaltrials.gov identified multiple studies assessing the role of LAMAs in asthma, including adults with asthma of a broad range of severity, children and adolescents, and ‘triple therapy’ with ICS, LABA, and LAMA in a variety of combinations.

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Conflicts of interest

L.R. did consulting for Forest, Inc for a planned development program for Aclidinium in asthma from September 2013 through September 2014.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Bousquet J, Busse WW. Section 1. EPR-3 versus GINA 2008 guidelines: asthma control and step 3 care: highlights of the Asthma Summit 2009: beyond the guidelines. *World Allergy Organ J* 2010; 3:16–22.
2. FDA urges safe use of certain inhaled asthma medicine: United States Food and Drug Administration [cited 7 October 2014]. <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm200923.htm>.
3. Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med* 2004; 170:836–844.
4. Flynn CA. Ipratropium bromide in acute asthma exacerbation. *J Fam Pract* 1999; 48:745–746.
5. Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. *Thorax* 2005; 60:740–746.

6. Dotson K, Dallman M, Bowman CM, Titus MO. Ipratropium bromide for acute asthma exacerbations in the emergency setting: a literature review of the evidence. *Pediatric Emerg Care* 2009; 25:687–692. (quiz 93-5).
7. Griffiths B, Ducharme FM. Combined inhaled anticholinergics and short-acting beta2-agonists for initial treatment of acute asthma in children. *Cochrane Database Syst Rev* 2013; 8:CD000060.
8. Iwamoto H, Yokoyama A, Shiota N, *et al*. Tiotropium bromide is effective for severe asthma with noneosinophilic phenotype. *Eur Respir J* 2008; 31:1379–1380.
9. Kapoor AS, Olsen SR, O'Hara C, *et al*. The efficacy of tiotropium as a steroid-sparing agent in severe asthma. *Can Respir J* 2009; 16:99–101.
10. Park HW, Yang MS, Park CS, *et al*. Additive role of tiotropium in severe asthmatics and Arg16Gly in ADRB2 as a potential marker to predict response. *Allergy* 2009; 64:778–783.
11. Peters SP, Kunselman SJ, Icitovic N, *et al*. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med* 2010; 363:1715–1726.
12. Bateman ED, Kornmann O, Schmidt P, *et al*. Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma. *J Allergy Clin Immunol* 2011; 128:315–322.
13. Kerstjens HA, Engel M, Dahl R, *et al*. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med* 2012; 367:1198–1207.
14. Buels KS, Fryer AD. Muscarinic receptor antagonists: effects on pulmonary function. *Handb Exp Pharmacol* 2012; pp. 317–341.
15. Novelli F, Costa F, Latorre M, *et al*. Tiotropium: a new therapeutic option in asthma. *Monaldi Arch Chest Dis* 2013; 79:109–115.
16. Bollmeier SG, Lee SY. The emerging role of tiotropium for patients with asthma. *Ann Pharmacother* 2013; 47:704–713.
17. Antoniu SA, Antohe I. Evaluation of inhaled tiotropium in asthma, uncontrolled with standard combination therapy. *Expert Opin Pharmacother* 2013; 14:967–969.
18. Adams KS, Lowe DK. Tiotropium for adults with inadequately controlled persistent asthma. *Ann Pharmacother* 2013; 47:117–123.
19. Yoshida M, Nakano T, Fukuyama S, *et al*. Effects of tiotropium on lung function in severe asthmatics with or without emphysematous changes. *Pulmon Pharmacol Ther* 2013; 26:159–166.
20. Rashid Q, Klein R. Tiotropium in the treatment of patients with asthma. *South Med J* 2014; 107:330–337.
- A recently published systematic review evaluating the role of tiotropium in asthma.
21. Tian JW, Chen JW, Chen R, Chen X. Tiotropium versus placebo for inadequately controlled asthma: a meta-analysis. *Respir Care* 2014; 59:654–666.
22. Gosens R, Zaagsma J, Meurs H, Halayko AJ. Muscarinic receptor signaling in the pathophysiology of asthma and COPD. *Respir Res* 2006; 7:73.
23. Scott GD, Fryer AD. Role of parasympathetic nerves and muscarinic receptors in allergy and asthma. *Chem Immunol Allergy* 2012; 98:48–69.
24. Price D, Fromer L, Kaplan A, *et al*. Is there a rationale and role for long-acting anticholinergic bronchodilators in asthma? *NPJ Prim Care Respir Med* 2014; 24:14023.
25. Kistemaker LE, Oenema TA, Meurs H, Gosens R. Regulation of airway inflammation and remodeling by muscarinic receptors: perspectives on anticholinergic therapy in asthma and COPD. *Life Sci* 2012; 91:1126–1133.
26. Meurs H, Oenema TA, Kistemaker LE, Gosens R. A new perspective on muscarinic receptor antagonism in obstructive airways diseases. *Curr Opin Pharmacol* 2013; 13:316–323.
- A comprehensive review outlining the role of muscarinic receptor antagonism in the management of obstructive airway diseases.
27. Terzano C, Petroianni A, Ricci A, *et al*. Early protective effects of tiotropium bromide in patients with airways hyperresponsiveness. *Eur Rev Med Pharmacol Sci* 2004; 8:259–264.
28. Damera G, Jiang M, Zhao H, *et al*. Acilidinium bromide abrogates allergen-induced hyperresponsiveness and reduces eosinophilia in murine model of airway inflammation. *Eur J Pharmacol* 2010; 649:349–353.
29. Bos IS, Gosens R, Zuidhof AB, *et al*. Inhibition of allergen-induced airway remodelling by tiotropium and budesonide: a comparison. *Eur Respir J* 2007; 30:653–661.
30. Sales ME. Muscarinic receptors as targets for anti-inflammatory therapy. *Curr Opin Investigat Drugs* 2010; 11:1239–1245.
31. Ohta S, Oda N, Yokoe T, *et al*. Effect of tiotropium bromide on airway inflammation and remodelling in a mouse model of asthma. *Clin Exp Allergy* 2010; 40:1266–1275.
32. Cazzola M, Page CP, Calzetta L, Matera MG. Pharmacology and therapeutics of bronchodilators. *Pharmacol Rev* 2012; 64:450–504.
33. Jacoby DB, Fryer AD. Anticholinergic therapy for airway diseases. *Life Sci* 2001; 68:2565–2572.
34. Gross NJ. Anticholinergic agents in asthma and COPD. *Eur J Pharmacol* 2006; 533:36–39.
35. Moulton BC, Fryer AD. Muscarinic receptor antagonists, from folklore to pharmacology: finding drugs that actually work in asthma and COPD. *Br J Pharmacol* 2011; 163:44–52.
36. Cazzola M, Page C, Matera MG. Long-acting muscarinic receptor antagonists for the treatment of respiratory disease. *Pulmon Pharmacol Ther* 2013; 26:307–317.
- A recent review of studies evaluating the role of LAMAs in respiratory diseases.
37. Rodrigo G, Rodrigo C, Burschtin O. A meta-analysis of the effects of ipratropium bromide in adults with acute asthma. *Am J Med* 1999; 107:363–370.
38. Vezina K, Chauhan BF, Ducharme FM. Inhaled anticholinergics and short-acting beta(2)-agonists versus short-acting beta2-agonists alone for children with acute asthma in hospital. *Cochrane Database Syst Rev* 2014; 7:CD010283.
- A recent updated systematic review by the Cochrane Collaboration airways group clarifying the role of combining short-acting cholinergics and short-acting beta agonists compared to short-acting beta agonists alone in children with acute asthma.
39. Westby M, Benson M, Gibson P. Anticholinergic agents for chronic asthma in adults. *Cochrane Database Syst Rev* 2004; CD003269.
40. Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *J Am Med Assoc* 2008; 300:1439–1450.
41. Salpeter SR. Do inhaled anticholinergics increase or decrease the risk of major cardiovascular events? A synthesis of the available evidence. *Drugs* 2009; 69:2025–2033.
42. Gelb AF, Karpel J, Wise RA, *et al*. Bronchodilator efficacy of the fixed combination of ipratropium and albuterol compared to albuterol alone in moderate-to-severe persistent asthma. *Pulmon Pharmacol Ther* 2008; 21:630–636.
43. Bateman ED, Bousquet J, Keech ML, *et al*. The correlation between asthma control and health status: the GOAL study. *Eur Respir J* 2007; 29:56–62.
44. Fardon T, Haggart K, Lee DK, Lipworth BJ. A proof of concept study to evaluate stepping down the dose of fluticasone in combination with salmeterol and tiotropium in severe persistent asthma. *Respir Med* 2007; 101:1218–1228.
45. Kerstjens HA, Disse B, Schroder-Babo W, *et al*. Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial. *J Allergy Clin Immunol* 2011; 128:308–314.
46. Reddel HK, Taylor DR, Bateman ED, *et al*. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009; 180:59–99.
47. Bel EH. Tiotropium for asthma: promise and caution. *N Engl J Med* 2012; 367:1257–1259.
48. Wise RA, Anzueto A, Cotton D, *et al*. Tiotropium Respimat inhaler and the risk of death in COPD. *N Engl J Med* 2013; 369:1491–1501.
49. Befekadu E, Onofrei C, Colice GL. Tiotropium in asthma: a systematic review. *J Asthma Allergy* 2014; 7:11–21.
- A recent systematic review summarizing five large clinical trials looking at the existing data regarding efficacy and safety of long-acting anticholinergics in asthma not controlled by inhaled corticosteroids alone.
50. Peters SP, Bleecker ER, Kunselman SJ, *et al*. Predictors of response to tiotropium versus salmeterol in asthmatic adults. *J Allergy Clin Immunol* 2013; 132:1068–1074; e1.
- Using data from the TALC study, an analysis of predictors of response to tiotropium versus salmeterol in adults with asthma not controlled by inhaled corticosteroids alone.
51. Jia CE, Zhang HP, Lv Y, *et al*. The Asthma Control Test and Asthma Control Questionnaire for assessing asthma control: systematic review and meta-analysis. *J Allergy Clin Immunol* 2013; 131:695–703.