

Journal Pre-proof

Tiotropium in Children and Adolescents With Asthma

Kevin R. Murphy, MD;, Bradley E. Chipps, MD

PII: S1081-1206(19)31460-7

DOI: <https://doi.org/10.1016/j.anai.2019.11.030>

Reference: ANAI 3090

To appear in: *Annals of Allergy, Asthma and Immunology*

Received Date: 21 August 2019

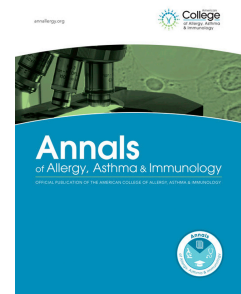
Revised Date: 19 November 2019

Accepted Date: 21 November 2019

Please cite this article as: Murphy KR, Chipps BE, Tiotropium in Children and Adolescents With Asthma, *Annals of Allergy, Asthma and Immunology* (2020), doi: <https://doi.org/10.1016/j.anai.2019.11.030>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.



TITLE: Tiotropium in Children and Adolescents With Asthma

AUTHORS: Kevin R. Murphy, MD;¹ Bradley E. Chipps, MD²

¹Boys Town National Research Hospital, Boys Town, NE, United States

²Capital Allergy & Respiratory Disease Center, Sacramento, CA, United States

CORRESPONDING AUTHOR DETAILS:

Bradley E. Chipps, MD

Capital Allergy & Respiratory Disease Center

5609 J Street, Suite C

Sacramento, CA 95819

United States

E-mail: BChipps@CapitalAllergy.com

Phone: 916-453-1454

Fax: 916-453-2786

CONFLICT OF INTEREST

Dr. Chipps reports personal fees from AstraZeneca, Boehringer Ingelheim, Circassia, Genentech, Novartis, Regeneron, Sanofi, and Teva, outside the submitted work. Dr. Murphy reports personal fees from AstraZeneca, Genentech, Greer, Meda, Mylan, Novartis, and Optinose, outside the submitted work.

FUNDING

This study was supported by Boehringer Ingelheim Pharmaceuticals, Inc. The funding source had no role in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

CLINICAL TRIAL REGISTRATION: Not applicable

KEYWORDS: adolescents, children, efficacy, safety, tiotropium

ABBREVIATIONS:

ACQ: Asthma Control Questionnaire

ACQ-IA: Interviewer-Administered Asthma Control Questionnaire

AE: adverse event

AUC_(0-3h): area under the curve from 0 to 3 h

FEV₁: forced expiratory volume in 1 second

FVC: forced vital capacity

GINA: Global Initiative for Asthma

ICS: inhaled corticosteroid

LABA: long-acting β_2 -agonist

LAMA: long-acting muscarinic antagonist

LTRA: leukotriene receptor antagonist

PEF: peak expiratory flow

RCT: randomized controlled trial

US: United States

WORD COUNT: 3109 words

49 **TABLES: 3**

50

51 **FIGURES: 2**

Journal Pre-proof

19-08-0418R2

Background: Asthma is a major cause of morbidity in children, despite the availability of various treatments. In adults, tiotropium—a long-acting muscarinic antagonist (LAMA)—as add-on therapy to an inhaled corticosteroid (ICS) with or without a long-acting β 2-agonist provides clinical benefit with a safety profile similar to placebo. **Objective:** To review published evidence on the efficacy and safety of tiotropium as add-on LAMA therapy in children and adolescents with asthma that is uncontrolled despite use of an ICS with or without additional controller medication(s).

Methods: We searched PubMed from inception until June 12, 2018, for randomized controlled trials (RCTs) involving children and adolescents aged 1 to 17 years treated with tiotropium Respimat® and reporting a primary outcome of any pulmonary function test and a secondary outcome of adverse events (AEs).

Results: Overall, 7 RCTs involving 1902 preschool children (aged 1-5 years; n = 102), school-age children (aged 6-11 years; n = 905), and adolescents (aged 12-17 years; n = 895) with moderate-to-severe asthma were included in the analysis. Once-daily tiotropium (5, 2.5, 1.25 μ g) improved lung function parameters, including peak and trough forced expiratory volume in 1 second, versus placebo. Commonly reported AEs across treatment groups included asthma worsening or exacerbations, decreased peak expiratory flow rate, nasopharyngitis, viral respiratory tract infection, and respiratory tract infection.

Conclusion: Once-daily tiotropium as add-on therapy is efficacious and safe in adolescents and children with moderate-to-severe asthma. These results support the expanded indication by regulatory authorities for add-on tiotropium in patients aged ≥ 6 years.

INTRODUCTION

Asthma, which is one of the most common pediatric chronic diseases, is a serious health concern that poses a substantial socioeconomic burden.^{1,2} In the United States (US), approximately 1 in 10 adolescents (aged 12-17 years) and children (aged 5-11 years) had asthma in 2016.³ An analysis of data from the 2001-2016 National Health Interview Survey showed that children aged 0 to 4 years had a lower prevalence of asthma but a higher prevalence of asthma attacks, emergency department or urgent care center visits, and hospitalization compared with those aged 12 to 17 years.⁴ Further, uncontrolled asthma significantly affects asthma-specific health-related quality of life, school attendance and productivity of children, and work productivity of their caregivers compared with controlled asthma.⁵⁻⁸ An analysis of data from Asthma Call-back Survey showed that more children with uncontrolled asthma, compared with those with well-controlled asthma, had activity limitation (78.5% versus 51.8%) and emergency department visits (27.1% versus 10.0%) because of asthma.⁹ Further, annual all-cause expenditures in children with asthma having indicators of poor control were significantly higher than in children having no indicators of poor asthma control.¹⁰

Goals of asthma management in children include achieving good symptom control, maintaining normal activity levels, and reducing the risk of impaired lung developmental growth, exacerbations, and side effects of medication.¹¹ Despite availability of various treatment options, namely, inhaled corticosteroids (ICSs) and short-acting β_2 -agonists, recurrent days with breathlessness, wheeze, or cough is a major cause of morbidity in children aged 1 to 5 years.¹² New, safe treatment options for asthma are thus needed in this age group, especially for children whose symptoms remain uncontrolled on ICSs.^{13,14} Importantly, infants have airway inflammation features more commonly seen in adolescents

and adults with asthma¹⁵ but children aged 0 to 17 years have a higher rate of visiting the physician office or hospital outpatient department and emergency department, than adults.¹⁶ Therefore, not only asthma needs to be managed differently in pediatric and adult patients, but patient and disease characteristics specific to each pediatric age group (adolescents [aged 12-18 years], school-age children [aged 6-11 years], and preschool children [aged ≤ 5 years]) also need to be considered.

The Global Initiative for Asthma (GINA) recommends a step-wise approach to asthma treatment not only for adults but for children and adolescents too.¹¹ For patients (aged ≥ 12 years) with a history of exacerbations, add-on tiotropium (as an optional controller in GINA step 4 and as a preferred controller in GINA step 5) is recommended. Of note, tiotropium is indicated for patients aged ≥ 6 years in the US and elsewhere.^{11,17,18} In addition to GINA, use of the Pediatric Asthma Yardstick provides guidance on when and how to step-up therapy for adolescents, school-age children, and preschool children with not well-controlled or poorly controlled asthma.¹⁹

Long-acting muscarinic antagonists (LAMAs), such as tiotropium, are anticholinergic compounds that block muscarinic receptors on airway smooth muscles, glands, and nerves, resulting in muscle relaxation, inhibition of gland secretion, and increased neurotransmitter release.²⁰ Tiotropium was approved by the US Food and Drug Administration in 2015 at a once-daily dose of 2.5 μ g for the long-term maintenance treatment of asthma in patients aged ≥ 12 years,²¹ based on results of 7 phase III randomized controlled trials (RCTs).²²⁻²⁶ The indication was extended in February 2017 to include patients aged 6 years and older,¹⁷ based on findings from additional RCTs involving children aged 6 to 11 years.^{27,28} Results of a systematic review of 5 RCTs of adults with uncontrolled, moderate-to-severe, persistent asthma (N = 1635)^{22,29-32} showed that tiotropium as add-on therapy to ICS or ICS/long acting

β_2 -agonist (LABA) maintained lung function, even when ICSs were tapered or LABA was discontinued.³³ Tiotropium is delivered using the Respimat[®] slow/soft-mist inhaler, a non-breath-actuated, propellant-free inhaler.³⁴ Unlike dry-powder inhalers, which depend on the patient's peak inspiratory flow for optimal medication delivery,³⁵ the slow/soft-mist inhaler delivers the medication dose to the airways independent of the patient's variable inspiratory flow.³⁴ Further, unlike pressurized metered-dose inhalers, a spacer is not needed to prevent oropharyngeal medication impaction.

By systematically reviewing RCTs of tiotropium Respimat[®] as add-on therapy to ICS in children and adolescents (aged 1-17 years) with asthma, we sought to answer the following question: what efficacy and safety evidence exists for tiotropium as add-on LAMA therapy in children and adolescents with asthma that is uncontrolled despite use of an ICS with or without additional controller medications?

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.³⁶

Search strategy

We searched PubMed from inception until June 12, 2018, for relevant RCTs using the following terms: tiotropium AND ((child OR children) OR infan* OR adolescen* OR pediater* OR paediatr*) AND asthma. Literature search results were limited to articles reported in English.

Trial selection

Trial inclusion criteria were RCTs involving children and adolescents aged 1 to 17 years treated with tiotropium Respimat[®], where any pulmonary function test was used as the

primary outcome and adverse events (AEs) were included as a secondary outcome. Trial inclusion criteria was based on expert consensus. Outcomes for lung function assessment included peak forced expiratory volume in 1 second (FEV_1) from 0 to 3 h ($FEV_{1(0-3h)}$), trough FEV_1 , FEV_1 area under the curve from 0 to 3 h ($AUC_{(0-3h)}$), peak forced vital capacity (FVC), trough FVC, FVC $AUC_{(0-3h)}$, morning peak expiratory flow (PEF), and evening PEF. Articles retrieved from PubMed were imported into an EndNote library. Titles and abstracts were screened by S.N-S. and M.B., and independently verified by the authors. Narrative and systematic review articles, retrospective chart reviews, case series, preclinical or observational studies, letters, editorials, errata, and reports of pooled data were excluded. A review and analysis of full-text articles of the RCTs were conducted to assess relevant articles based on patient population, intervention, study design, and outcomes. Articles meeting the inclusion criteria were selected for analysis. Discrepancies about inclusion of individual articles were resolved by consensus. Although the study by Vrijlandt et al, 2018 did not strictly meet the inclusion criteria, this study was included as it was the only published study on preschool children aged 1 to 5 years.³⁷ Relevant data were extracted from the articles. If data were not available, clinical trial reports were requested from the sponsor for additional data. Included articles and relevant data extraction was performed by S.N-S. and M.B. and were independently reviewed by the authors.

Assessment of risk of bias

Risk of bias in the included studies was assessed based on the Cochrane Collaboration's tool.^{38,39} For each study, risk of bias was assessed based on selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), selective outcome reporting, and other bias not reported elsewhere. Study protocols were requested from the sponsor to determine bias in selective reporting. Each

potential source of bias was graded as high, low, or unclear along with an explanation in the “Risk of bias” table (eTable 1; online only). Risk of bias was assessed by S.N-S. and M.B. and was independently reviewed by the authors. Discrepancies were resolved by consensus.

RESULTS

Trial selection

PubMed search yielded 56 articles, but only 7 met the prespecified inclusion criteria (Figure 1). After title and abstract review, 44 articles were excluded because they either were duplicates or did not meet the inclusion criteria (34 [77%] were review articles). The remaining articles and those that did not have abstracts available were considered for full-text review. Of 12 articles considered for full-text review, 5 were excluded because they did not meet the inclusion criteria (national guideline for asthma, $n = 1$; only adults were included in the studies, $n = 3$; and HandiHaler[®], a dry-powder inhaler [approved only for the treatment of bronchospasm associated with chronic obstructive pulmonary disease in the US]⁴⁰ was used to deliver tiotropium, $n = 1$).

Trial and patient characteristics

In total, 7 RCTs involving 1902 children and adolescents with moderate-to-severe asthma were selected for analysis (Table 1). Of the 7 trials, 3 included adolescents aged 12 to 17 years ($n = 895$),^{25,26,41} 3 included school-age children aged 6 to 11 years ($n = 905$),^{27,28,42} and 1 included preschool children aged 1 to 5 years ($n = 102$).³⁷ Five of the 7 RCTs were phase III (1 phase II/III) trials with a parallel-group design, and 2 were phase II trials with an incomplete-crossover design. Two trials included patients with mild-moderate asthma;^{28,37} 3, moderate symptomatic asthma;^{25,41,42} and 2, severe asthma.^{26,27} In all trials, male participants outnumbered female participants (male: 60%-70%). Patients received once-daily tiotropium

at a dose of 5, 2.5, or 1.25 µg using the Respimat[®] inhaler for 12 or 48 weeks and were compared with those receiving placebo via Respimat[®].^{25-28,37,41-40}

Risk of bias within trials

Risk of bias was deemed low for selection, performance, and attrition bias for all included trials (Figure 2). Risk of detection bias was unclear in 1 trial, and selective outcome reporting was low in 3 trials and unclear in 4 trials (eTable 1; online only). No other risks of bias were identified.

Efficacy and safety data

Initial phase II RCTs of tiotropium Respimat[®] in adolescents and school-age children with moderate symptomatic asthma yielded encouraging results (Table 1).^{28,41} In the first incomplete crossover trial, which involved adolescents with moderate symptomatic asthma, once-daily tiotropium Respimat[®] (5 µg, n = 80; 2.5 µg, n = 75; or 1.25 µg, n = 75), Vogelberg et al. 2014, found that add-on to medium-dose ICS with or without a leukotriene receptor antagonist (LTRA) improved lung function compared with placebo (n = 75).⁴¹ Compared with placebo, tiotropium 5 µg provided the greatest improvements in peak FEV₁, trough FEV₁, and FEV₁ AUC_(0-3h). All 3 doses of tiotropium significantly improved morning PEF compared with placebo; however, only the 5 and 2.5 µg doses yielded significant changes in evening PEF versus placebo. The rate of AEs was slightly higher in the tiotropium 5-µg group than in the tiotropium 2.5-µg, tiotropium 1.25-µg, or placebo group (Table 2). Similarly, in an RCT involving school-age children with moderate symptomatic asthma, Vogelberg et al. 2015, found that treatment with tiotropium Respimat[®] (5 µg, n = 76; 2.5 µg, n = 74; or 1.25 µg, n = 75), significant improved FEV₁ and morning and evening PEF (only

5- μ g dose) versus placebo (n = 76). The incidence of AEs was comparable across all treatment groups (Table 2).²⁸

Results from 4 phase III RCTs of tiotropium Respimat[®], 2 each involving adolescents^{25,26} and school-age children,^{27,42} confirmed previous findings. In a 48-week RCT (RubaTinA[®]-asthma), Hamelmann et al. 2016, found that once-daily tiotropium Respimat[®] (5 μ g, n = 135; 2.5 μ g, n = 125) add-on therapy to ICS maintenance treatment with or without an LTRA significantly improved lung function in adolescents with moderate asthma compared with placebo (n = 138).²⁵ Treatment with both tiotropium doses resulted in significant improvement in peak FEV_{1(0-3h)} after 24 weeks; however, only the 5- μ g dose significantly improved trough FEV₁ at week 24. Asthma control (assessed by the Asthma Control Questionnaire [ACQ]-6 and ACQ-7) improved over the 48-week treatment period with both doses of tiotropium, and the 2.5- μ g dose significantly reduced rescue medication use. The incidence of AEs was comparable across the treatment groups. In a 12-week study (PensieTinA[®]-asthma) involving adolescents with severe symptomatic asthma, Hamelmann et al. 2017, found that once-daily tiotropium Respimat[®] (5 μ g, n = 130; 2.5 μ g; n = 127) add-on to ICS plus other controller therapies resulted in numerical improvements in lung function and asthma control compared with placebo (n = 135).²⁶ Significant improvements in peak FEV_{1(0-3h)} and pre-dose morning and evening PEF were observed with tiotropium 2.5 μ g and 5 μ g, respectively. Numerical improvements in peak FEV_{1(0-3h)} were observed with tiotropium 5 μ g. Both tiotropium doses produced numerical improvements in trough FEV₁ and asthma control. The safety and tolerability profiles of tiotropium were comparable with those of placebo. Further, Szeffler et al. 2017, found that only tiotropium Respimat[®] 5 μ g (n = 130) added to ICS maintenance treatment with ≥ 1 controller medication significantly improved peak FEV_{1(0-3h)} and trough FEV₁, and resulted in numerical improvements in peak FVC_(0-3h) and trough FVC, compared with placebo in a 12-week trial (VivaTinA[®]-asthma) of

school-age children with severe symptomatic asthma.²⁷ In this trial, tiotropium 5 µg and 2.5 µg (n = 136) produced numerical decreases in daytime rescue medication use, and tiotropium 5 µg produced a decrease in Interviewer-Administered ACQ (ACQ-IA) scores. The incidence of AEs was lower in the tiotropium groups than in the placebo group, and most AEs were mild or moderate in severity. Finally, in a 48-week study (CanoTinA[®]-asthma), Vogelberg et al. 2018, found that tiotropium 5 µg (n = 135) and 2.5 µg (n = 135) significantly improved peak FEV_{1(0-3h)} and trough FEV₁ at weeks 24 and 48, and peak FVC at week 24, compared with placebo in children with moderate symptomatic asthma.⁴² Additionally, ACQ-IA scores improved with tiotropium. The incidence of AEs was lower in patients receiving tiotropium than those receiving placebo; most AEs were mild or moderate in intensity.

In addition to adolescents and school-age children, the efficacy and safety of tiotropium in preschool children aged 1 to 5 years with persistent asthmatic symptoms were evaluated in a small phase II/III RCT (NinoTinA[®]-asthma).³⁷ Vrijlandt et al. 2018, showed that although the change in mean daytime asthma symptom scores from baseline to week 12 did not significantly differ across treatment groups, more children in the placebo group (10/34 [29%]) than in the tiotropium groups (2.5 µg, 5/36 [14%]; 5 µg, 2/31 [6%]) had asthma exacerbations reported as AEs. Otherwise, and consistent with prior findings in patients aged ≥6 years, the safety profile of tiotropium was similar to that of placebo.

Overall, the most commonly reported AEs—based on mostly short-term safety data—in the tiotropium Respimat[®] groups across trials included asthma worsening or exacerbations, decreased PEF rate, nasopharyngitis, viral respiratory tract infection, and respiratory tract infection (Table 2). Within each age group (i.e adolescents or school age children), the percentage of asthma worsening or exacerbations, decreased PEF, and nasopharyngitis, was lower in patients with severe asthma than those with moderate asthma.

DISCUSSION

According to GINA recommendations, add-on tiotropium can be considered as an “other controller option” at step 4 and “preferred add-on treatment” at step 5 for adolescents and adults (aged ≥ 12 years) with a history of exacerbations.¹¹ However, based on recent clinical trial evidence, including trials described herein, the US FDA and the European Medicines Agency (EMA) expanded the indication for tiotropium as add-on maintenance treatment to patients aged ≥ 6 years (approved dose: US, 2.5 μg ; EU, 5 μg).^{17,18} Findings from this systematic review show that add-on tiotropium (5 and 2.5 μg) improved lung function and was safe (based on mostly short-term safety data) in adolescents and children. Similar frequencies of exacerbations reported as AEs were observed with tiotropium and placebo in studies of adolescents and school-age children in general, but the frequency with tiotropium was lower than that with placebo in preschool children. Patients with severe asthma had lower asthma worsening or exacerbations and other AEs possibly because they received higher doses of ICS/LABA leading to greater stability or due to undefined demographics. However, further studies with larger patient populations enabling statistical versus descriptive analyses are needed.³⁷

Traditionally, drug development in children is predicated by the efficacy and safety of medications in adults.⁴³ In adults, tiotropium Respimat[®] as add-on therapy to ICS with or without a LABA provided clinical benefit, with a safety profile comparable with that of placebo, in 5 phase III RCTs.²²⁻²⁴ In 2 replicate trials involving adults with severe asthma despite receiving ICS and LABAs (PrimoTinA[®]-asthma), once-daily tiotropium (5 μg) significantly improved peak and trough FEV₁ and increased the time to the first severe exacerbation compared with placebo.²² Similarly, in 2 other replicate trials including adults with moderate symptomatic asthma (MezzoTinA[®]-asthma), once-daily tiotropium (5 or 2.5 μg) add-on to medium-dose ICS significantly improved peak and trough FEV₁, FVC,

morning and evening PEF, and ACQ-7 responder rate compared with placebo.²³ Moreover, tiotropium was as efficacious as twice-daily salmeterol (50 µg) in the MezzoTinA[®]-asthma trials.²³ In the fifth trial (GraziaTinA[®]-asthma), which involved adults with symptomatic asthma receiving low- to medium-dose ICS, once-daily tiotropium (5 or 2.5 µg) significantly improved peak FEV_{1(0-3h)}, trough FEV₁, FEV₁ AUC_(0-3h), and morning and evening PEF.²⁴ Findings from the present systematic review, like those from systematic reviews of the adult tiotropium trials, reinforce the efficacy and safety of tiotropium in adolescents and children(link to video).^{33,44,45}

Further, by being able to evaluate all 7 phase II/III RCTs of tiotropium as add-on LAMA therapy conducted in children and adolescents with asthma that is uncontrolled despite ICS use, our findings confirm and expand upon previously published systematic reviews.^{46,47} In one systematic review and meta-analysis of the 3 RCTs involving approximately 1000 adolescents (mean age, 14 years) with moderate-to-severe asthma, tiotropium was deemed well tolerated and efficacious as add-on to maintenance ICS treatment or ICS plus a LABA.⁴⁶ Further, in another systematic review of 3 RCTs involving approximately 900 school-age children, tiotropium significantly improved lung function and decreased the number of patients with at least 1 exacerbation compared with placebo.⁴⁵ Finally, consistent with our findings, a pooled analysis of safety data from trials in adolescents and children with symptomatic moderate asthma showed that the most commonly reported AEs with tiotropium treatment included asthma worsening, exacerbations, decreased PEF, nasopharyngitis, viral respiratory tract infection, and respiratory tract infection (link to video).^{48,49}

Limitations to our findings include inadequate data regarding the efficacy and safety of tiotropium in preschool children. Results of only 1 RCT have been reported; robust data from additional trials are warranted. Moreover, statistical analysis (i.e., meta-analysis) of the

efficacy data was not feasible because of inclusion of children from different age groups and with a range of asthma severities. Other challenges encountered with trials in children include poor adherence and short study durations, which may affect the overall study results.⁴⁹ The inclusion of only English language studies could also contribute to reporting bias.⁵⁰ Despite these limitations, the strength of the evidence is compelling, especially when the burden of disease and unmet needs in current asthma care are taken into consideration.⁵¹

Results of this systematic review demonstrate that once-daily tiotropium (5 and 2.5 µg) as add-on LAMA therapy is efficacious and safe in adolescents and children with moderate-to-severe asthma and support the expanded indication by the FDA, EMA, and GINA for add-on tiotropium in patients aged ≥ 6 years. Results in the pediatric population are in line with those reported in adults. Tiotropium is currently considered as add-on treatment in GINA steps 4 and 5. Current scientific results will be additionally strengthened by real-world studies of tiotropium in the treatment of children and adolescents with asthma.

REFERENCES

1. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy*. 2004;59:469-78.
2. Centers for Disease Control and Prevention. Asthma's Impact on the Nation. Available at https://www.cdc.gov/asthma/impacts_nation/asthmafactsheet.pdf. Accessed on August 13, 2019.
3. Centers for Disease Control and Prevention. National Current Asthma Prevalence (2016). Available at https://www.cdc.gov/asthma/most_recent_data.htm. Accessed August 13, 2019.
4. Zahran HS, Bailey CM, Damon SA, Garbe PL, Breyse PN. Vital Signs: Asthma in Children — United States, 2001–2016. *Morbidity and Mortality Weekly Report (MMWR)*. 2018;67:149-55.
5. Liu AH, Gilsenan AW, Stanford RH, Lincourt W, Ziemiecki R, Ortega H. Status of asthma control in pediatric primary care: results from the pediatric Asthma Control Characteristics and Prevalence Survey Study (ACCESS). *J Pediatr*. 2010;157:276-81.e3.
6. Schmier JK, Manjunath R, Halpern MT, Jones ML, Thompson K, Diette GB. The impact of inadequately controlled asthma in urban children on quality of life and productivity. *Ann Allergy Asthma Immunol*. 2007;98:245-51.
7. Sullivan P, Ghushchyan VG, Navaratnam P, et al. School absence and productivity outcomes associated with childhood asthma in the USA. *J Asthma*. 2018;55:161-8.
8. Sullivan PW, Ghushchyan V, Navaratnam P, et al. The national burden of poorly controlled asthma, school absence and parental work loss among school-aged children in the United States. *J Asthma*. 2018;55:659-67.
9. Lozier MJ, Zahran HS, Bailey CM. Assessing health outcomes, quality of life, and healthcare use among school-age children with asthma. *J Asthma*. 2018:1-8.

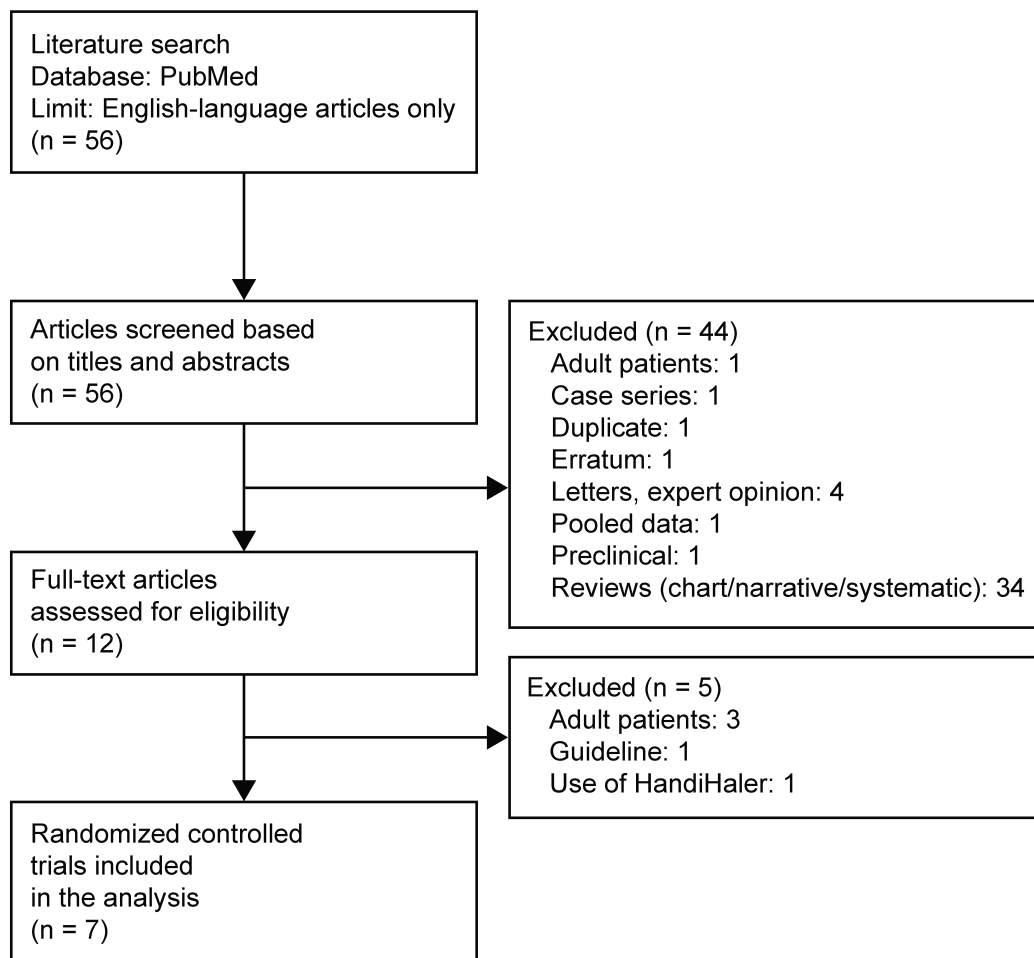
10. Sullivan PW, Ghushchyan V, Navaratnam P, et al. National Prevalence of Poor Asthma Control and Associated Outcomes Among School-Aged Children in the United States. *J Allergy Clin Immunol Pract*. 2018;6:536-44.e1.
11. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Updated 2019. Available at <https://ginasthma.org/wp-content/uploads/2019/06/GINA-2019-main-report-June-2019-wms.pdf>. Accessed August 13, 2019.
12. Bisgaard H, Szeffler S. Prevalence of asthma-like symptoms in young children. *Pediatr Pulmonol*. 2007;42:723-8.
13. Brand PL, Baraldi E, Bisgaard H, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J*. 2008;32:1096-110.
14. Pedersen SE, Hurd SS, Lemanske RF, Jr., et al. Global strategy for the diagnosis and management of asthma in children 5 years and younger. *Pediatr Pulmonol*. 2011;46:1-17.
15. Saglani S, Malmström K, Pelkonen AS, et al. Airway remodeling and inflammation in symptomatic infants with reversible airflow obstruction. *Am J Respir Crit Care Med*. 2005;171:722-27.
16. Akinbami LJ, Moorman JE, Bailey C, et al. Trends in asthma prevalence, health care use, and mortality in the United States, 2001-2010. *NCHS Data Brief*. 2012:1-8.
17. Spiriva Respimat prescribing information. Available at <https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Spiriva%20Respimat/spirivarespimat.pdf>. Accessed August 13, 2019.
18. Spiriva Respimat 2.5 microgram, inhalation solution. Summary of Product Characteristics. Available at <https://www.medicines.org.uk/emc/product/407/smpc>. Accessed August 13, 2019.

19. Chipps BE, Bacharier LB, Farrar JR, et al. The pediatric asthma yardstick: Practical recommendations for a sustained step-up in asthma therapy for children with inadequately controlled asthma. *Ann Allergy Asthma Immunol.* 2018;120:559-79.e11.
20. Moulton BC, Fryer AD. Muscarinic receptor antagonists, from folklore to pharmacology; finding drugs that actually work in asthma and COPD. *Br J Pharmacol.* 2011;163:44-52.
21. Spiriva Respimat[®] prescribing information Updated 2015. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207070s000lbl.pdf. Accessed August 13, 2019.
22. Kerstjens HA, Engel M, Dahl R, et al. Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med.* 2012;367:1198-207.
23. Kerstjens HA, Casale TB, Bleecker ER, et al. Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials. *Lancet Respir Med.* 2015;3:367-76.
24. Paggiaro P, Halpin DM, Buhl R, et al. The Effect of Tiotropium in Symptomatic Asthma Despite Low- to Medium-Dose Inhaled Corticosteroids: A Randomized Controlled Trial. *J Allergy Clin Immunol Pract.* 2016;4:104-13.e2.
25. Hamelmann E, Bateman ED, Vogelberg C, et al. Tiotropium add-on therapy in adolescents with moderate asthma: A 1-year randomized controlled trial. *J Allergy Clin Immunol.* 2016;138:441-50.e8.
26. Hamelmann E, Bernstein JA, Vandewalker M, et al. A randomised controlled trial of tiotropium in adolescents with severe symptomatic asthma. *Eur Respir J.* 2017;49: 1601100 [<https://doi.org/10.1183/13993003.01100-2016>].

27. Szeffler SJ, Murphy K, Harper III T, et al. A phase III randomized controlled trial of tiotropium add-on therapy in children with severe symptomatic asthma. *J Allergy Clin Immunol.* 2017;[10.1016/j.jaci.2017.01.014].
28. Vogelberg C, Moroni-Zentgraf P, Leonaviciute-Klimantaviciene M, et al. A randomised dose-ranging study of tiotropium Respimat® in children with symptomatic asthma despite inhaled corticosteroids. *Respir Res.* 2015;16:20.
29. Bateman ED, Kornmann O, Schmidt P, Pivovarova A, Engel M, Fabbri LM. Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma. *J Allergy Clin Immunol.* 2011;128:315-22.
30. Fardon T, Haggart K, Lee DK, Lipworth BJ. A proof of concept study to evaluate stepping down the dose of fluticasone in combination with salmeterol and tiotropium in severe persistent asthma. *Respir Med.* 2007;101:1218-28.
31. Kerstjens HA, Disse B, Schroder-Babo W, et al. Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial. *J Allergy Clin Immunol.* 2011;128:308-14.
32. Peters SP, Kunselman SJ, Icitovic N, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *N Engl J Med.* 2010;363:1715-26.
33. Befekadu E, Onofrei C, Colice GL. Tiotropium in asthma: a systematic review. *J Asthma Allergy.* 2014;7:11-21.
34. Dalby R, Spallek M, Voshaar T. A review of the development of Respimat Soft Mist inhaler. *Int J Pharm.* 2004;283:1-9.
35. Amirav I, Newhouse MT, Mansour Y. Measurement of peak inspiratory flow with in-check dial device to simulate low-resistance (Diskus) and high-resistance (Turbohaler) dry powder inhalers in children with asthma. *Pediatr Pulmonol.* 2005;39:447-51.

36. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg*. 2010;8:336-41.
37. Vrijlandt E, El Azzi G, Vandewalker M, et al. Safety and efficacy of tiotropium in children aged 1-5 years with persistent asthmatic symptoms: a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med*. 2018;6:127-37.
38. Cochrane handbook for systematic reviews of interventions. Version 5.1.0. Available at: <http://handbook-5-1.cochrane.org/>. Accessed August 13, 2019.
39. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928.
40. Spiriva HandiHaler® prescribing information. Available at <https://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Spiriva/Spiriva.pdf>. Accessed September 26, 2019.
41. Vogelberg C, Engel M, Moroni-Zentgraf P, et al. Tiotropium in asthmatic adolescents symptomatic despite inhaled corticosteroids: a randomised dose-ranging study. *Respir Med*. 2014;108:1268-76.
42. Vogelberg C, Engel M, Laki I, et al. Tiotropium add-on therapy improves lung function in children with symptomatic moderate asthma. *J Allergy Clin Immunol Pract*. 2018;[doi: 10.1016/j.jaip.2018.04.032.].
43. Zajicek A, Barrett JS. The grand challenges in obstetric and pediatric pharmacology. *Front Pharmacol*. 2013;4:170.
44. Rodrigo GJ, Castro-Rodriguez JA. What is the role of tiotropium in asthma?: a systematic review with meta-analysis. *Chest*. 2015;147:388-96.
45. Wang L, Zhou R, Xie X. Tiotropium added to low- to medium-dose inhaled corticosteroids (ICS) versus low- to medium-dose ICS alone for adults with mild to moderate uncontrolled persistent asthma: A systematic review and meta-analysis. *J Asthma*. 2018:1-10.

46. Rodrigo GJ, Castro-Rodriguez JA. Tiotropium for the treatment of adolescents with moderate to severe symptomatic asthma: a systematic review with meta-analysis. *Ann Allergy Asthma Immunol.* 2015;115:211-6.
47. Rodrigo GJ, Neffen H. Efficacy and safety of tiotropium in school-age children with moderate-to-severe symptomatic asthma: A systematic review. *Pediatr Allergy Immunol.* 2017;28:573-8.
48. Vandewalker ML, Hamelmann E, Engel M, et al. Once-daily tiotropium Respimat® add-on therapy has a safety profile comparable with placebo in children and adolescents. *J Allergy Clin Immunol.* 2017;139:AB94.
49. Hamelmann E, Szeffler SJ. Efficacy and safety of tiotropium in children and adolescents. *Drugs.* 2018;78:327-38.
50. Bassler D, Antes G, Egger M. Non-English reports of medical research. *JAMA.* 2000;284:2996-7.
51. Averell CM, Laliberté F, Duh MS, et al. Characterizing real-world use of tiotropium in asthma in the USA. *J Asthma Allergy.* 2019;12:309-21.



Vogelberg 2014 ³⁸	+	+	+	?	+	?	+
Vogelberg 2015 ²⁷	+	+	+	+	+	?	+
Hamelmann 2016 ²⁴	+	+	+	+	+	+	+
Hamelmann 2017 ²⁵	+	+	+	+	+	+	+
Szeffler 2017 ²⁶	+	+	+	+	+	?	+
Vogelberg 2018 ³⁹	+	+	+	+	+	?	+
Vrijlandt 2018 ⁴⁰	+	+	+	+	+	+	+
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias

Key

 Low risk of bias
 High risk of bias
 Unclear risk of bias

1 **FIGURE LEGENDS**

2

3 **FIGURE 1.** Flow chart showing selection of studies

4

5 **FIGURE 2.** Assessment of risk bias

6 The studies included in this systematic review are shown on the Y-axis and parameters for
7 assessing risk of bias are shown on the X-axis. The studies were categorized as possessing
8 unclear, low, or high risk of bias for each parameter assessed.