A comparison of tiotropium, long-acting β₂-agonists and leukotriene receptor antagonists on lung function and exacerbations in paediatric patients with asthma

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Abstract

Diagnosing and treating asthma in paediatric patients remains challenging, with many children and adolescents remaining uncontrolled despite treatment. Selecting the most appropriate pharmacological treatment to add onto inhaled corticosteroids (ICS) in children and adolescents with asthma who remain symptomatic despite ICS can be difficult. This literature review compares the efficacy and safety of long-acting β₂-agonists (LABAs), leukotriene receptor antagonists (LTRAs) and long-acting muscarinic antagonists (LAMAs) as add-on treatment to ICS in children and adolescents aged 4–17 years.

A literature search identified a total of 29 studies that met the inclusion criteria, including 21 randomised controlled trials (RCTs) of LABAs versus placebo, two RCTs of LAMAs (tiotropium) versus placebo, and four RCTs of LTRA (montelukast), all as add-on to ICS. In these studies, tiotropium and LABAs provided greater improvements in lung function than LTRAs, when compared with placebo as add-on to ICS. Although exacerbation data were difficult to interpret, tiotropium reduced the risk of exacerbations requiring oral corticosteroids when added to ICS, with or without additional controllers. LABAs and LTRAs had a comparable risk of asthma exacerbations with placebo when added to ICS. When adverse events (AEs) or serious AEs were analysed, LABAs, montelukast and tiotropium had a comparable safety profile with placebo.

In conclusion, this literature review provides an up-to-date overview of the efficacy and safety of LABAs, LTRAs and LAMAs as add-on to ICS in children and adolescents with asthma. Overall, tiotropium and LABAs have similar efficacy, and provide greater improvements in lung function than montelukast as add-on to ICS. All three controller options have comparable safety profiles.

Keywords: Asthma, Paediatrics, LAMA, LABA, LTRA
**Lay summary**

It can be difficult for doctors to decide which treatment is best to prescribe to children and adolescents with asthma to help reduce their symptoms. In this review, we weigh up the available evidence on three asthma treatments that work in different ways. We looked at two types of inhalers and one type of medicine that is either swallowed as a tablet or granules. The two inhalers helped to improve lung function more than the oral medication, which may be due to their different modes of action. All three treatments were found to be as safe as a placebo.

**Introduction**

Asthma is one of the most prevalent chronic diseases in childhood [1], yet diagnosing and treating asthma in children remains challenging. Poor control of asthma in children and adolescents is common and represents a considerable cause of morbidity [2, 3]. In addition to its physical effects, the disease can have an emotional impact on the patient and cause a great burden for patients’ families and the community [1]. There is, therefore, a need for more pharmacological options to improve asthma control in children and adolescents whose symptoms are not fully treated with inhaled corticosteroids (ICS).

Selecting the most appropriate add-on treatment to manage and reduce asthma symptoms in children and adolescents whose asthma remains uncontrolled despite treatment can be challenging. The Global Initiative for Asthma (GINA) recommends that patients with asthma who continue to experience symptoms and/or exacerbations on low-dose ICS have their ICS dose increased and combined with long-acting β2-agonists (LABAs) or other controllers in a step-wise fashion (Fig. 1). Further controller medications include long-acting muscarinic antagonists (LAMAs; e.g. tiotropium), leukotriene receptor antagonists (LTRAs), theophylline and biologics [4]. GINA also recommends as-needed low-dose ICS/formoterol as reliever therapy in all patients >12 years of age, with short-acting β2-agonists (SABAs) recommended as an alternative reliever medication [4], although it should be noted that the recommendation for children is to ensure additional ICS is taken whenever the SABA reliever is given [4]. The goals of asthma management are aligned across all age groups: namely, to achieve good symptom control, maintain normal activity levels, lung function and development, and minimise future risk of exacerbations and side effects associated with medication [4].

Previous studies have demonstrated the efficacy and safety of LABAs as add-on to ICS compared with placebo [5, 6]. LABAs are available both as single therapy to be taken as add-on to ICS, or as dual therapy, where ICS and LABA are delivered in the same device. Single-therapy LABAs are indicated as add-on treatment to ICS for patients aged from 4 years in Europe and the USA [7–10].

Tiotropium, an alternative add-on treatment to ICS, is a LAMA that is efficacious in clinical trials in adolescents and children with asthma as add-on to ICS [11, 12] or to ICS with other controllers [13, 14]. In the European Union, it is now indicated as add-on maintenance treatment in patients aged 6 years and older with severe asthma who experienced one or more severe asthma exacerbations in the past year [15]. In the USA, tiotropium is indicated in the long-term, once-daily maintenance treatment of asthma in patients aged 6 years and older [16].

The LTRA montelukast is indicated in the treatment of asthma as an add-on therapy in paediatric patients with mild-to-moderate persistent asthma who are inadequately controlled on ICS and in whom SABAs provide inadequate control [17]. It can also be tried as an alternative to ICS in patients with mild-to-persistent asthma who do not have a history of asthma attacks and have trouble using inhaled medications, and is indicated for the prophylaxis of asthma in patients aged at least 2 years [18]. Montelukast oral granules are indicated in patients aged between 6 months and 5 years [19].

Despite the availability of these controller medications, few studies have directly compared their efficacy in adolescents and children with asthma. A number of systematic reviews have compared the effects of LAMAs, LABAs and LTRAs as add-on to ICS in patients with asthma [6, 20–22], although reviews in children aged <12 years or adolescents aged 12–18 years are limited. Moreover, none have been published that compare the efficacy and safety of all three add-on treatments within one review in patients aged ≤18 years. More systematic reviews and treatment recommendations have been published for patients aged ≥12 years than those for younger patients. As such, there is a need for an up-to-date review of the literature related to the treatments available as add-on to ICS in paediatric patients with asthma.

The aim of this literature review is to compare the efficacy and safety of three controller options (LAMA, LABA and LTRA) as add-on to ICS in adolescents and children aged 4–17 years with asthma. We compare the magnitude of forced expiratory volume in 1 s (FEV1) improvements with each drug class, their effects on exacerbations, and the proportion of patients with adverse events (AEs) and serious AEs (SAEs).

**Methods**

We carried out an electronic literature search of the Cochrane Database of Systematic Reviews in December 2018 to identify any previously published systematic reviews, which were then manually checked for relevance.
We then searched PubMed for articles published since the search date detailed within the systematic review. The inclusion criteria for this review were randomised controlled trials (RCTs) of at least 4 weeks in duration in children and adolescents aged 4–17 years. The types of intervention included LABA, LAMA or LTRA versus placebo, or versus each other, added onto ICS, compared with the same dos of ICS alone. The primary outcome of interest was lung function, measured using FEV₁. For FEV₁, we included percent predicted as well as absolute values, as this has the advantage of removing physical confounding factors, particularly when comparing studies with different age groups of children. Secondary outcomes included exacerbations requiring oral corticosteroids (OCS), and proportion of patients reporting AEs and SAEs.

Data were extracted from published articles in PubMed and publicly available data online. We also checked the reference lists of the systematic reviews for any additional data for endpoints that were not described in the systematic reviews. Results were compared with data from tiotropium trials in paediatric patients (PensieTinA- [NCT01277523], VivaTinA- [NCT01634152], RubaTinA- [NCT01257230] and CanoTinA-asthma [NCT01634139]).

We used the following search strings:
Studies of LABA as add-on to ICS
((((((clinical trial[MeSH Terms]) OR clinical trial) OR clinical study))))
AND asthma[MeSH Terms])
AND (((((Asthma Control Questionnaire) OR ACQ)) OR ((forced expiratory volume) OR FEV)) OR ((exacerbation) OR worsening)) OR adverse event))))
AND ((((((((child*) OR paediat*) OR pediat*) OR adolesc*) OR infan*) OR young*) OR preschool*) OR "pre school"*) OR pre-school*)))
AND ((((((seretide) OR symbicort) OR advair) OR viani) OR flutiform))
OR (((((((glucocorticoids[MeSH Terms]) OR inhaled corticosteroid*) OR budesonide) OR beclomethasone) OR beclometasone) OR fluticasone) OR triamcinolone) OR flunisolide) OR ciclesonide))
AND ((((((adfrenergic beta 2 receptor antagonists[MeSH Terms]) OR (((beta*) AND agonist*))) AND (long-acting) OR "long acting"))) OR (((beta*) AND adrenergic*))) AND ((long-acting) OR "long acting")) OR ((bronchodilat*) AND (long-acting) OR "long acting")) OR salmeterol OR serevent OR "formoterol" OR foradil OR vilanterol)))))
AND ("2015/02/01"[Date - Publication]: “2018/12/19"[Date - Publication])

Studies of LTRA as add-on to ICS
((((((clinical trial[MeSH Terms]) OR clinical trial) OR clinical study))))
AND asthma[MeSH Terms])
AND (((((forced expiratory volume) OR FEV)) OR ((exacerbation) OR worsening)) OR adverse event))))
AND ((((((((child*) OR paediat*) OR pediat*) OR adolesc*) OR infan*) OR young*) OR preschool*) OR "pre school"*) OR pre-school*)))
AND ((((((glucocorticoids[MeSH Terms]) OR inhaled corticosteroid*) OR budesonide) OR beclomethasone) OR beclometasone) OR fluticasone) OR triamcinolone) OR flunisolide) OR ciclesonide))
AND ((( ((((((muscarinic ANT agonist*))) AND ((long-acting) OR "long acting"))) OR (((antagonists, muscarinic[MeSH Terms]) AND ((long-acting) OR "long acting")))))) OR LAMA) OR glycophyrinum) OR aclidinium) OR umeclidium) OR NVA237) OR seebri) OR LAS34273) OR turadorza) OR pressair) OR eklir) OR genuair) OR spirola) OR GSK573719))

The literature searches were reviewed from the title, abstract or descriptors, and all studies that were not RCTs or that clearly did not fit the inclusion criteria were excluded. Data were analysed from the articles deemed appropriate for inclusion. Where appropriate, we performed a meta-analysis using the Cochrane statistical package RevMan 5, assuming equivalence if the risk ratio estimate and its confidence interval (CI) were between 0.9 and 1.1. The risk of bias was assessed using a domain-based evaluation, in line with recommendations provided in the Cochrane Handbook for Systematic Reviews of Interventions [23]. Various domains, including allocation concealment and blinding, were judged as being low, unclear or high. Studies were deemed to be of high methodological quality when the reported randomisation and blinding procedures were adequate and at a low risk of bias, with balanced group attrition.

Results
Identification of relevant articles
A literature search identified four systematic reviews (Fig. 2). Of these, one compared RCTs of LABAs as add-on to ICS, published up to February 2015, and was included in the review [24]. Three of the systematic reviews compared LTRAs with placebo as add-on to ICS. Of these, two were included in this review [25, 26], with the most recent studies published up to July 2014. One systematic review comparing LTRAs with placebo [27] was excluded as data from the included studies were already covered in the 2010 systematic reviews. No systematic reviews were identified that compared LAMAs with placebo, or LABAs, LTRAs or LAMAs directly with one another. We reviewed the three systematic reviews and analysed the relevant studies for inclusion in this review.

Additional literature searches identified 73 articles, published since February 2015, comparing LABAs with placebo, of which two met the inclusion criteria for this review [28, 29]. Twenty-three articles published since July
2014 were identified comparing LTRA with placebo, of which one met the inclusion criteria for this review [30]. An additional 16 articles comparing LAMAs with placebo were identified, of which two met the inclusion criteria for this review [11, 31]. We also included two studies in which patients received tiotropium as add-on to ICS plus other controllers, which were not identified in the literature search as the search strings excluded additional controller medications to LAMA [13, 14]. There were no additional studies identified that compared LABAs, LTRAs or LAMAs directly with one another. In total, 29 studies were included in this review.

The designs of all included studies are summarised in Table 1. All studies were randomised, and most were double-blinded and parallel-group in design, ranging from 4 to 54 weeks in duration. Participants were 4–18 years of age. Primary outcomes included safety and lung function.

An overview of judgements on domains related to risk of bias is reported in Table 2. Most bias items were deemed to be of low or unclear risk.

FEV₁ results
The LABA studies included in the Cochrane meta-analysis present a combination of peak and trough FEV₁ measurements, and some articles do not specify at what time point the measurement was taken [24]. For this reason, we present both peak and trough FEV₁ response data where available.

FEV₁: absolute difference in litres
We performed a meta-analysis of nine LABA studies. There was a treatment difference in FEV₁ of 0.07 L (95% CI 0.05, 0.08) (Fig. 3). Excluding the two outliers (a vilanterol study that found no improvement [–0.06 to 0.02 L] [28] and a very small [n = 21] salmeterol study [0.42 L (95% CI 0.21, 0.63)] [46]), mean treatment differences were 0.04–0.13 L (Fig. 3). None of the included LTRA studies presented data for change from baseline in litres.

For the LAMA studies, we pooled the data for studies where tiotropium was the only add-on therapy (no additional LABA add-on therapy permitted) (Ruba-TinA-asthma® and CanoTinA-asthma®) [11, 31] and presented both peak and trough results for tiotropium Respimat® 5 μg and 2.5 μg (Fig. 4). Peak FEV₁ was defined as the maximum FEV₁ within 3 h after dosing and trough FEV₁ was defined as the pre-dose FEV₁ measured 24 h after the previous drug administration and 10 min prior to the evening dose of the patient’s usual asthma medication. We did the same for studies where tiotropium Respimat® was the third or even fourth controller (Pensie’TinA-asthma® and VivaTinA-asthma®) (Fig. 4). None of the included studies investigated tiotropium delivered via the HandiHaler® device [13, 14].

FEV₁ improvements versus placebo with tiotropium Respimat® as add-on to ICS in studies of children and adolescents with symptomatic moderate asthma were
| Study | Reference | Included in previous systematic review | Design | Patient age | Primary outcome |
|-------|-----------|----------------------------------------|--------|-------------|----------------|
| **LABA studies** | | | | | |
| Formoterol added to budesonide versus budesonide | | | | | |
| SD-039-0719 NCT00646529 | Berger 2010 [32] | Yes (Chauhan) | 26-week, randomised, open-label, parallel-group, multicentre trial | 6–11 years | Safety |
| SD-039-0725 NCT00646321 | Eid 2010 [33] | Yes (Chauhan) | 12-week, randomised, double-blind, parallel-group, multicentre trial | 6–15 years | PEF |
| Study 0688 | Pohunek 2006 [34] | Yes (Chauhan) | 12-week, randomised, double-blind, parallel-group, multicentre trial | 4–11 years | Morning PEF |
| SD-039-0714 ATTAIN CSR 2003 [35] | Yes (Chauhan) | 12-week, randomised, double-blind, parallel-group, multicentre trial | 12–17 years | Morning PEF |
| CHASE 3 NCT02091986 | Pearlman 2017 [29] | No | 12-week, randomised, double-blind, parallel-group, multicentre trial | 6–<12 years | FEV1 |
| Akpinarli 1999 [36] | Yes (Chauhan) | 6-week, randomised, double-blind, parallel-group, multicentre trial | 6–14 years | NR |
| SD-039-0718 NCT00651547 | Yes (Chauhan) | 12-week, randomised, double-blind, parallel-group, multicentre trial | 6–15 years | Morning PEF |
| SD-039-0682 | Morice 2008 [37] | Yes (Chauhan) | 12-week, randomised, double-blind, parallel-group, multicentre trial | 6–11 years | Morning PEF |
| **Salmeterol added to ICS versus ICS** | | | | | |
| SAS30031 | Malone 2005 [38] | Yes (Chauhan) | 12-week, randomised, double-blind, parallel-group, multicentre trial | 4–11 years | Safety |
| Carroll 2010 [39] | Yes | 8-week, randomised, double-blind, parallel-group, single-centre study | 7–18 years | Salbutamol response following cold air challenge |
| MASCOT | Lenney 2013 [40] | Yes | 48-week, randomised, double-blind, parallel-group, multicentre trial | 6–14 years | Exacerbations |
| Teper 2005 [41] | Yes (Chauhan) | 12-month, randomised, double-blind, parallel-group, single-centre trial | 6–14 years | NR |
| SFA100316 NCT00118690 | Murray 2011 [42] | Yes (Chauhan) | 4-week, randomised, double-blind, parallel-group, multicentre trial | 4–17 years | FEV1 following exercise |
| SFA100314 | Pearlman 2009 [43] | Yes (Chauhan) | 4-week, randomised, double-blind, parallel-group, multicentre trial | 4–17 years | FEV1 following exercise |
| Simons 1997 [44] | Yes (Chauhan) | 28-day, randomised, double-blind, crossover, single-centre trial | 12–18 years | NR |
| SAM40012a | Yes (Chauhan) | 6-month, randomised, double-blind, parallel-group, multicentre trial | 4–11 years | Symptom-free days/night |
| SALMP/AH91/D89 | Russell 1995 [45] | Yes (Chauhan) | 12-week, randomised, double-blind, parallel-group, multicentre trial | 4–16 years | Morning PEF % predicted |
| N/A | Langton Hewer 1995 | Yes (Chauhan) | 8-week, randomised, double-blind, parallel-group, multicentre trial | 12–17 years | Not identified |
| Study | Reference | Included in previous systematic review | Design | Patient age | Primary outcome |
|-------|-----------|----------------------------------------|--------|-------------|-----------------|
| [46] Verberne 1998 [47] | Yes (Chauhan) | single-centre trial | 54-week, randomised, double-blind, parallel-group, multicentre trial | 6–16 years | FEV<sub>1</sub> and response to methacholine |
| Meijer 1995 [48] | Yes (Chauhan) | 16-week, randomised, double-blind, parallel-group, single-centre trial | 7–15 years | NR |

Vilanterol added to fluticasone propionate versus fluticasone propionate

| NCT01573767 Oliver 2016 [28] | No | 4-week, randomised, double-blind, parallel-group, multicentre trial | 5–11 years | Evening PEF |

Tiotropium studies

Tiotropium added to ICS versus ICS

| NCT01257230 Harmelmann 2016 [11] | No | 48-week, randomised, double-blind, parallel-group, multicentre trial | 12–17 years | Peak FEV<sub>1</sub>, response |
| NCT01634139 | Vogelberg 2018 [31] | No | 48-week, randomised, double-blind, parallel-group, multicentre trial | 6–11 years | Peak FEV<sub>1</sub>, response |
| NCT01277523 Hamelmann 2017 [14] | No | 12-week, randomised, double-blind, parallel-group, multicentre trial | 12–17 years | Peak FEV<sub>1</sub>, response |
| NCT01634152 Szeffler 2017 [13] | No | 12-week, randomised, double-blind, parallel-group, multicentre trial | 6–11 years | Peak FEV<sub>1</sub>, response |

Montelukast studies

| Simons 2001 [49] | Yes (Castro-Rodriguez) | 12-week, randomised, double-blind, crossover, multicentre trial | 6–14 years | % change in FEV<sub>1</sub>, from baseline |
| Miraglia del Giudice 2007 [50] | Yes (Castro-Rodriguez) | 1-month, randomised, double-blind, crossover, single-centre study | 7–11 years | NR |
| Stelmach 2007 [51] | Yes (Zhao) | 4-week, randomised, double-blind, parallel-group, single-centre study | 6–18 years | 4 lung function parameters |
| NCT01266772 Stelmach 2015 [30] | No | 7-month, randomised, double-blind, parallel-group, single-centre study | 6–14 years | NR |

FEV<sub>1</sub> forced expiratory volume in 1 s, ICS inhaled corticosteroid, NR not reported, PEF peak expiratory flow
| Study                                      | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding (performance bias and detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|-------------------------------------------|--------------------------------------------|----------------------------------------|-----------------------------------------------|----------------------------------------|--------------------------------------|-----------|
| Akpinari 1999                             | ?                                         | ?                                      | +                                            | ?                                      | +                                    | ?         |
| Berger 2010                               | +                                         | +                                      | –                                            | +                                     | ?                                    | ?         |
| Carroll 2010                              | ?                                         | +                                      | +                                            | ?                                      | +                                    | ?         |
| Eid 2010a                                 | ?                                         | ?                                      | +                                            | ?                                      | –                                    | +         |
| Eid 2010b                                 | ?                                         | ?                                      | –                                            | +                                     | ?                                    | ?         |
| Langton Hewer 1995                       | ?                                         | ?                                      | +                                            | ?                                      | +                                    | ?         |
| Lenney 2013                               | +                                         | +                                      | +                                            | +                                     | +                                    |          |
| Malone 2006                               | +                                         | +                                      | –                                            | +                                     | +                                    |          |
| Meijer 1995                               | ?                                         | ?                                      | +                                            | ?                                      | ?                                    | ?         |
| Morice 2008a                              | +                                         | ?                                      | +                                            | ?                                      | –                                    | +         |
| Morice 2008b                              | +                                         | ?                                      | +                                            | ?                                      | –                                    | +         |
| Murray 2011                               | ?                                         | ?                                      | +                                            | +                                     | +                                    |          |
| Oliver 2016                               | +                                         | ?                                      | +                                            | ?                                      | +                                    |          |
| Pearlman 2009                             | +                                         | ?                                      | +                                            | +                                     | +                                    |          |
| Pohunek 2006a                             | +                                         | +                                      | ?                                            | ?                                      | ?                                    | +         |
| Pohunek 2006b                             | +                                         | +                                      | ?                                            | ?                                      | ?                                    | +         |
| Russell 1995                              | +                                         | +                                      | –                                            | +                                     | ?                                    |          |
| SAM40012                                  | +                                         | +                                      | ?                                            | ?                                      | ?                                    |          |
| SD 0390714                                | ?                                         | ?                                      | +                                            | ?                                      | ?                                    |          |
| SD 0390718                                | ?                                         | ?                                      | +                                            | ?                                      | ?                                    |          |
| Simons 1997                               | +                                         | ?                                      | +                                            | +                                     | +                                    | ?         |
| Teper 2005                                | ?                                         | ?                                      | +                                            | ?                                      | ?                                    |          |
| Verberne 1998a                            | +                                         | +                                      | ?                                            | +                                     | ?                                    |          |
| Verberne 1998b                            | +                                         | +                                      | ?                                            | +                                     | ?                                    |          |
| Tio added to ICS with other controllers   |                                            |                                        |                                               |                                        |                                      |          |
| Hamelmann 2016                            | +                                         | +                                      | +                                            | +                                     | +                                    |          |
| Vogelberg 2018                            | +                                         | +                                      | +                                            | +                                     | +                                    |          |
| Tio added to ICS                          |                                            |                                        |                                               |                                        |                                      |          |
| Hamelmann 2017                            | +                                         | +                                      | +                                            | +                                     | +                                    |          |
| Szefler 2017                              | +                                         | +                                      | +                                            | +                                     | +                                    |          |
| LTRA added to ICS versus ICS | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding (performance bias and detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|-----------------------------|------------------------------------------|--------------------------------------|-----------------------------------------------|----------------------------------------|-----------------------------------|-----------|
| Simons 2001                  | ?                                       | +                                    | +                                             | ?                                      |                                   | +         |
| Miraglia del Giudice 2007    | +                                       | +                                    | +                                             | ?                                      |                                   | +         |
| Stelmach 2007                | +                                       | ?                                    | +                                             | ?                                      |                                   | +         |
| Stelmach 2015                | +                                       | +                                    | +                                             | ?                                      |                                   | +         |

Key: + low risk of bias; − high risk of bias; ? unclear risk of bias
ICS inhaled corticosteroid, LABA long-acting β₂-agonist, LTRA leukotriene receptor antagonist, Tiotropium tiotropium
"a" and "b" refer to different treatment arms of the same study
0.159–0.168 L for peak FEV₁ and 0.105–0.118 L for trough FEV₁ (Fig. 4). For studies in children and adolescents with symptomatic severe asthma, FEV₁ improvements versus placebo were 0.074–0.117 L for peak FEV₁ and 0.064–0.071 L for trough FEV₁ (Fig. 4).

FEV₁ response: percent predicted
The Cochrane analysis of LABA studies (Table 3) found an improvement in FEV₁ percent predicted with LABAs added to ICS versus ICS of 2.99% (95% CI 0.86, 5.11; n = 534) [24]. Results from individual LABA studies are also detailed in Table 3. Improvements in peak FEV₁ percent predicted with tiotropium added to ICS versus ICS were 4.07–7.70%, and 2.85–5.05% for trough FEV₁; improvements with tiotropium added to ICS with other controllers were 1.64–6.33% for peak FEV₁ and 0.83–3.85% for trough FEV₁.

The treatment difference with montelukast added to ICS compared with ICS alone varied, with the systematic review finding an improvement of 0.09% (95% CI −0.07 to 0.25; n = 188) [25] and individual studies mostly ranging from 1.3 to 2.6%. One single-centre study found an improvement of 10.8% with montelukast compared with ICS, but this was a small, 4-week study (n = 24), and no confidence intervals or statistical comparison was available [50].

Exacerbations requiring OCS
The Cochrane analysis of LABA studies (n = 1669) found no difference in the risk of exacerbations requiring OCS between LABAs plus ICS compared with ICS alone (risk
The individual studies were quite variable, with study durations of 4–54 weeks. We found no additional studies reporting on exacerbations requiring OCS in our literature search.

Risk ratios were not available for the tiotropium studies, but the proportion of patients with exacerbations requiring OCS was low in all of the studies (Table 4). Tiotropium provided improvements in time to first exacerbation requiring OCS when added onto ICS versus placebo, with hazard ratios of 0.23–1.14, and 0.40–2.06 when added on to other controllers.

The systematic review of the LTRA studies showed no difference between montelukast and placebo on top of ICS, but the authors noted that there was evidence of statistical heterogeneity [25]. The network meta-analysis found no difference between montelukast and placebo as add-on to ICS (odds ratio 0.26; 95% CI 0.09, 0.76) [30].

Adverse events and serious adverse events

The proportion of patients experiencing AEs or SAEs with the addition of LABA to ICS was broadly similar, with some variations in the proportion of patients with AEs or SAEs between studies (Table 5).

There was no increase in the number of patients with AEs or SAEs with tiotropium compared with placebo as add-on to ICS or add-on to ICS plus other controllers (Table 5).

There were limited data on the number of patients with AEs in the montelukast analyses; the study that did report the proportion of patients with AEs showed no significant difference between montelukast and placebo as add-on to ICS (Table 5). There were insufficient data to make a comment on SAEs in the montelukast trials.
| Drug | Age, years | n | Mean difference FEV₁, % predicted (95% CI) active drug vs placebo |
|------|------------|---|---------------------------------------------------------------|
| LABA added to ICS versus ICS, FEV₁ response (Cochrane analysis: Chauhan 2015) | | | 534 | 2.99 (0.86, 5.11) |
| Formoterol added to ICS versus ICS | | | | |
| Akpinarli 1999 | 6–14 | 32 | 2.00 (−24.10, 28.10) |
| Salmeterol added to beclomethasone dipropionate versus beclomethasone dipropionate | | | | |
| Verberne 1998 | 6–16 | 117 | 3.08 (−0.49, 6.65) |
| Meijer 1995 | 7–15 | 39 | 3.60 (−2.94, 10.14) |
| Salmeterol added to fluticasone propionate versus fluticasone propionate | | | | |
| Carroll 2010 | 7–18 | 37 | 5.20 (−1.04, 11.44) |
| Lenney 2013 | 6–14 | 21 | 15.42 (1.51, 29.33) |
| Tiotropium in moderate asthma | | | | |
| Tiotropium 5 μg | 12–17 | 268 | Trough: 3.205 (0.209, 6.201) |
| Add-on to 400–800 μg/day budesonide (200–800 μg/day for patients aged 12–14 years) | 12–17 | 268 | Peak: 4.492 (1.700, 7.285) |
| Tiotropium 2.5 μg | 12–17 | 256 | Trough: 2.850 (−0.229, 5.929) |
| Add-on to 400–800 μg/day budesonide (200–800 μg/day for patients aged 12–14 years) | 12–17 | 257 | Peak: 4.066 (1.208, 6.924) |
| Tiotropium 5 μg | 6–11 | 260 | Trough: 4.439 (1.207, 7.671) |
| Add-on to 200–400 μg budesonide | 6–11 | 260 | Peak: 6.521 (3.717, 9.325) |
| Tiotropium 2.5 μg | 6–11 | 257 | Trough: 5.048 (1.811, 8.285) |
| Add-on to 200–400 μg budesonide | 6–11 | 257 | Peak: 7.698 (4.892, 10.505) |
| Tiotropium in severe asthma | | | | |
| Tiotropium 5 μg | 12–17 | 262 | Trough: 0.827 (−2.354, 4.008) |
| Add-on to high-dose ICS + ≥1 controller or medium-dose ICS + ≥2 controllers | | | Peak: 1.643 (−1.252, 4.539) |
| Tiotropium 2.5 μg | 12–17 | 258 | Trough: 3.283 (0.075, 6.491) |
| Add-on to high-dose ICS + ≥1 controller or medium-dose ICS + ≥2 controllers | | | Peak: 3.106 (0.188, 6.024) |
| Tiotropium 5 μg | 6–11 | 258 | Trough: 3.848 (0.576, 7.120) |
| Add-on to >400 μg budesonide + ≥1 controller or 200–400 μg budesonide + ≥2 controllers | 6–11 | 258 | Peak: 6.325 (3.264, 9.385) |
| Tiotropium 2.5 μg | 6–11 | 265 | Trough: 2.350 (−0.909, 5.609) |
| Add-on to >400 μg budesonide + ≥1 controller or 200–400 μg budesonide + ≥2 controllers | 6–11 | 265 | Peak: 3.587 (0.540, 6.634) |
| Montelukast | | | | |
| Castro-Rodriguez 2010 | 5–18 | 188 | 0.09 (−0.07, 0.25) |
| Meta-analysis: Montelukast 5 mg QD Add-on to 200–800 μg/day budesonide | | | |
| Simons 2001 | 6–14 | 279 | 1.3 (−0.1, 2.7) |
Efficacy and safety of tiotropium Respimat® as add-on to ICS and additional controller medications

In studies where tiotropium Respimat® was added onto ICS and additional controller medications (PensieTiNA-asthma* and VivaTiNA-asthma*) [13, 14], the effect size for both lung function and exacerbations requiring OCS was comparable with the studies where tiotropium was the only controller [11, 31], or where LABA or LTRA were added onto ICS [24, 28, 29, 31]. In addition, the studies demonstrated comparable safety with placebo [13, 14].

Discussion

In this literature review, the addition of once-daily tiotropium (with or without other controllers) and twice-daily LABAs to ICS in children and adolescents provided similar improvements in lung function [11, 13, 14, 24, 28, 29, 31], and greater improvements than with once-daily LABA vilanterol added onto ICS [28]. Data reporting on the effect of LTRAs as add-on to ICS on lung function were somewhat inconsistent, yet a previous systematic review found no improvement with montelukast compared with placebo when added to ICS [25], so it may be appropriate to suggest that twice-daily LABAs and tiotropium are more effective at improving lung function in adolescents and children as add-on to ICS. This assumption could be further clarified if future studies directly compared tiotropium, LABAs and LTRAs as add-on to ICS.

An additional endpoint that we analysed in this review was asthma exacerbations. However, the exacerbation data were more difficult to interpret, as the studies were of different durations and not necessarily powered to show a treatment difference in exacerbation frequency. Powering a study in paediatric patients to assess asthma exacerbations may present ethical considerations, with patients receiving placebo or care that is inconsistent with the best proven method, potentially being exposed to unnecessary risk and harm, especially where exacerbation events are expected [52]. In addition, not all studies included a risk ratio, making the comparison of data difficult. However, in the tiotropium trials, where exacerbations were included as a safety endpoint, it was possible to demonstrate that tiotropium provided a reduction in the risk of exacerbations requiring OCS when added onto ICS, either alone or with additional controller treatments, compared with placebo [11, 13, 14, 31]. Although the results from the individual studies of LABA as add-on to ICS varied, the previously published Cochrane review by Chauhan et al. suggested that LABAs and placebo have a comparable risk of asthma exacerbation [24]. In regards to the effect of LTRAs on asthma exacerbations, the data were more inconclusive. The one RCT included on LTRAs reported that montelukast reduced the risk of exacerbations compared with placebo. However, the sample size was small, with only 76 participants [30]. The two systematic reviews reported no reduction in the risk of exacerbations compared with placebo; however, the width of the CIs suggests a large spread of data [25, 26]. It could therefore be suggested that the highest quality of evidence was for the trials investigating LABA or LAMA as add-on to ICS.

The safety data showed no increase in the proportion of patients reporting AEs or SAEs with LABAs or with tiotropium when added to ICS [11, 13, 14, 24, 28, 29, 31]. The available data for LTRAs were limited, but suggested no increase in the proportion of patients with AEs with montelukast compared with

### Table 3 Mean difference in FEV₁ (Continued)

| Drug | Age, years | n | Mean difference FEV₁, % predicted (95% CI) active drug vs placebo |
|------|------------|---|------------------------------------------------------------------|
| Miraglia del Giudice 2007 Montelukast 5 μg QD + budesonide 200 μg BID vs budesonide 200 μg BID | 7–11 | 48 | 10.8 (NR) |
| Zhao 2015 Network meta-analysis: Montelukast 4–10 mg QD add-on to 100–200 μg/day budesonide | ≤18 | NR | | | | | |
| Stelmach 2007 Montelukast 5–10 μg QD + 200 μg budesonide BID vs 200 μg budesonide BID | 6–18 | 76 | 2.6 (NR) |
| Stelmach 2015 Montelukast 5 mg QD add-on to 200–600 μg budesonide | 6–14 | 76 | 2.5 (NR) |

BID twice daily, CI confidence interval, FEV₁ forced expiratory volume in 1 s, ICS inhaled corticosteroid, LABA long-acting β₂-agonist, NR not reported, QD once daily* Total n number for the treatment arms being compared. Time of measurement relevant to dosing (peak/trough) not specified. High-dose ICS defined as > 400 μg budesonide (aged 12–14 years)/800–1600 μg budesonide (aged 15–17 years). Medium-dose ICS defined as 200–400 μg budesonide (aged 12–14 years)/400–800 μg budesonide (aged 15–17 years). ICS dose was adjusted during the course of this study. Change from placebo was not significantly different (P = 0.229)
Table 4  Exacerbations requiring oral corticosteroids

| Drug | Time period | n<sup>a</sup> | Number of patients with exacerbations requiring OCS, n/N (%) | Risk ratio (95% CI) |
|------|-------------|---------------|---------------------------------------------------------------|-------------------|
| Cochrane analysis of LABA studies (Chauhan 2015) | 1669 | 0.95 (0.70, 1.28) |
| Formoterol added to ICS versus ICS | | | | |
| Eid 2010 Budesonide/formoterol 160/18 μg daily vs budesonide 160 μg QD | 12 weeks | 267 | 15/183 (8.2) | 13/84 (15.5) | 0.53 (0.26, 1.06) |
| Eid 2010 Budesonide/formoterol 160/9 μg daily vs budesonide 160 μg daily | 12 weeks | 252 | 33/168 (19.6) | 13/84 (15.5) | 1.27 (0.71, 2.28) |
| Salmeterol added to ICS versus ICS | | | | | |
| Langton Hewer 1995 Salmeterol 100 μg BID add-on to usual ICS (baseline mean 400 μg) | 8 weeks | 23 | 3/11 (27.2) | 3/12 (25.0) | 1.09 (0.28, 4.32) |
| Lenney 2005 Fluticasone propionate/salmeterol 100/50 μg BID vs fluticasone propionate 100 μg BID | 48 weeks | 26 | 5/15 (33.3) | 1/11 (9.1) | 3.67 (0.27, 27.12) |
| Malone 2005 Salmeterol/fluticasone 50/100 μg BID vs fluticasone 100 μg BID | 3 months | 203 | 2/101 (2.0) | 3/102 (2.9) | 0.67 (0.11, 3.94) |
| Murray 2011 Salmeterol/fluticasone 50/100 μg BID vs fluticasone 100 μg BID | 4 weeks | 231 | 2/113 (1.8) | 1/118 (0.8) | 2.09 (0.19, 22.71) |
| Pearlman 2009 Salmeterol/fluticasone 50/100 μg BID vs fluticasone 100 μg BID | 4 weeks | 248 | 1/124 (0.8) | 1/124 (0.8) | 1.00 (0.06, 15.81) |
| Simons 1997 Salmeterol 50 μg QD add-on to BDP 200–400 μg/day | 4 weeks | 32 | 0/16 (0.0) | 1/16 (6.3) | 0.33 (0.01, 7.62) |
| Verberne 1998 Salmeterol/BDP 50/200 μg BID vs BDP 200 μg BID | 54 weeks | 117 | 10/60 (16.7) | 10/57 (17.5) | 0.95 (0.43, 2.11) |
| Russell 1995 Salmeterol 50 μg BID add-on to ICS 400–2400 μg/day | 12 weeks | 198 | 16/99 (16.2) | 18/99 (18.2) | 0.89 (0.48, 1.64) |
| Tiotropium added to ICS versus ICS | | | | | |
| Hamelmann 2016 Tiotropium 5 μg add-on to 400–800 μg/day budesonide (200–800 μg/day for patients aged 12–14 years) | 48 weeks | 272 | 2/134 (1.5) | 9/138 (6.5) | 0.23 (0.05, 1.08) |
| Hamelmann 2016 Tiotropium 2.5 μg add-on to 400–800 μg/day budesonide (200–800 μg/day for patients aged 12–14 years) | 48 weeks | 263 | 5/125 (4.0) | 9/138 (6.5) | 0.63 (0.21, 1.87) |
| Vogelberg 2018 Tiotropium 5 μg add-on to 200–400 μg budesonide | 48 weeks | 266 | 7/135 (5.2) | 6/131 (4.6) | 1.14 (0.38, 3.39) |
| Vogelberg 2018 Tiotropium 2.5 μg add-on to 200–400 μg budesonide | 48 weeks | 266 | 7/135 (5.2) | 6/131 (4.6) | 1.14 (0.38, 3.38) |
| Tiotropium added to ICS plus other controller(s) versus ICS plus other controller(s) | | | | | |
| Hamelmann 2017 Tiotropium 5 μg add-on to high-dose ICS<sup>a</sup> + ≥1 controller or medium-dose ICS<sup>a</sup> + ≥2 controllers | 12 weeks | 265 | 2/130 (1.5) | 1/135 (0.7) | 2.06 (0.19, 22.70) |
| Hamelmann 2017 Tiotropium 2.5 μg add-on to high-dose ICS<sup>a</sup> + ≥1 controller or medium-dose ICS<sup>a</sup> + ≥2 controllers | 12 weeks | 262 | 1/127 (0.8) | 1/135 (0.7) | 1.06 (0.07, 16.95) |
| Szefler 2017 Tiotropium 5 μg add-on to > 400 μg budesonide + ≥1 controller or 200–400 μg budesonide + ≥2 controllers | 12 weeks | 264 | 7/130 (5.4) | 8/134 (6.0) | 1.01 (0.35, 2.88) |
| Szefler 2017 Tiotropium 2.5 μg add-on to > 400 μg budesonide + ≥1 controller or 200–400 μg budesonide + ≥2 controllers | 12 weeks | 270 | 3/136 (2.2) | 8/134 (6.0) | 0.40 (0.10, 1.55) |
Table 4 Exacerbations requiring oral corticosteroids (Continued)

| Drug                                      | Time period | n\(^a\) | Number of patients with exacerbations requiring OCS, n/N (%) | Exacerbations requiring OCS\(^b\) | Risk ratio (95% CI) |
|-------------------------------------------|-------------|---------|-------------------------------------------------------------|-----------------------------------|--------------------|
| Tiotropium 2.5 μg add-on to > 400 μg budesonide + ≥1 controller or 200–400 μg budesonide + ≥2 controllers | NR          | NR      | NR                                                          | NR                                | Risk ratio (95% CI) 0.53 (0.10, 2.74) |
| Montelukast added to ICS versus ICS       |             |         |                                                             |                                   |                    |
| Castro-Rodriguez 2010 systematic review   | NR          | NR      | NR                                                          | NR                                | Odds ratio (95% CI) 0.94 (0.58, 1.45) |
| Montelukast 5 mg add-on to 200–800 μg/day budesonide | 4–16 weeks  | NR      | NR                                                          | NR                                |                    |
| Zhao 2015 network meta-analysis           | NR          | NR      | NR                                                          | NR                                |                    |
| Montelukast 4–10 mg add-on to 100–200 μg/day budesonide | 4–16 weeks  | NR      | NR                                                          | NR                                |                    |
| Stelmach 2015                            | NR          | 76      | NR                                                          | NR                                | Odds ratio (95% CI) 0.26 (0.09, 0.76) |
| Montelukast 5 mg add-on to 200–600 μg budesonide\(^c\) | 7 months    | 76      | NR                                                          | NR                                |                    |

**BDP** beclomethasone dipropionate, **BID** twice daily, **CI** confidence interval, **ICS** inhaled corticosteroid, **LABA** long-acting β\(_2\)-agonist, **NR** not recorded, **OCS** oral corticosteroid, **QD** once daily

*Total n number for the treatment arms being compared. Risk ratio or odds ratio as noted. Data on file. > 400 μg budesonide (aged 12–14 years)/800–1600 μg budesonide (aged 12–17 years). 200–400 μg budesonide (aged 12–14 years)/400–800 μg budesonide (aged 15–17 years). Authors note evidence of statistical heterogeneity for this analysis. ICS dose was adjusted during the course of this study

placebo as add-on to ICS [49]. However, it should be noted that previous post-marketing studies have suggested that paediatric patients receiving montelukast are more likely to report neuropsychiatric AEs than those receiving ICS [53, 54]. Therefore, the results from this review indicate that LABAs, LTRAs and LAMAs all have a comparable safety profile to placebo, but other real-world and post-marketing evidence should also be considered.

This literature review aims to provide an up-to-date overview of the efficacy and safety of three classes of drugs that are options for adding onto ICS in adolescents and children with asthma. The strength of the study is that this is the first literature review and meta-analysis to collate and compare the efficacy and safety of LABAs, LTRAs and LAMAs in children and adolescents in one review. Previous reviews have compared the efficacy and safety of LABAs and LAMAs, or LABAs and LTRAs, in adolescents aged over 12 years and in adults, but none has compared all three therapeutic options in one review, and none has done so for this patient population in children and adolescents aged 4–17 years.

We have focused on a limited number of endpoints that are considered important in the treatment of asthma such as lung function, exacerbations and AEs. However, there is considerable variability in the methodology and definition of these endpoints between studies, making the comparison of data more difficult. There were only a limited number of montelukast studies in children that met the inclusion criteria, so LTRA data are lacking for some endpoints. For example, for the LABA studies, we were able to perform a meta-analysis of absolute change in lung function in litres, but LTRA studies only reported lung function change in percent predicted. Moreover, when extracting the FEV\(_1\) data from the various studies, the time point of the measurement in relation to drug administration (i.e. peak/trough) was not always clear. Only the LAMA studies reported whether FEV\(_1\) was peak (defined as the maximum FEV\(_1\) within 3 h after dosing) or trough FEV\(_1\) (defined as the pre-dose FEV\(_1\) measured 24 h after the previous drug administration and 10 min prior to the evening dose of the patient’s usual asthma medication). As Fig. 4 demonstrates, there are differences between the responses depending on when the measurement is taken, with peak FEV\(_1\) (Fig. 4a) values higher than the equivalent trough FEV\(_1\) (Fig. 4b) values. Therefore, it is possible that some of the between-study differences in FEV\(_1\) response for LABAs and LTRAs may be attributable to the time point at which the measurement was taken, but this cannot be confirmed.

In light of the extension of the tiotropium label and the most recent treatment guidelines for children with asthma [4], the results provide support for the use of tiotropium as add-on therapy in adolescents and children with asthma aged 4–17 years. The results are in agreement with those of a recently published systematic review that compared LABAs with LAMAs in patients aged over 12 years [22]. The authors reported that use of LAMA as add-on to ICS was associated with a lower risk of asthma exacerbations compared with placebo, and had a comparable benefit to LABA on lung function. The authors note that their review was designed and conducted in patients aged 12 years and over because tiotropium was not approved in
## Table 5 AEs and SAEs

| Drug                                      | Duration | n<sup>a</sup> | Number of patients with AE, n (%) | Number of patients with SAE, n (%) | Active | Comparator | Active | Comparator |
|-------------------------------------------|----------|---------------|-----------------------------------|-----------------------------------|--------|------------|--------|------------|
| **LABAs added to ICS versus ICS**        |          |               |                                   |                                   |        |            |        |            |
| Berger 2010                               | 26 weeks | 186           | 104 (84.6)                        | 54 (85.7)                         | 2 (1.6)| 1 (1.6)    |        |            |
| Budesonide/formoterol pMDI 320/9 μg BID   |          |               |                                   |                                   |        |            |        |            |
| Eid 2010                                  | 12 weeks | 184           | 120 (65.2)                        | 100 (59.2)                        | 2 (1.1)| 1 (0.6)    |        |            |
| Budesonide/formoterol 160/18 μg daily     |          |               |                                   |                                   |        |            |        |            |
| Eid 2010                                  | 12 weeks | 168           | 104 (61.9)                        | 100 (59.2)                        | 3 (1.8)| 1 (0.6)    |        |            |
| Budesonide/formoterol 160/9 μg daily      |          |               |                                   |                                   |        |            |        |            |
| Langton Hewer 1995                        | 8 weeks  | 24            | 10 (91)                           | 9 (75)                            | NR     | NR         |        |            |
| Salmeterol 100 μg BID                     |          |               |                                   |                                   |        |            |        |            |
| Malone 2005                               | 3 months | 203           | 101 (59)                          | 102 (57)                          | NR     | NR         |        |            |
| Salmeterol/fluticasone 50/100 μg BID      |          |               |                                   |                                   |        |            |        |            |
| Morice 2008a                              | 12 weeks | 419           | 100 (47)                          | 81 (39)                           | 2 (0.9)| 0          |        |            |
| Budesonide/formoterol 160/9 μg DPI BID    |          |               |                                   |                                   |        |            |        |            |
| Morice 2008b                              | 12 weeks | 410           | 92 (45)                           | 81 (39)                           | 3 (1.5)| 0          |        |            |
| Budesonide/formoterol 160/9 μg MDI BID    |          |               |                                   |                                   |        |            |        |            |
| Murray 2011                               | 4 weeks  | 231           | 20 (18)                           | 25 (21)                           | 0      | 0          |        |            |
| Salmeterol/fluticasone 50/100 μg BID      |          |               |                                   |                                   |        |            |        |            |
| Pearlman 2009                             | 4 weeks  | 248           | 37 (30)                           | 35 (28)                           | 0      | 0          |        |            |
| Salmeterol/fluticasone 50/100 μg BID      |          |               |                                   |                                   |        |            |        |            |
| SD 0390718                                | 12 weeks | 273           | 90 (70.3)                         | 92 (63.4)                         | 0      | 0          |        |            |
| Formoterol/budesonide 9/80 μg BID         |          |               |                                   |                                   |        |            |        |            |
| Verberne 1998a                            | 54 weeks | 117           | 59 (98)                           | 52 (93)                           | NR     | NR         |        |            |
| Salmeterol/beclomethasone dipropionate 50/200 μg BID | | | | | | | | |
| Russell 1995                              | 12 weeks | 206           | 74 (75)                           | 81 (76)                           | 10 (10)| 13 (12)    |        |            |
| Salmeterol 50 μg BID                      |          |               |                                   |                                   |        |            |        |            |
| SD 0390714                                | 12 weeks | 270           | 66 (49)                           | 65 (49)                           | 1 (0.7)| 1 (0.7)    |        |            |
| Formoterol/budesonide 4.5/160 μg BID      |          |               |                                   |                                   |        |            |        |            |
| SAM40012                                  | 6 months | 362           | 99 (55)                           | 111 (61)                          | 2 (1) | 1 (< 1)    |        |            |
| Salmeterol/fluticasone propionate 50/100 μg BID |          |               |                                   |                                   |        |            |        |            |
| Pearlman 2017                             | 12 weeks | 18            | 42 (66.7)                         | 40 (64.4)                         | 0      | 2 (2.2)    |        |            |
| Budesonide/formoterol 160/9 μg BID        |          |               |                                   |                                   |        |            |        |            |
| Budesonide/formoterol 160/4.5 μg BID      |          |               |                                   |                                   |        |            |        |            |
| Murray 2011                               | 4 weeks  | 183           | 41 (44.1)                         | 40 (44.4)                         | 0      | 2 (2.2)    |        |            |
| Olver 2016                                |          |               |                                   |                                   |        |            |        |            |
| Vilanterol 6.25 μg QD                     | 4 weeks  | 229           | 33 (29)                           | 25 (22)                           | NR     | NR         |        |            |
| Vilanterol 12.5 μg QD                     |          |               |                                   |                                   |        |            |        |            |
| Vilanterol 25 μg QD                       |          |               |                                   |                                   |        |            |        |            |
| Tiotropium added to ICS vs ICS            |          |               |                                   |                                   |        |            |        |            |
| Hamelmann 2016                            | 48 weeks | 272           | 84 (62.7)                         | 82 (59.4)                         | 3 (2.2)| 2 (1.4)    |        |            |
| Tiotropium 5 μg QD                        |          |               |                                   |                                   |        |            |        |            |
| Tiotropium 2.5 μg QD                      |          |               |                                   |                                   |        |            |        |            |
| Vogelberg 2018                            | 48 weeks | 263           | 79 (63.2)                         | 82 (59.4)                         | 2 (1.6)| 2 (1.4)    |        |            |
| Tiotropium 5 μg QD                        |          |               |                                   |                                   |        |            |        |            |
| Tiotropium 2.5 μg QD                      |          |               |                                   |                                   |        |            |        |            |
| Tiotropium added to ICS with other controllers vs ICS with other controllers | | | | | | | | |
| Hamelmann 2017                            | 12 weeks | 265           | 43 (33.1)                         | 48 (35.6)                         | 2 (1.5)| 0          |        |            |
patients aged less than 12 years at the time the study was undertaken [22]. In addition, it does not review the literature on LTRAs as an add-on treatment.

In conclusion, tiotropium and LABAs have similar efficacy, and provide greater improvements in lung function than montelukast as add-on to ICS in children and adolescents with asthma. All three controller options have comparable safety profiles. The results of our literature review in patients aged 4–17 years provide needed additional information, and further supports the use of tiotropium in children and adolescents with asthma. The clinical decision on the preferred add-on therapy should also take into account patient phenotype and comorbidities, dose regimen and frequency, the availability of combination therapy, and the delivery device, although more research is required in these younger age groups.

**Abbreviations**

AE: Adverse event; CI: Confidence interval; FEV1: Forced expiratory volume in 1 s; GINA: Global Initiative for Asthma; ICS: Inhaled corticosteroid; LABA: Long-acting β2-agonist; LAMA: Long-acting muscarinic antagonist; LTRA: Leukotriene receptor antagonist; OCS: Oral corticosteroid; RCT: Randomised controlled trial; SABA: Short-acting β2-agonist; SAE: Serious adverse event

**Acknowledgements**

Medical writing assistance, in the form of the preparation and revision of the draft manuscript, was supported financially by Boehringer Ingelheim and provided by Rosie Robson of MediTech Media, under the authors’ conceptual direction and based on feedback from the authors.

**Authors’ contributions**

The authors take full responsibility for the scope, direction, content of, and editorial decisions relating to the manuscript, were involved at all stages of development, and have approved the submitted manuscript.

**Funding**

This study was supported financially by Boehringer Ingelheim.

**Availability of data and materials**

All data generated or analysed during this study are included in this published article.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

CV reports personal fees from Allergopharma, ALK, Bencard, Boehringer Ingelheim, Novartis, Stallergenes, Sanofi Aventis, Engelhard and DBV Technology, and grants from the German Society of Research (DFG), outside the submitted work. LG reports personal fees from Boehringer Ingelheim and serves as a speaker and member of the pediatric advisory board for Boehringer Ingelheim outside of the submitted work. AL reports personal fees from Boehringer Ingelheim, Novartis, Stallergenes, Sanofi, Paladin and Trudell outside the submitted work. AdH is an employee of Boehringer Ingelheim. SG and EH have nothing to disclose.

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Received: 9 September 2019 Accepted: 5 January 2020
Published online: 13 January 2020

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