

TITLE: Tiotropium Compared with Ipratropium for Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease: A Review of the Clinical Effectiveness

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CONTEXT AND POLICY ISSUES

Chronic obstructive pulmonary disease (COPD) is a major respiratory illness affecting over 700,000 Canadians and is preventable and treatable, but not curable.¹ It is the fourth leading cause of death in Canada, with mortality rates increasing over the past fifteen years, especially in women.² According to the Canadian Institute for Health Information, COPD accounts for the highest rate of hospital admission and readmission among major chronic diseases in Canada. Exacerbations are the principal cause of hospitalizations.³

This disorder resonates largely in smokers, both former and current. It is characterized by progressive airway obstruction, inflammation, limited expiratory flow with subsequent lung hyperinflation and increasing frequency and severity of exacerbations.² COPD can be classified by both symptoms and by impairment of lung function tests, known as spirometry. The Canadian Thoracic Society defines moderate COPD as “shortness of breath from COPD causing the patient to stop after walking approximately 100m (or after a few minutes on the level)” and severe COPD as “shortness of breath from COPD resulting in the patient being too breathless to leave the house, breathless when dressing or undressing, or the presence of chronic respiratory failure or clinical signs of right heart failure.”² Post-bronchodilator forced expiratory volume in one second (FEV₁) to forced vital capacity (FVC) ratio less than 0.7 is diagnostic of COPD. A lower FEV₁ indicates poorer lung function and limited expiratory flow. COPD classification based on spirometry post-bronchodilator is as follows: for moderate COPD 50% ≤ FEV₁ <80% predicted, and for severe COPD 30% ≤ FEV₁ <50% predicted.²

Management should be patient focused, consisting of a combination of risk factor reduction, pharmacotherapy, education, pulmonary rehabilitation, and exercise programs to improve symptoms and activity levels, reduce exacerbations, and improve or maintain overall quality of life. Smoking cessation is the most effective intervention that reduces the risk of developing COPD and the only intervention that has been shown to slow the rate of lung function decline.² Pharmacotherapy is introduced in a step wise approach. Bronchodilators are the cornerstone of COPD therapy and include inhaled short and long acting β₂ agonists and short and long acting anticholinergics.² They act by decreasing airway smooth muscle tone, which increases

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expiratory flow rates and reduces hyperinflation with a subsequent reduction in dyspnea, improved exercise tolerance, and health status.² The two anticholinergics available in Canada are ipratropium bromide, a short acting agent available as nebulas and metered dose inhaler dosed up to four times a day and tiotropium bromide, a long acting agent available as capsules that are inhaled via a Handihaler device with once daily dosing.² Ipratropium and tiotropium are recommended separately for the treatment of COPD.²

A Rapid Response regarding this topic was produced by CADTH in 2009,⁴ with the conclusion that, "...spirometry measures typically did not differ between treatments over this time period. Further, symptoms of COPD did not differ between tiotropium and ipratropium and other important outcomes such as functional capacity and quality of life was not assessed..."⁴ There is still continuing pressure for policy makers to provide tiotropium as a general benefit. A review of the literature for new evidence regarding the clinical effectiveness of ipratropium compared to tiotropium may help to clarify if a change in policy is warranted.

RESEARCH QUESTION

What is the clinical effectiveness of tiotropium compared with ipratropium for the treatment of patients with moderate to severe chronic obstructive pulmonary disease?

KEY MESSAGE

Tiotropium appears to help improve objective lung function test measures, reduce the proportion of patients with ≥ 1 exacerbation, and improve COPD-related symptoms. There were conflicting results between the two included reports regarding a reduction in frequency of exacerbations. The use of tiotropium did not demonstrate a survival benefit

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2012, Issue 7), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses and randomized controlled trials. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between Nov 2009 and Jul 30, 2012.

Selection Criteria and Methods

One reviewer screened the titles and abstracts of the retrieved publications and evaluated the full-text publications for the final article selection, according to selection criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults with moderate to severe COPD
Intervention	Tiotropium bromide
Comparator	Ipratropium bromide
Outcomes	Clinical effectiveness: pulmonary function, chronic activity related dyspnea, health status
Study Designs	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized control trials (RCTs)

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria in Table 1, if they were published prior to 2009, duplicate publications of the same study, or included in a selected health technology assessment or systematic review. A systematic review was excluded if all its selected studies had been included in a newer systematic review.

Critical Appraisal of Individual Studies

The methodological quality of health technology assessments and systematic reviews were assessed using the Assessment of Multiple Systematic Reviews (AMSTAR) checklist.⁵ A numeric score was calculated and the strengths and limitations of the study were described.

SUMMARY OF EVIDENCE**Quantity of Research Available**

The literature search yielded 165 citations. Upon screening titles and abstracts, seven potentially relevant articles were retrieved for full-text review. Ten additional relevant reports were retrieved from other sources. Of the 17 potentially relevant articles, two were included in this review. There is one health technology assessment and one systematic review with meta-analysis. The study selection process is outlined in a PRISMA flowchart (Appendix 1).

Summary of Study Characteristics

A summary of the study characteristics can be found in Appendix 2.

Health Technology Assessment (HTA)⁶

The HTA by Neyt et al. was published in 2009 by the Belgian Health Care Knowledge Center. Reimbursement for tiotropium was granted on March 2004, with a planned re-evaluation of the reimbursement decision required 36 months later. The re-evaluation concluded there was no additional benefit with tiotropium use; however, reimbursement guidelines did not change. This HTA was conducted to assess new literature, with the purpose of evaluating the efficacy of tiotropium in COPD patients on outcomes relevant to patients. Sixteen RCTs were included in the systematic review and meta-analysis. Studies were identified that compared tiotropium to placebo, ipratropium, salmeterol, or salmeterol/fluticasone. Duration of studies ranged from

three to forty-eight months. Staging of COPD disease severity was based on the degree of airflow limitation as per the Global Initiative for Chronic Obstructive Lung Disease (GOLD).⁷ One included trial compared tiotropium to ipratropium in a study of 535 patients and follow up was 52 weeks. Patients were required to have a FEV₁ of $\leq 65\%$ of the predicted normal value and $\leq 70\%$ of FVC, ≥ 40 years of age, and smoking history of ≥ 10 pack years. Patients were excluded if they had a history of asthma, allergic rhinitis, or atopy or an elevated total blood eosinophil count, required supplemental oxygen, had a recent upper respiratory tract infection, or a significant disease other than COPD. Primary endpoints included exacerbations, hospitalizations, and mortality. Secondary endpoints included quality of life and dyspnea captured by the St. George's Respiratory Questionnaire (SGRQ) and Transitional Dyspnea Index (TDI), respectively.

Systematic Review⁸

Wu et al., in 2009, conducted a systematic review and meta-analysis to assess the safety and efficacy of tiotropium in Chinese patients with stable COPD. A comprehensive search of the literature for RCTs of tiotropium in Chinese patients produced 11 RCTs (n=1006 patients), with placebo (5 trials) and ipratropium (6 trials) as comparators. Patients had stable COPD defined by the diagnostic criteria of the China Medical Association in 2002, the GOLD Guidelines (2003 update), or the Taiwanese Society of Pulmonary and Critical Medicine 2003 with no history of an exacerbation in the month prior to study entry. The outcomes evaluated included FEV₁, FEV₁%, symptoms, frequency of exacerbations, and adverse events. Study duration ranged from four weeks to six months.

Summary of Critical Appraisal

The strengths and limitations of included studies are summarized in Appendix 3.

The methodological quality assessment of the two reports met most AMSTAR criteria. Both systematic reviews performed comprehensive literature searches with study selection and data extraction performed by two independent reviewers. Unmet AMSTAR criteria included (i) providing a list of excluded studies and (ii) appropriately considering the scientific quality of the included studies in formulating conclusions. Though both reviews, scored well per AMSTAR criteria, they are limited by the quality and quantity of included trials that directly compared tiotropium to ipratropium.

Summary of Findings

The main study findings and authors' conclusions from the reviews can be found in Appendix 4.

Health Technology Assessment⁶

Neyt et al. found when compared to ipratropium, tiotropium resulted in statistically significant reductions in the proportion of patients experiencing ≥ 1 exacerbation and the frequency of exacerbations and COPD related hospitalizations, and a statistically significant improvement in quality of life (St. George's Respiratory Questionnaire) and dyspnea (Transitional Dyspnea Index). No difference was observed for the proportion of patients with ≥ 1 hospitalization or mortality outcomes. Regarding safety, patients using tiotropium experienced statistically significant higher rates of dry mouth and urinary tract infections. Some data signaled a possible increased risk for arrhythmia, but statistical significance was not reported.

Systematic Review⁸

Wu et al found when compared to ipratropium, tiotropium resulted in statistically significant improvement in FEV₁, FEV₁%, and symptoms, assessed using *The Clinical Guidelines for New Medicines* enacted by the Department of Health of China. However, no statistical difference was observed in frequency of exacerbations or adverse events.

Limitations

The strengths and limitations of included studies are summarized in Appendix 3.

Despite the methodological strength of these large systematic reviews that focused on a variety of patient-focused and clinically important outcomes and use appropriate comparator dose of ipratropium, there are multiple limitations that influence both internal and external validity. The sample of patients in Neyt's review comes from a single study and as a result conclusions are based on a single finding. The duration of follow up was variable (Neyt, 52 weeks, Wu, 4 weeks to 6 months) and in some instances may be of inadequate length to observe the long term treatment or side effects, as COPD is a chronic progressive disease. The differing or lack of definitions of exacerbations in each review limits interpretability and generalizability. Specific limitations with respect to the single trial with ipratropium as a comparator (from Neyt) were inability to confirm adequate sequence generation and unclear allocation concealment. Patients and personnel were blinded, but it is unclear if outcome assessors were. The study did not include non-smokers, which limits relevance to a broader population and was sponsored by Boehringer Ingelheim, the manufacturer of tiotropium. Limitations from Wu include a symptom score tool specific to China (*The Clinical Guidelines for New Medicines* enacted by the Department of Health China) and no statement with regards to reliability and validity or a minimally clinical difference in score. There is also no quality of life, exercise tolerance, or mortality data. Both reviews were conducted in regions external to Canada based on different COPD guidelines, which may limit generalizability.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Based on two RCTs, a 2009 CADTH report concluded, "patients with moderate to severe COPD who were treated with tiotropium experienced larger increases in FEV₁ than in patients treated with ipratropium after 4-12 weeks of treatment. However, other spirometry measures typically did not differ between treatments over this time period. Further, symptoms of COPD did not differ between tiotropium and ipratropium and other important outcomes such as functional capacity and quality of life were not assessed. Thus, it is unclear whether the larger gain in FEV₁ that was experienced by patients treated with tiotropium was clinically important or significant from a patient perspective. As such, other factors such as ease of administration, dosing frequency, and cost may be important points to consider when making policy decisions about coverage for these two agents."p.5⁶

Since the above report, high quality evidence focusing on the clinical effectiveness of tiotropium compared with ipratropium for the treatment of patients with moderate to severe chronic obstructive pulmonary disease has failed to be captured. Some differences in outcomes observed in the two recent reports were statistically significant; however, validity of findings and clinical significance were unclear. Ease of administration, dosing frequency, and compliance were not assessed. Cost was assessed by Neyt; however, the model was specific to Belgium

and beyond the scope of this report. It does not appear that the two reviews substantially help to clarify a definitive course of action with regard to deciding to cover tiotropium as a benefit.

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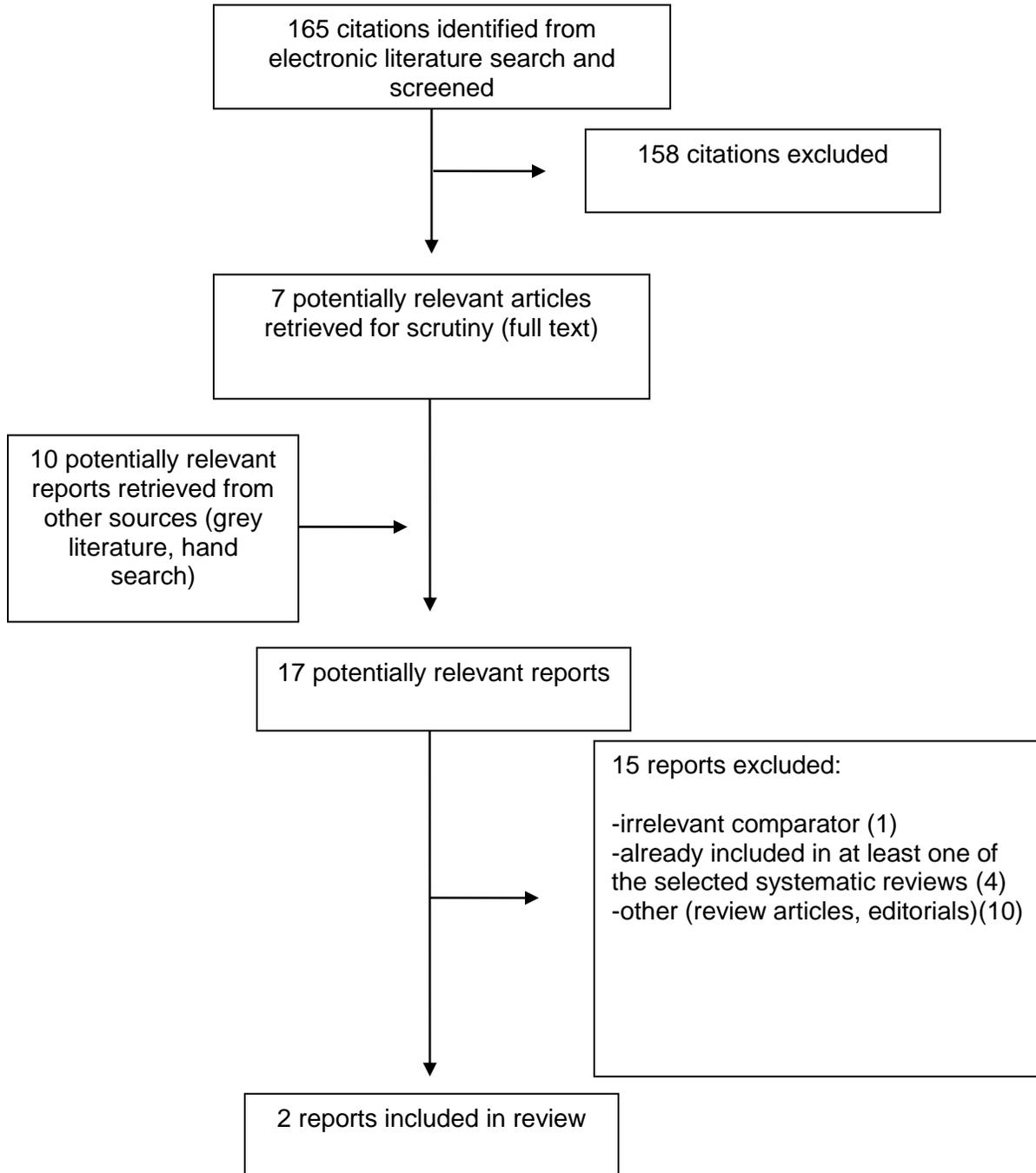
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APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Studies

First Author, Publication Year, Country	Study Design/ Length of Follow-up	Patient Characteristics, Sample Size (n)	Intervention	Comparator(s)	Clinical Outcomes
Neyt, 2009 ⁶ Belgium	HTA (SR and MA) Follow up: 3-48 months (1 trial with ipratropium =52 weeks)	16 RCTs (1 trial of tiotropium vs. ipratropium n=535 patients)	Tiotropium	Placebo Ipratropium Salmeterol +/- Fluticasone	<u>Primary</u> <ul style="list-style-type: none"> •Exacerbations •Hospitalization •Mortality <u>Secondary</u> <ul style="list-style-type: none"> •SGRQ •TDI
Wu, 2009 ⁸ China	SA & MA Follow up: 4 weeks to 6 months	11 RCTs Chinese patients with stable COPD (6 trials of tiotropium vs. ipratropium n= 759 patients)	Tiotropium	Placebo Ipratropium	<u>Primary</u> <ul style="list-style-type: none"> •FEV₁ •FEV₁% <u>Secondary</u> <ul style="list-style-type: none"> • Symptoms • Frequency of exacerbations • Adverse events & safety

HTA=health technology assessment; **SR**= systematic review; **MA**=meta-analyses; **RCTs**=randomized control trials; **SGRQ**=St. George Respiratory Questionnaire; **TDI**= Transitional Dyspnea Index; **COPD**= chronic obstructive pulmonary disease; **FEV₁**= forced expiratory volume in 1 second; **FEV₁%**= forced expiratory volume in 1 second/forced vital capacity

APPENDIX 3: Summary of Study Strengths and Limitations

First Author, Publication Year	Strengths	Limitations
HTA		
Neyt, 2009 ⁶	<ul style="list-style-type: none"> • The methodological quality of this SR was high as it scored 9 (Yes) out of 11 questions on the AMSTAR⁹ checklist • A comprehensive search was performed 	<ul style="list-style-type: none"> • List of excluded studies was not provided in the primary publication • It was unclear whether the scientific quality of the included studies was used appropriately in formulating conclusions. • The quality and quantity of studies was lacking and stated conclusion only addressed salmeterol comparator
Systematic Review and Meta-analysis		
Wu, 2009 ⁸	<ul style="list-style-type: none"> • The methodological quality of this SR was high as it scored 9 (Yes) out of 11 questions on the AMSTAR⁹ checklist • A comprehensive search was performed • Quality of the 6 studies with ipratropium as comparator ranged from 3-5 per Jadad's criteria¹⁰ (<3=low quality) • There was clinical homogeneity amongst the studies 	<ul style="list-style-type: none"> • List of excluded studies was not provided in the primary publication • It was unclear whether the scientific quality of the included studies were used appropriately in formulating conclusions • It was unclear what stage of COPD the patients were experiencing, which makes it challenging to assess the conclusion of tiotropium as a first line agent
<p>AMSTAR⁹ check list</p> <ol style="list-style-type: none"> 1. Was an "a priori" design provided? 2. Was there duplicate study selection and data extraction? 3. Was a comprehensive literature search performed? 4. Was the status of publication (i.e., grey literature) used as an inclusion criteria? 5. Was a list of studies (included and excluded) provided? 6. Were the characteristics of the included studies provided? 7. Was the scientific quality of the included studies assessed and documented? 8. Was the scientific quality of the included studies used appropriately in formulating conclusions? 9. Were the methods used to combine the findings of studies appropriate? 10. Was the likelihood of publication bias assessed? 11. Was the conflict of interest stated? 		

SR=systematic review; **AMSTAR**=A Measurement Tool to Assess the Methodological Quality of Systematic Reviews; **COPD**=chronic obstructive pulmonary disease

APPENDIX 4: Main Study Findings and Authors' Conclusions

First Author, Publication Year	Main Study Findings	Author's Conclusions
Neyt, 2009 ⁶	<p><u>Exacerbations</u> Proportion of patients experiencing ≥ 1 exacerbation -Tiotropium vs. Ipratropium</p> <ul style="list-style-type: none"> • OR 0.64, 95% CI 0.44-0.92 • Absolute difference 11%, 95% CI 2-20 <p>Exacerbation frequency -Tiotropium vs. Ipratropium</p> <ul style="list-style-type: none"> • -0.23 exacerbations per patient year, 95%CI -0.31- (-0.15) <p>Time to first exacerbation was statistically significantly longer in patients receiving tritropium (p=0.008)</p> <p><u>Hospitalizations for COPD Exacerbation</u> Proportion of patients with ≥ 1 hospitalization -Tiotropium vs. Ipratropium</p> <ul style="list-style-type: none"> • OR 0.59, 95% CI 0.32-1.09 <p>Hospitalization frequency -Tiotropium vs. Ipratropium</p> <ul style="list-style-type: none"> • OR -0.06 hospitalizations per patient year, 95%CI -0.09- (-0.03) <p>Mortality -Tiotropium vs. Ipratropium</p> <ul style="list-style-type: none"> • OR 1.52, 95% CI 0.41-5.69 <p>QOL (SGRQ) -Tiotropium vs. Ipratropium</p> <ul style="list-style-type: none"> • OR 1.99, 95% CI 1.38-2.89 • Absolute risk difference 17%, 95% CI 8-25 • NNT 6 (x52 weeks) <p>Dyspnea (TDI) -Tiotropium vs. Ipratropium</p> <ul style="list-style-type: none"> • OR 2.05, 95% CI 1.32-3.20 • Absolute risk difference 13%, 95% CI 6-20 • NNT 8 (x52 weeks) 	No conclusion was stated regarding the comparison between tiotropium and ipratropium.
Wu, 2009 ⁸	<p><u>FEV₁</u> -Tiotropium vs. Ipratropium</p> <ul style="list-style-type: none"> • WMD 307mL, 95% CI 273-340 • P<0.00001 	"Tiotropium improved pulmonary function and symptoms, reduced exacerbations and was

First Author, Publication Year	Main Study Findings	Author's Conclusions
	<p><u>FEV₁%</u> -Tiotropium vs. Ipratropium</p> <ul style="list-style-type: none"> • WMD 10.60%, 95% CI 6.53-14.67 • P<0.00001 <p><u>Symptom improvement</u> -Tiotropium vs. Ipratropium</p> <ul style="list-style-type: none"> • RR (fixed) 1.74, 95% CI 1.31-2.30 • P=0.0001 • NNT 6 per year <p><u>Frequency of exacerbations</u> -Tiotropium vs. Ipratropium</p> <ul style="list-style-type: none"> • RR (fixed) 0.70, 95% CI 0.13-3.75 • P=0.70 <p><u>Adverse events & safety</u> -Tiotropium vs. Ipratropium</p> <ul style="list-style-type: none"> • RR (fixed) 0.99, 95% CI 0.63-1.57 • P=0.98 	<p>well tolerated and safe. On the basis of its efficacy and safety profile, tiotropium appears to be a reasonable first-line choice for the management of Chinese patients with stable COPD. Additional long-term RCTs are required to further evaluate the efficacy and safety of tiotropium.” p.666</p>

OR=odds ratio; **CI**=confidence interval; **COPD**=chronic obstructive pulmonary disease; **QOL**= quality of life; **SGRQ**=St. George's Respiratory Questionnaire; **NNT**=number needed to treat; **TDI**=Transitional Dyspnea Index; **FEV₁**= forced expiratory volume in 1 second; **FEV₁%**= forced expiratory volume in 1 second/forced vital capacity; **WMD**=weighted mean difference; **RR**= relative risk; **RCTs**= randomized control trials