PMID	Digital Object ID	Citation	Article Title
30212239	10.1080/02770903.2018.1514047	J Asthma. 2018 Sep 13:1-9. doi: 10.1080/02770903.2018.1514047. [Epub ahead of print]	Comparison between montelukast and tiotropium as add-on therapy to inhaled corticosteroids plus a long-acting β2-agonist in for patients with asthma.
30193393	10.1055/a-0665-4379	Drug Res (Stuttg). 2018 Sep 7. doi: 10.1055/a-0665-4379. [Epub ahead of print]	A Single Institution Retrospective Study of the Clinical Efficacy of Tiotropium Respimat in Never-Smoking Elderly Asthmatics with Irreversible Airflow Limitation.
30085989	10.1097/JXX.0000000000000053	J Am Assoc Nurse Pract. 2018 Aug;30(8):460-463. doi: 10.1097/JXX.0000000000000053.	Tiotropium for asthma: **A summary of current guidelines and a case study**.

Abstract	Status	
Asthma often remains uncontrolled despite treatment with inhaled corticosteroids (ICS) alone or with ICS plus a long-acting β2-agonist (LABA). The recommended alternative is the addition of either montelukast or tiotropium. The aim of this study was to compare the effects of montelukast and tiotropium on airway inflammation and remodeling in persistent asthma.Eighty-seven patients with asthma were treated with budesonide and formoterol (640/18 μg); then, the patients were randomly allocated to three groups to receive oral montelukast (10 mg/day), inhaled **tiotropium (5 μg/day)**, or no add-on to the maintenance therapy for 48 weeks. Fractional exhaled nitric oxide (FeNO) and pulmonary function were measured, and quantitative computed tomography was performed.Compared to the maintenance therapy, add-on montelukast significantly decreased FeNO ($p < 0.05$) and improved airflow obstruction ($p < 0.05$), whereas airway dimensions remained unchanged. Changes in FeNO were significantly correlated with changes in FEV1 ($r = -0.71$, $p < 0.001$). In contrast, the addition of tiotropium significantly decreased airway wall area corrected for body surface area (WA/BSA) ($p < 0.05$), decreased wall thickness ($T/\sqrt{BSA}$) ($p < 0.05$) and improved airflow obstruction ($p < 0.05$) with no change in FeNO. Changes in WA/BSA and $T/\sqrt{BSA}$ were significantly correlated with the change in percentage predicted FEV1 ($r = -0.84$, $p < 0.001$ and $r = -0.59$, $p < 0.01$, respectively).Adding either montelukast or tiotropium to ICS/LABA may provide additive benefits with respect to the pulmonary function and airway inflammation or remodeling in patients with asthma.	excluded	did not meet inclusion criteria
In Japan, most asthma deaths occur among the elderly. We should improve the control of asthma in elderly patients to reduce the number of deaths due to asthma. This retrospective study aimed to evaluate the efficacy of tiotropium Respimat® (Tio-Res) in symptomatic, never-smoking, elderly asthmatics with irreversible airflow limitation despite the use of high-dose inhaled corticosteroids (ICS) plus long-acting β2-adrenoceptor agonists (LABA).The Asthma Control Test™ (ACT), pulmonary function tests, morning and evening peak flow (mPEF, ePEF, respectively, evaluated with an ASSESS® peak flow meter), and respiratory impedance (assessed with MostGraph®) were measured before and after a minimum of one year of Tio-Res 5 μg/day administration. Sixteen symptomatic, never-smoking asthmatics, aged 75 or over with irreversible airflow limitation despite the use of high-dose ICS plus LABA, were analyzed.All patients were female (mean age, 81.6 years). Tio-Res led to statistically significant improvements in the total ACT score (19.9 to 23.6), FVC and FEV1 (1.97 to 2.14 L and 1.13 to 1.23 L, respectively), and mPEF and ePEF (229.9 to 253.8 L/min and 259.8 to 277.4 L/min, respectively). Tio-Res also resulted in statistically significant improvements in respiratory resistance at 5 Hz (R5), respiratory resistance at 20 Hz (R20), R5-R20, low-frequency reactant indices at 5 Hz (X5), resonant frequency (Fres) and low-frequency reactance area (ALX).Our retrospective study suggests that Tio-Res improves symptoms, pulmonary function, and respiratory impedance in symptomatic asthmatics aged 75 or over with irreversible airflow limitation despite the use of high-dose ICS plus LABA.	excluded	did not meet inclusion criteria
The long-acting muscarinic antagonist tiotropium received an indication for the treatment of asthma from the FDA in 2015.This paper summarizes much of the published findings on tiotropium and asthma and explores the heterogeneity of the asthma population vis-à-vis recent changes in guidelines for management of COPD. The accompanying case study provides an illustration of how tiotropium might be added to a patient's regimen appropriately.Tiotropium has been shown in many studies to be beneficial to patients with asthma as an add-on medication. It should be considered as an agent by the clinician managing patients with both allergic and non-allergic asthma.	excluded	Case study

Not a Ph3 study	Use of Respimat	Evaluation of 2.5 ug dose	Reporting lung function	Reason for exclusion	Journal: Title	Journal: NLM ID
		No		Tiotropium 2.5 µg dose not evaluated	The Journal of asthma : official journal of the Association for the Care of Asthma	8106454
		No		Tiotropium Respimat 2.5 µg dose was not evaluated	Drug research	101602406
				Not an RCT (not a ph 3 RCT)	Journal of the American Association of Nurse Practitioners	101600770

Journal: Year	Journal: Month	Journal: Medline Date	Journal: Volume	Journal: Issue	Journal: Medline Pagination	Citation Medium	First Author (First Last)	All Authors (Last, Initials)	Affiliation
2018	Sep				1-9	Internet	Makoto Hoshino	Hoshino, M; Akitsu, K; Ohtawa, J	a Division of Clinical Allergy, Department of Internal Medicine, Atami Hospital , International University of Health and Welfare , Atami , Japan.
2018	Sep					Internet	Johsuke Hara	Hara, J; Kasahara , K; Ohkura, N; Yamamura, K; Sakai, T; Abo, M; Ogawa, N; Saeki, K; Koba, H; Watanabe, S; Uchida, Y; Tambo, Y; Sone, T; Kimura, H	Respiratory Medicine, Kanazawa University Hospital, Kanazawa, Ishikawa, Japan.
2018	Aug		30	8	460-463	Internet	Glenn Clinton Shedd	Shedd, GC; Blenis, RC	Emory University Nell Hodgson Woodruff School of Nursing, Atlanta, Georgia.

30069364	10.21037/jtd.2018.05.139	J Thorac Dis. 2018 Jun;10(6):3661-3669. doi: 10.21037/jtd.2018.05.139.	Clinical predictors of the effectiveness of tiotropium in adults with symptomatic asthma: **a real-life study**.
29605203	10.1016/j.rmed.2018.03.010	Respir Med. 2018 Apr;137:181-190. doi: 10.1016/j.rmed.2018.03.010. Epub 2018 Mar 7.	**In vitro and clinical characterization of the valved holding chamber AeroChamber Plus® Flow-Vu®** for administrating tiotropium Respimat® in 1-5-year-old children with persistent asthmatic symptoms.

Long-acting muscarinic antagonist (LAMA) tiotropium improved lung function and reduced risks of exacerbation when added on to inhaled corticosteroids (ICS) with or without long-acting B2 agonists (LABAs) in patients with uncontrolled asthma. However, studies predicting the effectiveness of tiotropium based on patients' clinical characteristics were limited.We conducted this retrospective study at a single medical center from July 2016 to July 2017, and used asthma control test (ACT) to evaluate the effectiveness of tiotropium add-on therapy in patients with uncontrolled asthma. The effectiveness was shown by an increase in ACT score from baseline of 3 or greater after 3 months of tiotropium add-on therapy.Patients with uncontrolled asthma despite the use of low- or medium- to high-dose of ICS plus LABA (n=160) were analyzed. Among patients having good response (n=112, ACT score increased ≥3 points) to tiotropium (TGR group) and patients having poor response (n=48, ACT increased <3 points) to tiotropium (TPR group), their baseline characteristics including age, asthma and chronic obstructive pulmonary disease (COPD) overlap (ACO), cigarette use, initial FEV1, serum IgE level, eosinophil count, and BMI were significantly different. Univariate analysis showed that old age, ACO, cigarette use, initial FEV1 <80%, and BMI >30 were predictors of the effectiveness of tiotropium. Patients with high serum total IgE level >430 μg/L and eosinophil count >0.6×109/L had a negative impact on response to tiotropium. Multivariate logistic regression analysis demonstrated that the independent factor of poor response to tiotropium was high serum IgE level >430 μg/L.Tiotropium add-on therapy in patients with uncontrolled asthma was effective. However, patients with serum total IgE level >430 μg/L were less likely to benefit from tiotropium.	excluded	did not meet inclusion criteria
When characterizing inhalation products, a comprehensive assessment including in vitro, pharmacokinetic (PK), and clinical data is required. We conducted a characterization of tiotropium Respimat® when administered with AeroChamber Plus® Flow-Vu® anti-static valved holding chamber (test VHC) with face mask in 1-5-year-olds with persistent asthmatic symptoms.In vitro tiotropium dose and particle size distribution delivered into a cascade impactor were evaluated under fixed paediatric and adult flow rates between actuation and samplings. The tiotropium mass likely to reach children's lungs was assessed by tidal breathing simulations and an ADAM-III Child Model. PK exposure to tiotropium in preschool children with persistent asthmatic symptoms (using test VHC) was compared with pooled data from nine Phase 2/3 trials in older children, adolescents, and adults with symptomatic persistent asthma not using test VHC.At fixed inspiratory flow rates, emitted mass and fine particle dose decreased under lower flow conditions; dose reduction was observed when Respimat® was administered by test VHC at paediatric flow rates. In <5-year-old children, such a dose reduction is appropriate. In terms of dose per kg/body weight, in vitro-delivered dosing in children was comparable with adults. Transmission and aerosol holding properties of Respimat® when administered with test VHC were fully sufficient for aerosol delivery to patients. At zero delay, particles <5 μm (most relevant fraction) exhibited a transfer efficacy of ≥60%. The half-time was>10 s, allowing multiple breaths. Standardized tidal inhalation resulted in an emitted mass from the test VHC of approximately one-third of labelled dose, independent of coordination and face mask use, indicating predictable tiotropium administration by test VHC with Respimat®. Tiotropium exposure in 1-5-year-old patients using the test VHC, when adjusted by height or body surface, was comparable with that in older age groups without VHCs; no overexposure was observed. Adverse events were less frequent with tiotropium (2.5 μg, n = 20 [55.6%]; 5 μg, n = 18 [58.1%]) than placebo (n = 25 [73.5%]).Our findings provide good initial evidence to suggest that tiotropium Respimat® may be administered with AeroChamber Plus® Flow-Vu® VHC in 1-5-year-old patients with persistent asthmatic symptoms. To confirm the clinical efficacy and safety in these patients, additional trials are required.The trial was registered under NCT01634113 at http://www.clinicaltrials.gov.	excluded	did not meet inclusion criteria

No		No		Tiotropium Respimat 2.5 μg dose was not evaluated; not a ph 3 RCT	Journal of thoracic disease	101533916
No				PK and other data eveluated from multiple studies	Respiratory medicine	8908438

2018	Jun		10	6	3661-3669	Print	Wen-Chien Cheng	Cheng, WC; Wu, BR; Liao, WC; Chen, CY; Chen, WC; Hsia, TC; Tu, CY; Chen, CH; Hsu, WH	Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, China Medical University Hospital, Taichung.
2018	04		137		181-190	Internet	Herbert Wachtel	Wachtel, H; Nagel, M; Engel, M; El Azzi, G; Sharma, A; Suggett, J	Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany. Electronic address: herbert.wachtel@boehringer-ingelheim.com.

29446377		Med Sci Monit. 2018 Feb 15;24:944-950.	Therapeutic Effects of a Long-Acting Cholinergic Receptor Blocker, Tiotropium Bromide, on Asthma.
29422778	10.1186/s12962-018-0089-8	Cost Eff Resour Alloc. 2018 Jan 30;16:3. doi: 10.1186/s12962-018-0089-8. eCollection 2018.	**Cost-effectiveness** of tiotropium versus omalizumab for uncontrolled allergic asthma in US.

BACKGROUND The aim of this study was to evaluate the therapeutic effects of tiotropium bromide on asthma. MATERIAL AND METHODS A total of 160 patients with moderate persistent asthma were randomly divided into 4 groups (n=40): the 3 control groups were given fluticasone propionate aerosol (group A), salmeterol-fluticasone propionate inhalant (group B), and tiotropium bromide inhalation powder combined with salmeterol-fluticasone propionate inhalant (group C), respectively, and the experimental group received **tiotropium bromide inhalation powder** combined with fluticasone propionate aerosol (group D) and salbutamol was used to relieve symptoms when necessary. RESULTS After 8 weeks of treatment, the pulmonary function of group D, which was significantly better than those of group A (P<0.05), was similar to those of groups B and C (P>0.05). Group D had significantly better asthma control test scores and nighttime symptom scores than in group A (P<0.05), without significant differences from those of group B or group C (P>0.05). The number of times salbutamol was used to alleviate symptoms was significantly different (P<0.05) between group D and group A (P<0.05), as well as between group C and group D (P<0.05). Groups D and B had similar results (P>0.05). IL-13 levels in induced sputum had significant differences (P<0.05). The levels in group D, which were higher than those of groups A and B (P<0.05), were similar to those of group C (P>0.05). CONCLUSIONS Tiotropium bromide combined with fluticasone propionate improved the respiratory function and quality of life, and is a new therapy for moderate, persistent asthma.	excluded	did not meet inclusion criteria
A significant minority of asthma patients remain uncontrolled despite the use of inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA). A number of add-on therapies, including monoclonal antibodies (namely omalizumab) and more recently tiotropium bromide have been recommended for this subgroup of patients. The purpose of this study was to assess the cost-effectiveness of tiotropium versus omalizumab as add-on therapies to ICS + LABA for patients with uncontrolled allergic asthma.A probabilistic Markov model of asthma was created. Total costs (in 2013 US $) and health outcomes of three interventions including standard therapy (ICS + LABA), add-on therapy with tiotropium, and add-on therapy with omalizumab, were calculated over a 10-year time horizon. Future costs and quality-adjusted life years (QALYs) were discounted at the rate of 3%. Multiple sensitivity analyses were conducted. Cost-effectiveness was evaluated at willingness-to-pay value of $50,000.The 10-year discounted costs and QALYs for standard therapy were $38,432 and 6.79, respectively. The corresponding values for add-on therapy with tiotropium and with omalizumab were $41,535 and 6.88, and $217,847 and 7.17, respectively. The incremental cost-effectiveness ratios (ICER) of add-on therapy with tiotropium versus standard therapy, and omalizumab versus tiotropium were $34,478/QALY, and $593,643/QALY, respectively. The model outcomes were most sensitive to the costs of omalizumab but were robust against other assumptions.Although omalizumab had the best health outcomes, add-on therapy with tiotropium was a cost-effective alternative to omalizumab and standard therapy for uncontrolled allergic asthma at willingness-to-pay of $50,000/QALY.	excluded	HEOR

	No			Tiotropium not delivered via Respimat®, 2.5 µg dose not evaluated	Medical science monitor : international medical journal of experimental and clinical research	9609063
				Not a ph 3 RCT (HEOR analysis)	Cost effectiveness and resource allocation : C/E	101170476

2018	Feb		24		944-950	Internet	Li Zhang	Zhang, L; Huang, G; Jin, L; Han, S	Department of Respiratory Medicine, Zhongda Hospital, Southeast University, Nanjing, Jiangsu, China (mainland).
2018			16		3	Print	Zafar Zafari	Zafari, Z; Sadatsafavi, M; Mark FitzGerald, J; ,	1Mailman School of Public Health, Columbia University, New York, USA.

29361462	10.1016/S2213-2600(18)30012-2	Lancet Respir Med. 2018 Feb;6(2):127-137. doi: 10.1016/S2213-2600(18)30012-2. Epub 2018 Jan 18.	Safety and efficacy of tiotropium in **children** aged 1-5 years with ***persistent*** asthmatic symptoms: a randomised, double-blind, placebo-controlled trial. **Nino®TinA-asthma (add-on to at least ICS)**
29174062	10.1016/j.jaip.2017.08.037	J Allergy Clin Immunol Pract. 2018 May - Jun;6(3):923-935.e9. doi: 10.1016/j.jaip.2017.08.037 . Epub 2017 Nov 22.	Tiotropium Respimat Add-on Is Efficacious in Symptomatic Asthma, Independent of T2 Phenotype.

Few studies have assessed the safety and efficacy of potential asthma medications in children younger than 5 years. We descriptively assessed the safety and efficacy of tiotropium, a long-acting anticholinergic drug, in children aged 1-5 years with persistent asthmatic symptoms.This exploratory 12-week, randomised, double-blind, placebo-controlled, parallel-group, phase 2/3, regulatory multicentre trial was done at 32 hospitals, clinics, and clinical research units in 11 countries in Asia, Europe, and North America. Children aged 1-5 years with at least a 6-month history of persistent asthmatic symptoms and a need for inhaled corticosteroids were eligible. Patients were randomly allocated using an interactive voice or web-based response system to receive once-daily tiotropium 2·5 μg, tiotropium 5 μg, or placebo as an add-on to inhaled corticosteroids with or without additional controller medication. Patients and investigators were masked to study group assignment. Tiotropium was given via the Respimat inhaler once daily as two puffs of 1·25 μg in the 2·5 μg group, two puffs of 2·5 μg in the 5 μg group, or two puffs of placebo. The primary outcomes were safety, which was assessed by comparing adverse events between the tiotropium and placebo groups, and efficacy, which was measured as the change in weekly mean combined daytime asthma symptom score from baseline to week 12. Statistical analyses of treatment effects were exploratory; although endpoints were defined, they were used for descriptive analyses only. The safety and primary analyses were done in all patients who received at least one dose of their assigned treatment. This study is registered with ClinicalTrials.gov (NCT01634113), and is completed.Between July 26, 2012, and Dec 4, 2014, 102 children were randomly assigned to the three treatment groups (36 to receive tiotropium 2·5 μg, 32 to receive tiotropium 5 μg, and 34 to receive placebo). 101 children completed the study and were included in the analyses. The changes in adjusted weekly mean combined daytime asthma symptom scores between baseline and week 12 were not significantly different between any of the groups. The adjusted mean difference between the tiotropium 2·5 μg group and placebo group was -0·080 (95% CI -0·312 to 0·152) and the difference between tiotropium 5 μg and placebo group was -0·048 (-0·292 to 0·195). Adverse events were less frequent with tiotropium treatment than with placebo (20 [56%] of 36 children with tiotropium 2·5 μg, 18 [58%] of 31 with tiotropium 5 μg, and 25 [74%] of 34 with placebo), although no formal statistical comparison between groups was performed. A greater proportion of children	Included	Inclusions
Adding tiotropium to existing inhaled corticosteroid (ICS) maintenance therapy with or without a long-acting β2-agonist (LABA) has been shown to be beneficial in patients with symptomatic asthma.To assess whether responses to tiotropium Respimat add-on therapy were influenced by patients' T2 status.In this exploratory study, data from 4 phase III trials were analyzed: once-daily tiotropium 5 μg or placebo as add-on to ICS + LABA (PrimoTinA-asthma; 2 replicate trials; NCT00772538/NCT00776984; n = 912); once-daily tiotropium 5 μg or 2.5 μg, twice-daily salmeterol 50 μg, or placebo as add-on to ICS (MezzoTinA-asthma; 2 replicate trials; NCT01172808/NCT01172821; n = 2100). The prespecified efficacy outcomes of these studies have been reported previously. Here, further exploratory subgroup analyses were performed to study whether these coprimary end points were influenced by serum IgE levels, blood eosinophil counts, and clinician judgment of allergic asthma. In addition, for the continuous parameters, namely, IgE and blood eosinophils, their influence on the treatment effect was modeled over the whole range of values.Tiotropium was efficacious in improving peak FEV1 within 3 hours postdose and trough FEV1, independent of T2 status. Tiotropium significantly reduced the risk of severe asthma exacerbations and asthma worsening, independent of T2 phenotype; Cox regression modeling supported a beneficial effect of tiotropium on exacerbations, independent of IgE levels or eosinophil counts. Numerical improvements in the 7-question Asthma Control Questionnaire (ACQ-7) responder rate with tiotropium versus placebo were observed in T2high and T2low patients; logistic regression modeling provided further evidence for improvement in ACQ-7 responder rates with tiotropium, independent of IgE levels or eosinophil counts.The results of our exploratory analyses suggest that the improvements seen with tiotropium Respimat as add-on to ICS ± LABA in patients with symptomatic asthma on lung function, exacerbation risk, and symptom control are independent of T2 phenotype.	excluded	did not meet inclusion criteria

					The Lancet. Respiratory medicine	101605555
		No	no	Primary endpoint not reported; 2.5 ug data not reported; subgroup anlaysis from pooled datasets	The journal of allergy and clinical immunology. In practice	101597220

2018	02		6	2	127-137	Internet	Elianne J L E Vrijlandt	Vrijlandt, EJLE; El Azzi, G; Vandewalker, M; Rupp, N; Harper, T; Graham, L; Szefler, SJ; Moroni-Zentgraf, P; Sharma, A; Vulcu, SD; Sigmund, R; Chawes, B; Engel, M; Bisgaard, H	Department of Pediatric Pulmonology and Pediatric Allergy, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, Netherlands.
		2018 May - Jun	6	3	923-935.e9	Internet	Thomas B Casale	Casale, TB; Bateman, ED; Vandewalker, M; Virchow, JC; Schmidt, H; Engel, M; Moroni-Zentgraf, P; Kerstjens, HAM	Division of Allergy and Immunology, Morsani College of Medicine, University of South Florida, Tampa, Fla. Electronic address: tbcasale@health.usf.edu.

28665534	10.1111/cea.12972	Clin Exp Allergy. 2017 Oct;47(10):1239-1245. doi: 10.1111/cea.12972. Epub 2017 Aug 1.	Bronchoprotective tolerance with indacaterol is not modified by concomitant tiotropium in persistent asthma.
28189771	10.1016/j.jaci.2017.01.014	J Allergy Clin Immunol. 2017 Nov;140(5):1277-1287. doi: 10.1016/j.jaci.2017.01.014 . Epub 2017 Feb 9.	A phase III randomized controlled trial of tiotropium add-on therapy in **children** with ***severe*** symptomatic asthma. **VivaTinA®-asthma (add-on to ICS)**

Tiotropium is a long acting muscarinic antagonist (LAMA), licensed as triple therapy with inhaled corticosteroid and long-acting beta-agonist (ICS/LABA). There may be a synergistic benefit between LAMA and LABA as a consequence of receptor cross-talk, which in turn could modify beta-2 receptor downregulation and associated tolerance induced by LABA.We hypothesize this mechanism may result in a reduction of airway hyperresponsiveness (AHR) when using triple therapy.We evaluated 14 non-smoking asthmatics using an open-label, randomized crossover design. ICS with Indacaterol and Tiotropium (IND/TIO) vs ICS with Indacaterol (IND) over 4 weeks with challenge performed after first and last doses at trough.We found no significant difference in mannitol sensitivity, expressed as the provocative dose of mannitol required to reach a 15% drop in FEV1 , or mannitol reactivity, expressed as the response dose ratio (RDR: max % fall in FEV1 /cumulative dose), when comparing ICS/IND/TIO to ICS/IND. Geometric mean fold differences for RDR comparing single and chronic dosing were 3.26-fold (95% CI 1.46-7.29) and 2.51-fold (95% CI 1.32-4.79) for IND and IND/TIO, respectively. Furthermore, salbutamol recovery post-challenge was significantly blunted after chronic compared to single dosing with either ICS/IND (P<.005) or ICS/IND/TIO (P<.05).Our data suggest that concomitant tiotropium does not modify the bronchoprotective tolerance induced by Indacaterol, in turn suggesting that cross-talk may not be clinically relevant when using triple therapy. This study was registered on clinicaltrials.gov as NCT02039011.	excluded	did not meet inclusion criteria
Studies in adults and adolescents have demonstrated that tiotropium is efficacious as an add-on therapy to inhaled corticosteroids (ICSs) with or without other maintenance therapies in patients with moderate or severe symptomatic asthma.We sought to assess the efficacy and safety of once-daily tiotropium Respimat add-on therapy to high-dose ICS with 1 or more controller medications, or medium-dose ICS with 2 or more controller medications, in the first phase III trial of tiotropium in children with severe symptomatic asthma.In this 12-week, double-blind, placebo-controlled, parallel-group trial, 401 participants aged 6 to 11 years were randomized to receive once-daily tiotropium 5 µg (2 puffs of 2.5 µg) or 2.5 µg (2 puffs of 1.25 µg), or placebo (2 puffs), administered through the Respimat device as add-on to background therapy.Compared with placebo, tiotropium 5 µg, but not 2.5 µg, add-on therapy improved the primary end point, peak FEV1 within 3 hours after dosing (5 µg, 139 mL [95% CI, 75-203; P < .001]; 2.5 µg, 35 mL [95% CI, -28 to 99; P = .27]), and the key secondary end point, trough FEV1 (5 µg, 87 mL [95% CI, 19-154; P = .01]; 2.5 µg, 18 mL [95% CI, -48 to 85; P = .59]). The safety and tolerability of tiotropium were comparable with those of placebo.Once-daily tiotropium Respimat 5 µg improved lung function and was well tolerated as add-on therapy to ICS with other maintenance therapies in children with severe symptomatic asthma.	Included	Inclusions

	No			Tiotropium not delivered via Respimat®	Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology	8906443
					The Journal of allergy and clinical immunology	1275002

2017	Oct		47	10	1239-1245	Internet	S Jabbal	Jabbal, S; Manoharan, A; Lipworth, BJ	Scottish Centre for Respiratory Research, Ninewells Hospital and Medical School, University of Dundee, Dundee, UK.
2017	Nov		140	5	1277-1287	Internet	Stanley J Szefler	Szefler, SJ; Murphy, K; Harper, T; Boner, A; Laki, I; Engel, M; El Azzi, G; Moroni-Zentgraf, P; Finnigan, H; Hamelmann, E	Department of Pediatrics, Children's Hospital of Colorado and the University of Colorado School of Medicine, The Breathing Institute, Aurora, Colo. Electronic address: Stanley.Szefler@childrenscolorado.org.

28039077	10.1016/j.pupt.2016.12.003	Pulm Pharmacol Ther. 2017 Feb;42:25-32. doi: 10.1016/j.pupt.2016.12.003. Epub 2016 Dec 28.	**Pharmacokinetics** of tiotropium administered by Respimat® in asthma patients: Analysis of pooled data from Phase II and III clinical trials.
27931291		Allergy Asthma Proc. 2016 Nov;37(6):147-153.	Effects of the addition of tiotropium on **airway dimensions** in symptomatic asthma.

Tiotropium is a long-acting inhaled antimuscarinic bronchodilator that has recently received marketing authorization for the indication of asthma with dose delivery via the Respimat® inhaler, in addition to its widely established role in the management of chronic obstructive pulmonary disease (COPD). This report presents a combined analysis of tiotropium plasma and urine pharmacokinetics at steady state from 8 Phase II/III clinical trials in asthma and delineates the effects of patient characteristics on systemic exposure based on the parameters fe0-24,ss (fraction of dose excreted unchanged in urine over 24 h post-dose at steady-state) and dose-normalized AUCtau,ss and Cmax,ss. Pharmacokinetics were also compared between asthma and COPD, incorporating data from 3 COPD Phase II/III clinical trials. Tiotropium pharmacokinetics in asthma were dose-proportional up to 5 µg dosed once daily. The following factors showed no statistically significant effects on tiotropium systemic exposure in asthma based on analysis of geometric mean ratios and 90% confidence intervals: age, asthma severity, lung function, reversibility testing, allergy status, smoking history, geographical region, and posology (5 µg once daily or 2.5 µg twice daily via Respimat®). Asian patients showed a moderately but significantly higher systemic exposure compared to White or Black patients. However, no differences in safety by race were observed. Total systemic exposure (AUCtau,ss) was similar between asthma and COPD, but Cmax,ss was 52% lower in asthma patients compared to COPD. It is concluded that in asthma, patient characteristics have no relevant effect on tiotropium systemic exposure. Since systemic exposure to inhaled drugs is an indicator of safety, the lower Cmax,ss compared to COPD is not considered a concern for tiotropium therapy of asthma.	excluded	did not meet inclusion criteria
Tiotropium, a once-daily, long-acting anticholinergic bronchodilator, has shown efficacy and safety as an add-on to maintenance therapy in patients with symptomatic asthma.The aim of the present study was to assess the effect of tiotropium on airway geometry and airway inflammation in patients with asthma who were symptomatic despite treatment with inhaled corticosteroid (ICS) plus a long-acting beta 2agonist (LABA).In total, 53 patients with symptomatic asthma who received ICS plus LABA and who had a prebronchodilator forced expiratory volume in 1 second of 6090% of the predicted value were randomized to the addition of tiotropium 5 g once daily (n = 25) or no add-on (n = 28) to maintenance therapy for 48 weeks. Quantitative computed tomography, fractional exhaled nitric oxide, and pulmonary function were measured.Compared with maintenance therapy, the addition of tiotropium significantly decreased airway wall area (WA) corrected for body surface area (BSA) (WA/BSA) (p 0.05) and wall thickness (T) (T/BSA, p 0.05), and improved airflow obstruction. No significant difference in the change of fractional exhaled nitric oxide was observed between the two treatment groups. Changes in WA/BSA and T/BSA were significantly correlated with the change in predicted forced expiratory volume in 1 second (r = 0.87, p 0.001, and r = 0.82, p 0.001, respectively).The addition of once-daily tiotropium to maintenance therapy improved airflow limitation and reduced airway T. A triple combination of tiotropium and ICS plus LABA may have additive protective effects of bronchodilation and remodeling.	excluded	did not meet inclusion criteria

No			no	Not a ph 3 RCT (PK study); pooled data	Pulmonary pharmacology & therapeutics	9715279
		No	no	Lung function data not reported; tiotropium Respimat 2.5 ug dose not reported	Allergy and asthma proceedings	9603640

2017	02		42		25-32	Internet	Ashish Sharma	Sharma, A; Kerstjens, HA; Aalbers, R; Moroni-Zentgraf, P; Weber, B; Dahl, R	Translational Medicine and Clinical Pharmacology, Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Strasse 65, Biberach 88400, Germany. Electronic address: Ashish.Sharma@boehringer-ingelheim.com.
2016	Nov		37	6	147-153	Internet	Makoto Hoshino	Hoshino, M; Ohtawa, J; Akitsu, K	Division of Clinical Allergy, Department of Internal Medicine, Atami Hospital, International University of Health and Welfare, Atami, Japan.

27888045	10.1016/j.pupt.2016.11.004	Pulm Pharmacol Ther. 2017 Feb;42:7-12. doi: 10.1016/j.pupt.2016.11.004. Epub 2016 Nov 22.	Effects of tiotropium on lung function in current smokers and never smokers with bronchial asthma.
27811070	10.1183/13993003.01100-2016	Eur Respir J. 2017 Jan 11;49(1). pii: 1601100. doi: 10.1183/13993003.01100-2016. Print 2017 Jan.	A randomised controlled trial of tiotropium in **adolescents** with ***severe*** symptomatic asthma. **Pensie®TinA-asthma (add on to ICS + ≥1 controller)**

The effects of tiotropium, an inhaled long-acting muscarinic antagonist, on lung function were investigated in current smokers and nonsmokers with asthma treated with inhaled corticosteroids (ICSs) and other asthma controllers: inhaled long-acting β2 agonists, leukotriene receptor antagonists, and/or theophylline. We conducted a double-blind, placebo-controlled study of an inhaled single dose of tiotropium in 9 asthmatics currently smoking and 9 asthmatics who have never smoked in a crossover manner. Lung function was measured before and 1, 3, and 24 h after inhalation of 18 μg of tiotropium or a placebo. The primary outcome was a change in forced expiratory volume in 1 s (FEV1) from the baseline, and the secondary outcomes were changes in peak expiratory flow rate (PEFR), V˙50, and V˙25. At baseline, asthmatics with and without a smoking history had a mean FEV1 of 2590 ml and 2220 ml and were taking a mean dose of ICSs of 1208 and 1000 μg/day, respectively. The increase from the baseline FEV1 was 169 ml and 105 ml higher at 3 h after tiotropium than after the placebo in current smokers and nonsmokers, respectively. PEFR, V˙50, and V˙25 were also significantly increased after tiotropium as compared with the placebo in both study groups. Changes in FEV1 and PEFR tended to be greater in asthmatics currently smoking than in subjects who have never smoked, although there were no statistical differences at any time points. Tiotropium resulted in improved lung function and symptoms both in current smoker and nonsmoker asthmatics. These findings suggest that tiotropium will provide a new strategy for the treatment of bronchial asthma.	excluded	did not meet inclusion criteria
We present results from the first phase III trial of once-daily tiotropium add-on to inhaled corticosteroids (ICS) plus one or more controller therapies in adolescents with severe symptomatic asthma.In this double-blind, parallel-group trial (NCT01277523), 392 patients aged 12-17 years were randomised to receive once-daily tiotropium 5 μg or 2.5 μg, or placebo, as an add-on to ICS plus other controller therapies over 12 weeks. The primary and key secondary end-points were change from baseline (response) in peak forced expiratory volume in 1 s (FEV1) within 3 h post-dosing (FEV1(0-3h)) and trough FEV1, respectively, after 12 weeks of treatment.Tiotropium 5 μg provided numerical improvements in peak FEV1(0-3h) response, compared with placebo (90 mL; p=0.104), and significant improvements were observed with tiotropium 2.5 μg (111 mL; p=0.046). Numerical improvements in trough FEV1 response and asthma control were observed with both tiotropium doses, compared with placebo. The safety and tolerability of tiotropium were comparable with those of placebo.Once-daily tiotropium Respimat add-on to ICS plus one or more controller therapies in adolescents with severe symptomatic asthma was well tolerated. The primary end-point of efficacy was not met, although positive trends for improvements in lung function and asthma control were observed.	Included	Inclusions

	No			Tiotropium not delivered via Respimat®	Pulmonary pharmacology & therapeutics	9715279
					The European respiratory journal	8803460

2017	02		42		7-12	Internet	Makoto Yoshida	Yoshida, M; Kaneko, Y; Ishimatsu, A; Komori, M; Iwanaga, T; Inoue, H	Division of Respiratory Medicine, National Hospital Organization Fukuoka Hospital, 4-39-1 Yakatabaru, Minami-ku, Fukuoka 811-1394, Japan. Electronic address: myoshida@mfukuoka2.hosp.go.jp.
2017	01		49	1		Internet	Eckard Hamelmann	Hamelmann, E; Bernstein, JA; Vandewalker, M; Moroni-Zentgraf, P; Verri, D; Unseld, A; Engel, M; Boner, AL	Klinik für Kinder- und Jugendmedizin, Kinderzentrum Bethel, Evangelisches Krankenhaus Bielefeld, Akademisches Lehrkrankenhaus der Universität Münster, Bielefeld, Germany eckard.hamelmann@evkb.de.

27578478	10.1016/j.rmed.2016.07.001	Respir Med. 2016 Sep;118:102-111. doi: 10.1016/j.rmed.2016.07.001. Epub 2016 Jul 2.	Safety and tolerability of once-daily tiotropium Respimat(®) as add-on to at least inhaled corticosteroids in adult patients with symptomatic asthma: **A pooled safety analysis**.
27578477	10.1016/j.rmed.2016.07.017	Respir Med. 2016 Sep;118:96-101. doi: 10.1016/j.rmed.2016.07.017. Epub 2016 Jul 30. Erratum in: Respir Med. 2017 Nov;132:268.	Duration of **bronchoprotection** of the long-acting muscarinic antagonists tiotropium & glycopyrronium against methacholine-induced bronchoconstriction in mild asthmatics.

Tiotropium, a long-acting anticholinergic bronchodilator, has demonstrated efficacy and safety as add-on therapy to inhaled corticosteroids (ICS), with or without other maintenance therapies, in patients with symptomatic asthma.To evaluate safety and tolerability of tiotropium delivered via the Respimat(®) device, compared with placebo, each as add-on to at least ICS therapy, in a pooled sample of adults with symptomatic asthma at different treatment steps.Data were pooled from seven Phase II and III, randomised, double-blind, parallel-group trials of 12-52 weeks' treatment duration, which investigated once-daily tiotropium Respimat(®) (5 µg, 2.5 µg) versus placebo as add-on to different background maintenance therapy including at least ICS. Adverse events (AEs) including serious AEs were assessed throughout treatment + 30 days after the last dose of trial medication.Of 3474 patients analysed, 2157 received tiotropium. The percentage of patients with AEs was comparable between treatment groups: tiotropium 5 µg, 60.8%; placebo 5 µg pool, 62.5%; tiotropium 2.5 µg, 57.1%; placebo 2.5 µg pool, 55.1%. Consistent with the disease profile, the most frequent AEs overall were asthma, decreased peak expiratory flow rate (both less frequent with tiotropium) and nasopharyngitis. Overall incidence of dry mouth, commonly associated with use of anticholinergics, was low: tiotropium 5 µg, 1.0%; placebo 5 µg pool, 0.5%; tiotropium 2.5 µg, 0.4%; placebo 2.5 µg pool, 0.5%. The percentage of cardiac disorder AEs was comparable between tiotropium and placebo: tiotropium 5 µg, 1.4%; placebo 5 µg pool, 1.4%; tiotropium 2.5 µg, 1.4%; placebo 2.5 µg pool, 1.1%. The proportions of patients with serious AEs were balanced across groups: tiotropium 5 µg, 4.0%; placebo 5 µg pool, 4.9%; tiotropium 2.5 µg, 2.0%; placebo 2.5 µg pool, 3.3%.Tiotropium Respimat(®) demonstrated safety and tolerability comparable with those of placebo, as add-on to at least ICS therapy, at different treatment steps in adults with symptomatic asthma.	excluded	did not meet inclusion criteria
The duration of bronchoprotection against methacholine-induced bronchoconstriction by long-acting muscarinic antagonists (LAMA's) in asthmatics and whether these drugs differ in their pharmacodynamic properties remain to be determined. The most recent published guidelines for methacholine challenge testing (MCT) suggest that LAMA's should be abstained from for 48 h prior to testing, perhaps one week in the case of tiotropium. The objectives were to determine and compare the duration of protection of a single dose of two different LAMA's, tiotropium and glycopyrronium, **against methacholine-induced bronchoconstriction**. Thirteen mild-to-moderate asthmatics [with a forced expiratory volume in 1 s (FEV1) > 65% of predicted and a baseline methacholine provocation concentration causing a 20% reduction in FEV1 (PC20) ≤ 8 mg/mL] completed this double-blind, double-dummy, crossover study. Methacholine challenges were performed before treatment (5 µg tiotropium or 50 µg glycopyrronium) and at 1, 24, 48, 72, 96 and 168 h post-treatment. The minimum duration between treatment administration was 11 days. Both drugs provided significant bronchoprotection, each producing greater than a 16-fold increase in mean PC20 by 1 h. Tiotropium still provided statistically significant protection at 7 days (p = 0.0282) while glycopyrronium provided bronchoprotection until day 7 (p = 0.0590). Tiotropium provided statistically superior bronchoprotection at 24 and 72 h compared to glycopyrronium. To minimize the occurrence of false negatives, MCT guidelines should be updated to recommend a minimum one-week abstinence period from all LAMA's. MCT was also able to statistically differentiate between tiotropium and glycopyrronium with respect to the degree and duration of bronchoprotection provided by each.NCT02622243.	excluded	did not meet inclusion criteria

No			no	Not a ph 3 RCT; lung function not reported (pooled safety analyses of 7 trials)	Respiratory medicine	8908438
No			no	Not an RCT; lung function not reported (methacholine-induced challenge; bronchoprotectio nendpoint)	Respiratory medicine	8908438

2016	09		118		102-111	Internet	Ronald Dahl	Dahl, R; Engel, M; Dusser, D; Halpin, D; Kerstjens, HAM; Zaremba-Pechmann, L; Moroni-Zentgraf, P; Busse, WW; Bateman, ED	Odense University Hospital, University of Southern Denmark, Sdr Boulevard, DK 5000, Odense C, Denmark. Electronic address: ronald.dahl2@rsyd.dk.
2016	09		118		96-101	Internet	Christianne M Blais	Blais, CM; Davis, BE; Cockcroft, DW	University of Saskatchewan, College of Medicine, Department of Physiology, 107 Wiggins Road, Saskatoon, SK S7N 5E5, Canada.

27492532	10.1016/j.rmed.2016.06.013	Respir Med. 2016 Aug;117:198-206. doi: 10.1016/j.rmed.2016.06.013. Epub 2016 Jun 14.	Tiotropium improves lung function, exacerbation rate, and asthma control, independent of baseline characteristics including age, degree of airway obstruction, and allergic status.
27182262	10.12669/pjms.322.8836	Pak J Med Sci. 2016 Mar-Apr;32(2):462-5. doi: 10.12669/pjms.322.8836.	Clinical efficacy of tiotropium in children with asthma.

Many patients with asthma remain symptomatic despite treatment with inhaled corticosteroids (ICS) with or without long-acting β2-agonists (LABAs). Tiotropium add-on to ICS plus a LABA has been shown to improve lung function and reduce exacerbation risk in patients with symptomatic asthma.To determine whether the efficacy of tiotropium add-on therapy is dependent on patients' baseline characteristics.Two randomized, double-blind, parallel-group, twin trials (NCT00772538 and NCT00776984) of **once-daily tiotropium Respimat(®) 5 µg add-on** to ICS plus a LABA were performed in parallel in patients with severe symptomatic asthma. Exploratory subgroup analyses of peak forced expiratory volume in 1 s (FEV1), trough FEV1, time to first severe exacerbation, time to first episode of asthma worsening, and seven-question Asthma Control Questionnaire responder rate were performed to determine whether results were influenced by baseline characteristics.912 patients were randomized: 456 received tiotropium and 456 received placebo. Tiotropium improved lung function, reduced the risk of asthma exacerbations and asthma worsening, and improved asthma symptom control, compared with placebo, independent of baseline characteristics including gender, age, body mass index, disease duration, age at asthma onset, and FEV1 % predicted at screening and reversibility.Once-daily tiotropium 5 µg compared with placebo improved lung function, reduced the risk of asthma exacerbations and asthma worsening, and improved asthma symptom control, independent of a broad range of baseline characteristics, as add-on to ICS plus LABAs in patients with severe symptomatic asthma.ClinicalTrials.gov; numbers NCT00772538 and NCT00776984 URL: www.clinicaltrials.gov.	excluded	did not meet inclusion criteria
To investigate the clinical efficacy of tiotropium in children with asthma. Eighty children with newly diagnosed moderate persistent asthma were enrolled into this study. The children were randomly assigned to the fluticasone propionate aerosol group or the fluticasone propionate aerosol plus tiotropium group for 12 weeks. Lung function was significantly improved in both groups at 4, 8, and 12 weeks compared with baseline ($P < 0.01$). Moreover, lung function was significantly improved in the tiotropium group compared with the control group ($P < 0.05$). However, there was no significant difference in the incidence of severe asthma between the two groups (36.3% and 26.8%, respectively; $P > 0.05$). Compared with the control group, the number of days and frequency of short-acting beta2-adrenoceptor agonist use was significantly reduced in the tiotropium group ($P < 0.05$). Awakenings during the night were also significantly decreased ($P < 0.00$). There were no severe adverse reactions in either of the study groups.Tiotropium could significantly improve lung function, reduce the use of short-acting beta2-adrenoceptor agonists, and improve sleep in children with asthma. Furthermore, few adverse reactions were reported.	excluded	did not meet inclusion criteria

		No	no	Tiotropium Respimat 2.5 µg dose not evaluated; primary endpoint not reported (PrimoTinA subgroup analyses)	Respiratory medicine	8908438
No	No			Not a ph 3 RCT; Tiotropium not delivered via Respimat®	Pakistan journal of medical sciences	100913117

2016	08		117		198-206	Internet	Huib A M Kerstjens	Kerstjens, HA; Moroni-Zentgraf, P; Tashkin, DP; Dahl, R; Paggiaro, P; Vandewalker, M; Schmidt, H; Engel, M; Bateman, ED	University of Groningen, Department of Pulmonary Medicine, Groningen Research Institute for Asthma and COPD, University Medical Center Groningen, Postbox 30.001, 9700 RB Groningen, The Netherlands. Electronic address: h.a.m.kerstjens@u
		2016 Mar-Apr	32	2	462-5	Print	Juan Huang	Huang, J; Chen, Y; Long, Z; Zhou, X; Shu, J	Juan Huang, Department of Pediatric Internal Medicine, Hubei Maternal and Child Health Care Hospital, Wuhan 430072, China.

26960245	10.1016/j.jaci.2016.01.011	J Allergy Clin Immunol. 2016 Aug;138(2):441-450.e8. doi: 10.1016/j.jaci.2016.01.011. Epub 2016 Mar 5.	Tiotropium add-on therapy in **adolescents** with ***moderate*** asthma: A 1-year randomized controlled trial. **RubaTinA®-asthma (add-on to at least ICS)**
26956858	10.3881/j.issn.1000-503X.2016.01.011	Zhongguo Yi Xue Ke Xue Yuan Xue Bao. 2016 Feb;38(1):62-8. doi: 10.3881/j.issn.1000-503X.2016.01.011.	Efficacy and Safety of Tiotropium in the Treatment of Severe Persistent Asthma: **Meta-analysis**.

Results from phase III clinical trials in adults and phase II clinical trials in children and adolescents demonstrate that tiotropium is an effective treatment when added to inhaled corticosteroid (ICS) maintenance therapy.We sought to assess the efficacy and safety of once-daily tiotropium Respimat added to ICSs with or without a leukotriene receptor antagonist in a phase III trial in adolescent patients with moderate symptomatic asthma.In this 48-week, double-blind, placebo-controlled, parallel-group study, 398 patients aged 12 to 17 years were randomized to receive 5 µg (2 puffs of 2.5 µg) or 2.5 µg (2 puffs of 1.25 µg) of once-daily tiotropium or placebo (2 puffs) administered through the Respimat device every evening, each as add-on treatment to ICS background therapy, with or without a leukotriene receptor antagonist; long-acting β2-agonist therapy was not permitted during the study.Improvement in peak FEV1 within 3 hours after dosing at 24 weeks (primary end point) was statistically significant with both tiotropium doses compared with placebo: 5 µg of tiotropium, 174 mL (95% CI, 76-272 mL); 2.5 µg of tiotropium, 134 mL (95% CI, 34-234 mL). Significant improvements in trough FEV1 at week 24 (a secondary end point) were observed with the 5-µg dose only. Trends for improvement in asthma control and health-related quality of life over the 48-week treatment period were observed.Once-daily tiotropium significantly improved lung function and was safe and well tolerated when added to at least ICS maintenance therapy in adolescent patients with moderate symptomatic asthma. Larger responses were observed with the 5-µg tiotropium dose.	Included	Inclusions
To evaluate the efficacy and safety of tiotropium in treatment of severe persistent asthma.Reports of randomized controlled trials (RCTs) describing tiotropium for treatment of severe persistent asthma published from January 1946 to February 2015 were searched in Cochrane Library, ClinicalTrials.gov, PubMed, Ovid Medline, CNKI, and CSJD. The data of the included RCTs were extracted and the data quality was evaluated. Meta-analyses were performed with Revman 5.3 software.Five RCTs including 1433 patients were analyzed. Meta-analysis of the data showed that compared with the placebo group, tiotropium treatment significantly improved the patients' peak forced expiratory volume in one second (FEV1) [weighted mean difference (WMD): 0.13 L, 95% confidence interval (CI): 0.10-0.16 L, P<0.00001], trough FEV1 (WMD: 0.09 L, 95%CI: 0.06-0.12 L, P<0.00001), peak forced vital capacity (FVC) (WMD: 0.10 L, 95%CI: 0.06-0.14 L, P<0.00001), trough FVC (WMD: 0.12 L, 95%CI: 0.08-0.17 L, P<0.00001), morning peak expiratory flow (PEF) (WMD: 9.21 L/min, 95%CI: 4.2-14.23 L/min, P=0.0003), evening PEF (WMD: 22.06 L/min, 95%CI 13.05-31.08 L/min, P<0.00001). The scores of asthma control questionnaire (ACQ) (WMD: 0.01, 95% CI: -0.07-0.09, P=0.86) or asthma quality of life questionnaire (AQLQ)(WMD: 0.06, 95% CI:-0.18-0.06, P=0.33) were not affected by tiotropium. No significant difference with adverse events between tiotropium group and placebo group were reported in these included studies (P>0.05).Tiotropium for severe persistent asthma treatment can improve FEV1, FVC, and PEF but may not improve the quality of life of the patients. Tiotropium is well tolerated and can be an add-on therapy for severe persistent asthma.	excluded	Review/meta analysis

					The Journal of allergy and clinical immunology	1275002
				Not a ph 3 RCT; meta-analysis	Zhongguo yi xue ke xue yuan xue bao. Acta Academiae Medicinae Sinicae	8006230

2016	08		138	2	441-450.e8	Internet	Eckard Hamelmann	Hamelmann, E; Bateman, ED; Vogelberg, C; Szefler, SJ; Vandewalker, M; Moroni-Zentgraf, P; Avis, M; Unseld, A; Engel, M; Boner, AL	Klinik für Kinder- und Jugendmedizin, Kinderzentrum Bethel, Evangelisches Krankenhaus Bielefeld GmbH, Akademisches Lehrkrankenhaus der Universität Münster, Bielefeld, Germany. Electronic address: eckard.hamelmann@evkb.de.
2016	Feb		38	1	62-8	Print	Li-li Lou	Lou, LL; Gong, HH; Zhang, MQ; Gao, JM	Department of Respiratory Medicine, PUMC Hospital, CAMS and PUMC,Beijing 100730,China.

26859538	10.1089/jamp.2015.1260	J Aerosol Med Pulm Drug Deliv. 2016 Oct;29(5):406-415. Epub 2016 Feb 9.	**Pharmacodynamics and Pharmacokinetics** Following Once-Daily and Twice-Daily Dosing of Tiotropium Respimat® in Asthma Using Standardized Sample-Contamination Avoidance.
26846267	10.1186/s12931-016-0327-6	Respir Res. 2016 Feb 4;17:13. doi: 10.1186/s12931-016-0327-6.	Combination therapy of tiotropium and ciclesonide attenuates airway inflammation and remodeling in a **guinea pig model of chronic asthma**.

This study was conducted to confirm the 24-hour bronchodilator efficacy and pharmacokinetic profile of once-daily tiotropium Respimat® 5 µg add-on to inhaled corticosteroids (ICS) in adults with symptomatic asthma. It used a trial protocol designed to minimize the risk of pharmacokinetic sample contamination resulting from improper sampling procedure, sample handling, or device handling during priming and subsequent inhalation procedure. A Phase II, randomized, double-blind, two-way crossover study (NCT01696071) comparing two daily dosing regimens of tiotropium for 4 weeks, once-daily 5 µg (evening dosing) or twice-daily 2.5 µg (morning and evening dosing), as add-on to maintenance therapy with ICS (400-800 µg budesonide or equivalent) as controller medication. There was no washout between treatment periods.An increase in the area under the curve of the 24-hour forced expiratory volume in 1 second profile from study baseline was observed following once-daily tiotropium 5 µg (217 mL) and twice-daily 2.5 µg (219 mL), with no difference between the two regimens (-2 mL [95% confidence interval: -38, 34]). In a subset of the study population, total tiotropium exposure, expressed as area under the plasma concentration versus time curve over 24 hours, was comparable between dosing regimens. Unexpected tiotropium plasma levels were observed in two patients, possibly because of contamination.The observed bronchodilator efficacy over 24 hours was similar with once-daily tiotropium 5 µg and twice-daily 2.5 µg as add-on to ICS therapy, supporting the suitability of once-daily dosing to provide sustained improvements in lung function in adults with symptomatic asthma.	excluded	did not meet inclusion criteria
The long-acting anticholinergic tiotropium has recently been registered for the treatment of asthma, and its use is associated with a reduction in exacerbation frequency. Anti-inflammatory and anti-remodeling effects of tiotropium have been demonstrated in in vitro and in vivo models. Because tiotropium treatment is used in combination with inhaled corticosteroids, potential additive effects between the two would be clinically relevant. Therefore, the aim of this study was to investigate additive effects between tiotropium and ciclesonide on airway inflammation and remodeling in guinea pig models of asthma.Guinea pigs (n = 3-8/group) were sensitized and challenged with ovalbumin in an acute (single challenge) and a chronic model (12 weekly challenges) of allergic asthma. Animals were treated with vehicle, nebulized tiotropium (0.01-0.3 mM) and/or intranasally instilled ciclesonide (0.001-1 mg/kg) before each challenge. Bronchoalveolar lavage fluid and lungs were collected for analysis of airway inflammation and remodeling.Tiotropium and ciclesonide treatment, alone or in combination, did not inhibit airway inflammation in the acute asthma model. In a dose-finding study, low doses of tiotropium and ciclesonide inhibited airway eosinophilia and airway smooth muscle thickening in the chronic asthma model. Threshold doses of 0.01 mM tiotropium (nebulizer concentration) and 0.01 mg/kg ciclesonide were selected to investigate potential additive effects between both drugs. At these doses, tiotropium and ciclesonide did not inhibit airway eosinophilia or airway smooth muscle thickening when administered alone, but significantly inhibited these allergen-induced responses when administered in combination.Combined treatment with low doses of tiotropium and ciclesonide inhibits airway inflammation and remodeling in a guinea pig model of chronic asthma, suggesting that combined treatment with anticholinergics and corticosteroids may have anti-inflammatory and anti-remodeling activity in allergic airway diseases. Since tiotropium is registered as a therapy for asthma added on to corticosteroid treatment, these beneficial effects of the combination therapy may be clinically relevant.	excluded	In vitro/Preclinical

No				Not a ph 3 RCT (PK/PD study)	Journal of aerosol medicine and pulmonary drug delivery	101475057
				Preclinical animal study	Respiratory research	101090633

2016	Oct		29	5	406-415	Internet	Kai-Michael Beeh	Beeh, KM; Kirsten, AM; Dusser, D; Sharma, A; Cornelissen, P; Sigmund, R; Moroni-Zentgraf, P; Dahl, R	1 Insaf Institut für Atemwegsforschung GmbH , Wiesbaden, Germany.
2016	Feb		17		13	Internet	Loes E M Kistemaker	Kistemaker, LE; Bos, IS; Menzen, MH; Maarsingh, H; Meurs, H; Gosens, R	Department of Molecular Pharmacology, University of Groningen, A. Deusinglaan 1, 9713 AV, Groningen, The Netherlands. l.e.m.kistemaker@rug.nl.

26650145	10.1513/AnnalsATS.201510-712PS	Ann Am Thorac Soc. 2016 Feb;13(2):173-9. doi: 10.1513/AnnalsATS.201510-712PS.	Tiotropium Respimat Is Effective for the Treatment of Asthma at a Dose Lower Than That for Chronic Obstructive Pulmonary Disease.
26563670	10.1016/j.jaip.2015.08.017	J Allergy Clin Immunol Pract. 2016 Jan-Feb;4(1):104-13.e2. doi: 10.1016/j.jaip.2015.08.017. Epub 2015 Nov 7.	The Effect of Tiotropium in Symptomatic Asthma Despite Low- to Medium-Dose Inhaled Corticosteroids: A Randomized Controlled Trial.**GraziaTinA®-asthma (add-on to low- to medium-dose ICS)**

Anticholinergic drug products are not part of the current treatment paradigm for asthma, despite their widespread availability for chronic obstructive pulmonary disease (COPD) and interest in their use for asthma. Published study results, mostly of short duration and primarily with ipratropium and tiotropium, have revealed inconsistent efficacy results. Consequently, the role of inhaled anticholinergic drugs in the treatment of asthma has been unclear. **This commentary** discusses and comments on data from five clinical trials in adults that were submitted by Boehringer Ingelheim to the U.S. Food and Drug Administration to support approval of tiotropium delivered by the Respimat device (Spiriva Respimat) for the treatment of asthma. These trials provided substantial evidence that supported the approval of Spiriva Respimat at a recommended dose of 2.5 µg once daily for asthma. Notably, in trials that evaluated two doses of tiotropium, 2.5 µg and 5 µg (the dose approved for COPD), pulmonary function measures for Spiriva Respimat 2.5 µg once daily were better overall than those obtained for the 5-µg once-daily dose, thus justifying selection of the lower dose for asthma. Spiriva Respimat represents the first new class of drug approved by the U.S. Food and Drug Administration for the treatment of asthma in more than a decade. The availability of Spiriva Respimat for asthma along with other novel therapies currently under development has the potential to impact asthma treatment guidelines.	excluded	Review/meta analysis
Tiotropium, a once-daily long-acting anticholinergic bronchodilator, has demonstrated efficacy in patients with asthma who were symptomatic despite treatment with medium- to high-dose inhaled corticosteroids (ICS).The objective of this study was to evaluate the efficacy and safety of once-daily tiotropium Respimat (5 µg or 2.5 µg), compared with placebo Respimat, as add-on therapy to low- to medium-dose ICS for adults with symptomatic asthma.A phase III, double-blind, placebo-controlled trial was conducted (NCT01316380). **Adults** with ***symptomatic*** asthma receiving low- to medium-dose ICS (200-400 µg budesonide or equivalent dose) and a pre-bronchodilator forced expiratory volume in 1 second (FEV1) ≥60% and ≤90% of predicted normal were randomized to 12 weeks of treatment with once-daily tiotropium Respimat 5 µg or 2.5 µg, or placebo Respimat, as add-on therapy to ICS. The primary endpoint was peak FEV1(0-3h) response.In total, 464 patients were randomized (61% female; mean age 43 years; mean baseline FEV1 78% of predicted normal). After 12 weeks, both tiotropium Respimat doses were superior to placebo (adjusted mean difference from placebo: 5 µg, 128 mL; 2.5 µg, 159 mL; both P < .001). Both doses of tiotropium Respimat were also superior to placebo with regard to the secondary endpoints of adjusted mean trough FEV1 and FEV1 area under the curve(0-3h) responses, and the other endpoints of morning and evening peak expiratory flow. Adverse events were comparable across the treatment groups.Once-daily tiotropium Respimat add-on therapy to low- to medium-dose ICS in adults with symptomatic asthma is an efficacious bronchodilator, and its safety and tolerability are comparable with those of placebo Respimat.	Included	Inclusions

				Review	Annals of the American Thoracic Society	101600811
					The journal of allergy and clinical immunology. In practice	101597220

2016	Feb		13	2	173-9	Internet	Stacy J Chin	Chin, SJ; Durmowicz, AG; Chowdhury, BA	Division of Pulmonary, Allergy, and Rheumatology Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland.
		2016 Jan-Feb	4	1	104-13.e2	Internet	Pierluigi Paggiaro	Paggiaro, P; Halpin, DM; Buhl, R; Engel, M; Zubek, VB; Blahova, Z; Moroni-Zentgraf, P; Pizzichini, E	Cardio-Thoracic and Vascular Department, Respiratory Pathophysiology, University of Pisa, Pisa, Italy. Electronic address: pierluigi.paggiaro@unipi.it.

26487277	10.1186/s12931-015-0290-7	Respir Res. 2015 Oct 20;16:128. doi: 10.1186/s12931-015-0290-7. No abstract available.	Erratum to: A randomised dose-ranging study of tiotropium Respimat® in children with symptomatic asthma despite inhaled corticosteroids.
26001185	10.1517/14656566.2015.1045877	Expert Opin Pharmacother. 2015 Jun;16(9):1403-9. doi: 10.1517/14656566.2015.1045877.	Tiotropium bromide as add-on therapy to inhaled corticosteroids for treating asthma.

	excluded	Erratum
Bronchial asthma is becoming increasingly prevalent worldwide. Although first-line therapy with inhaled corticosteroids (ICS) with or without long-acting β2 agonists (LABA) has significantly improved the clinical outcomes of asthma, they cannot provide all asthmatics with good control and thus alternatives or add-on drugs are required. Tiotropium is a long-acting muscarinic antagonist that has been used to treat chronic obstructive pulmonary disease and it has been approved for treating asthma in some countries. This agent has similar bronchodilatory effects to those of LABA and might also have anti-inflammatory and anti-remodeling effects.Some pivotal clinical trials have found tiotropium effective as an add-on medication for low-to-medium doses of ICS for treating symptomatic asthma and asthma that remains uncontrolled despite ICS plus LABA therapy.Whether or not tiotropium has anti-inflammatory and anti-remodeling effects in humans with asthma is an important issue. Predictors that would identify patients who would derive the maximal potential benefit from treatment with tiotropium in addition to their current therapy are also needed. Although the cardiovascular toxicity of tiotropium is less remarkable in asthma than in chronic obstructive pulmonary disease, longer and larger studies are still needed to confirm the safety of tiotropium for treating asthma.	excluded	Review/meta analysis

				Erratum for a ph 2 study (Vogelberg et al. Respir Res. 2015)	Respiratory research	101090633
				Expert opinion/review	Expert opinion on pharmacotherapy	100897346

2015	Oct		16		128	Internet	Christian Vogelberg	Vogelberg, C; Moroni-Zentgraf, P; Leonaviciute-Klimantaviciene, M; Sigmund, R; Hamelmann, E; Engel, M; Szefler, S	University Hospital Carl Gustav Carus, Technical University of Dresden, Fetscherstraße 74, 01307, Dresden, Germany. christian.vogelberg@uniklinikum-dresden.de.
2015	Jun		16	9	1403-9	Internet	Hiroto Matsuse	Matsuse, H; Yamagishi, T; Kodaka, N; Miura, A; Kurose, Y; Nakano, C; Oshio, T	Toho University Ohashi Medical Center, Division of Respirology, Department of Internal Medicine , 2-17-6 Ohashi Meguro-ku, Tokyo 153-8515 , Japan +81 3 3468 1251 ; +81 3 3468 5082 ; hiroto.matsuse@med.toho-u.ac.jp.

25894430	10.1371/journal.pone.0124109	PLoS One. 2015 Apr 20;10(4):e0124109. doi: 10.1371/journal.pone.0124109. eCollection 2015.	Long-Term Once-Daily Tiotropium Respimat® Is Well Tolerated and Maintains Efficacy over 52 Weeks in Patients with Symptomatic Asthma in Japan: A Randomised, Placebo-Controlled Study. **CadenTinA-asthma (add-on to at least ICS +/– LABA)**
25851298	10.1186/s12931-015-0175-9	Respir Res. 2015 Feb 7;16:20. doi: 10.1186/s12931-015-0175-9. Erratum in: Respir Res. 2015;16:128.	A randomised **dose-ranging study** of tiotropium Respimat® in children with symptomatic asthma despite inhaled corticosteroids.

This study assessed the long-term safety and efficacy of tiotropium Respimat, a long-acting inhaled anticholinergic bronchodilator, in asthma, added on to inhaled corticosteroids (ICS) with or without long-acting β2-agonist (LABA).285 patients with symptomatic asthma, despite treatment with ICS±LABA, were randomised 2:2:1 to once-daily tiotropium 5 µg, tiotropium 2.5 µg or placebo for 52 weeks (via the Respimat SoftMist inhaler) added on to ICS±LABA, in a double-blind, placebo-controlled, parallel-group study (NCT01340209).to describe the long-term safety profile of tiotropium. Secondary end points included: trough forced expiratory volume in 1 second (FEV1) response; peak expiratory flow rate (PEFR) response; seven-question Asthma Control Questionnaire (ACQ-7) score.At Week 52, adverse-event (AE) rates with tiotropium 5 µg, 2.5 µg and placebo were 88.6%, 86.8% and 89.5%, respectively. Commonly reported AEs with tiotropium 5 µg, 2.5 µg and placebo were nasopharyngitis (48.2%, 44.7%, 42.1%), asthma (28.9%, 29.8%, 38.6%), decreased PEFR (15.8%, 7.9%, 21.1%), bronchitis (9.6%, 13.2%, 7.0%), pharyngitis (7.9%, 13.2%, 3.5%) and gastroenteritis (10.5%, 3.5%, 5.3%). In the tiotropium 5 µg, 2.5 µg and placebo groups, 8.8%, 5.3% and 5.3% of patients reported drug-related AEs; 3.5%, 3.5% and 15.8% reported serious AEs. Asthma worsening was the only serious AE reported in more than one patient. At Week 52, adjusted mean trough FEV1 and trough PEFR responses were significantly higher with tiotropium 5 µg (but not 2.5 µg) versus placebo. ACQ-7 responder rates were higher with tiotropium 5 µg and 2.5 µg versus placebo at Week 24.The long-term tiotropium Respimat safety profile was comparable with that of placebo Respimat, and associated with mild to moderate, non-serious AEs in patients with symptomatic asthma despite ICS±LABA therapy. Compared with placebo, tiotropium 5 µg, but not 2.5 µg, significantly improved lung function and symptoms, supporting the long-term efficacy of the 5 µg dose.ClinicalTrials.gov NCT01340209.	Included	Inclusions
A considerable number of children with asthma remain symptomatic despite treatment with inhaled corticosteroids, resulting in significant morbidity, reduced quality of life, increased healthcare costs and lost school days. The aim of our study was to assess the efficacy, safety and tolerability of once-daily tiotropium Respimat® 5 µg, 2.5 µg and 1.25 µg add-on to medium-dose inhaled corticosteroids, with or without a leukotriene modifier, in children aged 6-11 years with symptomatic asthma.In this Phase II, double-blind, placebo-controlled, incomplete-crossover, dose-ranging study, patients were randomised to receive three of the four treatments evaluated: once-daily tiotropium Respimat® 5 µg, 2.5 µg or 1.25 µg or placebo Respimat®, in the evening during the 12-week (three × 4-week) treatment period.In total, 76, 74, 75 and 76 patients aged 6-11 years received tiotropium Respimat® 5 µg, 2.5 µg, 1.25 µg and placebo Respimat®, respectively. For the primary end point (peak forced expiratory volume in 1 second measured within 3 hours post-dosing), the adjusted mean responses with tiotropium Respimat® 5 µg (272 mL), 2.5 µg (290 mL) and 1.25 µg (261 mL) were significantly greater than with placebo Respimat® (185 mL; $p = 0.0002$, $p < 0.0001$ and $p = 0.0011$, respectively). The safety and tolerability of all doses of tiotropium Respimat® were comparable with those of placebo Respimat®, with no serious adverse events and no events leading to discontinuation.Tiotropium Respimat® add-on to medium-dose inhaled corticosteroids, with or without a leukotriene modifier, was efficacious in paediatric patients with symptomatic asthma and had comparable safety and tolerability with placebo Respimat®.ClinicalTrials.gov identifier NCT01383499.	Included	Inclusions

					PloS one	101285081
No				Not a ph 3 RCT (ph 2 dose-ranging study)	Respiratory research	101090633

2015			10	4	e0124109	Internet	Ken Ohta	Ohta, K; Ichinose, M; Tohda, Y; Engel, M; Moroni-Zentgraf, P; Kunimitsu, S; Sakamoto, W; Adachi, M	National Hospital Organization, Tokyo National Hospital, Tokyo, Japan.
2015	Feb		16		20	Internet	Christian Vogelberg	Vogelberg, C; Moroni-Zentgraf, P; Leonaviciute-Klimantaviciene, M; Sigmund, R; Hamelmann, E; Engel, M; Szefler, S	

25682232	10.1016/S2213-2600(15)00031-4	Lancet Respir Med. 2015 May;3(5):367-76. doi: 10.1016/S2213-2600(15)00031-4. Epub 2015 Feb 12.	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. **MezzoTinA-ashtma (add-on to at least ICS)**
25661281	10.1016/j.rmed.2014.12.005	Respir Med. 2015 Mar;109(3):329-38. doi: 10.1016/j.rmed.2014.12.005. Epub 2014 Dec 27.	Once-daily tiotropium Respimat(®) **5 µg** is an efficacious 24-h bronchodilator in adults with symptomatic asthma.

In patients with severe asthma, tiotropium improves lung function and exacerbation risk when added to high-dose inhaled corticosteroids plus long-acting β2 agonists. We aimed to assess the safety and efficacy of tiotropium in patients with moderate asthma who were symptomatic despite treatment with medium-dose inhaled corticosteroids.We did two 24-week, replicate, randomised, double-blind, placebo-controlled, parallel-group, active-comparator trials at 233 sites in 14 countries. Eligible patients were **aged 18-75 years** with symptomatic asthma and a pre-bronchodilator forced expiratory volume in 1 s (FEV1) of 60-90% predicted despite use of medium-dose inhaled corticosteroids, and had never smoked or were ex-smokers for 1 year or more with 10 pack-years or less. Patients were randomly assigned (1:1:1:1), with computer-generated pseudorandom numbers, to receive once-daily tiotropium 5 μg or 2·5 μg, twice-daily salmeterol 50 μg, or placebo, while maintaining inhaled corticosteroids. Patients and study investigators were masked to treatment allocation. Prespecified co-primary endpoints, assessed at week 24 in the full analysis set, were peak FEV1 response, measured within the first 3 h after evening dosing; trough FEV1 response; and responder rate assessed according to the seven-question Asthma Control Questionnaire (ACQ-7). These studies are registered with ClinicalTrials.gov, numbers NCT01172808 and NCT01172821.Between Aug 24, 2010, and Nov 13, 2012, we randomly assigned 2103 patients to the tiotropium 5 μg group (n=519), the tiotropium 2·5 μg group (n=520), the salmeterol group (n=541), or the placebo group (n=523); 1972 (94%) patients completed the study. Peak and trough FEV1 responses were significantly greater with tiotropium and salmeterol than with placebo and were similar in both studies. With pooled data, difference versus placebo in peak FEV1 was 185 mL (95% CI 146-223) in the tiotropium 5 μg group, 223 mL (185-262) in the tiotropium 2·5 μg group, and 196 mL (158-234) in the salmeterol group (all p<0·0001); difference in trough FEV1 was 146 mL (95% CI 105-188), 180 mL (138-221), and 114 mL (73-155; all p<0·0001), respectively. There were more ACQ-7 responders in the tiotropium 5 μg (OR 1·32, 95% CI 1·02-1·71; p=0·035) and 2·5 μg (1·33, 1·03-1·72; p=0·031) groups, and the salmeterol group (1·46, 1·13-1·89; p=0·0039), than in the placebo group. 48 (2%) of 2100 patients had serious adverse events (tiotropium 5 μg n=11, tiotropium 2·5 μg n=12, salmeterol n=11, placebo n=14).Once-daily tiotropium add-on to medium-dose inhaled corticosteroids reduces airflow	Included	Inclusions
Once-daily tiotropium Respimat(®) 5 μg is an efficacious add-on therapy to inhaled corticosteroids (ICS) with or without long-acting β2-agonists in patients with symptomatic asthma. The objective of this study was to investigate whether the dosing regimen of tiotropium (once- versus twice-daily), delivered via the Respimat(®) SoftMist™ inhaler, affected 24-h bronchodilator efficacy and safety versus placebo Respimat(®) in patients with asthma who were symptomatic despite medium-dose ICS therapy.A randomised, double-blind, placebo-controlled, crossover study with 4-week treatment periods of tiotropium 5 μg (once-daily, evening) and 2.5 μg (twice-daily, morning and evening). The primary efficacy end point was forced expiratory volume in 1 s (FEV1) area under the curve from 0 to 24 h (AUC)(0-24h) at the end of each treatment period. Secondary end points included peak forced expiratory volume in 1 s measured within 24 h of the last evening inhalation (peak FEV1(0-24h)), trough FEV1 measured prior to evening dosing, morning and evening peak expiratory flow (PEFam and PEFpm) and pharmacokinetic assessments.94 patients were randomised (mean age 44.3 years; mean asthma duration 21.3 years) and 89 (94.7%) completed the study. Significant and comparable bronchodilation was achieved over a 24-h period with both tiotropium dosing regimens. FEV1 AUC(0-24h) response (mean ± standard error) was significantly greater with both tiotropium dosing regimens (once-daily 5 μg: 158 ± 24 mL; twice-daily 2.5 μg; 149 ± 24 mL; both p < 0.01) when compared with placebo. Improvements in peak FEV1(0-24h), trough FEV1 and pre-dose PEFam/pm with both dosing regimens versus placebo were statistically significant (all p < 0.01), with no statistically significant differences between the tiotropium treatment regimens. Total systemic exposure and tolerability were comparable between treatment regimens.Lung function improvements with tiotropium Respimat(®) add-on to medium-dose ICS were sustained and similar for once-daily 5 μg and twice-daily 2.5 μg, supporting tiotropium Respimat(®) 5 μg as a once-daily bronchodilator that provides efficacy over the whole 24-h dosing interval in patients with symptomatic asthma. ClinicalTrials.gov identifier: NCT01152450.	excluded	did not meet inclusion criteria

				Although it is a pooled study (one of the exlusion criteria), it is included because two replicate trials with similar patient characteristics and treatment paradigms are pooled	The Lancet. Respiratory medicine	10160555 5
		No		Tiotropium Respimat 2.5 µg dose not evaluated	Respiratory medicine	8908438

2015	May		3	5	367-76	Internet	Huib A M Kerstjens	Kerstjens, HA; Casale, TB; Bleecker, ER; Meltzer, EO; Pizzichini, E; Schmidt, O; Engel, M; Bour, L; Verkleij, CB; Moroni-Zentgraf, P; Bateman, ED	University of Groningen, University Medical Center Groningen, Department of Pulmonary Medicine and Tuberculosis, and Groningen Research Institute for Asthma and COPD, Groningen, Netherlands. Electronic address: h.a.m.kerstjens@u
2015	Mar		109	3	329-38	Internet	Wolfgang Timmer	Timmer, W; Moroni-Zentgraf, P; Cornelissen, P; Unseld, A; Pizzichini, E; Buhl, R	CRS Clinical Research Services Mannheim GmbH, Grenadierstraße 1, 68167 Mannheim, Germany. Electronic address: w.timmer@inamed-cro.com.

25609985	10.2147/JAA.S76639	J Asthma Allergy. 2015 Jan 14;8:1-13. doi: 10.2147/JAA.S76639. eCollection 2015.	Long-acting muscarinic antagonist use in adults with asthma: **real-life prescribing and outcomes** of add-on therapy with tiotropium bromide.
25577543	10.1016/j.clinthera.2014.12.008	Clin Ther. 2015 Feb 1;37(2):418-26. doi: 10.1016/j.clinthera.2014.12.008. Epub 2015 Jan 8.	Assessment of montelukast, doxofylline, and tiotropium with budesonide for the treatment of asthma: which is the best among the second-line treatment? A randomized trial.

Randomized controlled trials indicate that addition of a long-acting muscarinic antagonist (LAMA) such as tiotropium may improve asthma control and reduce exacerbation risk in patients with poorly controlled asthma, but broader clinical studies are needed to investigate the effectiveness of LAMA in real-life asthma care.Medical records of adults with asthma (aged ≥18 years) prescribed tiotropium were obtained from the UK Optimum Patient Care Research Database for the period 2001-2013. Patients diagnosed with chronic obstructive pulmonary disease were excluded, but no other clinical exclusions were applied. Two primary outcomes were compared in the year before (baseline) and the year after (outcome) addition of tiotropium: exacerbations (asthma-related hospital emergency department attendance or inpatient admission, or acute oral corticosteroid course) and acute respiratory events (exacerbation or antibiotic prescription with lower respiratory consultation). Secondary outcomes included lung function test results and short-acting β2 agonist usage. The Wilcoxon signed-rank test was used for variables measured on the interval scale, the marginal homogeneity test for categorized variables, and the paired t-test for lung function indices.Of the 2,042 study patients, 83% were prescribed an inhaled corticosteroid and 68% a long-acting β2 agonist during the baseline year; 67% were prescribed both. Comparing baseline and outcome years, the percentage of patients having at least one exacerbation decreased from 37% to 27% (P<0.001) and the percentage having at least one acute respiratory event decreased from 58% to 47% (P<0.001). There were no significant changes in lung function, and usage of short-acting β2 agonists (in salbutamol/albuterol equivalents) increased from a median (interquartile range) of 274 (110, 548) to 329 (110, 603) μg/day (P=0.01).In this real-life asthma population, addition of LAMA therapy was associated with significant decreases in the incidence of exacerbations and antibiotic prescriptions for lower respiratory tract infections in the following year.	excluded	did not meet inclusion criteria
Data comparing various second-line treatments for asthma with subjective and objective assessment are lacking. This study aimed to compare the efficacy and safety of **montelukast, doxofylline, and tiotropium** with a low-dose budesonide in patients with mild to moderate persistent asthma.Patients, all of whom were concurrently using inhaled budesonide (400 μg), were treated for 6 months with formoterol (12 μg), montelukast (10 mg), doxofylline (400 mg), or **tiotropium (18 μg)**. Outcomes included forced expiratory volume in 1 second (FEV1), Saint George Respiratory Questionnaire (SGRQ) scores, asthma symptom scores (daytime and nighttime), and assessment of tolerability and rescue medication use.A total of 297 patients completed the study. In all 4 groups, significant improvements were observed in all the outcome measures, with formoterol treatment having greater and earlier improvements than the other 3 second-line controller medications with budesonide. Among the second-line treatments, monteradlukast improved the FEV1 from day 45 (P < 0.01), SGRQ scores from day 30 (P < 0.0001), daytime scores from day 30 (P < 0.05), nighttime scores from day 30 (P < 0.0001), and rescue medication use from day 15 (P < .0001) at a faster rate than doxofylline or tiotropium with budesonide. No patients discontinued the treatment because of adverse reactions.Among the tested second-line treatment regimens, the budesonide/montelukast combination was found to be superior to either the budesonide/doxofylline or budesonide/tiotropium combination in all the outcome measures without adversely affecting the tolerability of the patients. Further clinical studies with blinding techniques are likely to be useful.	excluded	did not meet inclusion criteria

No			no	Not a ph 3 RCT; lung function not reported	Journal of asthma and allergy	10154345 0
	No			Tiotropium not delivered via Respimat®	Clinical therapeutics	7706726

2015			8		1-13	Print	David Price	Price, D; Kaplan, A; Jones, R; Freeman, D; Burden, A; Gould, S; von Ziegenweidt, J; Ali, M; King, C; Thomas, M	Academic Centre of Primary Care, University of Aberdeen, Aberdeen; Research in Real-Life, Cambridge, UK.
2015	Feb		37	2	418-26	Internet	Muhasaparur Ganesan Rajanandh	Rajanandh, MG; Nageswari, AD; Ilango, K	Department of Pharmacy Practice, Faculty of Pharmacy, Sri Ramachandra University, Porur, Chennai, Tamil Nadu, India.

25335652	10.1111/crj.12230	Clin Respir J. 2016 Jul;10(4):421-7. doi: 10.1111/crj.12230. Epub 2014 Nov 9.	Tiotropium may improve asthma symptoms and lung function in asthmatic patients with irreversible airway obstruction: the **real-life data**.
25081651	10.1016/j.rmed.2014.06.011	Respir Med. 2014 Sep;108(9):1268-76. doi: 10.1016/j.rmed.2014.06.011. Epub 2014 Jul 17.	Tiotropium in asthmatic adolescents symptomatic despite inhaled corticosteroids: a randomised dose-ranging study.

Some patients with asthma have poorly controlled disease despite the use of high-dose inhaled corticosteroids (ICS), long-acting β2 agonists (LABAs) and antileukotrienes. The aim of the study was to assess the effectiveness of tiotropium as an add-on therapy to the standard treatment with high-dose ICS/LABA on asthma control and lung function in patients with severe asthma.Of the 633 asthmatic patients, 64 (10.1%) patients with severe asthma who were add-on treated at least for 3 months were evaluated. Number of exacerbations, emergency department visits, hospitalizations and lung functions of patients belonging to 12 months before starting add-on treatment were compared with those of 12 months after starting add-on treatment.The mean duration of add-on tiotropium treatment was 8.3 ± 0.5 months. For patients with severe asthma that was poorly controlled with standard combination therapy, tiotropium improved asthma control in 42.2%, decreased the number of emergency department visits in 46.9% and decreased the number of hospitalizations in 50.0% of them. The mean baseline forced expiratory volume in 1 s before add-on tiotropium was 57.5 ± 1.9% and forced vital capacity was 74.3 ± 15.6%. However, after 12 months of add-on tiotropium treatment, these rates became 65.5 ± 1.9% and 82.5 ± 15.1%, respectively. The addition of tiotropium significantly improved the percentages of the number of emergency department visits, the number of hospitalizations (P < 0.05).Our study has suggested that, for patients with poorly controlled asthma despite of the use of ICS/LABA, the addition of tiotropium to standard care may be beneficial.	excluded	did not meet inclusion criteria
Tiotropium, a once-daily long-acting anticholinergic agent, has been shown to be an efficacious and safe add-on treatment for adults with symptomatic asthma, despite treatment with inhaled corticosteroids (ICS). A large proportion of asthmatic adolescents have symptomatic disease despite a wide range of therapeutic options. We investigated the efficacy and safety of three doses of tiotropium, administered in the evening (via Respimat(®) SoftMist™ inhaler), versus placebo in asthmatic adolescents symptomatic despite ICS treatment.This randomised, double-blind, placebo-controlled, incomplete crossover study evaluated once-daily tiotropium 5 µg, 2.5 µg and 1.25 µg versus placebo in three 4-week treatment periods. Primary efficacy end point was change in peak forced expiratory volume in 1 s within 3 h post-dose from baseline (peak FEV1(0-3h)).From 139 enrolled patients, 105 were randomised to receive one of four treatment sequences. Peak FEV1(0-3h) response for tiotropium 5 µg was significantly greater versus placebo (p = 0.0043). Trough FEV1 responses were significantly greater for tiotropium 5 µg (p < 0.00001) and 1.25 µg (p = 0.0134) versus placebo, but not for 2.5 µg (p = 0.0975), while FEV1 area under the curve(0-3h) responses were significant for all doses (p = 0.00001-0.0398). Overall incidence of adverse events was balanced across treatment groups, with no dose-dependent observations. The majority of adverse events were mild to moderate in intensity.This first study of tiotropium in adolescents with symptomatic asthma demonstrates that tiotropium is well tolerated and efficacious as add-on to maintenance treatment with ICS. ClinicalTrials.gov identifier; NCT01122680.	Included	Inclusions

No				Not a ph 3 RCT	The clinical respiratory journal	101315570
No					Respiratory medicine	8908438

2016	Jul		10	4	421-7	Internet	Oznur Abadoglu	Abadoglu, O; Berk, S	Department of Chest Diseases, Subdepartment of Immunology and Allergy Diseases, Faculty of Medicine, Cumhuriyet Üniversity, Sivas, Turkey.
2014	Sep		108	9	1268-76	Internet	Christian Vogelberg	Vogelberg, C; Engel, M; Moroni-Zentgraf, P; Leonaviciute-Klimantaviciene, M; Sigmund, R; Downie, J; Nething, K; Vevere, V; Vandewalker, M	Technische Universität Dresden, University Hospital Carl Gustav Carus, Department of Pediatric Pneumology and Allergology, Fetscherstraße 74, 01307 Dresden, Germany. Electronic address: christian.vogelberg@uniklinikum-dresden.de.

24974107	10.1007/s40258-014-0107-8	Appl Health Econ Health Policy. 2014 Aug;12(4):447-59. doi: 10.1007/s40258-014-0107-8. Erratum in: Appl Health Econ Health Policy. 2016 Feb;14(1):119-25.	**Cost effectiveness** of tiotropium in patients with asthma poorly controlled on inhaled glucocorticosteroids and long-acting β-agonists.
24890738	10.1186/1465-9921-15-61	Respir Res. 2014 Jun 3;15:61. doi: 10.1186/1465-9921-15-61.	Tiotropium Respimat® in asthma: a double-blind, randomised, dose-ranging study in adult patients with moderate asthma.

A considerable proportion of patients with asthma remain uncontrolled or symptomatic despite treatment with a high dose of inhaled glucocorticosteroids (ICSs) and long-acting β2-agonists (LABAs). Tiotropium Respimat(®) added to usual care improves lung function, asthma control, and the frequency of non-severe and severe exacerbations, in a population of adult asthma patients who are uncontrolled despite treatment with ICS/LABA.This study estimated the cost effectiveness of tiotropium therapy as add-on to usual care in asthma patients that are uncontrolled despite treatment with ICS/LABA combination from the perspective of the UK National Health Service (NHS).A Markov model was developed which considers levels of asthma control and exacerbations. The model analysed cost and quality-adjusted life-years (QALYs); sensitivity and scenario analyses were also conducted to test the robustness of the base case outcomes. All costs are given at 2012 prices.The model found that in this category of asthma with unmet need, add-on tiotropium therapy generated an incremental 0.24 QALYs and £5,238 costs over a lifetime horizon, resulting in an incremental cost-effectiveness ratio of £21,906 per QALY gained. Sensitivity analysis suggested that findings were most dependent on the costs of managing uncontrolled asthma and the cost of treatment with tiotropium.In this modelled analysis of two clinical trials, tiotropium was found to be cost effective when added to usual care in patients who remain uncontrolled despite treatment with high-dose ICS/LABA. Further research should investigate the long-term treatment effectiveness of tiotropium.	excluded	HEOR
Tiotropium, a once-daily long-acting anticholinergic bronchodilator, when administered via Respimat® SoftMist™ inhaler (tiotropium Respimat®) significantly reduces the risk of severe exacerbations and improves lung function in patients with severe persistent asthma that is not fully controlled despite using inhaled corticosteroids (ICS) and long-acting β2-agonists. To further explore the dose-response curve in asthma, we investigated the efficacy and safety of three different doses of tiotropium Respimat® as add-on to ICS in symptomatic patients with moderate persistent asthma.In this randomised, double-blind, placebo-controlled, four-way crossover study, patients were randomised to tiotropium Respimat® 5 µg, 2.5 µg or 1.25 µg or placebo Respimat®, once daily in the evening. Each treatment was administered for 4 weeks, without washout between treatment periods. Eligibility criteria included ≥60% and ≤90% of predicted normal forced expiratory volume in 1 second (FEV1) and seven-question Asthma Control Questionnaire mean score of ≥1.5. Patients were required to continue maintenance treatment with stable medium-dose ICS for at least 4 weeks prior to and during the treatment period. Long-acting β2-agonists were not permitted during the treatment phase. The primary efficacy end point was peak FEV1 measured within 3 hours after dosing (peak FEV1(0-3h)) at the end of each 4-week period, analysed as a response (change from study baseline).In total, 149 patients were randomised and 141 completed the study. Statistically significant improvements in peak FEV1(0-3h) response were observed with each tiotropium Respimat® dose versus placebo (all $P < 0.0001$). The largest difference from placebo was with tiotropium Respimat® 5 µg (188 mL). Trough FEV1 and FEV1 area under the curve (AUC)(0-3h) responses were greater with each tiotropium Respimat® dose than with placebo (all $P < 0.0001$), and both were greatest with 5 µg. Peak forced vital capacity (FVC)(0-3h), trough FVC and FVC AUC(0-3h) responses, versus placebo, were greatest with tiotropium Respimat® 5 µg ($P < 0.0001$, $P = 0.0012$ and $P < 0.0001$, respectively). Incidence of adverse events was comparable between placebo and all tiotropium Respimat® groups.Once-daily tiotropium Respimat® add-on to medium-dose ICS improves lung function in symptomatic patients with moderate asthma. Overall, improvements were largest with tiotropium Respimat® 5 µg.ClinicalTrials.gov identifier NCT01233284.	Included	Inclusions

				HEOR analysis	Applied health economics and health policy	101150314
Yes					Respiratory research	101090633

2014	Aug		12	4	447-59	Internet	Jenny Willson	Willson, J; Bateman, ED; Pavord, I; Lloyd, A; Krivasi, T; Esser, D	Health Economics and Outcomes Research, Real-World Evidence Solutions, IMS Health, 210 Pentonville Road, London, N1 9JY, UK.
2014	Jun		15		61	Internet	Kai-Michael Beeh	Beeh, KM; Moroni-Zentgraf, P; Ablinger, O; Hollaenderova, Z; Unseld, A; Engel, M; Korn, S	insaf Respiratory Research Institute GmbH, Wiesbaden, Germany. k.beeh@insaf-wi.de.

24650447	10.1016/j.clinthera.2014.02.006	Clin Ther. 2014 Apr 1;36(4):526-33. doi: 10.1016/j.clinthera.2014.02.006. Epub 2014 Mar 17.	Pulmonary function assessment in mild to moderate persistent asthma patients receiving montelukast, doxofylline, and tiotropium with budesonide: a randomized controlled study.
24307202	10.1124/jpet.113.208439	J Pharmacol Exp Ther. 2014 Feb;348(2):303-10. doi: 10.1124/jpet.113.208439. Epub 2013 Dec 4.	Bronchoprotection by olodaterol is synergistically enhanced by tiotropium in a **guinea pig model** of allergic asthma.

There is no comparative study among asthma patients receiving first-line versus various second-line treatment regimens for mild to moderate persistent asthma.We assessed the pulmonary function in asthma patients receiving montelukast, doxofylline, and tiotropium with budesonide in a pilot group.Patients were recruited as per the study criteria and randomly allocated to 4 groups to receive **budesonide (400 µg) with formoterol (12 µg), doxofylline (400 mg), montelukast (10 mg), or tiotropium (18 µg)** for a period of 3 months. Outcomes included forced expiratory volume in 1 second (FEV1) and rescue medication use.A total of 167 patients were recruited; among them, 123 patients completed the study. At baseline, no significant difference (P > 0.05) was observed in any of the outcome measures. Significant within-group improvement in FEV1 was observed in all the groups. At day 90, between-group difference revealed that improvement in FEV1 was significantly (P < 0.05) high for budesonide plus formoterol followed by budesonide plus doxofylline, budesonide plus montelukast, and, lastly, budesonide plus tiotropium. Similarly, within-group comparison revealed a significant (P < 0.05) reduction in rescue medication use in all the groups. The intensity in decrease was more in budesonide plus formoterol group followed by budesonide plus doxofylline, budesonide plus montelukast, and budesonide plus tiotropium groups.On the basis of our findings, among the second-line treatment regimens, budesonide plus doxofylline and budesonide plus montelukast was found to be better than budesonide plus tiotropium in patients with mild to moderate persistent asthma. Further studies with a larger sample size are likely to be useful.	excluded	did not meet inclusion criteria
The novel once-daily β_2-agonist bronchodilator drug olodaterol has recently been shown to be effective in patients with allergic asthma for >24 hours. An increased cholinergic tone common to these patients may decrease the effectiveness of β_2-agonists. This could provide a rationale for combination therapy with olodaterol and the long-acting anticholinergic tiotropium to aim for a once-daily treatment regimen. In guinea pigs, we evaluated the protective effects of olodaterol, alone and in combination with tiotropium, on airway responsiveness to histamine, which is partially mediated by a cholinergic reflex mechanism. In addition, using a guinea pig model of acute allergic asthma, we examined the cooperative effects of these bronchodilators on allergen-induced early (EAR) and late (LAR) asthmatic reactions, airway hyper-responsiveness (AHR) to histamine, and airway inflammation. It was demonstrated that the protective effect of olodaterol against histamine-induced bronchoconstriction was synergistically enhanced and prolonged in the presence of tiotropium. In addition, tiotropium synergistically augmented both the reversal of and the protection against the allergen-induced AHR after the EAR by olodaterol. Olodaterol and tiotropium were highly effective in inhibiting the magnitude of the allergen-induced EAR and LAR, and both reactions were fully inhibited by the combination of these drugs. It is remarkable that these effects were not associated with an effect on inflammatory cell infiltration in the airways. In conclusion, the results indicate that combination therapy with olodaterol and tiotropium may be highly effective in the treatment of allergen-induced asthmatic reactions and AHR.	excluded	In vitro/Preclinical

	No			Tiotropium not delivered via Respimat, not placebo-controlled	Clinical therapeutics	7706726
				Preclinical animal study	The Journal of pharmacology and experimental therapeutics	0376362

2014	Apr		36	4	526-33	Internet	Muhasaparur G Rajanandh	Rajanandh, MG; Nageswari, AD; Ilango, K	Department of Pharmacy Practice, SRM College of Pharmacy, Tamil Nadu, India.
2014	Feb		348	2	303-10	Internet	Marieke Smit	Smit, M; Zuidhof, AB; Bos, SI; Maarsingh, H; Gosens, R; Zaagsma, J; Meurs, H	Department of Molecular Pharmacology, Groningen Research Institute of Pharmacy, and Groningen Research for Asthma and COPD, University of Groningen, Groningen, The Netherlands.

24090641	10.1016/j.pupt.2013.09.004	Pulm Pharmacol Ther. 2014 Feb;27(1):44-51. doi: 10.1016/j.pupt.2013.09.004. Epub 2013 Sep 30.	Tiotropium bromide inhibits relapsing allergic asthma in **BALB/c mice**.
24084072	10.1016/j.jaci.2013.08.003	J Allergy Clin Immunol. 2013 Nov;132(5):1068-1074.e1. doi: 10.1016/j.jaci.2013.08.003. Epub 2013 Sep 29.	Predictors of response to tiotropium versus salmeterol in asthmatic adults.
23207413		Pol Arch Med Wewn. 2012;122(11):525-6. No abstract available.	Tiotropium for severe asthma: a step forward or more of the same?

Recurrent relapses of allergic lung inflammation in asthmatics may lead to airway remodeling and lung damage. We tested the efficacy of tiotropium bromide, a selective long-acting, muscarinic receptor antagonist as an adjunct therapy in relapses of allergic asthma in mice. We compared the effectiveness of local intranasal administration of tiotropium and dexamethasone in acute and relapsing allergic asthma in BALB/c mice. Although tiotropium at low doses is a potent bronchodilator, we tested higher doses to determine effectiveness on inflammation and mucus hypersecretion. A 5-day course of twice daily intranasal tiotropium or dexamethasone (1 mg/kg (b.w.)) suppressed airway eosinophils by over 87% during disease initiation and 88% at relapse compared to vehicle alone. Both drugs were comparable in their capacity to suppress airway and parenchymal inflammation and mucus hypersecretion, though tiotropium was better than dexamethasone at reducing mucus secretion during disease relapse. Despite treatment with either drug, serum antigen-specific IgE or IgG1 antibody titres remained unchanged. Our study indicates that tiotropium at higher doses than required for bronchodilation, effectively suppresses inflammation and mucus hypersecretion in the lungs and airways of mice during the initiation and relapse of asthma. Tiotropium is currently not approved for use in asthma. Clinical studies have to demonstrate the efficacy of tiotropium in this respiratory disease.	excluded	In vitro/Preclinical
Tiotropium has activity as an asthma controller. However, predictors of a positive response to tiotropium have not been described.We sought to describe individual and differential responses of asthmatic patients to salmeterol and tiotropium when added to an inhaled corticosteroid, as well as predictors of a positive clinical response.Data from the double-blind, 3-way, crossover National Heart, Lung, and Blood Institute's Asthma Clinical Research Network's Tiotropium Bromide as an Alternative to Increased Inhaled Glucocorticoid in Patients Inadequately Controlled on a Lower Dose of Inhaled Corticosteroid (ClinicalTrials.gov number, NCT00565266) trial were analyzed for individual and differential treatment responses to salmeterol and tiotropium and predictors of a positive response to the end points FEV1, morning peak expiratory flow (PEF), and asthma control days (ACDs).Although approximately equal numbers of patients showed a differential response to salmeterol and tiotropium in terms of morning PEF (n = 90 and 78, respectively) and ACDs (n = 49 and 53, respectively), more showed a differential response to tiotropium for FEV1 (n = 104) than salmeterol (n = 62). An acute response to a short-acting bronchodilator, especially albuterol, predicted a positive clinical response to tiotropium for FEV1 (odds ratio, 4.08; 95% CI, 2.00-8.31; P < .001) and morning PEF (odds ratio, 2.12; 95% CI, 1.12-4.01; P = 0.021), as did a decreased FEV1/forced vital capacity ratio (FEV1 response increased 0.39% of baseline for every 1% decrease in FEV1/forced vital capacity ratio). Higher cholinergic tone was also a predictor, whereas ethnicity, sex, atopy, IgE level, sputum eosinophil count, fraction of exhaled nitric oxide, asthma duration, and body mass index were not.Although these results require confirmation, predictors of a positive clinical response to tiotropium include a positive response to albuterol and airway obstruction, factors that could help identify appropriate patients for this therapy.	excluded	did not meet inclusion criteria
	excluded	Editorial

				Preclinical animal study	Pulmonary pharmacology & therapeutics	9715279
	No			Tiotropium was not delivered via Respimat	The Journal of allergy and clinical immunology	1275002
				Opinion editorial	Polskie Archiwum Medycyny Wewnetrznej	0401225

2014	Feb		27	1	44-51	Internet	Berislav Bosnjak	Bosnjak, B; Tilp, C; Tomsic, C; Dekan, G; Pieper, MP; Erb, KJ; Epstein, MM	Division of Immunology, Allergy and Infectious Diseases, Experimental Allergy, Department of Dermatology, Medical University of Vienna, Vienna, Austria.
2013	Nov		132	5	1068-1074.e1	Internet	Stephen P Peters	Peters, SP; Bleecker, ER; Kunselman, SJ; Icitovic, N; Moore, WC; Pascual, R; Ameredes, BT; Boushey, HA; Calhoun, WJ; Castro, M; Cherniack, RM; Craig, T; Denlinger, LC; Engle, LL; Dimango, EA; Israel, E; Kraft, M; Lazarus, SC; Lemanske, RF;	Wake Forest School of Medicine, Winston-Salem, NC. Electronic address: sppeters@wakehealth.edu.
2012			122	11	525-6	Internet	Sally E Wenzel	Wenzel, SE	

23073336	10.1016/j.pupt.2012.09.007	Pulm Pharmacol Ther. 2013 Apr;26(2):159-66. doi: 10.1016/j.pupt.2012.09.007. Epub 2012 Oct 13.	Effects of tiotropium on lung function in severe asthmatics with or without emphysematous changes.
22938706	10.1056/NEJMoa1208606	N Engl J Med. 2012 Sep 27;367(13):1198-207. Epub 2012 Sep 2.	Tiotropium in asthma poorly controlled with standard combination therapy.

The effects of tiotropium, an inhaled long-acting anti-cholinergic agent, on lung function were investigated in obstructed severe asthmatics with and without emphysematous changes despite maximal recommended treatments with high-dose of inhaled glucocorticoids and inhaled long-acting β(2)-agonists. We conducted a double-blind, placebo-controlled study of an inhaled single-dose of tiotropium in 18 asthmatics with emphysema and 18 without emphysema in a crossover manner. The primary efficacy outcome was the relative change in forced expiratory volume in 1 s (FEV(1)) from baseline to 60 min, and the secondary outcome was a relative change in FEV(1) from baseline to 12 h. Subsequently, the patients were treated with tiotropium inhaled once daily for 12 weeks in an open label manner, and lung function and symptoms were evaluated. At baseline, patients with or without emphysema had a mean FEV(1) of 55.9% before tiotropium and 56.8% before placebo, or 77.4% before tiotropium and 77.6% before placebo of the predicted value and were taking a mean dose of inhaled glucocorticoids of 1444 or 1422 μg/day. Among patients with emphysema, the increase from baseline FEV(1) was 12.6 percentage points higher at 60 min after tiotropium than after placebo. Among patients without emphysema, the increase from baseline FEV(1) was 5.4 percentage points higher at 60 min after tiotropium than after placebo. Tiotropium resulted in improved lung function and symptoms in asthmatics with and without emphysema. These findings suggest that tiotropium will provide a new strategy for the treatment of bronchial asthma and of overlapping asthma and COPD.	excluded	did not meet inclusion criteria
Some patients with asthma have frequent exacerbations and persistent airflow obstruction despite treatment with inhaled glucocorticoids and long-acting beta-agonists (LABAs).In two replicate, randomized, controlled trials involving 912 patients with asthma who were receiving inhaled glucocorticoids and LABAs, we compared the effect on lung function and exacerbations of adding tiotropium (a total dose of 5 μg) or placebo, both delivered by a soft-mist inhaler once daily for 48 weeks. All the patients were symptomatic, had a post-bronchodilator forced expiratory volume in 1 second (FEV(1)) of 80% or less of the predicted value, and had a history of at least one severe exacerbation in the previous year.The patients had a mean baseline FEV(1) of 62% of the predicted value; the mean age was 53 years. At 24 weeks, the mean (±SE) change in the peak FEV(1) from baseline was greater with tiotropium than with placebo in the two trials: a difference of 86±34 ml in trial 1 (P=0.01) and 154±32 ml in trial 2 (P<0.001). The predose (trough) FEV(1) also improved in trials 1 and 2 with tiotropium, as compared with placebo: a difference of 88±31 ml (P=0.01) and 111±30 ml (P<0.001), respectively. The addition of tiotropium increased the time to the first severe exacerbation (282 days vs. 226 days), with an overall reduction of 21% in the risk of a severe exacerbation (hazard ratio, 0.79; P=0.03). No deaths occurred; adverse events were similar in the two groups.In patients with poorly controlled asthma despite the use of inhaled glucocorticoids and LABAs, the addition of tiotropium significantly increased the time to the first severe exacerbation and provided modest sustained bronchodilation. (Funded by Boehringer Ingelheim and Pfizer; ClinicalTrials.gov numbers, NCT00772538 and NCT00776984.).	excluded	did not meet inclusion criteria

	No			Tiotropium not delivered via Respimat,	Pulmonary pharmacology & therapeutics	9715279
		No		Tiotropium Respimat 2.5 µg dose not evaluated	The New England journal of medicine	0255562

2013	Apr		26	2	159-66	Internet	Makoto Yoshida	Yoshida, M; Nakano, T; Fukuyama, S; Matsumoto, T; Eguchi, M; Moriwaki, A; Takata, S; Machida, K; Kanaya, A; Matsumoto, K; Nakanishi, Y; Inoue, H	Research Institute for Diseases of the Chest, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan.
2012	Sep		367	13	1198-207	Internet	Huib A M Kerstjens	Kerstjens, HA; Engel, M; Dahl, R; Paggiaro, P; Beck, E; Vandewalker, M; Sigmund, R; Seibold, W; Moroni-Zentgraf, P; Bateman, ED	University of Groningen and the Department of Pulmonary Medicine and Tuberculosis, University Medical Center Groningen, and Groningen Research Institute for Asthma and COPD, Groningen, The Netherlands. h.a.m.kerstjens@umcg.nl

22727154	10.1016/j.anai.2012.05.005	Ann Allergy Asthma Immunol. 2012 Jul;109(1):29-35. doi: 10.1016/j.anai.2012.05.005. Epub 2012 May 25.	Effect of tiotropium bromide on airway remodeling in a **chronic asthma model**.
21807250	10.1016/j.jaci.2011.06.004	J Allergy Clin Immunol. 2011 Aug;128(2):315-22. doi: 10.1016/j.jaci.2011.06.004.	Tiotropium is noninferior to salmeterol in maintaining improved lung function in B16-Arg/Arg patients with asthma.

Recent evidence suggests that acetylcholine acting through muscarinic receptors may play an inhibitory role in the mechanisms that drive the structural changes in the airways called airway remodeling. The novel anticholinergic drug tiotropium bromide, which selectively antagonizes muscarinic receptors, especially the M3 subtype, and is long acting, could be beneficial in attenuating airway remodeling in chronic asthma.To investigate the effect of tiotropium bromide on parameters of airway remodeling, including smooth muscle hypertrophy and peribronchial thickening, in a mouse model of chronic asthma.To develop the murine models of acute and chronic asthma, BALB/c mice were sensitized and challenged to ovalbumin for 1 and 3 months, respectively. The effect of tiotropium bromide (0.1mM in 50 μL of phosphate-buffered saline) on pulmonary inflammation and remodeling was evaluated. The expression of muscarinic receptors M2 and M3 was analyzed.In the chronic asthma model, the tiotropium-treated group significantly decreased smooth muscle thickening and peribronchial collagen deposition. As for pulmonary inflammation, the chronic asthma model had a reduction of inflammatory cells and T(H)2 cytokines by tiotropium bromide, but the effects in the asthma acute model were reversed. In the chronic asthma model, expression of the M3 receptor was inhibited and that of the M2 receptor was elevated by the administration of tiotropium bromide.This study suggests that tiotropium bromide might have an inhibitory effect on airway remodeling in a murine model of chronic asthma. Differential effects on muscarinic receptor subtypes may explain why tiotropium bromide has different effects on acute and chronic asthma.	excluded	In vitro/Preclinical
The efficacy and safety of inhaled long-acting β(2)-adrenergic agonists in asthmatic patients with the B16-Arg/Arg genotype has been questioned, and the use of antimuscarinics has been proposed as an alternative in patients whose symptoms are not controlled by inhaled corticosteroids (ICSs).We compared the efficacy and safety of the long-acting anticholinergic tiotropium with salmeterol and placebo added to an ICS in B16-Arg/Arg patients with asthma that was not controlled by ICSs alone.In a double-blind, double-dummy, placebo-controlled trial, after a 4-week run-in period with 50 μg of twice-daily salmeterol administered through a metered-dose inhaler, 388 asthmatic patients were randomized 1:1:1 to 16 weeks of treatment with **5 μg of Respimat tiotropium** administered daily in the evening, 50 μg of salmeterol administered twice daily through a metered-dose inhaler, or placebo. Patients aged 18 to 67 years demonstrated reversibility to bronchodilators, and their symptoms were uncontrolled by regular ICSs (400-1000 μg of budesonide/equivalent). ICS regimens were maintained throughout the trial. The mean weekly morning peak expiratory flow (PEF) before randomization was 358 ± 115.7 L/min (range, 80.3-733.0 L/min).Changes in weekly PEF from the last week of the run-in period to the last week of treatment (primary end point: change in PEF) were -3.9 ± 4.87 L/min (n = 128) for tiotropium and -3.2 ± 4.64 L/min (n = 134) for salmeterol, and these were superior to placebo (-24.6 ± 4.84 L/min, n = 125, P < .05). Tiotropium was noninferior to salmeterol (estimated difference, -0.78 L/min [95% CI, -13.096 to 11.53]; P = .002; α = .025, 1-sided; noninferiority, 20 L/min). Tiotropium and salmeterol were numerically superior to placebo in some patient-reported secondary outcomes. Adverse events were comparable across treatments.Tiotropium was more effective than placebo and as effective as salmeterol in maintaining improved lung function in B16-Arg/Arg patients with moderate persistent asthma. Safety profiles were comparable.	excluded	did not meet inclusion criteria

				Preclinical animal study	Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology	9503580
		No		Tiotropium Respimat 2.5 µg dose not evaluated	The Journal of allergy and clinical immunology	1275002

2012	Jul		109	1	29-35	Internet	Ji Young Kang	Kang, JY; Rhee, CK; Kim, JS; Park, CK; Kim, SJ; Lee, SH; Yoon, HK; Kwon, SS; Kim, YK; Lee, SY	Division of Respiratory Medicine, Department of Internal Medicine, College of Medicine, Catholic University of Korea, Seoul, South Korea. sooklee@catholic.ac.kr
2011	Aug		128	2	315-22	Internet	Eric D Bateman	Bateman, ED; Kornmann, O; Schmidt, P; Pivovarova, A; Engel, M; Fabbri, LM	Department of Medicine, University of Cape Town, Cape Town, South Africa.

21636120	10.1016/j.jaci.2011.04.039	J Allergy Clin Immunol. 2011 Aug;128(2):308-14. doi: 10.1016/j.jaci.2011.04.039. Epub 2011 Jun 2.	Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial.
21226656	10.1517/14656566.2011.545054	Expert Opin Pharmacother. 2011 Feb;12(3):489-91. doi: 10.1517/14656566.2011.545054. Epub 2011 Jan 13.	Tiotropium in the treatment of asthma.

Some patients with severe asthma remain symptomatic and obstructed despite maximal recommended treatment. Tiotropium, a long-acting inhaled anticholinergic agent, might be an effective bronchodilator in such patients.We sought to compare the efficacy and safety of **2 doses of tiotropium (5 and 10 µg daily)** administered through the Respimat inhaler with placebo as add-on therapy in patients with uncontrolled severe asthma (Asthma Control Questionnaire score, ≥ 1.5; postbronchodilator FEV_1, ≤ 80% of predicted value) despite maintenance treatment with at least a high-dose inhaled corticosteroid plus a long-acting β_2-agonist.This was a randomized, double-blind, crossover study with three 8-week treatment periods. The primary end point was peak FEV_1 at the end of each treatment period.Of 107 randomized patients (54% female patients; mean, 55 years of age; postbronchodilator FEV_1, 65% of predicted value), 100 completed all periods. Peak FEV_1 was significantly higher with 5 µg (difference, 139 mL; 95% CI, 96-181 mL) and 10 µg (difference, 170 mL; 95% CI, 128-213 mL) of tiotropium than with placebo (both P < .0001). There was no significant difference between the active doses. Trough FEV_1 at the end of the dosing interval was higher with tiotropium (5 µg: 86 mL [95% CI, 41-132 mL]; 10 µg: 113 mL [95% CI, 67-159 mL]; both P < .0004). Daily home peak expiratory flow measurements were higher with both tiotropium doses. There were no significant differences in asthma-related health status or symptoms. Adverse events were balanced across groups except for dry mouth, which was more common on 10 µg of tiotropium.The addition of once-daily tiotropium to asthma treatment, including a high-dose inhaled corticosteroid plus a long-acting β_2-agonist, significantly improves lung function over 24 hours in patients with inadequately controlled, severe, persistent asthma.	excluded	did not meet inclusion criteria
Existing asthma therapies are not always able to achieve disease control. The addition of tiotropium bromide to inhaled corticosteroids might be effective in improving disease outcome. This paper discusses the results of a study evaluating the effects of tiotropium bromide added to inhaled corticosteroids when compared to other regimens in patients with uncontrolled asthma. The addition of tiotropium to the current inhaled corticosteroid dose is comparable to the addition of salmeterol: both are more effective in achieving disease control versus doubling the inhaled corticosteroid dose. It is well worth investigating the effects of tiotropium in asthma that is not adequately controlled with higher doses of inhaled corticosteroids.	excluded	Review/meta analysis

		No		Tiotropium Respimat 2.5 µg dose was not evaluated	The Journal of allergy and clinical immunology	1275002
				Expert opinion/review	Expert opinion on pharmacotherapy	100897346

2011	Aug		128	2	308-14	Internet	Huib A M Kerstjens	Kerstjens, HA; Disse, B; Schröder-Babo, W; Bantje, TA; Gahlemann, M; Sigmund, R; Engel, M; van Noord, JA	Department of Pulmonology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands. h.a.m.kerstjens@long.umcg.nl
2011	Feb		12	3	489-91	Internet	Sabina Antonela Antoniu	Antoniu, SA; Sampablo, I; Carone, M	University of Medicine and Pharmacy 'Gr.T.Popa' Iasi, Romania. sabina.antonela.antoniu@pneum.umfiasi.ro

20979471	10.1056/NEJMoa1008770	N Engl J Med. 2010 Oct 28;363(18):1715-26. doi: 10.1056/NEJMoa1008770. Epub 2010 Sep 19.	Tiotropium bromide step-up therapy for adults with uncontrolled asthma.
20337647	10.1111/j.1365-2222.2010.03478.x	Clin Exp Allergy. 2010 Aug;40(8):1266-75. doi: 10.1111/j.1365-2222.2010.03478.x. Epub 2010 Mar 12.	Effect of tiotropium bromide on airway inflammation and remodelling in a **mouse model of asthma**.

Long-acting beta-agonist (LABA) therapy improves symptoms in patients whose asthma is poorly controlled by an inhaled glucocorticoid alone. Alternative treatments for adults with uncontrolled asthma are needed.In a three-way, double-blind, triple-dummy crossover trial involving 210 patients with asthma, we evaluated the addition of tiotropium bromide (a long-acting anticholinergic agent approved for the treatment of chronic obstructive pulmonary disease but not asthma) to an inhaled glucocorticoid, as compared with a doubling of the dose of the inhaled glucocorticoid (primary superiority comparison) or the addition of the LABA salmeterol (secondary noninferiority comparison).The use of tiotropium resulted in a superior primary outcome, as compared with a doubling of the dose of an inhaled glucocorticoid, as assessed by measuring the morning peak expiratory flow (PEF), with a mean difference of 25.8 liters per minute (P<0.001) and superiority in most secondary outcomes, including evening PEF, with a difference of 35.3 liters per minute (P<0.001); the proportion of asthma-control days, with a difference of 0.079 (P=0.01); the forced expiratory volume in 1 second (FEV1) before bronchodilation, with a difference of 0.10 liters (P=0.004); and daily symptom scores, with a difference of -0.11 points (P<0.001). The addition of tiotropium was also noninferior to the addition of salmeterol for all assessed outcomes and increased the prebronchodilator FEV1 more than did salmeterol, with a difference of 0.11 liters (P=0.003).When added to an inhaled glucocorticoid, tiotropium improved symptoms and lung function in patients with inadequately controlled asthma. Its effects appeared to be equivalent to those with the addition of salmeterol. (Funded by the National Heart, Lung, and Blood Institute; ClinicalTrials.gov number, NCT00565266.).	excluded	did not meet inclusion criteria
Tiotropium bromide, a long acting muscarinic receptor inhibitor, is a potent agent for patients with bronchial asthma as well as chronic obstructive pulmonary disease.The aim of this study was to evaluate whether tiotropium bromide can inhibit allergen-induced acute and chronic airway inflammation, T helper (Th)2 cytokine production, and airway remodelling in a murine model of asthma.Balb/c mice were sensitized and challenged acutely or chronically to ovalbumin (OVA). The impact of tiotropium bromide was assessed using these mice models by histologic, morphometric, and molecular techniques. Moreover, the effect of tiotropium bromide on Th2 cytokine production from purified human peripheral blood mononuclear cells (PBMCs) was assessed.Treatment with tiotropium bromide significantly reduced airway inflammation and the Th2 cytokine production in bronchoalveolar lavage fluid (BALF) in both acute and chronic models of asthma. The levels of TGF-beta1 were also reduced by tiotropium bromide in BALF in a chronic model. The goblet cell metaplasia, thickness of airway smooth muscle, and airway fibrosis were all significantly decreased in tiotropium bromide-treated mice. Moreover, airway hyperresponsiveness (AHR) to serotonin was significantly abrogated by tiotropium bromide in a chronic model. Th2 cytokine production from spleen cells isolated from OVA-sensitized mice was also significantly inhibited by tiotropium bromide and 4-diphenylacetoxy-N-methylpiperidine methiodide, which is a selective antagonist to the M3 receptor. Finally, treatment with tiotropium bromide inhibited the Th2 cytokine production from PBMCs.These results indicate that tiotropium bromide can inhibit Th2 cytokine production and airway inflammation, and thus may reduce airway remodelling and AHR in a murine model of asthma.	excluded	In vitro/Preclinical

	No			Tiotropium not delivered via Respimat®	The New England journal of medicine	0255562
				Preclinical animal study	Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology	8906443

2010	Oct		363	18	1715-26	Internet	Stephen P Peters	Peters, SP; Kunselman, SJ; Icitovic, N; Moore, WC; Pascual, R; Ameredes, BT; Boushey, HA; Calhoun, WJ; Castro, M; Cherniack, RM; Craig, T; Denlinger, L; Engle, LL; DiMango, EA; Fahy, JV; Israel, E; Jarjour, N; Kazani, SD; Kraft, M; Lazarus	Wake Forest University Health Sciences, Center for Genomics and Personalized Medicine Research, Medical Center Blvd., Winston-Salem, NC 27157, USA. sppeters@wfubmc.edu
2010	Aug		40	8	1266-75	Internet	S Ohta	Ohta, S; Oda, N; Yokoe, T; Tanaka, A; Yamamoto, Y; Watanabe, Y; Minoguchi, K; Ohnishi, T; Hirose, T; Nagase, H; Ohta, K; Adachi, M	Department of Internal Medicine, Division of Allergy and Respiratory Medicine, School of Medicine, Showa University, Tokyo, Japan.

19183167	10.1111/j.1398-9995.2008.01876.x	Allergy. 2009 May;64(5):778-83. doi: 10.1111/j.1398-9995.2008.01876.x. Epub 2009 Jan 21.	Additive role of tiotropium in severe asthmatics and Arg16Gly in ADRB2 as a potential marker to predict response.
17920256	10.1016/j.rmed.2007.08.003	Respir Med. 2008 Jan;102(1):50-6. Epub 2007 Oct 24.	Improvements with tiotropium in COPD patients with concomitant asthma.

Recent findings have raised new interests about the use of anticholinergics, especially tiotropium, for the treatment of asthma. This study was performed to determine whether an additional improvement in lung function is obtained when tiotropium is administrated in addition to conventional therapies in severe asthmatics, and to identify factors capable of predicting the response to tiotropium, using a pharmacogenetic approach.A total of 138 severe asthmatics on conventional medications and with decreased lung function were randomly recruited. **Tiotropium 18 microg** was added once a day and lung functions were measured every 4 weeks. Responders were defined as those with an improvement of > or = 15% (or 200 ml) in the forced expiratory volume in 1 s (FEV1) that was maintained for at least 8 successive weeks. Eleven single nucleotide polymorphisms (SNPs) in CHRM1-3 (coding muscarinic receptors one to three) which were identified by re-sequencing, and Arg16Gly and Gln27Glu in ADRB2 (coding beta(2) adrenoreceptor) were scored in 80 of the 138 asthmatics.Forty-six of the 138 asthmatics (33.3%) responded to tiotropium treatment. Logistic regression analyses (controlled for age, gender, and smoking status) showed that Arg16Gly in ADRB2 [P = 0.003, OR (95% CI) = 0.21 (0.07-0.59) in a minor allele-dominant model] was significantly associated with response to tiotropium.As many as 30% of severe asthmatics on conventional medications with reduced lung function were found to respond to adjuvant tiotropium. The presence of Arg16Gly in ADRB2 may predict response to tiotropium.	excluded	did not meet inclusion criteria
Chronic obstructive pulmonary disease (COPD) and asthma have different diagnostic criteria and treatment paradigms. Both are common and can occur in the same patient. We sought to determine the spirometric effects of tiotropium in COPD patients with concomitant asthma.A 12-week randomized, double-blind, placebo-controlled, parallel group trial with **tiotropium 18 mcg daily** was performed. Patients continued usual respiratory medications except for inhaled anticholinergics.Physician diagnosis of COPD and asthma, age >or= 40 years, smoking >10 pack years, post-bronchodilator forced expiratory volume in 1s (FEV(1))<80% predicted, FEV(1)/forced vital capacity (FVC)<70%, >or= 12%, and >or= 200 ml increase in FEV(1) following inhaled bronchodilator, treatment with inhaled steroids >or= 1 year. Spirometry was measured serially for 6h on days 1, 29 and 85.Four hundred and seventy-two patients were randomized. Baseline characteristics were balanced. Mean age=59.6 years, 61.4% were men, and FEV(1)=1.55l (53.0% predicted). Improvements at 12 weeks with tiotropium were observed for the primary endpoint FEV(1) area under the curve (AUC) from 0 to 6h (difference=186+/-24 ml, p<0.001) and for morning pre-dose FEV(1) (difference=98+/-23 ml, p<0.001). Significant differences in favor of tiotropium were observed for pre-dose FVC (difference=128+/-34 ml, p<0.001) and FVC AUC 0-6h (difference=232+/-35 ml, p<0.001). Compared to baseline, the mean weekly number of daily puffs of prn salbutamol was reduced by 0.05+/-0.12 puffs/day in the placebo group and by 0.50+/-0.12 puffs/day in the tiotropium group at week 12 (p<0.05).Patients with COPD and concomitant asthma achieve spirometric improvements with tiotropium along with symptomatic benefit as seen by reduced need for rescue medication.	excluded	did not meet inclusion criteria

	No			Tiotropium not delivered via Respimat	Allergy	7804028
	No			Tiotropium not delivered via Respimat	Respiratory medicine	8908438

2009	May		64	5	778-83	Internet	H-W Park	Park, HW; Yang, MS; Park, CS; Kim, TB; Moon, HB; Min, KU; Kim, YY; Cho, SH	Department of Internal Medicine, Seoul National University College of Medicine, Seoul 110-744, Korea.
2008	Jan		102	1	50-6	Print	H Magnussen	Magnussen, H; Bugnas, B; van Noord, J; Schmidt, P; Gerken, F; Kesten, S	Krankenhaus Grosshansdorf, Zentrum für Pneumologie und Thoraxchirurgie, Schleswig-Holstein Universität, Grosshansdorf, Germany. magnussen@pulmoresearch.de

17178217	10.1016/j.rmed.2006.11.001	Respir Med. 2007 Jun;101(6):1218-28. Epub 2006 Dec 18.	A **proof of concept study** to evaluate stepping down the dose of fluticasone in combination with salmeterol and tiotropium in severe persistent asthma.
8887578	10.1164/ajrccm.154.4.8887578	Am J Respir Crit Care Med. 1996 Oct;154(4 Pt 1):876-80.	Prolonged effect of tiotropium bromide on **methacholine-induced bronchoconstriction** in asthma.

We conducted a double blind, randomised, placebo-controlled, crossover study evaluating the effects of halving inhaled steroid dosage plus salmeterol, or salmeterol and tiotropium. Eighteen life-long non-smoking severe asthmatics [mean FEV(1) 1.49 l (51%)] were run-in for 4 weeks on HFA-fluticasone propionate 1000 microg daily, and were subsequently randomised to 4 weeks of either (a) HFA-fluticasone propionate 500 microg BD/salmeterol 100 microg BD/HFA-**tiotropium bromide18 microg** od; or (b) fluticasone propionate 500 microg BD/salmeterol 100 microg BD matched placebo. Measurements of spirometry and body plethysmography were made. Adding salmeterol to half the dose of fluticasone led to a mean improvement (95% CI) vs. baseline in morning PEF of 41.5 (14.0-69.0)l/min [p<0.05]; and RAW of 0.98 (0.14-1.8)cm H(2)O/l/s [p<0.05]. Adding salmeterol/tiotropium produced similar improvements in PEF and RAW, but also improved FEV(1) by 0.17 (0.01-0.32)l [p<0.05]; FVC 0.24 (0.05-0.43)l [p<0.05] and reduced exhaled NO by 2.86 (0.12-5.6)ppb [p<0.05]. RV and TLC were not altered by either treatment; there were no significant changes in symptoms or quality of life compared with baseline. Addition of salmeterol/tiotropium to half the dose of fluticasone afforded small, but significant improvements in pulmonary function. These effects were not associated with commensurate changes in subjective symptoms or quality of life.	excluded	did not meet inclusion criteria
Inhaled anticholinergic drugs are effective in the treatment of chronic obstructive pulmonary diseases (COPD), of acute asthma, and of some patients with nocturnal asthma. Tiotropium bromide (tiotropium) is a novel anticholinergic agent with a long duration of action and kinetic selectivity for M1- and M3-subtypes of muscarinic receptors. We investigated the duration of protection of a single dose of inhaled tiotropium against methacholine-induced bronchoconstriction in 12 male atopic asthmatic volunteers in a double-blind, placebo-controlled study. On four separate occasions 8 to 24 d apart, methacholine PC20 was measured serially for up to 48 h after placebo and after three doses of tiotropium (10, 40, and 80 microg). Each dose of tiotropium produced mild bronchodilatation as measured by an increase in FEV1 of between 5.5 and 11.1% from baseline, that was sustained for 24 h. There was significant dose-dependent protection against methacholine challenge at 2 h of 5.0 +/- 1.1, 7.1 +/- 0.5, and 7.9 +/- 0.7 (mean +/- SEM) doubling doses after 10, 40, and 80 microg respectively, and this persisted for 48 h. There were no adverse effects reported at any dose. The prolonged bronchodilator response and protection against methacholine challenge suggest that tiotropium may be useful in the treatment of COPD and nocturnal asthma and that once-daily dosing may be sufficient.	excluded	did not meet inclusion criteria

	No			Tiotropium not delivered via Respimat	Respiratory medicine	8908438
	No			Tiotropium not delivered via Respimat	American journal of respiratory and critical care medicine	9421642

2007	Jun		101	6	1218-28	Print	Tom Fardon	Fardon, T; Haggart, K; Lee, DK; Lipworth, BJ	Asthma and Allergy Research Group, Division of Medicine and Therapeutics, Ninewells Hospital and Medical School, University of Dundee, Dundee, Scotland, UK.
1996	Oct		154	4 Pt 1	876-80	Print	B J O'Connor	O'Connor, BJ; Towse, LJ; Barnes, PJ	Clinical Studies Unit, Royal Brompton National Heart and Lung Hospital, London, United Kingdom.

Included	10
Needs confirmation	1
Excluded	43

Table S1. Baseline characteristics of patients in the phase 3 RCTs.

Study	Total (n)		Female		Age (y)		Asthma duration (y)		Pre-bronchodilator FEV_1 % predicted		Dose of stable maintenance ICS (µg)[†]		ACQ-7 scores	
	2.5 µg TioR	Pbo	2.5 µg TioR	Pbo	2.5 µg TioR	Pbo	2.5 µg TioR	Pbo	2.5 µg TioR	Pbo	2.5 µg TioR	Pbo	2.5 µg TioR	Pbo
Vrijlandt 2018[24]	36	34	17 (47.2)	13 (38.2)	3.1 (1.5)	3.2 (1.4)	1.8 (1.1)[††]	1.4 (0.9)[††]	MD	MD	228 (111)	276 (230)	MD	MD
Szefler 2017[15]	136	134	40 (29.4)	41 (30.6)	8.8 (1.7)	9.1 (1.6)	5.0 (2.5)	4.8 (2.4)	76.8 (7.7)	76.2 (8.1)	439 (218)	480 (240)	1.9 (0.3)*	2.0 (0.4)*
Hamelmann 2017[16]	127	135	47 (37.0)	56 (41.5)	14.4 (1.8)	14.1 (1.7)	8.0 (3.9)	8.0 (3.7)	75.9 (7.6)	75.0 (8.2)	727.8 (343.6)	736.6 (347.9)	2.2 (0.4)	2.2 (0.5)
Hamelmann 2016[17]	125	138	44 (35.2)	50 (36.2)	14.2 (1.8)	14.2 (1.7)	7.7 (4.0)	7.7 (4.2)	78.1 (7.9)	77.6 (7.5)	557 (346)	527 (275)	2.1 (0.5)	2.0 (0.4)
Paggiaro 2016[18]	154	155	82 (53.2)	103 (66.5)	43.8 (14.0)	42.8 (12.1)	15.0 (0.3–61.0)**	15.0 (0.3–57.0)**	73.2 (8.6)	73.7 (8.5)	384.4 (93.4)	383.0 (77.1)	2.1 (0.4)	2.1 (0.4)
Ohta 2015[19]	114	57	72 (63.2)	38 (66.7)	44.7 (12.1)	47.8 (13.0)	21.0 (0.8–57.8)**	26.8 (0.8–63.0)**	MD	MD	673.2 (247.4)	644.2 (220.9)	1.94 (0.43)	1.90 (0.32)
Kerstjens 2015[20]	519	523	316 (61.0)	311 (59.0)	43.4 (12.9)	42.8 (13.0)	22.1 (14.3)	21.1 (13.7)	72.8 (8.3)	73.0 (8.3)	655.9 (213.2)	668.3 (217.3)	2.17 (0.49)	2.18 (0.50)
Vogelberg 2018[21]	135	131	38 (28.1)	46 (35.1)	9.0 (1.6)	9.0 (1.6)	4.42 (2.43)	4.24 (2.30)	77.0 (7.8)	78.9 (7.1)	312 (109)	301 (102)	1.9 (0.3)*	1.9 (0.3)*

Data are expressed as n (%) or mean (SD) unless stated otherwise.
Baseline patient characteristics by individual treatment group were not reported for the 3 phase 2 dose-ranging studies (Vogelberg 2014, Vogelberg 2015, and Beeh 2014).
*Data presented for ACQ-IA.
**Data presented as median (range).
[†]Budesonide or equivalent dose.
[††]Adjusted for treatment and baseline.
ACQ-7 = Asthma Control Questionnaire 7; ACQ-IA = Interviewer-Administered Version of the ACQ; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; MD = missing data; Pbo = placebo; RCT = randomized controlled trial; SD = standard deviation; TioR = tiotropium Respimat®.

Figure S2. Risk of bias summary.