Is there a rationale and role for long-acting anticholinergic bronchodilators in asthma?

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Despite current guidelines and the range of available treatments, over a half of patients with asthma continue to suffer from poor symptomatic control and remain at risk of future worsening. Although a number of non-pharmacological measures are crucial for good clinical management of asthma, new therapeutic controller medications will have a role in the future management of the disease. Several long-acting anticholinergic bronchodilators are under investigation or are available for the treatment of respiratory diseases, including tiotropium bromide, aclidinium bromide, glycopyrronium bromide, glycopyrrolate and umeclidinium bromide, although none is yet licensed for the treatment of asthma. A recent Phase III investigation demonstrated that the once-daily long-acting anticholinergic bronchodilator tiotropium bromide improves lung function and reduces the risk of exacerbation in patients with symptomatic asthma, despite the use of inhaled corticosteroids (ICS) and long-acting β2-agonists (LABAs). This has prompted the question of what the rationale is for long-acting anticholinergic bronchodilators in asthma. Bronchial smooth muscle contraction is the primary cause of reversible airway narrowing in asthma, and the baseline level of contraction is predominantly set by the level of 'cholinergic tone'. Patients with asthma have increased bronchial smooth muscle tone and mucus hypersecretion, possibly as a result of elevated cholinergic activity, which anticholinergic compounds are known to reduce. Further, anticholinergic compounds may also have anti-inflammatory properties. Thus, evidence suggests that long-acting anticholinergic bronchodilators might offer benefits for the maintenance of asthma control, such as in patients failing to gain control on ICS and a LABA, or those with frequent exacerbations.

INTRODUCTION

Asthma affects over 300 million individuals worldwide, a figure that is estimated to grow by 100 million by 2025.1 A chronic inflammatory disease of the Airways, asthma has multifactorial pathophysiological causes and considerable heterogeneity in the classification of the disease by phenotype, aetiology, severity and interventional control.

Current guidelines recommend stepwise management to gain and maintain control, in which the clinical definition of full 'control' is daytime symptoms or use of reliever medication less than twice a week, no limitations of activity, no nocturnal symptoms and normal lung function.2 Furthermore, the American Thoracic Society and the European Respiratory Society state that any definition or measure of control must take into account the management of a patient's future risk.3 Thus, in clinical management of asthma, consideration must be given to reducing the frequency of exacerbations, preserving lung function, preventing reduced lung growth in children and minimising the adverse effects of any treatment.4

For those receiving low-dose inhaled corticosteroids (ICS), current step-up treatment involves the addition of a long-acting β2-agonist (LABA) or leukotriene receptor antagonist as controller therapy. In patients unable to attain or maintain control with ICS and LABA—those in Global Initiative for Asthma treatment steps 3–5 (Figure 1)—upward titration of ICS dose, leukotriene modifiers, sustained-release theophylline, oral glucocorticosteroids and anti-immunoglobulin E (omalizumab) are all further or alternative treatment options.5

Despite these guidelines and the wide range of therapies available, poor control of current asthma symptoms, and of future asthma exacerbations, continues to affect >50% of patients,5–9 with exacerbations placing significant strain on their quality of life and on health-care systems.10 Risk factors associated with future exacerbations include previous exacerbations, poor control, inhaler technique and adherence, co-morbid allergic rhinitis, gastro-oesophageal reflux disease, psychological dysfunction, smoking and obesity.10 The same factors, in addition to incorrect diagnosis, poor choice of inhaler, variation in individual treatment responses or genetic components, have been attributed to the underlying poor control.11 There are a number of actions available in the primary care setting to reduce the impact of these factors (Figure 1).10,11

In the light of such concerns around risk and poor control, it is appropriate to consider the rationale for investigating additional controller medications. A number of new therapies are under investigation,12 including long-acting anticholinergic bronchodilators (the focus of this review), anti-prostaglandin D2 CRTH2 antagonists,13 phosphodiesterase-4 inhibitors,5 anti-leukotriene 5-lipoxygenase-activating protein antagonists14 and the monoclonal antibodies mepolizumab and lebrikizumab (which are raised against interleukin-515 and interleukin-13,16 respectively).

Short-acting anticholinergic agents, particularly ipratropium bromide (ipratropium) and oxtipronium bromide (oxitropium), have
be used in asthma for many years, although they have not become widespread because they are generally considered to be less effective than short-acting β₂-agonists (SABAs) for acute bronchodilation. This, coupled with a perception that longer-acting antagonism of cholinergic receptors induces little bronchodilation above that induced by LABAs, has meant that, in contrast to chronic obstructive pulmonary disease, long-acting anticholinergic bronchodilators have not been considered or thoroughly investigated as potential controller medication in asthma. Early studies demonstrated mild bronchodilation and protection, over 48 h, against methacholine-induced bronchoconstriction in male patients with asthma, and, in patients with severe persistent asthma, small improvements in lung function were observed with the LABA salmeterol plus the long-acting anticholinergic bronchodilator tiotropium bromide (tiotropium), with a halved dose of fluticasone propionate.

Recently, Phase I–III clinical investigation with long-acting anticholinergic bronchodilators in asthma has begun: two Phase II trials of umecclidinium bromide (umeclidinium) have 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 in patients with poorly controlled asthma despite the use of ICS or ICS plus a LABA.

In this review, we consider the pathophysiological and clinical rationales for use of long-acting anticholinergic agents in the broader management of asthma, and the clinical evidence reported to date. Please see Box 1 for a description of the literature search and appraisal methods.

**Figure 1.** Combined approaches for the management of control in asthma. FLAP, 5-lipoxygenase-activating protein; ICS, inhaled corticosteroids; IL, interleukin; LABA, long-acting β₂-agonist; PDE4, phosphodiesterase-4; SABA, short-acting β₂-agonist.

### Long-acting anticholinergic bronchodilators in asthma

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The symptoms of asthma, and of acute exacerbations, are attributed to airway narrowing that occurs as a consequence of chronic inflammation and associated hyper-responsiveness. Local influx of inflammatory cells and high levels of inflammatory mediators result in airway oedema, airway thickening, mucus hypersecretion and bronchial smooth muscle contraction (Table 1). Although multiple pathophysiological mechanisms are thought to contribute to the characteristic narrowing of airways and the hyper-responsiveness found in asthma (Table 1), bronchial smooth muscle contraction represents the primary cause of reversible airway obstruction in asthma. The degree of basal airway smooth muscle contraction (airway smooth muscle ‘tone’) is under autonomic nervous regulation (Figure 2), although the mechanisms are not fully understood. During normal ventilation, adrenergic sympathetic nerves and parasympathetic cholinergic and non-cholinergic nerves are all active, but cholinergic activity is thought to be the predominant driver of bronchoconstriction (Figure 2, Box 2). Acute treatment with the anticholinergic compounds atropine and ipratropium is known to reduce basal airway smooth muscle tone.

Patients with asthma have increased basal airway smooth muscle tone, and there is evidence to suggest that this is a result of increased basal activity of pulmonary parasympathetic cholinergic nerves, hereinafter described as ‘cholinergic tone’. Moffino et al. demonstrated that bronchoconstriction induced by breathing is significantly inhibited by ipratropium in asthmatic...
Clinical evidence around long-acting anticholinergic bronchodilators

We performed searches in November 2013 of PubMed, Google Scholar and Cochrane databases and ClinicalTrials.gov (www.clinicaltrials.gov).

PubMed searches

All terms restricted to title and abstract, with restriction of results to clinical trials:
- (1) Asthma* AND (anticholinergic OR antimuscarinic OR cholinergic OR muscarinic OR parasympathetic)
- (2) Asthma* AND (tiotropium OR umeclidinium OR aclidinium OR glycopyrronium OR darotropium OR QVA149 OR glycopyrrolate)
- In November 2013 the searches yielded 209 results; search 2 yielded 25 results. PubMed search results were manually reviewed for articles or studies relevant to the topic of short-acting muscarinic agonists or long-acting muscarinic agonists for acute or maintenance therapy

Cochrane database searches

- ‘Asthma AND anticholinergic’, limited to title, abstract and keywords, yielding 39 hits, the titles and abstracts of which were manually reviewed
- In November 2013 the searches yielded one review\(^1\) relating to the use of anticholinergics for asthma management, and eight reviews of anticholinergics in a variety of acute settings

www.clinicaltrials.gov searches

- Asthma AND tiotropium OR umeclidinium OR aclidinium OR glycopyrronium OR darotropium OR glycopyrrolate OR QVA149

Pathophysiology and pharmacology

PubMed and Google scholar searches

- The following terms in Boolean strings: asthma; respiratory; cholinergic; muscarinic; parasympathetic; autonomic; tone; pathophysiology; anticholinergic; antimuscarinic; β-agonist; phenotype; genotype; inflammation; bronchoconstriction; and bronchodilation
- As this article is not a systematic review, certain articles within the pathophysiology and pharmacology sections were reviewed and cited based on their adjudged relevance to the topic

Box 1  Literature evaluation methods

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patients but not in healthy volunteers. It is thought that cholinergic tone, at least, is driven by afferent nervous activity arising in the airways,\(^29,36,37\) and it has been hypothesised that local airway inflammatory mediators may have a role in inducing afferent activity and an autonomic reflex response, thereby driving an increase in cholinergic tone (Figure 2).\(^7,21,38,39\) Other proposed mechanisms for increased cholinergic tone in asthmatic patients include abnormal muscarinic receptor expression,\(^40\) increased release of acetylcholine from cholinergic nerve endings\(^41\) and reduced levels of neuromodulators that attenuate cholinergic neurotransmission.\(^42,43\)

The degree to which cholinergic tone contributes to airway narrowing in asthma, either at basal state or during exacerbations, is unclear. However, the fact that airway hyper-responsiveness can persist in asthmatic patients, possibly even in the absence of airway inflammation following long-term ICS use,\(^44\) suggests that other pathophysiologic factors, such as increased cholinergic and smooth muscle tone, have a role in asthma.\(^39,45\) It has been proposed that acetylcholine has a prominent role in allergen-induced airway smooth muscle remodelling.\(^46–48\) In a guinea pig model of ongoing allergic asthma, treatment with tiotropium inhibited increases in airway smooth muscle mass and contractility induced by allergic challenge; it has thus been hypothesised that

![Figure 2. Autonomic regulation of airway smooth muscle tone.](Image)

**Table 1.** Mechanisms of airway narrowing and hyper-responsiveness in asthma\(^4\)

| Process | Consequence |
|---------|-------------|
| Increased volume and/or contractility of airway smooth muscle cells | Excessive contractility of airway smooth muscle |
| Secretion of multiple bronchoconstriction mediators such as histamine, prostaglandin D\(_2\) and neurotransmitters | Airway smooth muscle contraction |
| Uncoupling of airway smooth muscle contraction as a result of inflammatory changes in the airway wall | Excessive narrowing of the airways; loss of maximum plateau of contraction when a bronchodilator is administered |
| Oedema due to microvascular leakage in response to inflammatory mediators and structural changes to airway smooth muscle | Thickening of airway wall; amplification of airway narrowing due to contraction of airway smooth muscle for geometric reasons |
| Sensitisation of sensory nerves leading to afferent activity and autonomic reflex | Increased parasympathetic, cholinergic and airway smooth muscle tone, with consequent exaggerated bronchoconstriction in response to sensory stimuli |

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Box 2 Possible pathophysiological reasons why long-acting anticholinergic bronchodilators may be beneficial for the control of asthma

- Cholinergic activity is the predominant driver of bronchial smooth muscle contraction, the primary cause of reversible airway obstruction in asthma.
- Patients with asthma have increased basal airway smooth muscle tone, possibly as a result of increased cholinergic tone.
- Acute treatment with anticholinergic compounds reduces basal airway smooth muscle tone.
- Local airway inflammatory mediators may have a role in inducing increased cholinergic tone.
- Cholinergic activity may have a prominent role in airway smooth muscle remodelling.
- Cholinergic receptors on lung submucosal cells regulate mucus secretion.
- Increased cholinergic and smooth muscle tone may contribute to airway hyper-responsiveness.
- Cholinergic antagonists may have non-neuronal anti-inflammatory actions.
- Patients with asthma may have abnormal muscarinic receptor expression.
- Patients with asthma may have increased release of acetylcholine from cholinergic nerve endings.
- Patients with asthma may have reduced levels of neuromodulators that attenuate cholinergic neurotransmission.

Anticholinergic drugs could help prevent airway smooth muscle remodelling in human asthma.

Cholinergic activity is also believed to regulate non-smooth muscle and non-neuronal cells within the lungs, including inflammatory cells and those controlling mucus secretion. In a guinea pig model, tiotropium was shown to reduce allergen-induced mucus gland hypertrophy and goblet cell number, suggesting that anticholinergic bronchodilators might also reduce airflow obstruction by reducing mucus hypersecretion. Expression of cholinergic receptors on inflammatory cells raises the additional question of whether there are any non-neuronal anti-inflammatory actions of cholinergic antagonists, although a review of studies on chronic obstructive pulmonary disease failed to identify robust evidence of this.

PHARMACOLOGY OF ANTICHOLINERGIC BRONCHODILATORS

Anticholinergic bronchodilators are antagonistic to parasympathetic activity and exert their effects on acetylcholine receptors on airway smooth muscle and pulmonary parasympathetic nerves (Figure 2). Acetylcholine receptors fall into two families—nicotinic and muscarinic—and it is the M1, M2 and M3 subtypes of the latter that are thought to be primarily involved in the regulation of bronchoconstriction. All subtypes of muscarinic receptors are widely expressed in the brain, the parasympathetic nervous system and the body’s smooth muscle tissues. M1 receptors are broadly distributed throughout the parasympathetic ganglia and regulate cholinergic transmission. M2 receptors are found in prejunctional membranes of neuromuscular junctions of airway smooth muscle and regulate negative feedback to reduce acetylcholine transmission. In a pulmonary context, M3 receptors are predominantly expressed in smooth muscle cells, where they regulate contraction, and also within lung submucosal glands, where they regulate mucus secretion (Figure 2). Thus, it is preferable for antimuscarinic bronchodilators to have a relatively high affinity for M1, and M3 receptors and low affinity for the M2 receptor.

CLINICAL EVIDENCE OF ANTICHOLINERGIC BRONCHODILATORS IN ASTHMA

Historically, short-acting anticholinergic bronchodilators have not been considered appropriate for the control of asthma, except in some cases for the acute treatment of asthma attacks in patients with chronic stable asthma, and in those who experience adverse events from SABAs, such as tachycardia, arrhythmia and tremor. Although short-acting anticholinergics are considered less effective rapid bronchodilators than SABAs such as salbutamol, there are data to suggest that, for acute exacerbations, ipratropium in combination with a SABA as reliever medication improves lung function to a greater extent than a SABA alone. In a double-blind, randomised trial, Rodrigo and Rodriguez investigated the effects of high-dose ipratropium plus the SABA albuterol (registered generic name for salbutamol in the USA) in adults with acute asthma, in the emergency

Currently, there are five anticholinergic drugs available for bronchodilation in respiratory disease. Ipratropium and oxitropium are short-acting non-selective antagonists of M1, M2 and M3 receptors. In contrast, tiotropium, aclidinium bromide (aclidinium) and glycopyrronium bromide (glycopyrronium) are long-acting compounds, with comparative selectivity for the M1/M3, M2/M3 and M3 receptors, respectively. Short-acting anticholinergics are generally considered less effective acute bronchodilators than SABAs, and their short duration of action makes them broadly unsuitable as controller medication. Thus, evidence of increased cholinergic tone in patients with asthma indicates that the longer-acting bronchodilator compounds may be more suitable as controller medications in asthma.

There is some rationale to suggest that the addition of long-acting anticholinergic bronchodilators to LABAs might provide advantages in the treatment of asthma (Box 2). It is reasonable to hypothesise that by simultaneously antagonising parasympathetic smooth muscle contraction and stimulating adrenergic smooth muscle relaxation, it is possible to achieve greater bronchodilation compared with either strategy in isolation. To date, there has been little thorough clinical investigation of this hypothesis in asthma, but a study in a guinea pig model found that bronchodilation induced by the LABA carmoterol was significantly augmented by the addition of tiotropium. In vitro studies have also found that the LABA indacaterol can synergistically increase the inhibitory effects of glycopyrronium on methacholine-induced airway smooth muscle contraction. As discussed below, improvements in lung function have been observed in asthmatic patients receiving tiotropium as add-on therapy to LABA plus ICS.
department. Patients receiving high-dose ipratropium plus albuterol had a greater improvement in peak expiratory flow and forced expiratory volume in 1 s compared with patients who received albuterol alone. The risk of hospital admission was 49% lower in the ipratropium/albuterol arm. Further, a meta-analysis has indicated that the addition of a short-acting anticholinergic to a SABA is associated with a significant reduction in the risk of hospitalisation in children. Thus, in adults or children, the main justification for the use of short-acting anticholinergic drugs in acute asthma is reduction of the elevated airway smooth muscle and cholinergic tone during an acute crisis, although administration of multiple doses has been associated with a reduction in hospitalisations and risk of hospitalisation of patients. It has been indicated for the treatment of chronic obstructive pulmonary disease for over a decade, no long-acting anticholinergic bronchodilators are currently approved in asthma. A number of compounds exist, including aclidinium, glycopyronium, glycopyrrolate and darotropium bromide, but, as mentioned, presently only tiotropium and umeclidinium have clinical trials in asthma listed on ClinicalTrials.gov. The latter has been under investigation in two dose-ranging Phase II trials in patients with asthma, as a monotherapy (NCT01641692) and in combination with fluticasone furoate (NCT01573624), although to our knowledge no results from these trials have yet been published.

Early studies with long-acting anticholinergics in asthma were small and underpowered, and failed to detect meaningful responses. However, studies of tiotropium and of glycopyrrolate indicated that long-acting anticholinergics can provide sustained bronchodilation and bronchoprotection. To date, more thorough clinical evaluation has been performed with tiotropium only, in six Phase II or III studies, involving over 3,500 patients (Table 2). In an investigator-initiated three-way crossover trial (14 weeks per treatment) in 210 patients with asthma inadequately controlled by low-dose ICS (twice-daily beclomethasone 80 μg), tiotropium delivered via the Spiriva HandiHaler device (Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT, USA) was shown to be superior to a doubling of ICS dose and equal to the addition of salmeterol, as assessed by improvements in lung function (Table 2). Subsequent published investigation of tiotropium have all involved administration via the Respimat SoftMist Inhaler (Boehringer Ingelheim Pharma, Ingelheim am Rhein, Germany). In an 8-week crossover trial, once-daily tiotropium at a dose of 5 or 10 μg improved lung function, compared with placebo, in 107 patients with severe persistent poorly controlled asthma already receiving ICS and LABA (Table 2). In a 16-week trial in patients with arginine/arginine homozygosity at amino acid 16 of the β2-adrenergic receptor (B16-Arg/Arg) and moderate poorly controlled asthma (already receiving ICS), once-daily tiotropium at a dose of 5 μg was superior to placebo and non-inferior to twice-daily salmeterol at a dose of 50 μg for maintenance of improvements in lung function (Table 2). The rationale for performing the latter study was based on suggestions that the addition of a short-acting β2-agonist is worse, and the efficacy lower, in patients with the B16-Arg/Arg polymorphism, although prospective investigation has revealed that there are no such concerns. A subsequent Phase II dose-ranging study tested tiotropium at doses of 5 μg, 2.5 μg and 1.25 μg as add-on to ICS and found the 5 μg dose to provide the greatest bronchodilator effect. Data from the first Phase III trial on a long-acting anticholinergic bronchodilator in asthma were published in 2012. In two replicate trials including a total of 912 patients with poorly controlled asthma despite the use of LABA and high-dose ICS (>800 μg budesonide or equivalent), tiotropium 5 μg administered via the Respimat SoftMist inhaler as add-on therapy significantly reduced the risk of severe exacerbations compared with placebo (values provided in Table 2).

IS THERE A ROLE FOR LONG-ACTING ANTICHOLINERGIC BRONCHODILATORS IN ASTHMA?

Is it possible to determine to which patients, and in which clinical situations, long-acting anticholinergic bronchodilators might offer clinical benefits? Phase III investigation has found that tiotropium add-on therapy offers advantages to adults with severe asthma who are failing to gain control on ICS and LABA combinations. This, and the fact that the benefit/risk ratio of ICS falls at high ICS doses, suggests that addition of long-acting anticholinergic bronchodilators to ICS plus a LABA is likely to be a useful option for patients with poorly controlled severe asthma, and an alternative to further increases in ICS dose.

Whether long-acting anticholinergics will be appropriate as alternatives to LABAs is a harder question to answer. Nevertheless, tiotropium add-on to medium-dose ICS has been shown to provide lung function and ACQ-7 improvements that were statistically significant over placebo in ACQ-7 responder rate was observed in all three active arms, although, as is common in analyses of ACQ-7 in asthma clinical trials, there was also a large placebo effect. We await the full primary publication from this trial.
There are some physiological (Box 2) and clinical rationales that allow us to suggest groups of patients for whom long-acting anticholinergic bronchodilators might be appropriate. A few small studies with short-acting anticholinergic bronchodilators have indicated that responses to anticholinergics are more likely in older patients or in those with intrinsic (non-allergic) asthma. It has also been suggested that patients intolerant of β₂-adrenergic agents or with nocturnal asthma might respond better to anticholinergic bronchodilators. Further, there is 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 hence may be candidates for additional treatments such as long-acting anticholinergic bronchodilators, as may groups in which steroid resistance is known to occur, such as smokers or obese patients.

It is currently unclear why long-acting anticholinergic bronchodilators might reduce the rate of exacerbations. However, one can hypothesise that a contributing factor to

| Authors | Severity | Duration per treatment, weeks | N | Study drug(s) | Comparator(s) | Primary and key secondary end points | Difference from comparator |
|---------|----------|-------------------------------|---|--------------|---------------|-------------------------------------|---------------------------|
| Peters et al. | Mild to moderate asthma inadequately controlled by low-dose ICS | 14 | 210 | Once-daily tiotropium 18 μg, via Spiriva HandiHaler | Doubling ICS dose | Morning PEF | 25.8 l/min (95% CI: 14.4–37.1; P < 0.001) |
| Kerstjens et al. | Severe asthma inadequately controlled by high-dose ICS + LABA | 8 | 107 | Once-daily tiotropium 5 μg, via Respimat SoftMist | Placebo | Tiotropium 5 μg, peak FEV₁ | 139 ml (95% CI: 96–181; P = 0.0001) |
| Bateman et al. | Mild to moderate asthma uncontrolled by ICS alone | 16 | 38 | Once-daily tiotropium 5 μg, via Respimat SoftMist | Placebo (following run-in with salmeterol) | Morning pre-dose PEF | –20.70 l/min (95% CI: –33.24 to –8.16; P = 0.001 for superiority) |
| Kerstjens et al. | Poorly controlled asthma despite use of ICS + LABA | 48 | 912 | Once-daily tiotropium 5 μg, via Respimat SoftMist | Placebo | Peak FEV₁ at week 24 | 86 ± 34 ml (P = 0.01) (trial 1); 154 ± 32 ml (P < 0.001) (trial 2) |

Abbreviations: ACQ-7, seven-question Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; FEV₁, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; LABA, long-acting β₂-agonist; NS, not significant; PEF, peak expiratory flow.

*Only studies published in journal primary publication format have been included (Kerstjens et al. and Beeh et al. not shown).**

All lung function values are mean change from baseline, unless otherwise stated.

Table 2. Comparison of lung function and clinical findings from clinical trials with long-acting anticholinergic bronchodilators in asthma

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exacerbations might be an increase in afferent sensory nerve activity, resulting in an increase in parasympathetic tone and subsequent bronchoconstriction. If this were the case, treatment with long-acting anticholinergic therapies may attenuate such autonomic effects and provide additional bronchodilation.

CONCLUSIONS
It has long been apparent from clinical and preclinical investigations of the pathophysiology of asthma that cholinergic parasympathetic tone contributes to contraction of bronchial smooth muscle and narrowing of the airways. The extent to which increased parasympathetic tone is a consequence of reflex to the inflammatory state or is a pathophysiological mechanism in itself is unclear. Regardless, the raised parasympathetic tone does provide a rationale for the use of long-acting anticholinergic bronchodilators in asthma, and recent Phase III trial results have demonstrated clinical benefits and lung function improvements with tiotopium as add-on therapy to ICS alone or ICS plus LABA in adult patients with poorly controlled asthma. In light of the evidence, we believe that anticholinergic bronchodilators will be a useful add-on therapy for patients at high risk of future worsening or exacerbations, and in patients whose asthma remains uncontrolled on a broad range of treatments and/or for whom other alternative therapies are unsuitable.

Whether tiotropium or other long-acting anticholinergic bronchodilators will offer clinical advantages in younger patients, or in those with less severe asthma than studied thus far, is under investigation. As we gain clinical experience in asthma with long-acting anticholinergics, if approved, it will be interesting to see whether and to what extent certain subgroups and phenotypes benefit from their use as controller medications.

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REFERENCES
1 Masoli M, Fabian D, Holt S, Beasley R. The Global Initiative for Asthma. Global burden of asthma. Available at: http://www.ginasthma.org/ local/uploads/files/ GINA BurdenReport_1.pdf (accessed 6 December 2013).
2 Global Initiative for Asthma. Global strategy for asthma management and prevention. Updated 2012. Available at: http://www.ginasthma.org/ local/uploads/ files/GINA_Report_2012Feb13.pdf (accessed 6 December 2013).
3 Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW 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.
4 National Heart, Lung, and Blood Institute. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma. Available at: http://www.nhlbi.nih.gov/ guidelines/asthma/asthgdln.htm (accessed 15 November 2013).
5 Baines PJ. New therapies for asthma: is there any progress? Trends Pharmacol Sci 2010; 31: 335–343.
6 Canonica GW, Baena-Cagnani CE, Blais MS, Dahl R, Kaliner MA, Valovirta EJ, GAPP Survey Working Group. Unmet needs in asthma: Global Asthma Physician and Patient (GAPP) Survey: global adult findings. Allergy 2007; 62: 668–674.
7 Bateman ED, Boushey HA, Bouquet J, Busse WW, Clark TJ, Pauwels RA 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.
8 Adams RJ, Fuhlbrigge A, Guibert T, Lozano P, Martinez F. Inadequate use of asthma medication in the United States: results of the asthma in America national population survey. J Allergy Clin Immunol 2002; 110: 58–64.
9 Partridge MR, van der Molen T, Mynset SE, Busse WW. Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. BMC Pulm Med 2006; 6: 13.
10 Sims EJ, Price D, Haughney J, Ryan D, Thomas M. Current control and future risk in asthma management. Allergy Immunol Respir Med 2011; 3: 217–225.
11 Haughney J, Price D, Kaplan A, Chrystyn H, Horne R, May N et al. Achieving asthma control in practice: understanding the reasons for poor control. Respir Med 2008; 102: 1681–1693.
12 O’Byrne PM, Naij N, Gauvreau GM. Severe asthma: future treatments. Clin Exp Allergy 2012; 42: 706–711.
13 Baines N, Pavord I, Chuchalin A, Bell J, Hunter M, Lewis T et al. A randomized, double-blind, placebo-controlled study of the CRTH2 antagonist OC000459 in moderately persistent asthma. Clin Exp Allergy 2012; 42: 38–48.
14 Iwona S, Tomasz G. Antileukotriene treatment in children with asthma - new patents. Recent Pat Inflamm Allerg Drug Discov 2008; 2: 202–211.
15 Pavord ID, Korn S, Howarth P, Bleeker ER, Buhl R, Keene ON et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 2012; 380: 651–659.
16 Corren J, Lemanske RF Jr, Hanania NA, Korenblat PE, Parsey MV, Aron JR et al. Lebrikizumab treatment in adults with asthma. N Engl J Med 2011; 365: 1088–1098.
17 Restrepo RD. Use of inhaled anticholinergic agents in obstructive airway disease. Respir Care 2007; 52: 833–851.
18 Meier CR, Jick H. Drug use and pulmonary death rates in increasingly symptomatic asthma patients in the UK. Thorax 1997; 52: 612–617.
19 Westby MJ, Benson MK, Gibson PG. Anticholinergic agents for chronic asthma in adults. Cochrane Database Syst Rev 2004; 3:CD003269.
20 Novelli F, Malagrinò L, Dente FL, Paggiaro P. Efficacy of anticholinergic drugs in asthma. Expert Rev Respir Med 2012; 6: 309–319.
21 Vogelmeier C, Hederer B, Gaab T, Schmidt H, Rutten-van Mölken MP, Beek KM et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med 2011; 364: 1093–1103.
22 Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 2008b; 359: 1543–1554.
23 O’Connor BJ, Towie LJ, Barnes PJ. Prolonged effect of tiotropium bromide on methacholine-induced bronchoconstriction in asthma. Am J Respir Crit Care Med 1996; 154(4 Pt 1): 876–880.
24 Fardon T, Haggart K, Lee DKC, Lipworth BJ. A proof of concept study to evaluate stepping down the dose of fluticasone in combination with salmeterol and tiotropium bromide in asthma. Respir Med 2007; 101: 1218–1228.
25 Bateman ED, Kornmann O, Schmidt P, Pivovarova A, Engel M, Fabbri LM. 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.
26 Kersiøns HAM, Disse B, Schröder-Babo W, Bantje TA, Gahlemann M, Sigmund R et al. Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial. J Allergy Clin Immunol 2011; 128: 308–314.
27 Peters SP, Kunselmann SJ, Ictovnic T, Moore WC, Pascual R, Ameredes BT et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. N Engl J Med 2010; 363: 1715–1726.
28 Kersiøns HAM, Engel M, Dahl R, Paggiaro P, Beck E, Vandevalker M et al. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med 2012; 367: 1198–1207.
29 Canning BJ. Reflex regulation of airway smooth muscle tone. J Appl Physiol 2006; 101: 971–985.
30 Moffina NA, Slutsky AS, Jüla-Serda G, Hoffstein V, Szalai JP, Chapman KR et al. Assessment of airway tone in asthma. Comparison between double lung transplant patients and healthy subjects. Am J Respir Crit Care Med 1993; 148: 1238–1243.
31 Barnes PJ. Neural mechanisms in asthma. Br Med Bull 1992; 48: 149–168.
32 Cazzola M, Page CP, Calzetta L, Matare MG. Pharmacology and therapeutics of bronchodilators. Pharmacol Rev 2012; 64: 450–504.
33 Douglas NJ, Sudlow MF, Flenley DC. Effect of an inhaled atropine-like agent on normal airway function. J Appl Physiol 1979; 46: 256–262.
34 Rodrigo G, Rodrigo C, Burchín O. A meta-analysis of the effects of ipratropium bromide in adults with acute asthma. Am J Med 1999; 107: 363–370.
35 Hashimoto A, Maeda H, Yokoyama M. Augmentation of parasympathetic nerve response in patients with extrinsic bronchial asthma—evaluation by coefficient of variance of R-R interval with modified long-term ECG monitoring system. Kobe J Med Sci 1996; 42: 347–359.
36 Kesler BS, Canning BJ. Regulation of baseline cholinergic tone in guinea-pig airway smooth muscle. J Physiol 1999; 518: 843–855.
37 Jammes Y, Mei N. Assessment of the pulmonary origin of bronchoscopic vagal tone. J Physiol 1979; 291: 305–316.
38 Barnes PJ. Neuroeffector mechanisms: the interface between inflammation and neuronal responses. J Allergy Clin Immunol 1996; 98(S1 Pt 2): 573–581.
39 Goyal M, Jaseja H, Verma N. Increased parasympathetic nerve tone as the underlying cause of asthma: a hypothesis. Med Hypotheses 2010; 74: 661–664.
40 Ayala LE, Ahmed T. Is there loss of protective muscarinic receptor mechanism in asthma? Chest 1989; 96: 1285–1291.
41 Barnes PJ. Modulation of neurotransmission in airways. Physiol Rev 1992; 72: 699–729.
42 Kanazawa H, Kawaguchi T, Shoji S, Fujii T, Kudoh S, Hirata K et al. Synergistic effect of nitric oxide and vasoactive intestinal peptide on bronchoprotection against histamine in anesthetized guinea pigs. Am J Respir Crit Care Med 1997; 155: 747–750.
43 Park HW, Yang MS, Park CS, Kim TB, Moon HB, Min KU 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.
44 Lundgren R, Söderberg M, Horstedt P, Stenling R. Morphological studies of bronchial mucosal biopsies from asthmatics before and after ten years of treatment with inhaled steroids. Eur Respir J 1988; 1: 883–889.
45 An SS, Bai TR, Bates JHT, Black JL, Brown RH, Brusasco V et al. Airway smooth muscle dynamics: a common pathway of airway obstruction in asthma. Eur Respir J 2007; 29: 834–840.
46 Gossens R. Inhibition of induced-airway inflammatory remodeling by tiotropium and budesonide: a comparative study. Abstract A269 presented at the 103rd Annual International Conference of the American Thoracic Society. San Francisco, CA, USA, 2007.
74 Bleecker ER, Nelson HS, Kraft M, Corren J, Meyers DA, Yancey SW et al. β₂-receptor polymorphisms in patients receiving salmeterol with or without fluticasone propionate. *Am J Respir Crit Care Med* 2010; 181: 676–687.

75 Beeh KM, Ablinger O, Moroni-Zentgraf P, Hollaenderova Z, Pivovarova A, Engel M et al. Tiotropium in asthma: a dose-finding study in adult patients with moderate persistent asthma. Poster A1283 presented at the American Thoracic Society International Conference: Philadelphia, PA, USA, 2013.

76 Kerstjens HAM, Bleecker E, Meltzer E, Casale T, Pizzichini E, Schmidt O et al. Tiotropium as add-on therapy to inhaled corticosteroids for patients with symptomatic asthma: lung function and safety. *Eur Respir J* 2013; 42(Suppl 57): 980s (abs 4629).

77 Kerstjens HAM, Bleecker E, Meltzer E, Casale T, Pizzichini E, Schmidt O et al. Tiotropium as add-on to inhaled corticosteroids significantly improves asthma control as reflected by the ACQ responder rate. *Eur Respir J* 2013; 42(Suppl 57): 876s (abs 4130).

78 Bateman ED, Esser D, Chirila C, Fernandez M, Fowler A, Moroni-Zentgraf P et al. Systematic review and meta-analysis of the magnitude of the effect on the AQLQ and ACQ in asthma clinical trials. Poster P4113 presented at the European Respiratory Society Annual Congress: Barcelona, Spain, 2013.

79 Powell H, Gibson PG. Inhaled corticosteroid doses in asthma: an evidence-based approach. *Med J Aust* 2003; 178: 223–225.

80 Szefer SJ, Martin RJ, King TS, Boushey HA, Cherniack RM, Chinchilli VM et al. Significant variability in response to inhaled corticosteroids for persistent asthma. *J Allergy Clin Immunol* 2002; 109: 410–418.

81 Price DB, Kaplan A, Jones R, Freeman D, Burden A, Gould SE et al. Real-life prescribing and outcomes of long-acting anticholinergic therapy in adult asthma patients in UK clinical practice. *Am J Respir Crit Care Med* 2013; 187 (abs A2729).

82 Ullah MI, Newman GB, Saunders KB. Influence of age on response to ipratropium and salbutamol in asthma. *Thorax* 1981; 36: 523–529.

83 Connolly MJ. Ageing, late-onset asthma and the beta-adrenoceptor. *Pharmacol Ther* 1993; 60: 389–404.

84 Partridge MR, Saunders KB. Site of action of ipratropium bromide and clinical and physiological determinants of response in patients with asthma. *Thorax* 1981; 36: 530–533.

85 Berry M, Morgan A, Shaw DE, Parker D, Green R, Brightling C et al. Pathological features and inhaled corticosteroid response of eosinophilic and non-eosinophilic asthma. *Thorax* 2007; 62: 1043–1049.

86 Pavord ID, Brightling CE, Woltmann G, Wardlaw AJ. Non-eosinophilic corticosteroid unresponsive asthma. *Lancet* 1999; 353: 2213–2214.

87 Bradding P, Green RH. Subclinical phenotypes of asthma. *Curr Opin Allergy Clin Immunol* 2010; 10: 54–59.

88 Lazarus SC, Chinchilli VM, Rollings NJ, Boushey HA, Cherniack R, Craig TJ et al. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. *Am J Respir Crit Care Med* 2007; 175: 783–790.

89 Chaudhuri R, Livingston E, McMahon AD, Lafferty J, Fraser I, Spears M et al. Effects of smoking cessation on lung function and airway inflammation in smokers with asthma. *Am J Respir Crit Care Med* 2006; 174: 127–133.