BRN Reviews REVIEW ARTICLE

Therapeutic Role of Tiotropium in Chronic Obstructive Airways Diseases

David M.G. Halpin, MA, DPhil, MBBS, FRCP

Department of Respiratory Medicine, Royal Devon and Exeter Hospital, Exeter, United Kingdom

ABSTRACT

Chronic obstructive airways disease (COPD) and asthma are major causes of morbidity around the world. This review examines the evidence on the effectiveness of tiotropium as a treatment for COPD and asthma. It discusses the role of acetylcholine in airway physiology and the effects of muscarinic antagonism on airways smooth muscle, mucous secretion and inflammation. In COPD, tiotropium increases forced expiratory volume in 1 second (FEV_1) and reduces hyperinflation; it improves breathlessness, exercise capacity and health status, and it reduces exacerbation rates. Tiotropium also reduces the rate of decline in FEV_1 over 4 years in patients with an FEV_1 over 50% predicted. In asthma, when added to inhaled steroids alone or in combination with long-acting beta agonists, tiotropium improves lung function, improves asthma control and reduces exacerbations. These effects have been seen in children, adolescents and adults with asthma. Tiotropium is well tolerated, with a low incidence of adverse events. **(BRN Rev. 2018;4:135-52)**

Corresponding author: David M.G. Halpin, d.halpin@nhs.net

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Correspondence to:
David M.G. Halpin
Department of Respiratory Medicine, Royal Devon and Exeter Hospital, Exeter, United Kingdom
E-mail: d.halpin@nhs.net

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INTRODUCTION

Asthma and chronic obstructive pulmonary disease (COPD) are both common chronic diseases characterised by airflow obstruction. COPD is now the third most common cause of death worldwide[1] and the Global Burden of Disease project estimated that COPD affected 174 million people worldwide in 2015 causing 3.2 million deaths, an increase of 11.6% compared with 1990. Asthma affected 358 million people worldwide and caused 400,000 deaths, a decrease of 26.7% from 1990[2].

Long-acting bronchodilators are the mainstay of treatment for COPD[3] and now play an important role alongside inhaled corticosteroids (ICS) in reducing symptoms in patients with uncontrolled asthma[4]. Tiotropium bromide was the first long-acting muscarinic antagonist (LAMA) to be approved for maintenance treatment of COPD. It has been available since 2002, and it is widely prescribed in over 110 countries worldwide with patient experience of over 25 million patient-years[5]. It is available in two formulations: dry powder (18 µg once daily) delivered via the HandiHaler inhaler, and aqueous solution (5 µg, two puffs 2.5 µg once daily) delivered via the Respimat Soft Mist Inhaler. Since 2014, tiotropium in the Respimat has also been licensed in the European Union (EU) for add-on maintenance treatment of adults with symptomatic asthma and it is still the only LAMA to have this indication. This review examines the evidence on the efficacy and safety of tiotropium in COPD and asthma, considers this in the context of the evidence on the efficacy of other LAMAs in COPD and briefly examines the efficacy of tiotropium when combined with the long-acting β2-agonists (LABA) olodaterol.

Acetylcholine is synthesized from choline and acetyl coenzyme A mainly by the enzyme choline acetyltransferase which is expressed parasympathetic neuron in the airways but also in airway epithelial cells[6-8]. Human airways contain M1, M2, and M3 muscarinic receptors. M3 receptors mediate acetylcholine's effects on airway smooth muscle tone and mucous secretion from mucosal glands. M2 receptors have an inhibited auto-regulatory effect on the release of acetylcholine from both pre- and post-ganglionic nerve terminals but are also widely expressed by other cells such as fibroblasts and smooth muscle cells[9]. Non-neuronal acetylcholine released from epithelial cells acts as a paracrine/autocrine hormone maintaining cellular homeostasis and epithelial repair, regulating ciliary activity and mucociliary clearance and modulating the activity of inflammatory cells promoting their survival and cytokine release[7,10].

Tiotropium antagonises all three muscarinic receptors present in the airways, but it has a higher selectivity for M3 receptors than for M2 receptors, and it dissociates more slowly from M3 receptors than from M2 receptors giving it its long duration of action[11].

M3 antagonism leads to airway smooth muscle relaxation and a reduction in mucus secretion, which is important, as hypersecretion may contribute to airflow limitation in asthma and COPD, and it is a risk factor for accelerated loss of lung function and exacerbations[12]. Animal studies have suggested tiotropium might improve airflow limitation by reducing airway mucus as well as its effects on smooth muscle[13], and in patients with COPD, tiotropium was associated with a reduction in sputum volume[14].

Both asthma and COPD are characterised by chronic inflammation and structural changes to the airways, although the underlying inflammatory processes differ between each disease[15]. Inflammation is an important therapeutic target for these diseases and in invitro and in animal models, tiotropium also appears to have anti-inflammatory properties due to M3 antagonism. In animal models pretreatment with tiotropium reduces eosinophilic inflammation in response to allergen exposure and partly prevents aspects of airway remodelling, inhibiting mucus gland hypertrophy and decreasing the number of MUC5AC-positive goblet cells, as well as reducing airway smooth muscle thickening[13-16]. In animal models, tiotropium also inhibits neutrophil chemotactic activity, and decreases levels of cytokines (interleukin [IL]-4, IL-5, IL-13 & tumour necrosis factor alpha [TNF-α]) and leukotriene B4 in bronchoalveolar lavage fluid[17,18] as well as inhibiting airway remodelling and pulmonary inflammation in a guinea pig model of COPD[18].

Tiotropium may also have an indirect effect on inflammation in COPD through the suppression of repeated airway smooth muscle contraction, which reduces the inflammatory activity[9,11]. In humans, tiotropium attenuates reactive oxygen species (superoxide anions) and leukotriene B4 production by peripheral blood neutrophils obtained from patients with COPD[18].

CLINICAL EFFECTS OF TIOTROPIUM IN COPD

The goal of COPD therapy is to obtain improve symptoms, exercise capacity and quality of life as well as minimising or preventing exacerbations, with minimal adverse events[3]. Tiotropium is widely used around the world to help deliver these goals. There is now experience of over 50 million patient-years of treatment[19], including more than 2.5 million patient-years' experience with the Respimat[20]. Its use is supported by evidence from over 200 clinical trials and of many these trials include patients typical of those seen in primary care[21,22]. Populations studied have included patients with mild to very severe airflow obstruction[22], patients naïve to maintenance therapy[23,24], patients with common and relevant comorbidities, such as cardiovascular disease[22,25-27] as well those with mild-to-moderate renal impairment[22].

As well as the individual clinical trials, a number of systematic reviews with meta-regression analysis of pooled data have summarised the efficacy of tiotropium in patients with COPD[19,28-34] as well as its safety[35,36]. This review will not duplicate these reviews but will highlight the main findings.

Randomised trials have demonstrated lung function improvements with tiotropium versus placebo and active comparators. Lung function improvement is seen in patients with all levels of spirometric impairment and in all Global Initiative for Chronic Obstructive Lung Disease (GOLD) groups[20,37-39]. Whether administered in the HandiHaler or Respimat device tiotropium results in similar spirometric improvements[40]. The magnitude of the effect of tiotropium on FEV_1 (whether peak or trough) compared to placebo or other bronchodilators is remarkably consistent despite differences in the characteristics of the patients studied. Figure 1 shows the effect of tiotropium on trough FEV_1 compared with placebo across eighteen of the principal studies, which varied in the severity of airflow obstruction and GOLD group

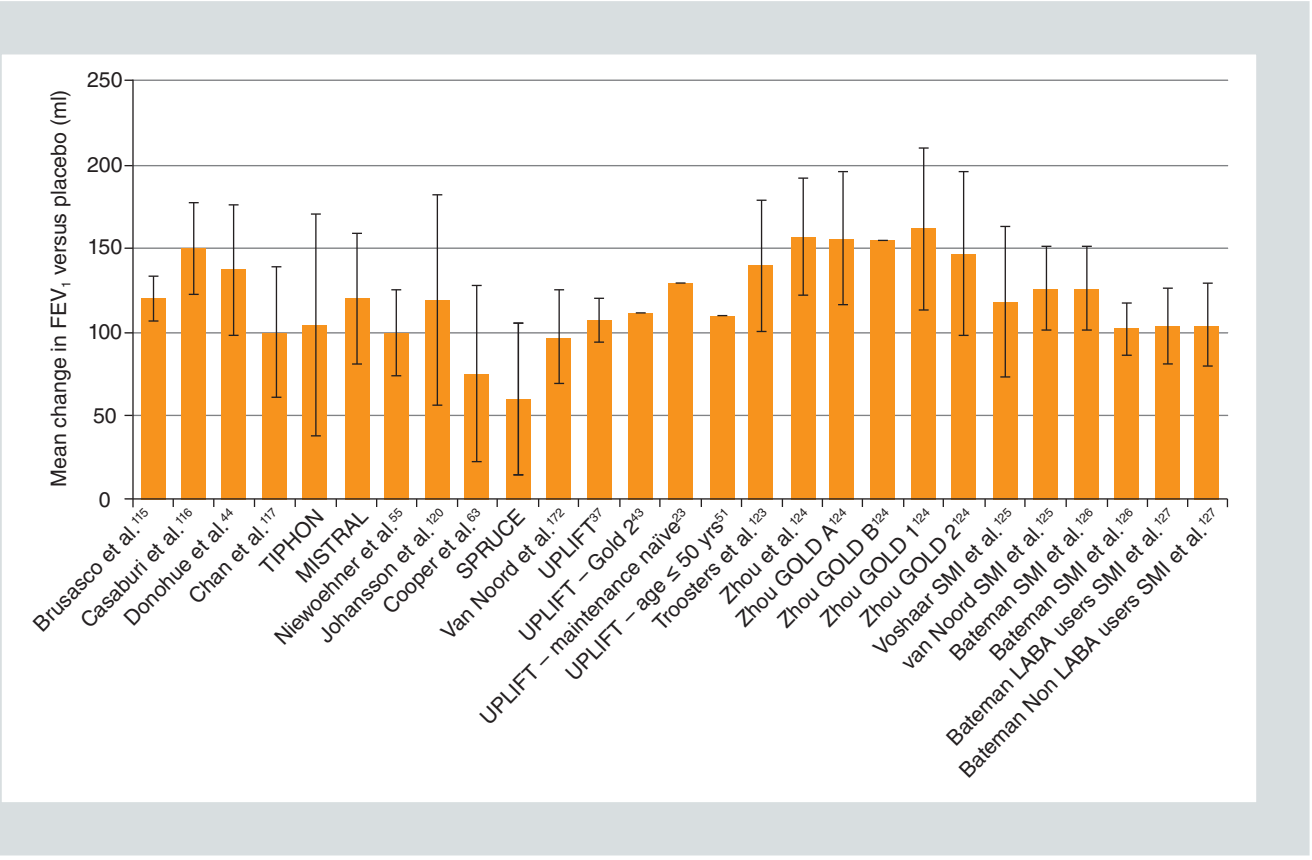

Figure 1. Mean effect of tiotropium on trough FEV_1 (± 95% CI) compared to placebo across eighteen studies and subgroups within these studies. For details of the studies, including inclusion criteria and permitted medications see table 1.
FEV_1: forced expiratory volume in 1 second.

of the patients included, concomitant and prior use of maintenance therapy, age and whether the Handihaler or Respimat soft mist inhaler were used to deliver the tiotropium. The details of the studies are listed in table 1.

As well as the changes in spirometry, tiotropium produces sustained reductions of lung hyperinflation at rest and during exercise[41] that lead to improvements in both exertional dyspnoea and exercise endurance as a result of the improved ability to increase tidal volume (Fig. 2).

Among the many trials examining the efficacy of tiotropium, the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) study stands out as it studied the effects compared to placebo against a background of usual therapy including LABA and ICS in nearly six thousand patients over 4 years[37]. There were improvements in trough FEV_1 when tiotropium was added of between 87 to 103 ml pre-bronchodilator and between 47 to 65 ml post-bronchodilator group and these improvements were maintained over four years. Improvements in FEV_1 were observed across the spectrum of disease in GOLD Stages 2–4[37] and GOLD 2011 Groups A–D COPD[38] and were similar in current and ex-smokers[42].

In the UPLIFT study the primary endpoint, the rate of decline in lung function, was not significantly different between patients treated with tiotropium and those receiving standard

Table 1. Details of double blind studies examining the effect of tiotropium on trough forced expiratory volume in 1 second (FEV_1) compared to placebo showing duration, basic inclusion criteria, other inhaled medication patients were allowed to use during the study, the percentage using these medications at randomisation and the estimated mean change in FEV_1 and 95% confidence interval compared to placebo. (SMI – Respimat soft mist inhaler used to administer tiotropium)

Study	Population	Duration (weeks)	Background therapy	Mean Δ trough FEV_1 (95% CI) (mL)
Brusasco et al.[115]	FEV1 ≤ 65% pred FEV_1/FVC ≤ 0.7	24		120 (106, 133)
Casaburi et al.[116]	FEV_1 ≤ 65% pred FEV_1/FVC ≤ 0.7	52	ICS (42%)	150 (123, 177)
Donohue et al.[44]	FEV_1 ≤ 60% pred FEV_1/FVC ≤ 0.7	24	ICS (66%)	137 (98, 176)
Chan et al.[117]	FEV1 ≤ 65% pred FEV1/FVC ≤ 0.7 ≥ 1 exac in last 2 yr	48	ICS (68%) LABA (53%)	100 (61, 139)
TIPHON[118]	FEV_1 20-70% pred FEV_1/FVC ≤ 0.7	39	ICS (33%)	104 (37,170)
MISTRAL[119]	FEV_1 30-65% pred FEV_1/FVC ≤ 0.7 ≥ 1 exac in last yr	52	ICS (64%)	120 (80, 159)
Niewoehner et al.[55]	FEV_1 ≤ 60% pred FEV_1/FVC ≤ 0.7	24	ICS (60%) LABA (38%)	100 (75, 125)
Johansson et al.[120]	FEV_1 ≥ 60% pred FEV_1/FVC ≤ 0.7 MRC ≥ 2	12	none	119 (56, 182)
Cooper et al.[63]	FEV_1 ≤ 65% pred FEV_1/FVC ≤ 0.7 MRC ≥ 2	96	ICS (63%) LABA (29%)	60 (15, 105)
SPRUCE[121]	FEV_1 30-65% pred FEV_1/FVC ≤ 0.7 No SAMA or LAMA in last year			
van Noord et al.[122]	FEV_1 ≤ 60% pred FEV_1/FVC ≤ 0.7	30	ICS (55%)	97 (72, 125)
UPLIFT[37]	FEV_1 ≤ 70% pred FEV_1/FVC ≤ 0.7	208	ICS (74%) LABA (72%)	107 (93, 120)
UPLIFT – GOLD 2[43]	FEV_1 50-70% pred FEV_1/FVC ≤ 0.7	208	ICS (58%) LABA (56%)	101 to 119
UPLIFT – maintenance naïve[23]	FEV_1 ≤ 70% pred FEV_1/FVC ≤ 0.7	208		99 to 160
UPLIFT – age ≤ 50 yrs[51]	FEV_1 ≤ 70% pred FEV_1/FVC ≤ 0.7	208	ICS (58%) LABA (57%)	82 to 148
Troosters et al.[123]	FEV_1 50-80% pred FEV_1/FVC ≤ 0.7	24		140 (90, 180)
Zhou et al.[124]	FEV_1 > 50% pred FEV_1/FVC ≤ 0.7	104	none	157 (123, 192)
Zhou et al.[124] GOLD A	FEV_1 > 50% pred FEV_1/FVC ≤ 0.7	104	none	156 (116, 196)
Zhou et al.[124] GOLD B	FEV_1 > 50% pred FEV_1/FVC ≤ 0.7	104	none	155 (85, 224)
Zhou et al.[124] GOLD 1	FEV_1 > 80% pred FEV_1/FVC ≤ 0.7	104	none	162 (115, 210)
Zhou et al.[124] GOLD 2	FEV_1 50-80% pred FEV_1/FVC ≤ 0.7	104	none	147 (98, 196)

(continued)

TABLE 1. *Continuation*

Study	Population	Duration (weeks)	Background therapy	Mean Δ trough FEV_1 (95% CI) (mL)
Voshaar et al.[125] SMI	FEV_1 ≤ 60% pred FEV_1/FVC ≤ 0.7	12	ICS (50%)	118 (73, 163)
van Noord et al.[122] SMI	FEV_1 ≤ 60% pred FEV_1/FVC ≤ 0.7	30	ICS (55%)	126 (101, 151)
Bateman et al.[126] SMI	FEV_1 ≤ 60% pred FEV_1/FVC ≤ 0.7	48	ICS (52%)	127 (101, 151)
Bateman et al.[127] SMI	FEV_1 ≤ 60% pred FEV_1/FVC ≤ 0.7	48	ICS (56%) LABA (53%)	102 (85, 118)
Bateman et al.[127] LABA users SMI	FEV_1 ≤ 60% pred FEV_1/FVC ≤ 0.7	48	ICS (90%) LABA (100%)	104 (82, 127)
Bateman et al.[127] Non LABA users SMI	FEV_1 ≤ 60% pred FEV_1/FVC ≤ 0.7	48	ICS (17%)	101 (74, 129)

CI: confidence interval; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; ICS: inhaled corticosteroids; LABA: long-acting $beta_2$ agonists; LAMA: long-acting muscarinic antagonist; MRC: medical research council; pred: predicted; SAMA: short-acting muscarinic antagonists; SMI: soft mist inhaler. MISTRAL study: Mesure de l'Influence de Spiriva® sur les Troubles Respiratoires Aigus à Long terme. SPRUCE study: Efficacy and safety of tiotropium in COPD patients in primary care–the SPiRiva Usual CarE. TIPHON study: Effect of a 9-month treatment of SPIRIVA® on Health Related Quality of Life in patients with Chronic Obstructive Pulmonary Disease. Validation of a new HRQoL questionnaire appropriate to common daily practice. UPLIFT study: Understanding potential long-term impacts on function with tiotropium study.

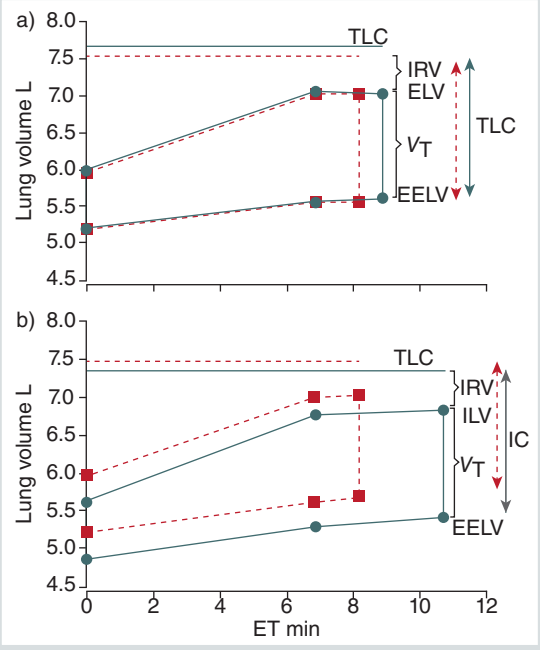

FIGURE 2. Operating lung volumes at rest and during exercise at baseline (■—) and after 42 days (●—) of treatment with placebo (a; n = 91) and tiotropium (b; n = 96) *(reproduced with permission from O'Donnell DE et al.[41] under the Creative Commons Attribution Non-Commercial License).*
EELV: end-expiratory lung volume; EILV: end-inspiratory lung volume; ET: endurance time; IC: inspiratory capacity; IRV: inspiratory reserve volume;; TLC: total lung capacity; V_T: tidal volume.

therapy in the whole population[37]; however, the rate of decline was significantly lower with tiotropium in patients with GOLD Stage 2 COPD[43].

As well as trials comparing tiotropium to placebo there have been studies comparing tiotropium to other long acting bronchodilators. These have shown greater FEV_1 improvements compared to twice-daily salmeterol[44] and non-inferiority to once-daily indacaterol[45]. Comparisons versus other LAMAs in patients with moderate-to-severe COPD have generally shown similar effects on lung function[46-48], although one study showed significantly greater improvements with umeclidinium versus tiotropium 12–24 hours post-dose[49].

Tiotropium consistently improves symptoms and health status compared with placebo (for a comprehensive review of studies, see Kaplan et al[50].) Figure 3 shows the effect of tiotropium on health status as measured using the St Georges Respiratory Questionnaire (SGRQ) compared

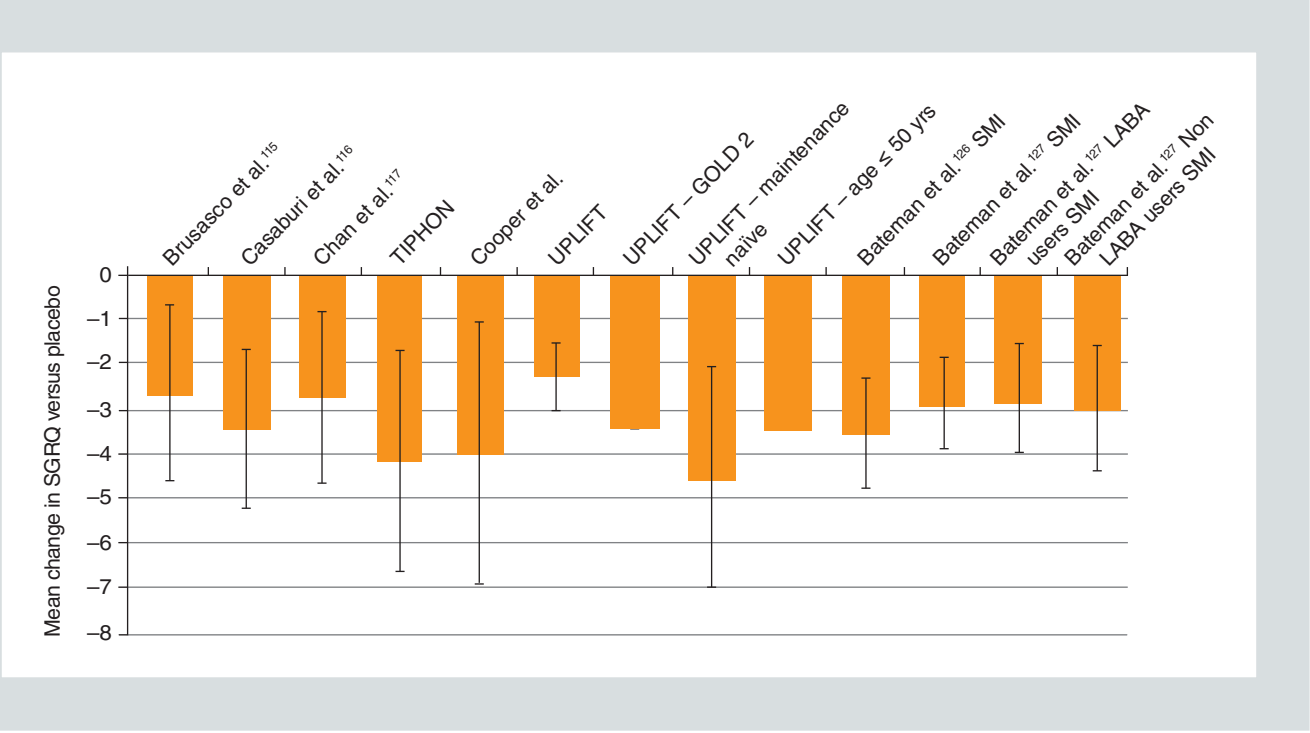

FIGURE 3. Mean effect of tiotropium on St George's Respiratory Questionnaire (SGRQ) (± 95% CI) compared to placebo. For details of the studies, including inclusion criteria and permitted medications see table 2.
SGRQ: St George's Respiratory Questionnaire.

with placebo across eight studies, which again varied in the severity of airflow obstruction and GOLD group of the patients included, concomitant and prior use of maintenance therapy, age and whether the Handihaler or Respimat soft mist inhaler were used to deliver the tiotropium. The details of the studies are listed in table 2. The magnitude of the mean effect is generally less than the 4 units considered the minimum clinically important difference, but the proportion of patients achieving a 4-unit change was significantly higher in all cases with tiotropium (Fig. 4 and Table 2).

In the UPLIFT study SGRQ was significantly improved by tiotropium compared with standard maintenance therapy on a background of standard care throughout the 4-year study period[37], including in GOLD 2 patients[43], those who were naïve to maintenance therapy (i.e. not receiving LABA, ICS, theophyllines or anticholinergics) at baseline[23] and those under the age of 50[51].

Figure 5 shows the effect of tiotropium on breathlessness measured using the transitional dyspnoea index (TDI) compared to placebo in the four trials which have examined this. There is less heterogeneity in the characteristics and patients studied in these trials, although there is some variation in the concomitant and prior use of maintenance therapy and both the Handihaler or Respimat soft mist inhaler were used to deliver the tiotropium. The details of the studies are listed in table 3. In each case the magnitude of the mean effect reaches or exceeds the 1-unit change considered the minimum clinically important difference.

Table 2. Details of double blind studies examining the effect of tiotropium on St George's Respiratory Questionnaire (SGRQ) compared to placebo showing duration, basic inclusion criteria, other inhaled medication patients were allowed to use during the study, the percentage using these medications at randomisation, and the estimated mean change in SGRQ and the odds ratio of having a 4-unit change with 95% confidence intervals compared to placebo (SMI – Respimat soft mist inhaler used to administer tiotropium)

Study	Population	Duration (weeks)	Background therapy	Mean Δ SGRQ (95% CI) from baseline	Odds Ratio of achieving a 4 unit change in SGRQ with tiotropium (95% CI)
Brusasco et al.[115]	FEV_1 ≤ 65% pred FEV_1/FVC ≤ 0.7	24		–2.70 (–4.64, –0.76)	1.48 (1.09, 2.00)
Casaburi et al.[116]	FEV_1 ≤ 65% pred FEV_1/FVC ≤ 0.7	52	ICS (42%)	–3.44 (–5.24, –1.64)	2.25 (1.68, 3.02)
Chan et al.[117]	FEV_1 ≤ 65% pred FEV_1/FVC ≤ 0.7 ≥ 1 exac in last 2 yr	48	ICS (68%) LABA (53%)	–2.79 (–4.69, –0.89)	1.43 (1.05, 1.95)
TIPHON[118]	FEV1 20-70% pred FEV_1/FVC ≤ 0.7	39	ICS (33%)	–4.18 (–6.67, –1.69)	1.56 (1.09, 2.22)
Cooper et al.[63]	FEV_1 ≤ 65% pred FEV_1/FVC ≤ 0.7 MRC ≥ 2	96	ICS (60%) LABA (59%)	–4.03 (–6.97, –1.09)	1.48 (0.94, 2.32)
UPLIFT[37]	FEV_1 ≤ 70% pred FEV_1/FVC ≤ 0.7	208	ICS (74%) LABA (72%)	–2.28 (–3.02, –1.54)	1.45 (1.27, 1.67)
UPLIFT – GOLD 2[43]	FEV_1 50-70% pred FEV_1/FVC ≤ 0.7	208	ICS (58%) LABA (56%)	–2.7 to –4.0	N/A
UPLIFT – maintenance naïve[23]	FEV_1 ≤ 70% pred FEV_1/FVC ≤ 0.7	208		–4.57 (–7.06, –2.09)	N/A
UPLIFT – age ≤ 50 yrs[51]	FEV_1 ≤ 70% pred FEV_1/FVC ≤ 0.7	208	ICS (58%) LABA (57%)	–3.0 to –4.1	N/A
Bateman et al.[126] SMI	FEV_1 ≤ 60% pred FEV_1/FVC ≤ 0.7	48	ICS (52%)	–3.65 (–4.81, –2.49)	1.52 (1.24, 1.86)
Bateman et al.[127] SMI	FEV_1 ≤ 60% pred FEV_1/FVC ≤ 0.7	48	ICS (56%) LABA (53%)	–2.9 (–3.9, –2.0)	1.39 (1.21, 1.59)
Bateman et al.[127] LABA users SMI	FEV_1 ≤ 60% pred FEV_1/FVC ≤ 0.7	48	ICS (90%) LABA (100%)	–2.8 (–4.0, –1.5)	1.42 (1.18, 1.71)
Bateman et al.[127] Non LABA users SMI	FEV_1 ≤ 60% pred FEV_1/FVC ≤ 0.7	48	ICS (17%)	–3.0 (–4.4, –1.5)	1.36 (1.11, 1.66)

CI: confidence interval; exac: exacerbations; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; ICS: inhaled corticosteroids; LABA: long-acting $beta_2$ agonists; MRC: medical research council; pred: predicted; SGRQ: St George's Respiratory Questionnaire; SMI: soft mist inhaler; yr: year.

As well as improving lung function and health status and reducing breathlessness, tiotropium reduces COPD exacerbation rates in patients with all disease severities and comorbid risk factors. The effects on all exacerbations and specifically on hospitalised exacerbations have been comprehensively reviewed[29,52].

Overall tiotropium reduced the rate of exacerbations by between 14% and 52% depending on the population studied, what concomitant therapy was allowed and how exacerbations were recorded[29]. Evidence suggests that the effect is not simply due to sustained bronchodilation[29]. Potential mechanisms that may contribute to the preventive effects of tiotropium on COPD exacerbations are a reduction in the inflammatory stimulus repeated hyperinflation and deflation[53], in a similar way to lung volume reduction surgery[54], re-setting the threshold of

Table 3. Details of double blind studies examining the effect of tiotropium on transitional dyspnoea index (TDI) compared to placebo showing duration, basic inclusion criteria, other inhaled medication patients were allowed to use during the study, the percentage using these medications at randomisation, and the estimated mean change in TDI with 95% confidence intervals compared with placebo (SMI – Respimat soft mist inhaler used to administer tiotropium)

Study	Population	Duration (weeks)	Background therapy	Mean Δ TDI (95% CI) from baseline
Brusasco et al.[115]	FEV_1 ≤ 65% pred FEV_1/FVC ≤ 0.7	24		1.1 (0.5, 1.7)
Casaburi et al.[116]	FEV_1 ≤ 65% pred FEV_1/FVC ≤ 0.7	52	ICS (42%)	1.0 (0.4, 1.6)
Chan et al.[117]	FEV_1 ≤ 65% pred FEV_1/FVC ≤ 0.7 ≥ 1 exac in last 2 yr	48	ICS (68%) LABA (53%)	1.0 (0.4, 1.6)
Bateman et al.[126] SMI	FEV_1 ≤ 60% pred FEV_1/FVC ≤ 0.7	48	ICS (52%)	1.05 (0.73, 1.38)

CI: confidence interval; exac: exacerbations; ICS: inhaled corticosteroids; LABA: long-acting beta 2 agonists; pred: predicted; SGRQ: St George's Respiratory Questionnaire; SMI: soft mist inhaler; TDI: transitional dyspnoea index; yr: year.

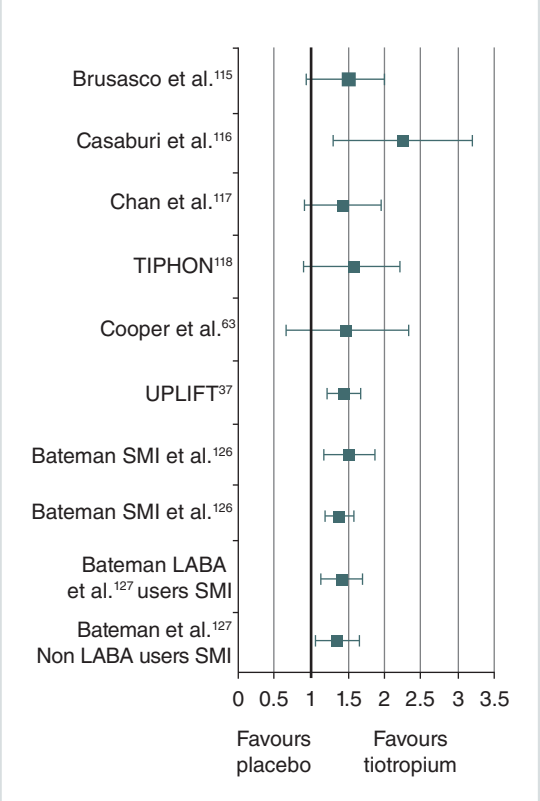

Figure 4. Odds ratio for patients achieving a 4-unit improvement in St George's Respiratory Questionnaire (SGRQ) (± 95% CI) with tiotropium compared to placebo. For details of the studies, including inclusion criteria and permitted medications see table 2.
SGRQ: St George's Respiratory Questionnaire.

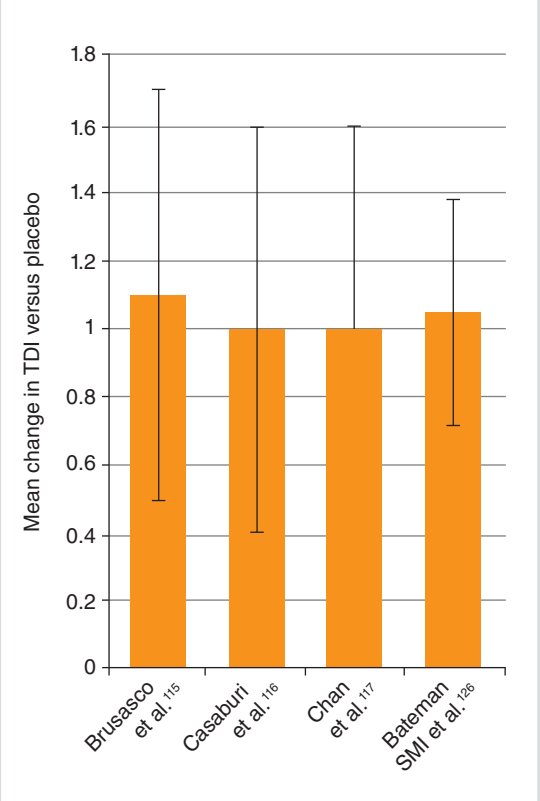

Figure 5. Mean effect of tiotropium on transitional dyspnoea index (TDI) (± 95% CI) compared to placebo. For details of the studies, including inclusion criteria and permitted medications see table 3.
TDI: transitional dyspnoea index.

lung function/dynamics (end-expiratory lung volume [EELV] and residual volume) at which an exacerbation is triggered, reduction of mucus secretion[55] and suppression of acetylcholine-mediated inflammatory responses[56].

In UPLIFT, tiotropium significantly delayed time to first exacerbation and first severe (hospitalised) exacerbation and reduced the number of exacerbations by 14% over 4 years versus standard respiratory therapy ($p < 0.001$)[37]. In a post-hoc analysis exacerbation risk was reduced with tiotropium across all GOLD stages[38].

Studies have shown that tiotropium is significantly more effective at reducing exacerbations than either once or twice daily LABAs[29,45,57,58]. The Investigation New Standards For Prophylaxis In Reduction Of Exacerbations (INSPIRE) study showed tiotropium had a similar effect on exacerbation rate to salmeterol/fluticasone, but patients treated with salmeterol/fluticasone had an increased incidence of pneumonia (8% versus 4% with tiotropium; $p = 0.008$)[59].

The effect of tiotropium on exacerbations is similar whether the Respimat or HandiHaler devices are used[40] and the reduction in exacerbations provided by tiotropium may additionally have beneficial effects on cardiovascular disease and mortality as well as on COPD itself[60].

The effects of tiotropium on lung function lead to an improvement in exercise capacity endurance, particularly when combined with pulmonary rehabilitation[4,61-64].

Glycopyrronium bromide, aclidinium and umeclidinium are also LAMAs licensed for once or twice daily use in COPD. They each have data showing effects on lung function, health status, breathlessness and exacerbations compared to placebo[65,66].

The efficacy of twice-daily (bid) aclidinium bromide has been examined in 12 placebo randomised controlled trials lasting between 4 and 52 weeks. In a meta-analysis of these studies, aclidinium resulted in a significantly greater improvement in pre-dose FEV_1 than placebo with a mean difference of 0.10 L (95% confidence interval [CI]: 0.08, 0.10), an improvement in TDI compared with placebo of 0.72 (95% CI: 0.33, 1.11), and an improvement in SGRQ total score compared to placebo of –2.51 (95% CI: –3.50 to –1.51)[67]. There was no significant difference between the number of patients treated with aclidinium and placebo having an exacerbation (odds ratio [OR] 0.83, 95% CI: 0.66, 1.05).

Studies have examined the effects of two doses of umeclidinium (62.5 µg [the licensed dose] and 125 µg), but the results have been pooled when meta-analysed[68]. Umeclidinium produced an overall mean improvement in trough FEV_1 of 0.13L (95% CI: 0.11 , 0.14) compared to placebo and no significant difference compared to tiotropium (0.04L 95% CI: –0.01, 0.09). TDI was improved by 0.63 (95% CI: 0.27, 0.99) by umeclidinium compared to placebo but the mean effect was smaller, although not significantly different, compared to tiotropium (–0.20 95% CI: –0.75, 0.35). There is considerable heterogeneity in the effect of umeclidinium on health status measured by SGRQ compared to placebo, with 3 studies showing no effect, but an overall mean change of –2.15 (95% CI: –4.11, –0.18) and a less, but non-significantly different, effect compared to tiotropium (mean difference 1.38 [95% CI: –1.28, 4.04]). Umeclidinium delayed the time to first exacerbation compared to placebo (hazard ratio [HR] 0.53 (95% CI: 0.40,

0.70), but there are no direct comparisons of the effect of umeclidinium and tiotropium on exacerbations.

A meta-analysis of the Glycopyrronium Bromide in COPD AirWays (GLOW)1, GLOW2 and the Dual bronchodilation with QVA149 versus single bronchodilator therapy (SHINE) studies has examined the effect of glycopyrronium 50 µg once daily compared to placebo after 24 weeks. The GLOW 2 study is the only randomised trial to examine effects over 52 weeks. After 24 weeks glycopyrronium produced a mean improvement in the pooled studies in FEV_1 of 0.135 L (95%: CI –0.123, 0.138)[30]. At 52 weeks in GLOW2 the mean improvement was 0.108L (95% CI: 0.070, 0.146). Compared to placebo after 24 weeks glycopyrronium significantly improved TDI by 1.01 (95% CI: 0.79, 1.22) and SGRQ by –3.14 (95% CI: –3.83, –2.45)[30]. The GLOW5 trial, a 12-week blinded, double-dummy study comparing glycopyrronium with tiotropium, showed no difference between the two LAMAs in their effect on trough FEV_1, TDI and SGRQ[48]. The study was too short to examine any difference in the effect on exacerbations.

Despite the effectiveness of tiotropium and other LAMAs, a significant proportion of patients remain breathless despite treatment with long-acting bronchodilator monotherapy[69]. GOLD recommends that for such patients, therapy should be escalated to dual therapy using two bronchodilators with different mechanisms of action[3]. For such patients, tiotropium is now available in combination with the new LABA olodaterol in the Respimat and a large phase III clinical trial programme of over 8000 patients[70,71] has shown significant improvements in lung function compared to monotherapy[72], irrespective of whether patients received prior LAMA or LABA maintenance treatment[73-75]. Other effects of the combination include reduced breathlessness and reduced rescue medication, as well as improvement in quality of life and exercise endurance[73,75], with the combination having a similar safety profile similar to the monotherapy components[73].

Dual bronchodilator therapy is recommended by GOLD as the preferred choice for patients in Group D (i.e. higher levels of symptoms and higher risk of exacerbations)[3]. Escalation to triple therapy with LABA, LAMA and ICS is recommended if patients continue to exacerbate, but de-escalation by withdrawing ICS from triple therapy is also recommended as dual bronchodilator therapy can be as effective as triple therapy in preventing exacerbations. The Withdrawal Of Inhaled Glucocorticoids And Exacerbations of COPD (WISDOM) trial showed that withdrawal of the fluticasone in three steps over a 12-week period from triple therapy consisting of tiotropium (18 µg once daily), salmeterol (50 µg twice daily), and fluticasone propionate (500 µg twice daily) did not result in an increase rate of exacerbations[76]. Withdrawal of fluticasone did lead to a mean fall in FEV_1 of 38 ml after 18 weeks and 43 ml after 52 weeks, but there was no significant effect on modified Medical Research Council dyspnoea (mMRC) scores. There was an increased SGRQ score (i.e. worsening) of 0.55 points in the glucocorticoid-withdrawal group and a reduction of 0.42 points in the glucocorticoid-continuation group at week 27 ($p = 0.08$) and an increase of 1.15 and a decrease of 0.07, respectively, at week 52 ($p = 0.047$). The patients studied had an FEV_1 < 50% predicted and had had at least one exacerbation in the previous 12 months; they were all treated with triple therapy for 6 weeks

before the ICS withdrawal began, but only 39% of them had been on triple therapy prior to enrolment. In total 47% had been on a LAMA, 65% on a LABA and 70% on an ICS. In this population, dual bronchodilator therapy with tiotropium and salmeterol facilitated ICS withdrawal without increasing the risk of exacerbations, but a key question is whether there are sub-groups of patients who do better if maintained on ICS. A post hoc analysis of the WISDOM study has shown that patients with a history of two or more exacerbations per year plus an eosinophil count ≥ 300 cells/ml have a lower risk of exacerbation if continued on ICS[77].

CLINICAL EFFECTS OF TIOTROPIUM IN ASTHMA

Despite major advances in the management of asthma many patients, including children and adolescents remain uncontrolled and remain at risk of exacerbations[78-80]. LABA/ICS can achieve well-controlled asthma in around 70% of patients but not all[81]. Anticholinergic bronchodilators are the oldest documented therapy for asthma[82].

The effects of tiotropium in asthma were first explored over 20 years ago when the sustained bronchodilator effects and protective effects against methacholine challenge were shown[83]. More recently, the National Heart, Lung, and Blood Institute Asthma Clinical Research Network (ACRN) in the United States (US) undertook a study to investigate the effects of adding tiotropium to an inhaled glucocorticoid, compared to doubling of the dose of the inhaled glucocorticoid or adding the LABA salmeterol[84]. Tiotropium improved lung function by 0.10 L (95% CI: 0.03, 0.17) and symptom control measured by the asthma control questionnaire (ACQ) by −0.18 (95% CI: −0.34, −0.03) compared with doubling the ICS dose and increased the pre-bronchodilator FEV_1 more than salmeterol (mean difference 0.11L [95% CI: 0.04 to 0.18]).

The effects of tiotropium administered via the Respimat in asthma have now been studied in an extensive clinical trial programme including over 6000 patients, including children, adolescents and adults with uncontrolled mild to moderate and severe asthma[85-98]. The findings supported of the individual studies have been supported by systematic reviews and meta-analyses[99-101]. The addition of tiotropium to ICS only, or ICS plus LABA results in statistically and clinically significant improvements in lung function, clinically significant reductions in exacerbation risk and improved asthma control[102].

In the two PrimoTinA-asthma studies 5 µg tiotropium administered via the Respimat was added to therapy with LABA and ICS (≥ 800 µg of budesonide or the equivalent) in people with uncontrolled asthma (ACQ ≥ 1.5)[90]. Two of the co-primary end points were changes in peak FEV_1 (within 3 hours of administration) and trough FEV_1 at 24 weeks. Tiotropium resulted in an increase in peak FEV_1 (0–3 h) of 86 ml (95% CI: 20, 152) in trial 1 and 154 ml (95% CI: 91, 217) in trial 2 and an increase in trough FEV_1 of 88 ml (95% CI: 27, 149) in trial 1 and 111 ml (95% CI: 53, 169) in trial 2. In a pre-specified pooled analysis of the two trials there was a 21% reduction in the risk of having an exacerbation in patients treated with tiotropium (HR, 0.79, 95% CI: 0.62, 1.00). This was the third co-primary end point.

After 48 weeks tiotropium resulted in an increase in peak FEV_1 (0–3h) of 73 ml (95% CI: 5, 140) in trial 1 and 152 ml (95% CI: 87, 217)

in trial 2. The changes in trough FEV_1 after 48 weeks were 42 ml (95% CI: –21, 104) in trial 1 and 92 ml (95% CI: 32, 151) in trial 2. Improvements in asthma control and quality of life were also observed in both trials with marked improvements in the placebo groups particularly in trial 1. At week 24, the mean difference in ACQ-7 scores and Asthma Quality Of Life Questionnaire (AQLQ) score between groups was only statistically significant in trial 2 but did not exceed the minimal clinically important differences for the ACQ-7 of 0.5 or AQLQ of 0.5.

Pre-specified post hoc subgroup analyses of the PrimoTinA-asthma trials showed that the improvements in peak FEV_1 with tiotropium tended to be larger in patients with a lower FEV_1 and in ex-smokers, but were not related to level of reversibility, age, body-mass index, allergic status, asthma duration, ACQ-7 score at baseline, or prior use of systemic glucocorticoids[103].

A further two replicated, double-dummy trials, the MezzoTinA-asthma studies have examined the effects of tiotropium in patients with moderate symptomatic asthma (ACQ-7 score ≥ 1.5) and persistent airflow obstruction (post-bronchodilator FEV_1, 60-90%) despite treatment with medium-dose ICS (400-800 µg of budesonide or the equivalent)[91]. Patients received once-daily tiotropium 5 or 2.5 µg, twice-daily salmeterol 50 µg, or matching placebo for 24 weeks. Tiotropium significantly improved pooled peak FEV_1 by 185 ml (95% CI: 146, 223) with 5 µg and 223 ml (95% CI: 185, 262) with 2.5 µg. The improvements in peak FEV_1 were maintained over 24 hours. Both doses also led to significant improvements in asthma control, as assessed by ACQ-7 responder rate: OR, 1.32 (95% CI: 1.02, 1.71) for 5 µg and 1.33 (95% CI: 1.03, 1.72) for 2.5 µg. The effects of tiotropium were similar to those of salmeterol, which increased peak FEV_1 by 196 ml (95% CI: 158, 234) and increased the proportion showing an ACQ response (OR: 1.46; 95% CI: 1.13, 1.89), while 5 µg tiotropium prolonged the time to the first severe asthma exacerbation (HR 0.72 [95% CI: 0.45, 1.14]) but this was not statistically significant, possibly reflecting the low rate of exacerbations in these patients.

The Grazzia-TinA-asthma trial examined the effect of tiotropium in adults with symptomatic asthma (ACQ-7 score ≥ 1.5) and persistent airflow obstruction (post-bronchodilator FEV_1 60-90%) on low- to-medium dose ICS (200-400 µg of budesonide or the equivalent) therapy[92]. Both 2.5 µg and 5 µg of tiotropium improved peak FEV_1 (0–3 h) compared to placebo (adjusted mean difference 128 ml (95% CI: 57, 199) for 5 µg; 159 ml (95% CI: 88, 230) for 2.5 µg. Both doses also improved the secondary endpoints of trough FEV_1 and FEV_1 area under the curve (0–3h), and morning and evening PEF compared to placebo.

A post-hoc analysis of the PrimoTinA-asthma and MezzoTinA-asthma studies has examined whether the coprimary endpoints were influenced by serum immunoglobulin E (IgE) levels, blood eosinophil counts, or clinician judgment of allergic asthma. In addition, the influence of the continuous parameters of IgE and blood eosinophils was modelled over the whole range of values[104]. Tiotropium was found to be efficacious in improving peak and trough FEV_1 and reducing the risk of severe asthma exacerbations and asthma worsening, independent of T2 status. The effect of tiotropium on exacerbations was independent of IgE levels or eosinophil counts when analysed continuously and numerical improvements the ACQ responder

rate were observed in both $T2_{high}$ and $T2_{low}$ patients.

An observational study of patients with asthma treated in primary care in the United Kingdom (UK) has also shown tiotropium leads to a reduction in the percentage of patients having at least one exacerbation from 37% to 27% after 1 year[105]. Tiotropium has been shown to be a cost-effective approach to asthma care, principally as a result of the reduced expenditure on exacerbations and improved quality of life[106] and the Global Initiative for Asthma (GINA) guidelines now recommend tiotropium as an add-on therapy for Steps 4 and 5 of the treatment pathway, independent of patient phenotype[107].

Overall in adults seven trials have assessed the effect of 5 µg of tiotropium and four the effect of 2.5 µg as add on therapy to at least ICS in asthma. For some outcomes in some studies 5 µg was not superior to 2.5 µg, but taking all outcomes into account, including morning and evening peak flow results and the safety data (see below), the European Medicines Agency (EMA) and other regulators decided that 5 µg should be the recommended dose. However, in the US the Food and Drug Administration (FDA) took a different view, perhaps reflecting their caution regarding the dose of inhaled long-acting bronchodilators and decided that 2.5µg should be the recommended dose.

SAFETY OF TIOTROPIUM IN COPD AND ASTHMA

When delivered via Respimat 5 µg, approximately 40% of the inhaled dose of tiotropium reaches the lungs and 33% reaches systemic circulation[108]; similar systemic exposures and urinary excretion levels are seen with HandiHaler[109,110]. Gastrointestinal absorption of LAMAs is low and the structure of tiotropium also prevents crossing of the blood–brain barrier, avoiding the risk of central neurologic effects[111].

The safety profile of tiotropium in people with COPD using both the HandiHaler and the Respimat has been well characterised. In patients across all disease severities and with a range of common comorbidities there is a low incidence of adverse events[36]. Dry mouth is a predictable but relatively infrequent side effect of anticholinergics: in a meta-analysis of 16 trials the cumulative incidence of dry mouth with tiotropium was 7.4%, compared with 3.9% with ipratropium, 1.6% with salmeterol and 2.0% with placebo[33].

Pooled analyses of clinical trials of tiotropium have shown reduced rates of cardiac adverse events and cardiovascular mortality versus placebo[36,60]. Long-term data from UPLIFT demonstrated no increase in all-cause and cardiovascular mortality, nor any increased risk of myocardial infarction or stroke versus standard care[37]. In fact, there was a reduction in cardiac adverse events in people treated with tiotropium[112]. The Tiotropium Safety and Performance in Respimat (TIOSPIR) study also demonstrated conclusively that there was no difference in the cardiac or other safety signal between tiotropium HandiHaler and tiotropium Respimat[40] in people with COPD.

In line with previous studies, a recent study in Taiwan has shown that patients with COPD who are established on long acting bronchodilator therapy (both LABA and LAMA) are at a reduced risk of cardiovascular disease,

but it has suggested that for the first 30 days after initiation of long acting bronchodilator therapy patients may be at an increased risk[113]. This needs to be examined in other cohorts.

The safety of tiotropium in asthma has been evaluated in more than 6,000 patients as add-on to ICS and ICS plus LABA, with treatment durations up to 1 year. In studies of patients with uncontrolled severe asthma including 912 patients, the incidence of adverse events was similar in the tiotropium and placebo groups and no deaths were reported[114].

SUMMARY

Tiotropium is an effective inhaled anti-muscarinic which improves lung function and patient reported outcomes, including health status, and reduces exacerbations in people with COPD, as well as slowing disease progression in those with GOLD grade 2 disease. In children, adolescents and adults with asthma it improves lung function and control when added to at least ICS therapy. There is no evidence of any significant adverse effects and in particular there are no cardiovascular safety concerns. It is a very important and effective therapy for people with chronic obstructive airways diseases.

CONFLICT OF INTEREST

Dr. David Halpin reports personal fees from AstraZeneca, personal fees and non-financial support from Boehringer Ingelheim, personal fees from GlaxoSmithKline, personal fees and non-financial support from Novartis, personal fees from Pfizer, personal fees from Chiesi, outside the submitted work.

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