CHEST

# What Is the Role of Tiotropium in Asthma?
## A Systematic Review With Meta-analysis

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**BACKGROUND:** The role of tiotropium for the treatment of asthma has not yet been clearly defined. The aim of this systematic review was to assess the efficacy and safety of tiotropium in patients with asthma.

**METHODS:** Randomized placebo-controlled trials were included. Primary outcomes were peak and trough $FEV_1$ and morning and evening peak expiratory flow (PEF).

**RESULTS:** Thirteen studies (4,966 patients) were included. Three different therapeutic protocols were identified. Tiotropium as an add-on to inhaled corticosteroids (ICSs) showed statistically and clinically significant increases in PEF (22-24 L/min) and $FEV_1$ (140-150 mL). Additionally, tiotropium decreased the rate of exacerbations (number needed to treat for benefit [NNTB], 36) and improved asthma control. The use of tiotropium in patients poorly controlled despite the use of medium to high doses of ICS was not inferior to salmeterol. Finally, the use of tiotropium as an add-on to ICS/salmeterol combination increased pulmonary function to a clinically significant magnitude, reduced asthma exacerbations (relative risk, 0.70; 95% CI, 0.53-0.94; $P < .02$; $I^2 = 0\%$; NNTB, 17), and improved asthma control compared with ICS/salmeterol. Tiotropium was well tolerated, and no potential safety signals were observed.

**CONCLUSIONS:** Tiotropium resulted noninferiorly to salmeterol and superiorly to placebo in patients with moderate to severe asthma who were not adequately controlled by ICS or ICS/salmeterol. Major benefits were concentrated in the increase in lung function and in the case of patients with severe asthma, in the reduction of exacerbations. CHEST 2015; 147(2):388-396

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**ABBREVIATIONS:** ACQ-7 = Asthma Control Questionnaire 7; AE = adverse event; AQLQ = Asthma Quality of Life Questionnaire; ICS = inhaled corticosteroid; LABA = long-acting $\beta_2$-agonist; MCID = minimal clinically important difference; NNTB = number needed to treat for benefit; OD = once daily; PEF = peak expiratory flow; RCT = randomized controlled trial; SAE = serious adverse event

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Since the early 1970s, there has been a renewed interest in the use of anticholinergics, given the need to develop alternatives to therapy with $\beta_2$-agonist agents. In acute severe asthma, the addition of ipratropium bromide to $\beta_2$-agonists has been shown to reduce hospital admissions and improve respiratory function more than $\beta_2$-agonists alone,[1,2] whereas in chronic asthma, use of short-acting anticholinergic agents resulted in less bronchodilation than have $\beta_2$-agonists.[3]

A group of studies evaluated the potential benefits and safety of the use of tiotropium bromide (the first long-acting anticholinergic agent) for the treatment of symptomatic asthma.[4-6] The evidence from these and other studies were partially analyzed by two published reviews. The first was a systematic review without meta-analysis that included five randomized controlled trials (RCTs),[7] and the second[8] was a systematic review with a meta-analysis based on six RCTs. Both reviews concluded that tiotropium may play a beneficial role in the treatment of inadequately controlled asthma, compared with placebo, without an increase in adverse events (AEs). However, based on the small number of studies and the low accuracy of their conclusions, we conducted a new systematic review to clarify the role of tiotropium in the treatment of patients with asthma. The objective was to assess the efficacy and safety of tiotropium in symptomatic patients with asthma with various levels of severity and therapeutic protocols.

## Materials and Methods

### *Search and Selection Criteria*

This study was registered with the International Prospective Register of Systematic Reviews (PROSPERO) (http://www.crd.york.ac.uk/PROSPERO) as CRD42014009840. We adopted PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to perform this review.[9] We identified published studies from Medline, Embase, CINAHL, Scopus, and CENTRAL (Cochrane Central Register of Controlled Trials) (September 2014) databases and ClinicalTrials.gov using the following search terms: "tiotropium OR Ba 679 BR OR Spiriva AND asthma." Additionally, we performed a search of relevant files from the drug manufacturer's database. The search was without language restriction and included unpublished studies. Trials published solely in abstract form were excluded because the methods and results could not be fully analyzed.

To be included, studies had to meet all the following criteria: (1) adults and adolescents aged $>12$ years with symptomatic stable asthma of any severity and receiving inhaled corticosteroids (ICSs) or an ICS plus long-acting $\beta_2$-agonist (LABA); (2) RCT (parallel group or crossover) of $\geq 4$ weeks duration; (3) comparison of inhaled tiotropium (5 μg once daily [OD] through a Respimat inhaler [Boehringer Ingelheim GmbH], 18 μg through a HandiHaler [Boehringer Ingelheim GmbH], or any device) with any treatment; and (4) report of at least one of the following outcomes: pulmonary function in terms of peak or trough $FEV_1$ and morning or evening peak expiratory flow (PEF) rate as primary outcomes and rescue medication use (puffs/d), asthma symptom-free days per week, quality of life (Mini-Asthma Quality of Life Questionnaire [AQLQ] total score),[10] asthma control (Asthma Control Questionnaire 7 [ACQ-7] total score),[11] ACQ-7 responder rate determined by the percentage of patients with an improvement (decrease) in the ACQ-7 total score of at least 0.5 points, asthma exacerbations (number of patients with one or more episodes that required the use of systemic corticosteroids), withdrawals (total and due to AEs), and safety (AEs and serious adverse events [SAEs]) as secondary outcomes. For both the AQLQ and the ACQ-7, the minimal clinically important difference (MCID) is 0.5 units.[10,11] An SAE was defined as any untoward medical occurrence that sometimes results in death, is life threatening, requires inpatient hospitalization, or results in persistent or significant disability or incapacity.[12]

### *Data Extraction and Assessment of Risk of Bias*

We independently analyzed titles, abstracts, and citations and from the full text, independently assessed all studies for inclusion based on the criteria for population intervention, study design, and outcomes. After obtaining full reports about potentially relevant trials, we assessed eligibility. We both were independently involved in all stages of study selection, data extraction, and risk-of-bias assessment. The latter was assessed according to recommendations outlined in the Cochrane handbook[13] for the following items: (1) adequacy of sequence generation, (2) allocation concealment, (3) blinding of participants and investigators, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective outcome reporting, and (7) other bias. Disagreements were discussed and resolved by consensus.

### *Data Analysis*

Analysis was by intention to treat and included all participants to minimize bias. Outcomes were pooled using mean differences (inverse variance method) or Mantel-Haenszel risk ratios. The precision of the estimates was quantified by 95% CI. When effect estimates were significantly different between groups, the number needed to treat for benefit (NNTB) or for harm was obtained. Heterogeneity was measured by the $I^2$ test[14] ($\leq 25\%$, absent; 26%-39%, unimportant; 40%-60%, moderate; 60%-100%, substantial). A fixed-effects model was used when there was no evidence of significant heterogeneity in the analysis; if significant heterogeneity was found, a random-effects model was used.[15] As an a priori subgroup analysis, we explored the influence of asthma severity. Subgroups were compared using the residual $\chi^2$ test from the Peto ORs.[16] Potential publication bias was analyzed quantitatively by means of Egger regression using a significance level of $P<.1$.[17] Otherwise, $P<.05$ (two-tailed test) was considered significant. The meta-analysis was performed with Review Manager version 5.3.3 software (The Nordic Cochrane Centre, The Cochrane Collaboration).

## Results

The process of study selection is outlined in Figure 1. Thirteen RCTs including 4,966 patients met the entry criteria.[4,6,18-28] One study included data from two replicate trials.[20] Two replicated trials were presented separately in two different studies.[26,27] Four studies included two different comparisons.[6,18,26,27] Characteristics of the trials are shown in Table 1. The selected studies were grouped into three treatment protocols: (1) tiotropium OD as add-on to ICS in patients with mild to moderate asthma,[6,18,21-28] (2) tiotropium OD added to ICS vs bid LABA plus ICS in patients with moderate