



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

Liqun Wang, Ruirui Zhou & Xiaohui Xie

To cite this article: Liqun Wang, Ruirui Zhou & Xiaohui Xie (2018): 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, Journal of Asthma, DOI: [10.1080/02770903.2018.1424192](https://doi.org/10.1080/02770903.2018.1424192)

To link to this article: <https://doi.org/10.1080/02770903.2018.1424192>



Published online: 08 Feb 2018.



Submit your article to this journal [↗](#)



Article views: 79



View related articles [↗](#)



View Crossmark data [↗](#)



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

Liqun Wang, MPharm, Ruirui Zhou, MPharm, and Xiaohui Xie, MS

Department of Pharmacy Administration and Clinical Pharmacy, School of Pharmaceutical Sciences, Peking University, Beijing, China

ABSTRACT

Objective: To assess the efficacy and safety profile of tiotropium when added to low- to medium-dose inhaled corticosteroid (ICS) regimen versus low- to medium-dose ICS alone for adults with mild to moderate uncontrolled persistent asthma. **Data Sources:** The online databases Pubmed, Embase and the Cochrane Library were searched for relevant data published up to November 14, 2017; we also conducted a supplementary search using clinicaltrials.gov. **Study Selections:** Only randomized control trials were included in this review. **Results:** Four studies met our inclusion criteria for this review. In our review, two crossover studies were rated as “high risk” in the domain of “other bias” because a washout was not performed between each intervention. Lung function was significantly improved in the patient group receiving low- to medium-dose ICS with tiotropium. Results were consistent between each of three subgroups (tiotropium dry powder inhaler 18 µg or Respimat Soft Mist inhaler 5 µg, Respimat Soft Mist inhaler 2.5 µg, and Respimat Soft Mist inhaler 1.25 µg). Although no significant difference in Asthma Control Questionnaire (ACQ) score was found between the two treatment groups, substantial heterogeneity was observed. The incidence of serious adverse events between the two treatment groups was not statistically significant. **Conclusions:** Tiotropium as a once daily add-on to low- to medium-dose ICS may be efficacious and well-tolerated treatment in adults with moderate uncontrolled asthma. However, as only a few studies were identified, more studies of better design and long-term trial duration are required in the future.

ARTICLE HISTORY

Received 25 August 2017
Revised 21 December 2017
Accepted 1 January 2018

KEYWORDS

Asthma; mild; moderate; tiotropium; Long-acting muscarinic antagonist; LAMA; systematic review; meta-analysis; efficacy; safety

1. Introduction

Asthma, a common chronic respiratory disease, is characterized by variable respiratory symptoms and variable expiratory airflow limitation (1). According to the World Health Organization (WHO), approximately 235 million people currently suffer from asthma worldwide (2). In order to achieve good symptom control and minimize future risk in the long-term, the Global Initiative for Asthma (GINA) has adopted a stepwise approach for pharmaceutical in asthma treatment (1). Inhaled corticosteroids (ICSs) are the cornerstone of asthma maintenance and are used for management of uncontrolled persistent asthma in step two through five of the GINA treatment protocol (1). If ICS alone is insufficient for asthma control, an increase of the ICS dosage or adding a long-acting beta2 agonist (LABA) has been established as the preferred treatment based on several randomized controlled trials (1). Alternatives to LABA

that supplement ICS are leukotriene receptor antagonists (LTRA) and sustained-release theophylline for treatment of mild to moderate asthma (1).

Tiotropium, a long-acting muscarinic antagonist (LAMA), is an established treatment for chronic obstructive pulmonary disease (COPD). Some research has demonstrated the efficacy of this antagonist and good patient tolerance when added to ICS. GINA has incorporated tiotropium into the Global Strategy for Asthma Management and Prevention as an add-on treatment for patients older than 12 years with a history of asthmatic exacerbations in steps four and five, steps identified as treating severe asthma (1). Although severe asthma has a large economic burden, considerable morbidity, and mortality compared to mild to moderate asthma, patients with mild to moderate asthma make up a higher proportion of the asthmatic population. These patients are at risk of serious symptoms and acute exacerbations if their

asthma remains poorly controlled, increasing suffering and economic burdens (1,3,4). It is necessary, therefore, that attention be given to the study of novel treatment for mild to moderate asthma.

To our knowledge, few systematic reviews have analyzed the effect of tiotropium as a potential alternative add-on for asthma treatment in lower GINA treatment steps. Two systematic reviews with meta-analyses published in the Cochrane Library (5,6) compared the efficacy and safety of tiotropium added to ICS with that of same dose or higher dose ICS alone for the treatment of asthmatic adults, but regardless of asthma severity. Rodrigo et al. (7) pooled clinical data on tiotropium and performed subgroup analysis when it was added to at least ICS for asthma treatment across all levels of disease severity. Importantly, one of the studies of the mild to moderate asthma subgroup included intervention arms in which leukotriene receptor antagonists (LTRAs) were permitted during the trials (8); another study in the same subgroup only enrolled patients who were B16-Arg/Arg positive (9). With the inclusion of LTRAs in the trials, the effect of tiotropium may be unclear, and the universality of the research of a patient group with a specific genotype may be limited. We aimed to correct these problems and include recently published trials.

The objective of this systematic review and meta-analysis was to assess the efficacy and safety profile of tiotropium when added to low- to medium-dose ICS versus low- to medium-dose ICS alone for adults with mild to moderate uncontrolled persistent asthma, and to further investigate the application of tiotropium as an add-on to ICS in lower steps of asthma treatment.

2. Methods

2.1. Search strategy

Electronic databases, including Pubmed, Embase, and the Cochrane Library were searched for articles of interest with terms relevant to “tiotropium”, “ICS”, and “asthma”, from conception to November 14, 2017. In addition, we searched clinicaltrials.gov for more study data. The search strategy is as follows: 1) tiotropium; 2) inhaled and (steroid or glucocorticoid or corticosteroid) or ICS or (budesonide or beclomethasone or fluticasone or ciclesonide or triamcinolone or mometasone or flunisolide) ; 3) asthma; 4) all three terms combined.

2.2. Study selection

Two reviewers independently screened for parallel or crossover randomized control trials (RCTs) on the efficacy and safety of tiotropium when added to low- to medium-dose ICS for adults with mild to moderate

uncontrolled persistent asthma. Publication language was restricted to English. Disagreements about study relevance were resolved by discussion between two reviewers, or by the third reviewer if necessary.

Relevant RCTs were included in this review only if they fulfilled the following inclusion criteria: 1) patients who were male or female adults (age ≥ 18) with uncontrolled persistent asthma, who were not current smokers who never smoked or had a smoking history of less than 10 pack years; 2) at least two medication regimens included in study analysis, i.e., tiotropium once daily added to stable low- to medium-dose ICS, and the same or higher dose ICS alone; 3) RCTs in which salbutamol hydrofluoroalkane metered-dose inhaler as a reliever and additional temporary treatments (e.g., systemic corticosteroids) for acute exacerbations were permitted, while trials with maintenance treatments (such as LABA, LTRA, sustained-release theophylline, LAMA other than tiotropium) were not included; 4) articles that reported at least one of following outcomes: lung function, such as forced expiratory volume in one second (FEV1), peak expiratory flow (PEF), and forced vital capacity (FVC), or other relevant measurements, Asthma Control Test (ACT) score or Asthma Control Questionnaire (ACQ) score, and serious adverse events (AEs).

Without access to original patient records before recruitment, we had to accept the determination of asthma severity made by original study investigators. The dose range of low- to medium-dose ICS for adults was consistent with GINA guidelines: Beclomethasone dipropionate 200–1000 μg (chlorofluorocarbon propellant, CFC) or 100–400 μg (hydrofluoroalkane propellant, HFA), budesonide (dry powder inhaler, DPI) 200–800 μg , ciclesonide (HFA) 80–320 μg , fluticasone furoate (DPI) 100 μg , fluticasone propionate (DPI and HFA) 100–500 μg , mometasone furoate 110–440 μg , triamcinolone acetonide 400–2000 μg (1). Serious AEs were identified based on clinicaltrials.gov definition: an AE that results in death, is life-threatening, requires inpatient hospitalization or extends a current hospital stay, results in an ongoing or significant incapacity or interferes substantially with normal life functions, or causes a congenital anomaly or birth defect (10). Medical events that do not result in death, are not life-threatening, or do not require hospitalization, may be considered serious adverse events if they put the participant in danger or require medical or surgical intervention to prevent one of the results listed above (10).

Trial exclusion criteria included: 1) studies in which the trial duration was less than 4 weeks; 2) studies in which a few patients achieved satisfactory symptom control after the run-in period; 3) studies on special population, such as pregnant women, patients with aspirin-induced asthma or exercise-induced asthma, and population with specific

genotypes; 4) subjects with serious disease or other respiratory diseases (e.g., COPD); 5) articles that were published repeatedly, or those articles of which full-text or essential data were unavailable.

2.3. Data extraction and quality assessment

The following information were collected: title, authors, year of publication, study design, study population, eligibility criteria, asthma triggers, asthma severity, demographic characteristics of subjects, sample size, trial duration, medication of each group, adherence to medication, inhaler devices, technique for using the inhaler devices, efficacy, and safety outcomes. When a trial included multiple trial arms, we extracted relevant data only from those arms of interest.

The Cochrane Collaboration's tool for assessing risk of bias was used to evaluate the methodological quality of the RCTs included in this review. The risk of bias was assessed as "Low risk", "High risk", or "Unclear risk" in each of seven domains: 1) sequence generation (selection bias); 2) allocation concealment (selection bias); 3) blinding of participants and personnel (performance bias); 4) blinding of outcome assessment (detection bias); 5) incomplete outcome data (attrition bias); 6) selective outcome reporting (reporting bias); 7) other bias (11). "Risk of bias graph" was exported by Review Manager (RevMan) 5.3.

Data extraction and quality assessment were completed independently by two reviewers, and differences

of opinion were discussed or resolved by the third reviewer.

2.4. Data synthesis and analysis

The change of lung function measurements from baseline was defined as the primary outcome, while the changes in ACQ score and incidence of serious adverse events as the secondary ones. Treatment effects were estimated by using the mean difference (MD) for continuous outcome measures, and the risk ratio (RR) for binary outcomes, with 95% confidence interval (CI). Heterogeneity was measured by I^2 statistic, and heterogeneity was considered to be substantial when I^2 was greater than 50%, in which case the cause of heterogeneity should be explored and discussed. Subgroup analyses were carried out based on the dose of tiotropium for primary outcome, and the random-effects model was used for all analyses. The meta-analysis was conducted with RevMan software.

3. Results

3.1. Literature search and description of included studies

All of four articles (12–15) were identified that met all inclusion criteria and were included in the quantitative synthesis. The study selection process is presented in Figure 1. Of the included studies, three were designed as

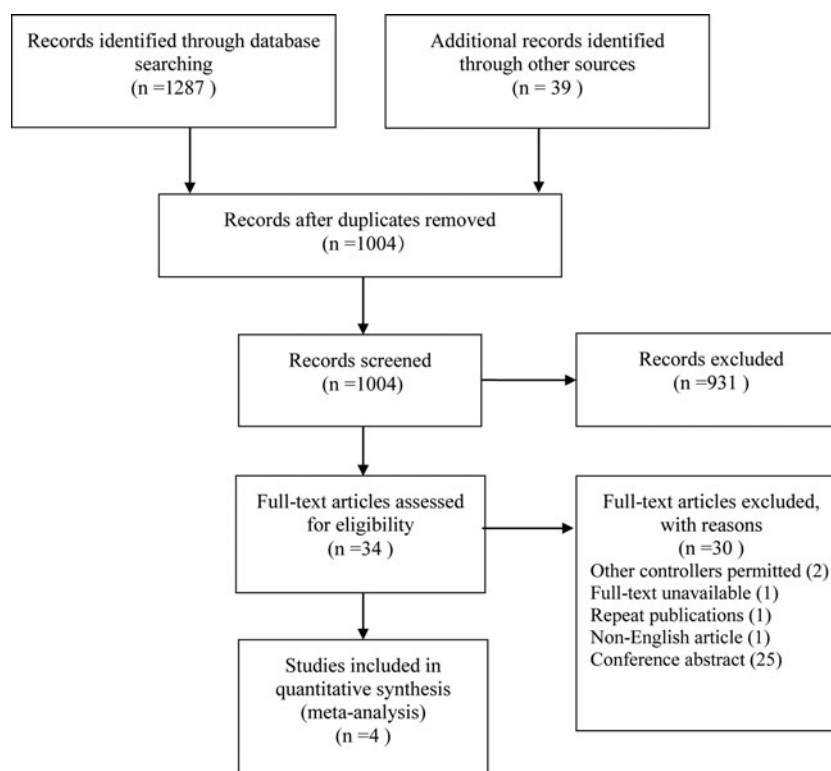


Figure 1. Flowchart for identification of eligible studies.

crossover trials, while the remaining one was of parallel design. Nine hundred and seventeen adults with mild to moderate asthma enrolled in these four trials and met the following inclusion criteria: 1) the age of at least 18 years; 2) all patients with uncontrolled asthma, having symptoms 6 or more days/week (d/wk) or using a rescue inhaler 6 or more d/wk or being awakened by symptoms 2 or more nights/week, or with mean ACQ score 1.5 or more before randomization; 3) prebronchodilator FEV1 greater than 40% or 60% and less than 70% or 90% of the predicted value; 4) no current smokers (never smoked or less than 10 pack years); 5) no patients with significant diseases or lung diseases other than asthma. Participants received either tiotropium or placebo, or both in exclusive periods, plus low- to medium-dose ICS. Tiotropium was administered by DPI at a dose of 18 µg in one study and in the other three by Respimat Soft Mist inhaler (RSMI) at the dose of 5 µg, 2.5 µg, or 1.25 µg. Lung function parameters, such as morning PEF (PEF am), peak FEV1, etc., were defined as primary or major outcomes, and were compared to baseline measurements after treatment. The trial characteristics are shown in Table 1.

3.2. Quality assessment

The two crossover-design studies were given a high risk of bias rating in the “other bias” domain, because of failure in study procedure to wash out between two interventions. An overview of risk of bias assessment is shown in Figure 2.

3.3. Primary outcome: lung function

We defined the following three tiotropium dose subgroups: 1) tiotropium DPI 18 µg or RSMI 5 µg (DPI18&RSMI5); 2) RSMI 2.5 µg (RSMI2.5); 3) RSMI 1.25 µg (RSMI1.25). Results were measured as changes in FEV% of predicted value, peak FEV1, trough FEV1, PEF am, and PEF pm, compared to baseline. These measurements were used to demonstrate the effect of the three treatments on lung function.

FEV% of predicted value significantly improved by an additional 3.46% (95% CI 2.29 to 4.63, $p < 0.00001$) and 2.60% (95% CI 0.38 to 4.82, $p = 0.02$) in DPI18&RSMI5 and RSMI2.5 groups, respectively, compared with ICS treatment alone. No heterogeneity was observed in any or across the subgroups, and the overall MD of changes for FEV1% of predicted value was 3.27% (95% CI 2.24 to 4.31, $p < 0.00001$) between tiotropium plus ICS and ICS alone. (Figure 3)

Patients taking tiotropium plus ICS also had a significant improvement in peak FEV1, trough FEV1, PEF am, and PEF pm (Figure 3 and Figure 4).

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Beeh 2014	+	?	?	?	+	+	-
Paggiaro 2016	+	?	+	?	+	+	+
Peters 2010	?	?	+	+	+	+	+
Timmer 2015	?	?	?	?	+	+	-

Figure 2. Risk of bias assessment by using the Cochrane Collaboration's tool. Low risk (+); unclear risk (?); high risk (-).

3.4. Secondary outcomes

There were no statistically significant differences of changes in ACQ score found between two of the treatment groups (MD -0.03, 95% CI -0.17 to 0.11, $P = 0.65$), but $I^2 = 73\%$ indicated significant heterogeneity. (Figure 5)

Subjects treated with tiotropium plus ICS were more likely to have serious AEs than those given ICS alone with an RR of 1.03, but the difference was not statistically significant (95% CI 0.36 to 2.94, $P = 0.95$) (Figure 6).

4. Discussion

Asthma control is suboptimal in a significant proportion of asthmatic patients despite adherence to treatment guidelines (16), therefore clinical research on this topic has been conducted in an attempt to investigate strategies for better asthma control, and tiotropium has become one of the hot spots.

Because management of severe asthma is the focus of research, international guidelines, consensus statements, and recommendations (17), research efforts are mounting to investigate the role of tiotropium in severe asthma management. Tiotropium treatment has been

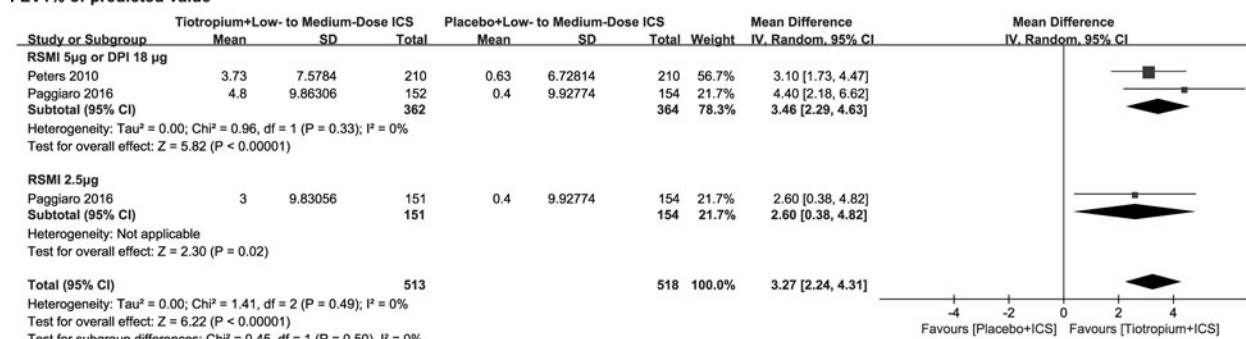
Table 1. Characteristics of the included studies.

Studies	Study design	Trial duration, weeks	Duration of washout period, weeks	Number of subjects, <i>n</i> (male: female)	Age, mean (SD)	Asthma triggers	Severity of asthma	FEV ₁ % of the predicted value, mean (SD)	ACQ score, mean (SD)
Peters 2010	crossover	14	2	210 (69:141)	42.2 (12.3)	N/A	moderate	71.5 (14.9)	1.64 (0.73)
Beeh 2014	crossover	4	No	149 (67:82)	49.3 (13.3)	N/A	moderate	71.3 (7.1)	N/A
Timmer 2015	crossover	4	No	94 (39:55)	44.3 (13.2)	N/A	moderate	73.4 (7.9)	2.317 (0.504)
Paggiaro 2016	parallel	12	–	464 (183:281)	42.9 (13.0)	N/A	mild to moderate	73.9 (8.4)	2.1 (0.4)

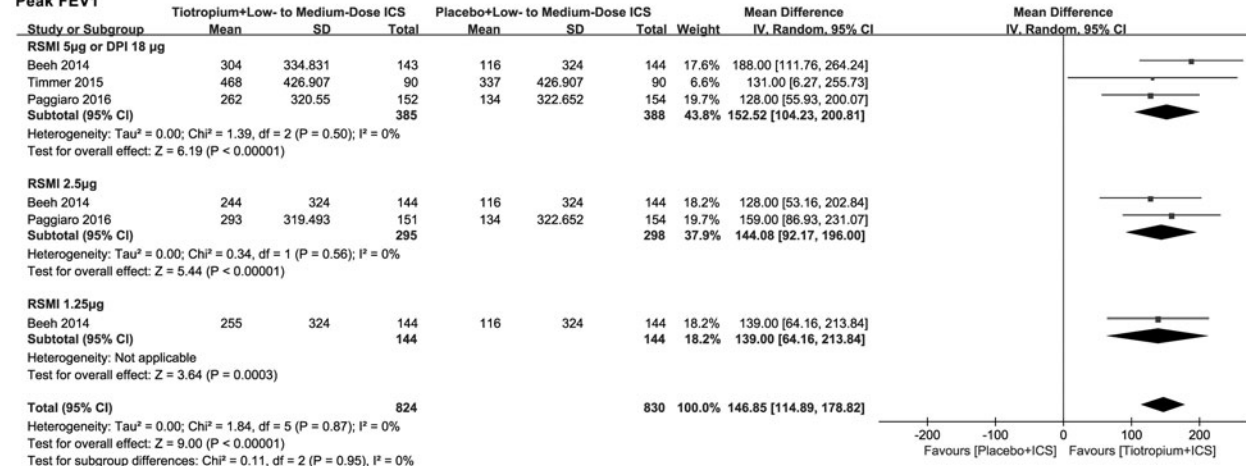
Studies	Intervention groups (IG)	Control groups (CG)	Inhaler devices	Adherence to medication	Technique for using the inhaler devices
Peters 2010	Tiotropium 18 µg/d + 160 µg/d beclomethasone	Placebo + 320 µg/d beclomethasone	Tiotropium: DPI ICS: HFA	IG: 84.1 ± 16% CG: 92.6 ± 12.3% (for tiotropium)	N/A
Beeh 2014	Tiotropium 5 µg/d, 2.5 µg/d or 125 µg/d + 400–800 µg/d budesonide or equivalent	Placebo + 400–800 µg/d budesonide or equivalent	Tiotropium: RSMI ICS: N/A	N/A	Using RSMI correctly
Timmer 2015	Tiotropium 5 µg/d + 400–800 µg/d budesonide or equivalent	Placebo + 400–800 µg/d budesonide or equivalent	Tiotropium: RSMI ICS: N/A	N/A	Using RSMI correctly
Paggiaro 2016	Tiotropium 5 µg/d or 2.5 µg/d + 200–400 µg/d budesonide or equivalent	Placebo + 200–400 µg/d budesonide or equivalent	Tiotropium: RSMI ICS: N/A	N/A	Using RSMI correctly

SD: standard deviation; ACQ: Asthma Control Questionnaire; N/A: no data available; DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant; RSMI: Respimat Soft Mist Inhaler.

FEV1% of predicted value



Peak FEV1



Trough FEV1

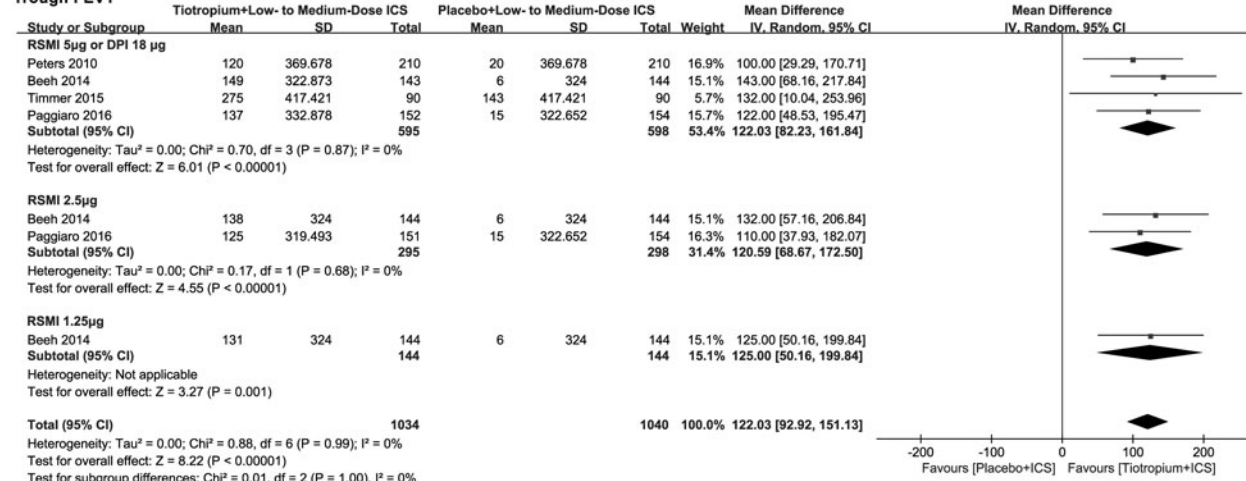


Figure 3. Forest plot demonstrating the mean differences for changes of FEV1% of predicted value, peak FEV1, and trough FEV1 from trials comparing Tiotropium + low- to medium-dose ICS and Placebo + low- to medium-dose ICS for adults with mild to moderate asthma.

incorporated into the GINA guidelines as a recommended alternative add-on option only for severe asthma (1). Considering the high proportion of patients with mild and moderate asthma, their substantial symptom and economic burden, the efficacy and safety of the tiotropium in this population merits investigation.

Four studies were identified that fulfilled our inclusion criteria after a systematic literature search and rigorous study selection. Several studies on tiotropium with low- to medium-dose ICS for adults with mild to moderate asthma were excluded due to admission of additional

LTRA treatment throughout the trials, a treatment which might affect the efficacy measurements of tiotropium. The limited number of eligible studies indicates that the issue of alternative add-on medications for adult patients with mild to moderate asthma has drawn little attention, suggesting that more clinical research should be made in this field to address the majority of the asthmatic population.

As is shown in Table 1, several critical factors were found absent in the eligible articles. Patients' asthma triggers were unclear in all studies. Effects of asthma

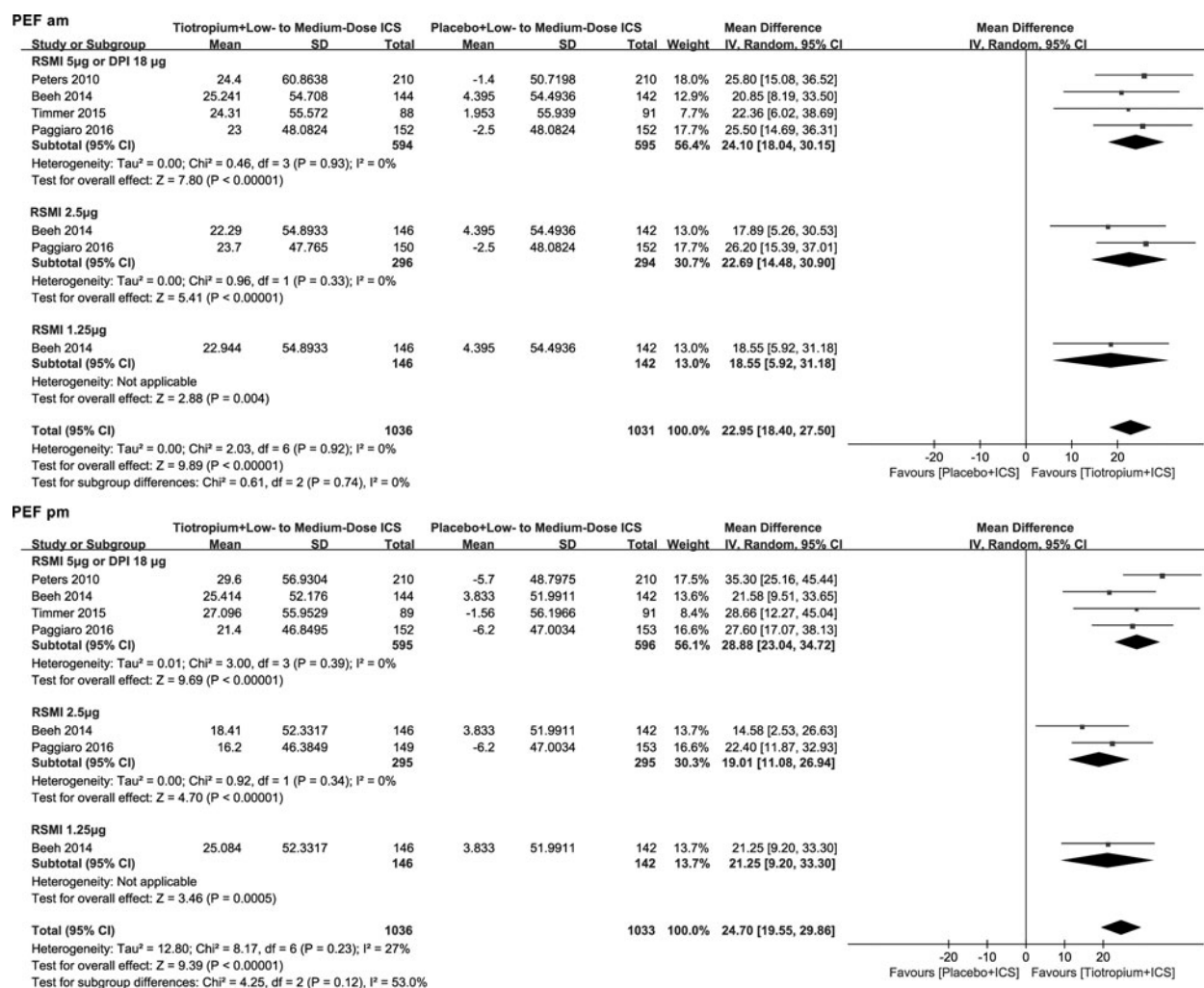


Figure 4. Forest plot demonstrating the mean differences for PEF am and PEF pm from trials comparing Tiotropium + low- to medium-dose ICS and Placebo + low- to medium-dose ICS for adults with mild to moderate asthma.

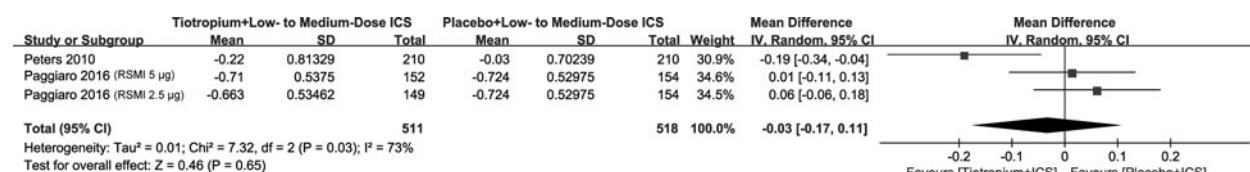


Figure 5. Forest plot demonstrating the mean differences for ACQ score from trials comparing Tio-tropium + low- to medium-dose ICS and Placebo + low- to medium-dose ICS for adults with mild to moderate asthma.

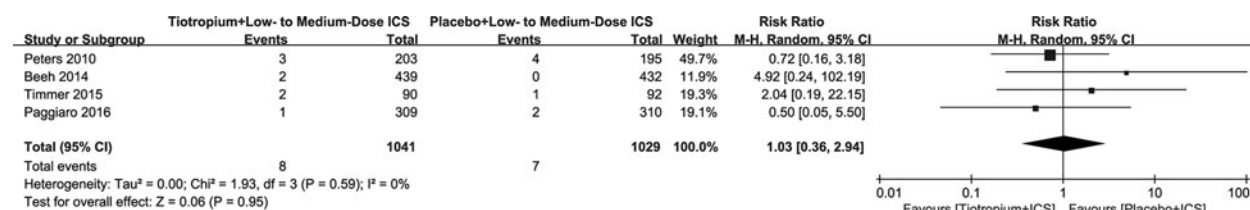


Figure 6. Forest plot demonstrating the relative risk of serious AEs from trials comparing Tiotro-pium + low- to medium-dose ICS and Placebo + low- to medium-dose ICS for adults with mild to moderate asthma.

treatment usually vary with different triggers, and persistent exposure to triggers also affects treatment efficacy. One study reported adherence to tiotropium treatment, while the remaining three did not report any medication adherence in the treatment arms of the study. Poor adherence to treatment is one of the major factors of suboptimal asthma control and exacerbation, significantly influencing the treatment efficacy. Only one study described the inhaler types used for both tiotropium and ICS, while the remaining three studies only described the inhaler type of tiotropium treatment. Similarly, three studies ensured that patients used tiotropium inhalers correctly, but no study reported patients' techniques of using ICS inhaler or whether ICS Metered Dose Inhaler (MDI) with a valved holding chamber was used. ICS plays an overwhelming role in asthma treatment, and optimal adherence to ICS and proper techniques of using ICS inhaler is the basis needed for accurate and reliable results. Moreover, there is potential bias without explicit exclusion of comorbidities that also need steroids (e.g., allergic rhinitis). Failure to adequately report all of these factors in the included studies could weaken the reliability of trial results to some extent.

Additionally, the duration of the included trials was too short to satisfactorily investigate the complete efficacy and safety profile of tiotropium treatment in the long term. Many asthmatic patients require pharmaceutical intervention for a long time, and some even require life-long treatments. According to the GINA guidelines, one major long-term goal of asthma management is to minimize future risks, like exacerbations, fixed airflow limitation, and side-effects of treatment (1). The durations of two included studies were 4 weeks each, and potential severe exacerbations or side-effects of treatment were not observable in such short follow-up period. Trials of an adequate duration will lead to more conclusive results and deserves attention in future studies.

In our risk of bias assessment, two crossover studies were rated as "high risk" in the domain of "other bias" because washout was not performed between each intervention, creating a carry-over effect that might lead to bias. Carryover in crossover trials refers to the situation in which the effects of an intervention given in one period persist into a subsequent period; including a washout period between interventions is a major method used to reduce carryover (11). Because it was unclear if there was serious carry-over bias in the two included crossover studies without a washout period, all measurements from periods in which intervention medication was given and in which control medication was given, are analyzed as if these crossover trials were parallel trials. This method of analysis may be incorrect but it is conservative, so studies are under-weighted rather than over-weighted (11).

In quantitative synthesis, we incorporated patients using tiotropium DPI 18 µg and RSMI 5 µg into a single group because one clinical trial suggests that tiotropium RSMI 5 µg provides similar bronchodilator efficacy to tiotropium DPI 18 µg in COPD patients (18). A previous review indicates that tiotropium RSMI 5 µg is considered to be equivalent to DPI 18 µg in asthma patients (19). Because only one included study involved patients with mild asthma, no dependable conclusion has been reached about the efficacy and safety profile of tiotropium when added to low- to medium-dose ICS for adults with mild uncontrolled persistent asthma, which is an important issue for future research. However, the present results are significant for understanding the role of tiotropium as an add-on medication for adults with moderate persistent asthma.

Through quantitative synthesis, this review confirmed that tiotropium plus low- to medium-dose ICS permits a more significant improvement in lung function than low- to medium-dose ICS alone for adults with moderate asthma. Additionally, tiotropium for moderate asthma exhibited a long-term effect as both of PEF pm and PEF am improved more than that in the ICS alone group. All lung function measurements, the effect of all type and dose of tiotropium (DPI 18 µg, RSMI 5 µg, 2.5 µg, and 1.25 µg) had no significant difference.

There was no significant difference in ACQ score, but substantial heterogeneity ($I^2 = 73\%$) observed. The results from two studies that included in analysis of ACQ score were different. One study indicated that add-on tiotropium benefits asthmatic patients, while the other suggested that the control group decrease in ACQ score seemed higher than that in tiotropium group but no significant difference was observed. These conflicting results might have been caused by different trial duration. The duration of the former trial is two weeks longer than that of latter one, and it might require a long period of time to improve symptoms and thus to decrease ACQ score by taking tiotropium. Moreover, ACQ is a patient self-assessment, and respiratory symptoms may be nonspecific, which means subjectivity and potential discrepancies in judgment may exist in different studies. Therefore, it seemed inappropriate to pool ACQ score data from these two studies, and it would be interesting to investigate this issue further with longer trial duration and rigorous training of patients.

Finally, this review suggests that tiotropium added to low- to medium-dose ICS does not increase or reduce serious AEs compared with ICS alone.

This review has worked to depict the scope, research status, and knowledge gap of recent studies on tiotropium plus ICS for mild to moderate asthma. We also highlighted some limitations of current research, which

should be avoided in future studies of high quality. To the best of our knowledge, this is the first systematic review and meta-analysis focusing on a population with mild to moderate uncontrolled asthma, with a comparison between tiotropium plus low- to medium-dose ICS and low- to medium-dose ICS alone. The result of this meta-analysis supports the assumption that tiotropium is efficacious and well tolerated for adults in the lower steps of asthma treatment as an alternative add-on medication, although the number of included studies was small and their qualities were suboptimal.

Several limitations should be considered in this review: 1) RCTs of parallel and crossover design, with two crossover trials without washout between each intervention, were included together, which might result in bias; 2) the design, performance, and analyses of included studies varied, despite no statistical heterogeneity being found in the main analyses; there may be some other unconsidered heterogeneity; 3) of the four included trials, three enrolled patients with moderate asthma, while one enrolled patients with mild to moderate asthma. As only one study involved mild asthma, the results for patients with mild asthma need to be interpreted with caution and should be investigated further in future studies. Moreover, including patients with mild persistent asthma in the meta-analysis may have an influence on assessing the benefit and risk of tiotropium for moderate persistent asthmatic patients.

5. Conclusion

In conclusion, this review indicates that tiotropium once daily with low- to medium-dose ICS may be efficacious and well tolerated in adults with moderate uncontrolled asthma. Of note, this add-on treatment may improve lung function, providing evidence for the possibility of tiotropium as an add-on option for non-severe asthma. Among the various types and doses of tiotropium analyzed (DPI 18 µg, RSMI 5 µg, 2.5 µg and 1.25 µg), there were no significant differences in efficacy to improve lung function. The limited number of studies of suboptimal quality may have created possible bias, and further studies of improved design and longer duration are required to confirm our results.

Acknowledgements

The authors would like to thank Xiaotong Yu and Yitong Wang for their suggestions for this paper.

Declaration of interest

There is no conflict of interest.

Funding

No financial support was obtained for this study.

References

1. GINA. Global Strategy for Asthma Management and Prevention. GINA[Internet]. 2017. [cited 2017 August 3]. Available from: <http://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-and-prevention/>.
2. WHO. Asthma. WHO[Internet]. 2017. [cited 2017 August 3]. Available from: <http://www.who.int/mediacentre/factsheets/fs307/en/>.
3. Lee YJ, Kwon SH, Hong SH, Nam JH, Song HJ, Lee JS, et al. Health care utilization and direct costs in mild, moderate, and severe adult asthma: a descriptive study using the 2014 South Korean Health Insurance Database. *Clin Ther*. 2017;39(3):527–36. doi:10.1016/j.clinthera.2017.01.025.
4. Network TGA. Global Asthma Report 2014. The Global Asthma Network[Internet]. 2014. [cited 2017 August 3]. Available from: <http://www.globalasthmareport.org/>.
5. Anderson DE, Kew KM, Boyter AC. Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus the same dose of ICS alone for adults with asthma. *Cochrane Database Syst Rev*. 2015(8). Article. No.: CD011397. DOI:10.1002/14651858.CD011397.pub2.
6. Evans DJ, Kew KM, Anderson DE, Boyter AC. Long-acting muscarinic antagonists (LAMA) added to inhaled corticosteroids (ICS) versus higher dose ICS for adults with asthma. *Cochrane Database Syst Rev*. 2015(7) Article. No.:CD011437. DOI: 10.1002/14651858.CD011437.pub2.
7. Rodrigo GJ, Castro-Rodriguez JA. What is the role of tiotropium in asthma?: a systematic review with meta-analysis. *Chest*. 2015;147(2):388–96. doi:10.1378/chest.14-1698.
8. Vogelberg C, Engel M, Moroni-Zentgraf P, Leonaviciute-Klimantaviciene M, Sigmund R, Downie J, et al. Tiotropium in asthmatic adolescents symptomatic despite inhaled corticosteroids: a randomised dose-ranging study. *Respir Med*. 2014;108(9):1268–76. doi:10.1016/j.rmed.2014.06.011.
9. Bateman E, Kornmann O, Schmidt P, Pivovarov A, Engel M, Fabbri L. Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma. *J Allergy Clin Immunol*. 2011;128(2):315–22. doi:10.1016/j.jaci.2011.06.004.
10. clinicaltrials. Glossary of Common Site Terms. clinicaltrials[Internet]. 2017. [cited 2017 August 3] Available from: <https://clinicaltrials.gov/ct2/about-studies/glossary>
11. JPT H, S G. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration[Internet]. 2011 March [cited 2017 August 3]. Available from: www.handbook.cochrane.org.
12. Peters SP, Kunselman SJ, Icitovic N, Moore WC, Pascual R, Ameredes BT, et al. Tiotropium bromide step-up therapy for adults with uncontrolled asthma. *New Engl J Med*. 2010;363(18):1715–26. doi:10.1056/NEJMoa1008770.
13. Beeh K, Moroni-Zentgraf P, Ablinger O, Hollaenderova Z, Unseld A, Engel M, et al. Tiotropium Respimat® in asthma: a double-blind, randomised, dose-ranging study in adult

- patients with moderate asthma. *Respir Res.* 2014;15:61. doi:10.1186/1465-9921-15-61.
14. Timmer W, Moroni-Zentgraf P, Cornelissen P, Unseld A, Pizzichini E, Buhl R. Once-daily tiotropium Respimat(R) 5 mug is an efficacious 24-h bronchodilator in adults with symptomatic asthma. *Respir Med.* 2015;109(3):329–38. doi:10.1016/j.rmed.2014.12.005.
 15. Paggiaro P, Halpin D, Buhl R, Engel M, Zubek V, Blahova Z, et al. The effect of tiotropium in symptomatic asthma despite low- to medium-dose inhaled corticosteroids: a randomized controlled trial. *J Allergy Clin Immunol: In Pract.* 2016;4(1):104–13.e2. doi:10.1016/j.jaip.2015.08.017.
 16. Busse WW, Dahl R, Jenkins C, Cruz AA. Long-acting muscarinic antagonists: a potential add-on therapy in the treatment of asthma? *Eur Respir Rev: An Off J Eur Respir Society.* 2016;25(139):54–64. doi:10.1183/16000617.0052-2015.
 17. Ding B, Small M. Disease burden of mild asthma: findings from a cross-sectional real-world survey. *Adv Ther.* 2017;34(5):1109–27. doi:10.1007/s12325-017-0520-0.
 18. Anzueto A, Wise R, Calverley P, Dusser D, Tang W, Metzendorf N, et al. The Tiotropium safety and performance in respimat® (TIOSPIR®) trial: spirometry outcomes. *Respir Res* [Internet]. 2015;16:107. Available from: <http://online.library.wiley.com/o/cochrane/clcentral/articles/075/CN-01092075/frame.html>. doi:10.1186/s12931-015-0269-4.
 19. Adams KS, Lowe DK. Tiotropium for adults with inadequately controlled persistent asthma. *Ann pharmacother.* 2013;47(1):117–23. doi:10.1345/aph.1R502.