

Leukotriene-Receptor Antagonists Versus Placebo in the Treatment of Asthma in Adults and Adolescents

A Systematic Review and Meta-Analysis

Michael Miligkos, MD, MS; Raveendhara R. Bannuru, MD, PhD; Hadeel Alkofide, MS, PhD; Sucharita R. Kher, MD; Christopher H. Schmid, PhD*; and Ethan M. Balk, MD, MPH*

Background: Leukotriene-receptor antagonists (LTRAs) are recommended as an alternative treatment in patients with mild asthma, but their effect compared with placebo is unclear.

Purpose: To determine the benefits and harms of LTRAs as monotherapy or in combination with inhaled corticosteroids compared with placebo in adults and adolescents with asthma.

Data Sources: MEDLINE and the Cochrane Central Register of Controlled Trials from inception through June 2015.

Study Selection: Peer-reviewed, English-language, randomized, controlled trials in patients with asthma that reported the effect of LTRAs versus placebo on measures of asthma control.

Data Extraction: Three researchers extracted data on study population, interventions, outcome measures, and adverse events. One researcher assessed risk of bias.

Data Synthesis: Of the 2008 abstracts that were screened, 50 trials met eligibility criteria. Random-effects meta-analyses of 6 trials of LTRA monotherapy showed that LTRAs reduced the risk for an exacerbation (summary risk ratio [RR], 0.60 [95% CI, 0.44 to 0.81]). In 4 trials of LTRAs as add-on therapy to inhaled corti-

costeroids, the summary RR for exacerbation was 0.80 (CI, 0.60 to 1.07). Leukotriene-receptor antagonists either as monotherapy or add-on therapy to inhaled corticosteroids increased FEV₁, whereas FEV₁ percentage of predicted values was only improved in trials of LTRA monotherapy. Adverse event rates were similar in the intervention and comparator groups.

Limitation: Variation in definitions and reporting of outcomes, high risk of bias in some studies, heterogeneity of findings, possible selective outcome reporting bias, and inability to assess the effect of asthma severity on summary estimates.

Conclusion: Leukotriene-receptor antagonists as monotherapy improved asthma control compared with placebo, but which patients are most likely to respond to treatment with LTRAs remains unclear.

Primary Funding Source: National Institutes of Health.

Ann Intern Med. doi:10.7326/M15-1059

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For author affiliations, see end of text.

* Drs. Schmid and Balk contributed equally to this work.

This article was published online first at www.annals.org on 22 September 2015.

Asthma is one of the most common chronic diseases and has considerable socioeconomic burdens, including both high direct costs related to health care use and indirect costs related to time lost from work or school (1). In the United States, the annual cost is estimated at roughly \$56 billion. Approximately 300 million persons worldwide, and 25 million Americans, are affected by asthma. Worldwide, the number is expected to increase to 400 million by 2025 (2).

Successful long-term management of asthma includes the use of medications that target the underlying inflammatory process. Although inhaled corticosteroids (ICSs) constitute the current gold standard of maintenance treatment, leukotriene-receptor antagonists (LTRAs) have the advantages of oral once- or twice-daily dosing and apparent avoidance of the adverse effects associated with long-term corticosteroid therapy (3). In addition, their mechanisms of action theoretically predict a good response in patients with specific asthma “phenotypes.” Allergic rhinitis (AR) is present in many patients with asthma, and LTRAs may improve asthma-related outcomes by treating both conditions concurrently (4). Moreover, aspirin-induced asthma (AIA), which is clinically characterized by chronic eosinophilic rhinosinusitis, nasal polyposis, aspirin hypersensitivity, and development of persistent asthma, is associated with increased airway leukotrienes and is frequently poorly responsive to ICSs (5).

Guidelines recommend the use of LTRAs as monotherapy for patients with mild persistent asthma, as an alternative or as add-on therapy to ICSs, and as an alternative to either increasing the ICS dose or adding a long-acting β_2 -agonist (6). However, the relative benefits and harms of LTRAs compared with placebo have not been established.

We did a systematic review of randomized, controlled trials (RCTs) that compared the efficacy and safety of LTRAs with placebo in adults and adolescents with asthma for both objective and patient-reported outcome measures used to assess asthma control.

METHODS

Data Sources and Search

We searched MEDLINE and the Cochrane Central Register of Controlled Trials from inception through June 2015. We developed a search strategy with a combination of Medical Subject Headings terms and keywords relevant to study design (*randomized, controlled trial*), disease of interest (*asthma*), and interven-

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tion of interest (*leukotriene receptor antagonists*) (Appendix Table 1, available at www.annals.org).

Study Selection

We included peer-reviewed publications of RCTs if they fulfilled the following criteria: comparison of an LTRA either as monotherapy or add-on therapy to ICSs with placebo in adults and adolescents (aged ≥ 12 years) with asthma; oral administration of usual licensed doses of an LTRA daily (10 mg of montelukast once daily for persons aged ≥ 15 years, 20 mg of zafirlukast twice daily for those aged ≥ 12 years, or 225 mg of pranlukast twice daily for those aged ≥ 12 years); minimum treatment duration of 4 weeks; inclusion of at least 1 prespecified outcome measure that reflects asthma control (such as asthma exacerbations, pulmonary function tests, daytime asthma symptom scores, asthma-specific quality of life, nocturnal awakenings, use of short-acting β_2 -agonist, and adverse events); and English-language publication. The primary outcome measure was the number of exacerbations that required systemic corticosteroids, an unscheduled visit to a physician, or a visit to an emergency department. Quality of life was assessed with asthma-specific quality-of-life and mini-asthma quality-of-life questionnaires (7, 8). The scales range from 1 to 7 (or 0 to 6), and higher values indicate better quality of life. The minimal difference considered clinically important is 0.5 (7, 8). Because of the inclusion of children and adolescents in some studies of montelukast, we included studies in which at least some children and adolescents received 10 mg of montelukast daily and excluded those in which no participants received 10 mg. Two investigators (M.M. and H.A.) independently reviewed the titles and abstracts of the citations for potentially relevant articles using Abstrackr (Brown University) (9); the full-text publications of potentially relevant articles were retrieved and rescreened by the same 2 investigators. Disagreements were resolved by consensus.

Data Extraction and Quality Assessment

Data from each eligible study were independently extracted by 2 of 3 investigators (M.M., H.A., and R.B.); any disagreements were resolved by consensus. We extracted data on study design and methodology, patient characteristics, interventions, comparators, outcome measures, and adverse events by using a standardized electronic form in the Systematic Review Data Repository (10).

We assessed the methodological quality of the eligible studies with the Cochrane Collaboration's risk-of-bias tool for randomized trials (11). This tool includes 13 risk-of-bias items (Appendix Table 2, available at www.annals.org). A judgment of "low," "high," or "unclear" was assigned for the first 7 items (sequence generation, allocation concealment, patients' blinding, caregivers' blinding, outcome assessors' blinding, attrition, and selective outcome reporting), whereas a judgment of "yes," "no," or "unsure" was assigned for the remainder (intention-to-treat analysis, baseline balance, co-intervention similarity, compliance, and presence of other biases). After reviewing all risk-of-bias items, we

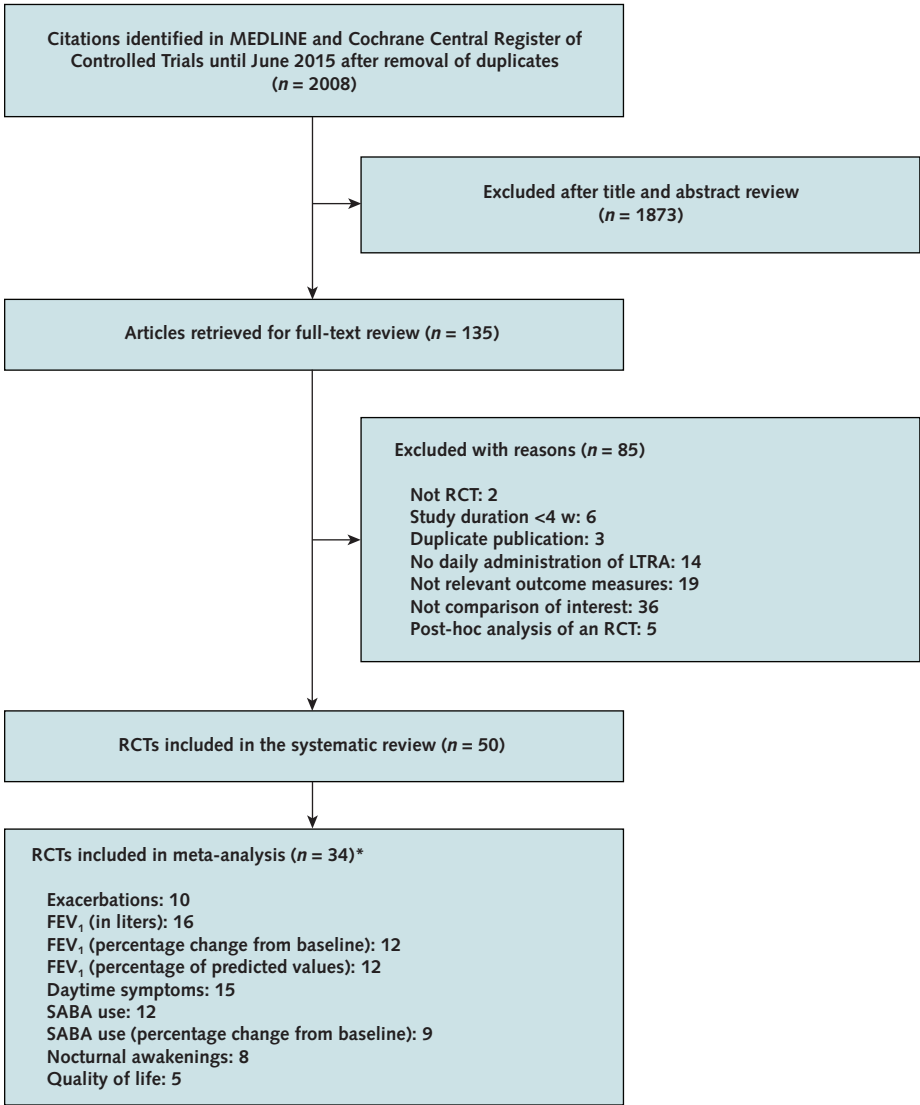
assigned an overall quality grade of good, fair, or poor to each RCT. Studies were considered poor quality if they had any of the following: absence of blinding, differential loss to follow-up, baseline imbalances, or absence of a washout period in the case of crossover trials. Studies that reported sufficient details about the implementation of blinding (such as double-blinding and use of identical capsules) had low risk of bias for this specific item, whereas studies with insufficient reporting (for example, reporting of a phrase such as "double-blind") had unclear risk of bias. We compared the proportions of withdrawals in each group by using the chi-square test and considered a *P* value less than 0.1 to indicate differential loss to follow-up. The assessments were completed by 1 author (M.M.).

Data Synthesis and Analysis

We estimated treatment effects for binary outcomes by using the risk ratio (RR) with corresponding 95% CIs. For the continuous outcome measures, the difference in mean changes from baseline between LTRAs and placebo was calculated for each study. We computed study treatment effects for daytime symptom scores and asthma-specific quality-of-life scores using the Hedges *g* statistic, corrected for small samples (12). When only the baseline and final SDs were reported, we calculated SDs of change from baseline in each group, assuming a correlation coefficient of 0.5 (13). When means and measures of dispersion were not reported in the text, they were approximated from figures with the use of Engauge Digitizer Qt4 (Source-Forge) (14). We imputed missing group SDs in 1 study (and for 1 outcome measure) by using the median of all available SDs from other studies, which were measured on the same scale.

We estimated the summary treatment effects by using the random-effects model estimated by the empirical Bayes method (15). We calculated a summary RR, summary mean difference, and summary standardized mean difference between LTRAs and placebo, where appropriate. We assessed statistical heterogeneity using the I^2 statistic (16). Crossover trials were included in the analyses only if they provided appropriate data to approximate a paired analysis. The overall analysis included only the reported end point values at the longest follow-up within each trial. We explored the effect of prespecified factors on the effect estimates with random-effects model metaregression when an outcome of interest was reported by at least 3 RCTs in each subgroup. The prespecified factors were type of LTRA, treatment duration, asthma severity, and presence of comorbid AR and AIA. The RCTs were classified into 2 categories based on concomitant use of ICSs in the intervention groups, LTRA monotherapy (that is, no ICS use) and LTRAs as add-on therapy to ICSs (that is, concomitant ICS use either by all patients or by a proportion of patients in the intervention groups). We did post hoc sensitivity analyses excluding studies of poor reporting quality. Because the treatment duration varied among trials, we grouped the time points of out-

Figure 1. Summary of evidence search and selection.



ICS = inhaled corticosteroid; LTRA = leukotriene-receptor antagonist; RCT = randomized, controlled trial; SABA = short-acting β_2 -agonist.
* Some RCTs contributed data to >1 meta-analysis.

come assessments in the individual trials into the 6 following intervals: 4 to 7, 8 to 11, 12 to 15, 16 to 23, 24 to 30, and greater than 30 weeks. This grouping was designed for optimum capture of all available data in the trials but also reflects the periodic monitoring of asthma control used in clinical practice (17). All analyses were done with OpenMeta[Analyst] (Brown University) (18).

Role of the Funding Source

This review was funded by the National Institutes of Health. The funding source had no role in the design or conduct of the study, the preparation of the manuscript, or the decision to submit the manuscript for publication.

RESULTS

Literature Search

Figure 1 summarizes our search yield. We screened 2008 citations. A total of 135 articles were retrieved for full-text review; of those, 50 RCTs met our inclusion criteria (19–68).

Trial Characteristics

Table 1 summarizes the characteristics of the included RCTs, which were published between 1994 and 2014. Five RCTs included both children and adolescents (53, 56–58, 60), and 1 RCT included both children and adults (27). The demonstration of reversibility of airway obstruction after administration of short-acting β_2 -agonists led to an asthma diagnosis in most trials.

Table 1. Trial Characteristics

Study, Year (Reference)	Region	Treatment Groups	Concomitant Treatments	Treatment Duration, wk	Patients, n	Age, y*	Men, %	FEV ₁ Predicted at Baseline (SD), %*	FEV ₁ Predicted Range of Inclusion, %
Altman et al, 1998 (19)	United States	Montelukast	Theophylline, ICS†, SABA	6	57	Median: 33	79	62 (13)	40-80
		Placebo			58	Median: 36	78	59 (13)	
American Lung Association Asthma Clinical Research Centers, 2007 (20)	United States	Montelukast	ICS†, LABA, SABA	24	164	40	28	77 (17)	>50
		Placebo			164	40	26	80 (16)	
Awad et al, 2002 (21)	India	Zafirlukast	SABA	12	116	35	47	62 (11)	45-80
		Placebo			99	35	50	64 (12)	
Baena-Cagnani et al, 2003 (22)	United States	Montelukast	SABA	4	311	34	39	86	>70
		Placebo			302	32	33	86	
Barnes and Pujet, 1997 (23)	Europe	Pranlukast	BEC (≤1000 µg/d)†, SABA	4	46	39	59	68 (12)	50-80
		Placebo			44	38	66	67 (11)	
Baumgartner et al, 2003 (24)	North and South America	Montelukast	SABA	6	313	36	34 overall	69 (12)	50-85
		Placebo			103	36		68 (12)	
Busse et al, 2001 (25)	United States	Zafirlukast	SABA	12	111	12-75 overall	50 overall	66-67 overall	50-80
		Placebo			114				
Cakmak et al, 2004 (26)	Turkey	Zafirlukast-BUD (400 µg/d)	SABA	6	11	30	55	88 (14)	≥70
		Placebo-BUD (400 µg/d)			10	28	20	89 (14)	
Capriles Hulett et al, 2014 (27)	Venezuela	Montelukast	ND	24	46	18	37	ND	ND
		Placebo			42	17	36	ND	
Dahlén et al, 2002 (28)	United States, Europe	Montelukast	Theophylline, ICS†, SABA	4	40	Median: 49	38	70	ND
		Placebo			40	Median: 47	28	70	
Fish et al, 1997 (29)	United States	Zafirlukast	SABA	13	514	18-55 (80%)	57	78 (16)	≥55
		Placebo			248		59	79 (17)	
Gao et al, 2013 (30)	China	Montelukast	FCS (500 µg/d), LABA (100 µg/d)	24	19	45.3	53	57 (4)	≤80
		Placebo			19	48.8	42	51 (4)	
Green et al, 2006 (31)	United Kingdom	Montelukast-BUD (200 µg/d)	SABA	4	49	Median: 42	51	75 (3)	ND
		Placebo-BUD (200 µg/d)							
Helenius et al, 2004 (32)	Finland	Montelukast	SABA	4	16	18	100	101 (12)	ND
		Placebo							
Huang et al, 2003 (33)	Taiwan	Zafirlukast	BUD (800-1600 µg/d), SABA	4	20	59	53	68 (1)	60-80
		Placebo			18	57	50	69 (1)	
Israel et al, 2002 (34)	United States	Montelukast	SABA, antihistamines	6	339	34	48	67 (11)	50-80
		Placebo			111	33	47	67 (12)	
Jayaram et al, 2005 (35)	Canada	Montelukast	BUD (1857 µg/d), SABA	4	14	61	57	62 (15)	ND
		Placebo							
Jayaram et al, 2005 (36)	Canada, Brazil	Montelukast	SABA	8	19	31	58	77 (16)	ND
		Placebo			13	39	71	80 (23)	
Kanazawa et al, 2004 (37)	Japan	Pranlukast-BEC (800 µg/d)	SABA	4	10	28	60	87	ND
		Placebo-BEC (800 µg/d)							
Kannies et al, 2002 (38)	Germany	Montelukast	BEC (tapered doses), SABA	12	26	38	50	95 (10)	>80
		Placebo			24	43	46	92.3 (9)	
Kraft et al, 2006 (39)	United States	Montelukast	SABA	4	19	38	32	83 (3)	ND
		Placebo							
Laviolette et al, 1999 (40)	North America, Europe, Africa, Australia, Asia	Montelukast-BEC (400 µg/d)	SABA	16	193	Median: 40	56	72 (12)	50-85
		Placebo-BEC (400 µg/d)			200	Median: 39	52	71 (12)	
		Montelukast			201	38	49	72 (12)	
		Placebo			48	41	40	71 (11)	

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Table 1—Continued

Study, Year (Reference)	Region	Treatment Groups	Concomitant Treatments	Treatment Duration, wk	Patients, n	Age, y*	Men, %	FEV ₁ Predicted at Baseline (SD), %*	FEV ₁ Predicted Range of Inclusion, %
Leff et al, 1998 (41)	United States	Montelukast Placebo	SABA, antihistamines	12	54 56	25 25	52 52	83 (11) 84 (11)	ND
Löfdahl et al, 1999 (42)	United States, Canada, Europe	Montelukast Placebo	ICS (various doses), SABA	12	113 113	40 41	42 54	85 (11) 82 (13)	>70
Malmstrom et al, 1999 (43)	Europe, Africa, Australia, Central and South America	Montelukast Placebo	Theophylline, SABA	12	387 257	Median: 35 Median: 36	40 43	65 (10) 66 (11)	50–85
Minoguchi et al, 2002 (44)	Japan	Montelukast Placebo	Theophylline, SABA	4	26	37	50	83 (16)	ND
Nakamura et al, 1998 (45)	Japan	Pranlukast Placebo	SABA	4	10 7	Median: 35 Median: 32	80 43	Median: 71 Median: 80	≥50
Nathan et al, 1998 (46)	United States	Zafirlukast Placebo	SABA, nasal corticosteroids	13	231 223	33 32	45 41	66.6 overall	45–80
Nathan et al, 1999 (47)	United States	Zafirlukast Placebo	SABA	13	96 95	32 30	55 53	77 (15) 78 (17)	>55
Nathan et al, 2005 (48)	United States	Montelukast Placebo	FCS (100 µg/d), LABA (50 µg/d), SABA	4	282 290	34 36	33 28	81 (10) 81 (10)	ND
Pizzichini et al, 1999 (49)	United States, Canada	Montelukast Placebo	SABA	4	19 21	31 28	63 57	69 (11) 69 (15)	ND
Price et al, 2013 (50)	United States, Europe, Asia, Africa	Montelukast Placebo	SABA	24	347 336	38 38	53 51	74 (10) 74 (9)	60–85
Reid et al, 2008 (51)	Australia	Zafirlukast Placebo Zafirlukast-BUD (1600 µg/d) Placebo-BUD (1600 µg/d)	SABA	12 16	14 7 Median: 37 8	Median: 42 Median: 29 Median: 56 Median: 45	57 43 77 25	85 80 76	≥60
Reiss et al, 1998 (52)	United States	Montelukast Placebo	ICS†, SABA	12	408 273	Median: 31 Median: 31	43 47	67 (11) 69 (11)	50–85
Schäper et al, 2011 (53)	Germany	Montelukast Placebo	ICS†, SABA	6	24	Median: 56	71	88	ND
Spahn et al, 2006 (54)	United States	Montelukast Placebo	SABA	8	11 10	13 14	64 36	88 (10) 83 (10)	60–90
Spector et al, 1994 (55)	United States	Zafirlukast Placebo	SABA	6	70 70	37 36	74 71	66 69	40–75
Spector and Tan, 2004 (56)	United States	Montelukast Placebo	SABA, nasal corticosteroids	4	8 6	42 36	50 67	>50	50–85
Stelmach et al, 2007 (57)	Poland	Montelukast-BUD (200 µg/d) Placebo-BUD (200 µg/d) Montelukast Placebo	SABA	4	29 29 29 29	11 12 10 11	69 69 62 70	95 (11) 94 (10) 96 (11) 95 (10)	ND
Stelmach et al, 2002 (58)	Poland	Montelukast Placebo	SABA	4	18 36	12 12	60 44	77 (4) 75 (5)	ND
Stelmach et al, 2002 (59)	Poland	Montelukast Placebo	SABA	6	16 19	14 13	67 59	85 (9) 81 (7)	ND
Storms et al, 2004 (60)	United States	Montelukast-FCS (200 µg/d) Placebo-FCS (200 µg/d)	SABA	4	39 44	33 31	28 45	88 (10) 88 (11)	≥70
Strunk et al, 2008 (61)	United States	Montelukast	BUD (800–1600 µg/d), LABA, SABA	30	19 19	11 overall	58 overall	102 (14)	ND

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Table 1—Continued

Study, Year (Reference)	Region	Treatment Groups	Concomitant Treatments	Treatment Duration, wk	Patients, n	Age, y*	Men, %	FEV ₁ Predicted at Baseline (SD), %*	FEV ₁ Predicted Range of Inclusion, %
Tohda et al, 2002 (62)	Japan	Montelukast Placebo	BEC (various doses), SABA	24	93 98	16–70	58 58	87 (18) 86 (25)	ND
Ulrik and Diamant, 2009 (63)	Denmark	Montelukast Placebo	SABA	12	16 15	34 33	44 40	79 (14) 83 (10)	>70
Vaquero et al, 2003 (64)	Spain	Montelukast-BUD (400–1600 µg/d) Placebo-BUD (400–1600 µg/d)	SABA	16	326 313	42 44	62 61	81 (19) 81 (21)	≥55
Wise et al, 2009 (65)	United States	Montelukast Placebo Montelukast Placebo	ICS†, SABA	4	120 121 119 120	37 39 37 39	19 27 29 32	87 (12) 87 (15) 86 (13) 87 (13)	>75
Yoo et al, 2001 (66)	South Korea	Pranlukast Placebo	ICS†, SABA	4	98 99	45 45	61 54	73 73	60–80
Yoshida et al, 2000 (67)	Japan	Pranlukast Placebo	Theophylline, SABA	4	32	41	44	77 (7)	ND
Zeidler et al, 2006 (68)	United States	Montelukast Placebo	SABA	4	20	36	56	86 (12)	≥60

BEC = beclomethasone; BUD = budesonide; FCS = fluticasone; ICS = inhaled corticosteroid; LABA = long-acting β_2 -agonist; ND = no data; SABA = short-acting β_2 -agonist.

* Data are means unless otherwise indicated.

† Used by only a proportion of participants (20%–90%).

Definitions of categories of asthma severity varied among trials. The main exclusion criteria were active upper respiratory tract infection, recent use of oral corticosteroids, and recent emergency department visit or hospitalization due to worsening asthma.

Overall, 9872 patients were randomly assigned to receive either LTRA or placebo. Montelukast was administered in 36 RCTs, zafirlukast was administered in 9, and pranlukast was administered in 5. Leukotriene-receptor antagonists were used solely as monotherapy in 25 trials. Inhaled corticosteroids were used as concomitant treatments by all patients in 16 trials, whereas ICSs were used only by a proportion of participants in 8 trials. In 4 RCTs, the ICS dose was gradually reduced during follow-up according to specific criteria described in the trials. Short-acting β_2 -agonists were permitted on an “as-needed” basis in all trials. Mean FEV₁ at baseline was between 59% and 102% of predicted values. Sixteen RCTs reported inclusion of patients with a history of atopy, 11 reported presence of concomitant AR, and 2 reported inclusion of patients with AIA. Patients with exercise-induced bronchoconstriction were included in 5 trials. We included 41 parallel and 9 crossover RCTs, and 29 RCTs were multicenter. Treatment duration ranged from 4 to 30 weeks. Appendix Table 3 (available at www.annals.org) lists all included trials and shows which studies contributed data to the meta-analysis of each outcome.

Assessment of Risk of Bias

Among the 50 RCTs, 22 were assessed to be of good quality, 13 of fair quality, and 15 of poor quality (Appendix Table 4, available at www.annals.org). Generation of a randomized sequence and allocation concealment were not clearly reported in most trials. All but 1 RCT reported double-blinding; the other RCT was

single-blinded. Six RCTs had differential loss to follow-up. Intention-to-treat analyses were not widely used. Randomized, controlled trials were generally balanced with regard to baseline characteristics and co-interventions. Among the 9 crossover trials, 6 had at least a 1-week washout period that was considered adequate, 1 had no washout period, and 2 did not clarify whether they had a washout period.

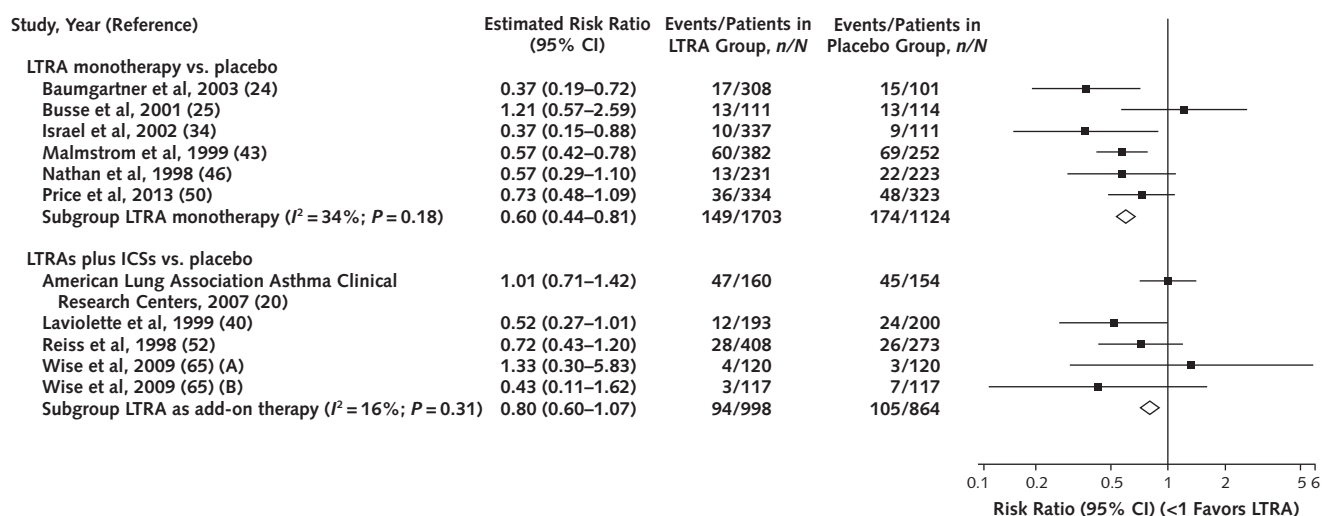
Studies Not Included in the Meta-Analysis

A summary of the results from the trials that were included in the systematic review but not meta-analyzed is presented in Appendix Table 5 (available at www.annals.org). In general, the main reasons for excluding studies from the meta-analysis were inadequate reporting (such as reporting only nonsignificance of difference in effects rather than providing actual numbers) or missing data (such as missing effect estimates). In addition, 6 crossover trials were not included in the meta-analyses. These RCTs either did not provide appropriate data to approximate a paired analysis or data from the first and second period were provided separately. However, most of the excluded RCTs reported nonsignificant results for the secondary outcomes of interest.

Asthma Exacerbations

In our analysis, we only included RCTs with clear and prespecified criteria of asthma exacerbation. Four trials that reported only withdrawals due to an exacerbation that required either oral corticosteroids or an emergency department visit were not quantitatively summarized.

In 6 RCTs of LTRA monotherapy, the definition of an exacerbation was consistent with our definition. This analysis included 1703 patients who received an LTRA

Figure 2. Forest plot for asthma exacerbation.

Meta-analyses of the overall risk ratio (diamonds) were done separately for LTRA monotherapy vs. placebo and LTRAs as add-on therapy to ICSs vs. placebo and ICSs. The size of the squares representing each study's effect size is proportional to the weight of each study in the meta-analysis. The P value is for chi-square heterogeneity. LTRA = leukotriene-receptor antagonist.

and 1124 patients who received placebo. Overall, patients treated with LTRAs as monotherapy had a 40% decreased risk for an exacerbation compared with those treated with placebo (summary RR, 0.60 [95% CI, 0.44 to 0.81]) (Figure 2). Statistical heterogeneity was moderate ($I^2 = 34\%$). The effect of treatment duration on the summary estimate could not be assessed because of the limited number of RCTs of no ICS use. We could not assess the effect of the type of LTRA on the summary estimate because montelukast was administered in 4 RCTs and zafirlukast in only 2 trials. We could not examine the effect of AR or AIA on the summary estimate because of incomplete reporting in the RCTs included.

In 4 RCTs of LTRAs as add-on therapy to ICSs, the definition of an exacerbation was consistent with our definition (1 RCT included 2 separate comparisons of LTRAs vs. placebo in different patients). All patients received ICSs in only 1 RCT; in 3 RCTs, only some (25% to 75%) patients received ICSs. The risk for exacerbations between the intervention groups did not significantly differ (summary RR, 0.80 [CI, 0.60 to 1.07]). Statistical heterogeneity was low ($I^2 = 16\%$).

Table 2 shows the results from the meta-analyses of the secondary outcome measures.

FEV₁

Forty-five trials reported the effect of LTRAs compared with placebo on FEV₁. Thirty-seven trials reported FEV₁ in liters and 16 as percentage of predicted values. A mean difference in change from baseline in FEV₁ in liters was computed for 8 trials of no ICS use and 9 trials in which doses of ICSs were equal. A mean difference in percentage change from baseline in FEV₁ was computed for 6 trials of no ICS use and 5 trials of

equal ICS use. A mean difference in change from baseline in percentage of predicted FEV₁ was computed for 9 trials of no ICS use and 4 trials of equal ICS use.

In trials of LTRA monotherapy, LTRAs significantly improved FEV₁ in liters and percentage of predicted values (Appendix Figures 1 to 3, available at www.annals.org). Metaregression showed no association between treatment duration and the pooled effect for FEV₁ in liters ($P = 0.11$) (Appendix Figure 4, available at www.annals.org). The effects of zafirlukast and montelukast did not significantly differ ($P = 0.32$) (Appendix Figure 5, available at www.annals.org). In the trials of LTRAs used as add-on therapy to ICSs, LTRAs significantly improved FEV₁ in liters but not percentage of predicted FEV₁ compared with placebo (Appendix Figures 6 to 8, available at www.annals.org). There was no association between treatment duration and the pooled effect for FEV₁ in liters ($P = 0.71$) (Appendix Figure 9, available at www.annals.org). The limited number of studies precluded metaregression of the pre-specified factors for FEV₁ percentage change from baseline and percentage of predicted FEV₁.

Daytime Symptoms

Daytime symptom scores were reported in 23 RCTs. Seven trials of LTRA monotherapy and 8 trials of LTRAs as add-on therapy contributed data to the meta-analyses. Various scales were used with lower values indicating fewer symptoms. Leukotriene-receptor antagonists significantly reduced daytime symptoms in trials where they were used as add-on therapy to ICSs, whereas the reduction did not reach statistical significance in trials of LTRA monotherapy (Appendix Figures 10 and 11, available at www.annals.org).

Table 2. Summary Effects of LTRAs Versus Placebo

Concomitant ICS Use, by Outcome Measure	RCTs, <i>n</i>	Summary Effect (95% CI)*	Heterogeneity Assessed by <i>I</i> ² , %	Poor-Quality RCTs, <i>n</i>
Change from baseline in FEV₁				
Reported in liters				
No	8	0.11 (0.06 to 0.16)	15	2
Equal	9†	0.12 (0.08 to 0.15)	48	2
Reported in percentages				
No	6	4.91 (2.13 to 7.69)	54	1
Equal	5	7.03 (2.54 to 11.53)	80	1
Unequal	1	−2.70 (−7.85 to 2.45)	NA	1
Reported in percentage of predicted values				
No	9	6.17 (3.25 to 9.10)	68	2
Equal	4	1.35 (−1.46 to 4.17)	0	1
Change from baseline in daytime symptoms				
No	7	SMD: −0.21 (−0.54 to 0.12)	81	1
Equal	8	SMD: −0.19 (−0.32 to −0.06)	29	1
Change from baseline in SABA use reported in puffs/d				
No	8	−0.67 (−0.85 to −0.49)	0	3
Equal	5	−0.61 (−1.05 to −0.17)	36	1
Change from baseline in SABA use reported in percentages				
No	6	−21.10 (−36.12 to −6.09)	84	2
Equal	3	−12.15 (−18.41 to −5.90)	0	1
Change from baseline in nocturnal awakenings per week				
No	6	−0.66 (−1.25 to −0.07)	83	3
Equal	2	−0.78 (−1.07 to −0.49)	0	0
Change from baseline in ASQL				
No	1	0.27 (0.11 to 0.42)	NA	1
Equal	4†	SMD: 0.08 (−0.03 to 0.18)	0	0

ASQL = asthma-specific quality of life; ICS = inhaled corticosteroids; LTRA = leukotriene receptor antagonist; NA = not applicable; RCT = randomized, controlled trial; SABA = short-acting β_2 -agonist; SMD = standardized mean difference.

* Values are mean differences unless otherwise indicated.

† 1 RCT included 2 independent comparisons of LTRAs vs. placebo in different patients.

Use of Short-Acting β_2 -Agonists

The effect of LTRAs on short-acting β_2 -agonist use compared with placebo was examined in 30 RCTs. We computed a mean difference in change from baseline in β_2 -agonist use for 8 trials of LTRA monotherapy and 5 trials of LTRAs used as add-on therapy to ICSs. A mean difference in percentage change from baseline was computed for 6 trials of LTRA monotherapy and 3 trials of LTRAs used as add-on therapy. Overall, LTRAs led to reduced β_2 -agonist use (Appendix Figures 12 to 15, available at www.annals.org).

Nocturnal Awakenings

Nocturnal awakenings were reported in 15 RCTs. Only 6 RCTs of LTRA monotherapy and 2 RCTs of LTRAs used as add-on therapy to ICSs could be meta-analyzed because of missing data in the original trials (primarily missing number of analyzed participants). Overall, LTRAs reduced nocturnal awakenings per week (Appendix Figures 16 and 17, available at www.annals.org).

Asthma-Specific Quality of Life

Eleven trials examined the effect of LTRAs compared with placebo on asthma-specific quality of life. However, only 4 trials (1 RCT included 2 independent comparisons) of LTRAs used as add-on therapy contributed data to our meta-analysis. There was only 1 trial of

LTRA monotherapy. Leukotriene-receptor antagonists did not improve quality of life compared with placebo (Appendix Figure 18, available at www.annals.org).

Sensitivity Analysis

Overall, 7 poor-quality trials were included in the meta-analyses. In 5 trials of no ICS use, LTRAs significantly reduced asthma exacerbations (summary RR, 0.60 [CI, 0.40 to 0.90]; $I^2 = 46\%$). In 3 trials of equal ICS use, we saw results similar to those of our main analysis (summary RR, 0.79 [CI, 0.52 to 1.20]; $I^2 = 32\%$). For the secondary outcomes of interest, exclusion of poor-quality RCTs did not significantly alter the results (Appendix Table 6, available at www.annals.org). Likewise, exclusion of 2 crossover trials with no washout period from the respective meta-analyses did not affect the results (Appendix Table 6).

Adverse Events and Tolerability

The proportions of patients with adverse events were generally similar in the intervention and comparator groups (Appendix Table 7, available at www.annals.org). Across all trials, no serious adverse events were reported. Five trials explicitly reported no adverse events. Withdrawals from adverse events or worsening asthma were generally similar across groups (Appendix Table 8, available at www.annals.org).

DISCUSSION

Administration of LTRAs to adults and adolescents with asthma significantly reduced the risk for an exacerbation. In trials of LTRA monotherapy, LTRAs significantly improved asthma control compared with placebo, whereas only some measures of asthma control were significantly improved in trials of LTRAs used as add-on therapy to ICSs. This effect was consistent across all types of LTRAs. The incidence of adverse events and withdrawals due to adverse events and worsening asthma was similar for LTRAs and placebo, which reflects a favorable safety and tolerability profile for LTRAs.

Several systematic reviews have examined the state of evidence about the use of LTRAs in adults and adolescents with asthma, but only a few have included RCTs that compared LTRA with placebo. Joos and colleagues (69) included RCTs of at least 12-weeks duration that examined the benefits and harms of montelukast as add-on therapy to ICSs compared with ICSs with or without placebo. They concluded that adding montelukast to ICSs improved control of mild to moderate asthma compared with ICS monotherapy. However, no meta-analysis was used in this study because of the inclusion of a limited number of RCTs. Ducharme and colleagues (70) included RCTs of at least 4-weeks duration that compared LTRAs with placebo as add-on therapy to ICSs, but only 2 of the 6 included RCTs reported use of usual licensed doses. Currie and colleagues (71) examined the bronchoprotective effects of LTRAs compared with placebo after administration of bronchial stimuli. However, these provocative challenges are mainly used to establish the diagnosis of asthma. In contrast, our systematic review was more expansive and more applicable to current clinical practice in many ways. Our study included outcome measures that correspond to the components proposed by international guidelines to periodically assess and monitor asthma control in patients with an established diagnosis of asthma (72). More specifically, we included RCTs of at least 4-weeks duration because the level of asthma control is assessed over at least a 4-week period (6). We also excluded RCTs where LTRAs were not administered daily because we intended to examine their effect as long-term controller medications (6). Therefore, we excluded RCTs that only assessed the pharmacodynamic profile of single doses of LTRAs after provocative challenges or exercise. In a systematic review of LTRA safety data that included both RCTs and their extension studies, Storms and colleagues (73) concluded that the incidence of adverse events between patients who received montelukast and those who received placebo did not significantly differ. Although our systematic review included only RCTs with a relatively short length of follow-up, the reported adverse events and their relative frequencies were similar to those reported in the meta-analysis by Storms and colleagues.

Despite the broader scope and improved generalizability of our systematic review compared with previ-

ous reviews, our study had limitations at both the individual-study and systematic-review level that need to be remembered while interpreting our results. Trials used different definitions of asthma exacerbation, and some studies did not explicitly define it. Consequently, the severity of the exacerbations could not be fully assessed across studies. Therefore, because of the clinical importance of our specific definition of an asthma exacerbation, we only meta-analyzed studies that clearly defined and reported this outcome. We did not quantitatively summarize 12 studies (4 with a definition consistent with ours) that reported only withdrawals because the number of patients at risk could not be determined (that is, absence of any prespecified criteria for withdrawal due to an exacerbation). The definitions of asthma severity in the individual trials were also inconsistent, and we could not assess the effect of baseline asthma severity on summary treatment effects. Nevertheless, the use of ICSs in some trials may indicate that patients with more severe disease were included. Our conclusions about the magnitude of the treatment effect are limited because of the small number of RCTs included in each analysis compared with the total number of RCTs included in the systematic review. Part of this difference arises because studies used different analytic scales for the same outcome measure, which prevented combination of all available data. For instance, change from baseline in FEV₁ was provided as an absolute number in some trials and as a percentage in others. Another set of studies reported a nonsignificant difference, without providing the actual numbers, for clinical outcomes. These studies were generally either not primarily designed to assess outcome measures relevant to clinical practice or had a relatively small sample size. In either case, this leads to outcome reporting bias; therefore, the summary effect sizes from the meta-analyses may be overstated.

The between-study statistical heterogeneity found for most outcomes remained largely unexplained, partly because of the limited number of trials included in each analysis. A potential association between AR and the magnitude of the summary treatment effect remains unclear because of insufficient reporting in the individual studies. Moreover, no subgroup analyses in the individual studies were reported. Only 2 trials reported inclusion of patients with AIA. Another limitation of the study is the inclusion of only peer-reviewed and English-language publications; therefore, we cannot exclude publication bias.

This systematic review investigates the use of all marketed LTRAs in usual licensed doses as asthma controller medications compared with placebo. Our findings suggest that LTRAs may be efficacious and safe, either as an alternative treatment in adult and adolescent patients who cannot or prefer not to take ICSs or as add-on treatment in patients with concomitant ICS use. However, which patients are more likely to respond to LTRAs remains unclear. Asthma is a complex disease with various clinical, inflammatory, and trigger-related phenotypes that may overlap (73). It is hypothesized that proper identification of these phenotypes

would lead to better disease management. Moreover, because not all patients respond well to ICSs, the need for alternative treatments that would benefit specific subpopulations increases. Therefore, professional organizations or expert panels should recommend standardized study protocols, definitions of phenotypes, and outcome measures (such as asthma control test and asthma control questionnaire) (74, 75) for the purpose of research and encourage future researchers to implement these standards.

From Laboratory of Biomathematics, University of Thessaly School of Medicine, Larissa, Greece; Center for Treatment Comparison and Integrative Analysis, Tufts Medical Center, Sackler School of Biomedical Sciences, and Tufts Clinical and Translational Science Institute, Tufts University, Boston, Massachusetts, and Center for Evidence-based Medicine, Brown University School of Public Health, Providence, Rhode Island.

Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Grant Support: By the National Center for Research Resources Award (UL1RR025752) and the National Center for Advancing Translational Sciences, National Institutes of Health (UL1TR000073 and UL1TR001064).

Disclosures: Dr. Bannuru reports grants from the Agency for Healthcare Research and Quality outside the submitted work. Authors not named here have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M15-1059.

Reproducible Research Statement: Study protocol, statistical code, and data set: Available from Dr. Miligkos (e-mail, mmiligkos@med.uth.gr).

Requests for Single Reprints: Michael Miligkos, MD, MS, Laboratory of Biomathematics, University of Thessaly School of Medicine, 22 Papakyriazi Street, 41222, Larissa, Greece; e-mail, mmiligkos@med.uth.gr.

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Dr. Miligkos: Laboratory of Biomathematics, University of Thessaly School of Medicine, 22 Papakyriazi Street, 41222, Larissa, Greece.

Dr. Bannuru: Center for Treatment Comparison and Integrative Analysis (CTCIA), Tufts Medical Center, 800 Washington Street, Boston, MA 02111.

Dr. Alkofide: Sackler School of Biomedical Sciences, Tufts University, 35 Kneeland Street, Boston, MA 02111.

Dr. Kher: Division of Pulmonary, Critical Care and Sleep Medicine, 800 Washington Street, Boston, MA 02111.

Drs. Schmid and Balk: Center for Evidence Based Medicine, Brown University School of Public Health, Box G-S121-8, Providence, RI 02912.

Author Contributions: Conception and design: M. Miligkos, R.R. Bannuru, H. Alkofide, S.R. Kher, C.H. Schmid, E.M. Balk. Analysis and interpretation of the data: M. Miligkos, R.R. Bannuru, H. Alkofide, C.H. Schmid, E.M. Balk.

Drafting of the article: M. Miligkos, R.R. Bannuru, H. Alkofide. Critical revision of the article for important intellectual content: M. Miligkos, R.R. Bannuru, H. Alkofide, C.H. Schmid, E.M. Balk.

Final approval of the article: M. Miligkos, R.R. Bannuru, H. Alkofide, S.R. Kher, C.H. Schmid, E.M. Balk.

Provision of study materials or patients: M. Miligkos, R.R. Bannuru.

Statistical expertise: M. Miligkos, R.R. Bannuru, H. Alkofide, C.H. Schmid, E.M. Balk.

Collection and assembly of data: M. Miligkos, R.R. Bannuru, H. Alkofide.

Appendix Table 1. Search Strategy

1. Leukotriene antagonists.sh.
2. Leukotriene receptor antagonist*.af.
3. (leukotriene and receptor antagonist*.af.
4. Leukotriene modifier*.af.
5. (leukotriene receptor and antagonist*).af.
6. Montelukast.af.
7. Zafirlukast.af.
8. Pranlukast.af.
9. Singulair.af.
10. Accolate.af.
11. Onon.af.
12. Azlaire.af.
13. Or/1-12
14. Exp Asthma/
15. Asthma*.af.
16. Samter* syndrome.af.
17. Aspirin intolerance.af.
18. Aspirin sensitivity.af.
19. Aspirin hypersensitivity.af.
20. Exercise induced broncho*.af.
21. (Exercise induced and broncho*).af.
22. Nasal polyp*.af.
23. Or/14-22
24. Randomized controlled trial.pt.
25. Controlled clinical trial.pt.
26. Randomized controlled trials/
27. Random Allocation/
28. Double-blind method/
29. Single-blind method/
30. Clinical trial.pt.
31. Clinical Trials.mp. or exp Clinical Trials/
32. (clinic\$ adj25 trial\$).tw.
33. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (mask\$ or blind\$)).tw.
34. Placebos/
35. Placebo\$.tw.
36. Random\$.tw.
37. Trial\$.tw.
38. (randomized control trial or clinical control trial).sd.
39. Latin adj square.tw.
40. Comparative Study.tw. or Comparative Study.pt.
41. Exp Evaluation studies/
42. Follow-up Studies/
43. Prospective Studies/
44. (control\$ or prospective\$ or volunteer\$).tw.
45. Cross-over Studies/
46. Or/24-45
47. And/13, 23, 46

Appendix Table 2. Risk-of-Bias Items Assessed for Randomized, Controlled Trials

1. What is the risk of selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence? [Low, Unclear, High]
2. What is the risk of selection bias (biased allocation of interventions) due to inadequate concealment of allocations before assignment? [Low, Unclear, High]
3. For each main outcome or class of outcomes, what is the risk of performance bias due to knowledge of the allocated interventions by participants and personnel during the study (lack of study participant and personnel blinding)? [Low, Unclear, High]
4. Was the care provider blinded to the intervention? [Low, Unclear, High]
5. For each main outcome or class of outcomes, what is the risk of detection bias due to knowledge of the allocated interventions by outcome assessment (lack of outcome assessor blinding)? [Low, Unclear, High]
6. For each main outcome or class of outcomes, what is the risk of attrition bias due to amount, nature, or handling of incomplete outcome data? [Low, Unclear, High]
7. What is the risk of reporting bias due to selective outcome reporting? [Low, Unclear, High]
8. Were all randomized participants analyzed in the group to which they were allocated? [Yes, No, Unsure]
9. Were the groups similar at baseline regarding the most important prognostic indicators? [Yes, No, Unsure]
10. Were co-interventions avoided or similar? [Yes, No, Unsure]
11. Was the compliance acceptable in all groups? [Yes, No, Unsure]
12. Was the timing of the outcome assessment similar in all groups?*[Yes, No, Unsure]
13. Are there other risks of bias? [Yes, No]

* Incorporated into question 13 for the purpose of the current study.

Appendix Table 3. List of Included Trials and Contribution to Meta-analysis of Each Outcome

Study, Year (Reference)	Exacerbations	FEV ₁	Daytime Symptoms	SABA Use	Nocturnal Awakenings	Asthma-Specific Quality of Life
Altman et al, 1998 (19)		✓ (% change from baseline)	✓	✓ (change from baseline)		
American Lung Association Asthma Clinical Research Centers, 2007 (20)	✓	✓ (change from baseline in liters)				✓
Awad et al, 2002 (21)		✓ (change from baseline in liters) ✓ (change from baseline in FEV ₁ predicted)	✓			
Baena-Cagnani et al, 2003 (22)				✓ (% change from baseline)		
Barnes and Pujet, 1997 (23)		✓ (change from baseline in liters)	✓	✓ (change from baseline)		
Baumgartner et al, 2003 (24)	✓	✓ (% change from baseline)		✓ (% change from baseline)		
Busse et al, 2001 (25)	✓	✓ (% change from baseline)	✓	✓ (change from baseline)	✓	
Cakmak et al, 2004 (26)						
Capriles Hulett et al, 2014 (27)		✓ (% change from baseline)	✓	✓ (change from baseline)		✓
Dahlén et al, 2002 (28)		✓ (change from baseline in liters)		✓ (change from baseline)	✓	
Fish et al, 1997 (29)		✓ (change from baseline in FEV ₁ % predicted)				
Green et al, 2006 (31)						
Helenius et al, 2004 (32)						
Huang et al, 2003 (33)						
Israel et al, 2002 (34)	✓	✓ (change from baseline in liters) ✓ (change from baseline in FEV ₁ % predicted) ✓ (change from baseline in liters)		✓ (% change from baseline)		
Jayaram et al, 2005 (35)						
Jayaram et al, 2005 (36)		✓ (change from baseline in FEV ₁ % predicted)	✓	✓ (change from baseline)		
Kanazawa et al, 2004 (37)		✓ (change from baseline in liters)				
Kannies et al, 2002 (38)		✓ (change from baseline in liters)	✓	✓ (change from baseline)		
Kraft et al, 2006 (39)						
Lavolette et al, 1999 (40)	✓	✓ (% change from baseline)	✓	✓ (% change from baseline)	✓	
Leff et al, 1998 (41)		✓ (change from baseline in liters)				
Löfdahl et al, 1999 (42)		✓ (% change from baseline)	✓	✓ (% change from baseline)		✓
Malmstrom et al, 1999 (43)						
Minoguchi et al, 2002 (44)	✓	✓ (% change from baseline)	✓	✓ (% change from baseline)	✓	
Nakamura et al, 1998 (45)						
Nathan et al, 1998 (46)	✓	✓ (change from baseline in liters) ✓ (change from baseline in FEV ₁ % predicted)		✓ (change from baseline)	✓	
Nathan et al, 1999 (47)						
Nathan et al, 2005 (48)						
Pizzichini et al, 1999 (49)		✓ (% change from baseline)	✓	✓ (% change from baseline)		
Reid et al, 2008 (51)		✓ (change from baseline in liters)		✓ (change from baseline)		
Reiss et al, 1998 (52)	✓	✓ (% change from baseline)	✓	✓ (% change from baseline)	✓	
Schäper et al, 2011 (53)						
Spahn et al, 2006 (54)	✓	✓ (change from baseline in FEV ₁ % predicted)	✓	✓ (change from baseline)	✓	
Spector et al, 1994 (55)		✓ (% change from baseline)		✓ (change from baseline)		
Spector et al, 2004 (56)						
Stelmach et al, 2007 (57)		✓ (change from baseline in FEV ₁ % predicted)				
Stelmach et al, 2002 (58)		✓ (change from baseline in FEV ₁ % predicted)				
Stelmach et al, 2002 (59)		✓ (change from baseline in FEV ₁ % predicted)				
Storms et al, 2004 (60)		✓ (change from baseline in FEV ₁ % predicted)				
Strunk et al, 2008 (61)						
Tohda et al, 2002 (62)						
Ulrik and Diamant, 2009 (63)						
Vaquero et al, 2003 (64)		✓ (% change from baseline)	✓	✓ (% change from baseline)		✓
Wise et al, 2009 (65)	✓	✓ (change from baseline in liters)				✓
Yoo et al, 2001 (66)		✓ (change from baseline in liters)	✓			
Yoshida et al, 2000 (67)						
Zeidler et al, 2006 (68)		✓ (change from baseline in FEV ₁ % predicted)		✓ (change from baseline)	✓	

SABA = short-acting β_2 -agonist.

Appendix Table 4. Risk of Bias in Included Trials

Study, Year (Reference)	Sequence Generation	Allocation Concealment	Blinding/ Patients	Blinding/ Caregivers	Blinding/ Assessors*	Attrition†	Selective Outcome Reporting	Intention-to-Treat Analysis‡	Baseline Balance	Co-interventions Similarity	Adherence	Other Biases	Overall Grade
Altman et al, 1998 (19)	Unclear	Unclear	Low	Low	Low	Unclear	Low	Yes	Yes	Yes	Unclear	No	Fair
American Lung Association Asthma Clinical Research Centers, 2007 (20)	Low	Unclear	Low	Low	Low	Low	Unclear	No	Yes	Yes	Yes	No	Good
Awad et al, 2002 (21)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Yes	Yes	Unclear	Unclear	No	Fair
Baegna-Cagnani et al, 2003 (22)	Low	Unclear	Low	Low	Low	High	Unclear	Yes	Yes	Yes	Unclear	No	Poor
Barnes and Pujet, 1997 (23)	Unclear	Unclear	Low	Low	Low	Low	Low	Yes	Yes	Yes	Unclear	No	Good
Baumgartner et al, 2003 (24)	Low	Unclear	Low	Low	Low	Low	Unclear	Yes	Yes	Yes	Yes	No	Good
Busse et al, 2001 (25)	Low	Unclear	Low	Low	Low	Low	Unclear	Yes	Yes	Yes	Unclear	No	Good
Cakmak et al, 2004 (26)	High	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	No	Unclear	Unclear	No	Poor
Capriles Hulett et al, 2014 (27)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear	Unclear	Yes	No	Poor
Dahlén et al, 2002 (28)	Low	Unclear	Low	Low	Low	Low	Unclear	Yes	Yes	Yes	Unclear	No	Good
Fish et al, 1997 (29)	Unclear	Unclear	Low	Low	Low	High	Unclear	Yes	Yes	Yes	Unclear	No	Poor
Gao et al, 2013 (30)	Unclear	Unclear	Low	Low	Low	Unclear	Unclear	No	Yes	Yes	Unclear	No	Good
Green et al, 2006 (31)	Unclear	Unclear	Low	Low	Low	Unclear	Unclear	Yes	NA	Yes	Yes	No	Fair
Helenius et al, 2004 (32)	Unclear	Unclear	Low	Low	Low	Unclear	Unclear	Yes	NA	Unclear	Yes	No	Fair
Huang et al, 2003 (33)	Unclear	Unclear	Low	Low	Low	Low	Unclear	No	Yes	Yes	Unclear	No	Good
Israel et al, 2002 (34)	Low	Low	Low	Low	Low	Low	Low	No	Yes	Yes	Unclear	No	Good
Jayaram et al, 2005 (35)	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	No	NA	Yes	Yes	No washout period	Poor
Jayaram et al, 2005 (36)	Unclear	Unclear	Low	Low	Low	Low	Unclear	No	Unclear	Yes	Yes	No	Good
Kanazawa et al, 2004 (37)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Yes	Unclear	No	Fair
Kannies et al, 2002 (38)	Unclear	Unclear	Low	Low	Low	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear	Fair
Kraft et al, 2006 (39)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	NA	Yes	Unclear	No	Fair
Laviolette et al, 1999 (40)	Low	Unclear	Low	Low	Low	Low	Low	No	Yes	Yes	Yes	No	Good
Leff et al, 1998 (41)	Unclear	Unclear	Low	Low	Low	Low	Unclear	No	Yes	Yes	Unclear	No	Good
Löfdahl et al, 1999 (42)	Low	Unclear	Unclear	Unclear	Unclear	High	Low	Unclear	Yes	No	Unclear	No	Poor
Malmstrom et al, 1999 (43)	Low	Unclear	Low	Low	Low	High	Low	No	Yes	Yes	Yes	No	Poor
Minoguchi et al, 2002 (44)	Unclear	Unclear	Low	Low	Low	Low	Unclear	No	NA	Yes	Unclear	No	Good
Nakamura et al, 1998 (45)	Unclear	Unclear	Low	Low	Low	Low	Unclear	No	No	Yes	Unclear	No	Poor
Nathan et al, 1998 (46)	Unclear	Unclear	Low	Low	Low	Low	Unclear	No	Yes	Yes	Unclear	No	Good
Nathan et al, 1999 (47)	Unclear	Unclear	Low	Low	Low	High	Unclear	No	Yes	Yes	Unclear	No	Good
Nathan et al, 2005 (48)	Unclear	Unclear	Low	Low	Low	Low	Unclear	No	Yes	Yes	Unclear	No	Poor
Pizzichini et al, 1999 (49)	Low	Unclear	Low	Low	Low	Low	Unclear	Yes	Yes	Yes	Unclear	No	Good
Price et al, 2013 (50)	Low	Low	Low	Low	Low	Low	Low	No	Yes	Yes	Unclear	No	Good
Reid et al, 2008 (51)	Low	Low	Low	Low	Low	Low	Unclear	Unclear	No	Yes	Yes	No	Good
Reiss et al, 1998 (52)	Low	Unclear	Low	Low	Low	High	Low	No	Yes	Yes	Unclear	No	Poor
Schäper et al, 2011 (53)	Unclear	Unclear	Unclear	High	High	Low	Unclear	Yes	NA	Unclear	Unclear	No washout period reported, differential duration of treatment periods	Poor
Spahn et al, 2006 (54)	Unclear	Unclear	Low	Low	Low	Low	Unclear	Yes	Unclear	Yes	Unclear	No	Fair
Spector et al, 1994 (55)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	No	Yes	Yes	Unclear	No	Fair
Spector and Tan, 2004 (56)	Unclear	Unclear	Low	Low	Low	Low	Unclear	Unclear	No	Yes	Unclear	No	Fair
Stelmach et al, 2007 (57)	Low	Unclear	Low	Low	Low	Low	Unclear	No	Yes	Yes	Unclear	No	Good
Stelmach et al, 2002 (58)	Low	Unclear	Low	Low	Low	Low	Unclear	No	Yes	Yes	Unclear	No	Good
Stelmach et al, 2002 (59)	Low	Unclear	Unclear	Unclear	Unclear	Low	Unclear	No	Yes	Yes	Unclear	No	Fair
Storms et al, 2004 (60)	Low	Low	Low	Low	Low	Low	Unclear	No	Yes	Yes	Unclear	No	Good
Strunk et al, 2008 (61)	Unclear	Unclear	Low	Low	Low	High	Unclear	Yes	Unclear	No	Yes	Stopped early	Poor
Tohda et al, 2002 (62)	Unclear	Unclear	Low	Low	Low	Low	Unclear	No	Yes	No	Unclear	No	Good
Ulrik and Diamant, 2009 (63)	Unclear	Unclear	Low	Low	Low	Low	Unclear	Yes	Yes	Yes	Yes	No	Good
Vaquero et al, 2003 (64)	Low	Unclear	Low	Low	Low	Low	Unclear	No	Yes	Yes	Unclear	No	Good
Wise et al, 2009 (65)	Low	Unclear	Low	Low	Low	Low	Unclear	No	Yes	Yes	Unclear	No	Good
Yoo et al, 2001 (66)	Low	Unclear	Low	Low	Low	Unclear	Unclear	No	Yes	Yes	Unclear	No	Fair
Yoshida et al, 2000 (67)	Unclear	Unclear	Low	Low	Low	Unclear	Unclear	Unclear	NA	Unclear	Unclear	No	Fair
Zeidler et al, 2006 (68)	Unclear	Unclear	Low	Low	Low	Unclear	Unclear	No	NA	Yes	Unclear	No washout period reported	Poor

NA = not applicable.

* Blinding of the outcome assessors with regard to patient-reported outcomes was considered adequate if patients were reported to be blinded.

†We compared the proportions of withdrawals in each group using the chi-square test, and a *P* value <0.1 was indicative of differential loss to follow-up.

‡An analysis was considered as intention-to-treat if the number of participants who were randomized was equal to the number of participants who were analyzed.

Appendix Table 5. Effect of LTRAs Versus Placebo in Trials Not Included in the Meta-analyses

Outcome Measure	Study, Year (Reference)	LTRA (95% CI)	Placebo (95% CI)	Reported P Value (Difference in Effects)	Reason for Exclusion
FEV₁ (L) change from baseline					
	Baena-Cagnani et al, 2003 (22)	0.18	0.05	$P < 0.01$	Data provided only for patients with FEV ₁ % predicted less than 80%
	Cakmak et al, 2004 (26)	ND	ND	NS	No effect estimates reported
	Green et al, 2006 (31)	-0.05 (-0.13 to 0.03)	-0.07 (-0.20 to 0.05)	NS	Inadequate reporting (crossover trial)
	Helenius et al, 2004 (32)	-0.01	0.02	NS	Inadequate reporting (crossover trial)
	Nathan et al, 1999 (46)	0.23	0.04	$P < 0.05$	Patients with PEF $\geq 10\%$
		0.15	0.07	NS	Patients with PEF $< 10\%$
	Schäper et al, 2011 (53)	0.2	-0.5	NS overall	1st period of crossover
		0.2	-0.2		2nd period of crossover
	Spector and Tan, 2004 (56)	ND	ND	NS	No effect estimates reported
	Tohda et al, 2002 (62)	ND	ND	NS	No effect estimates reported
	Ulrik and Diamant, 2009 (63)	ND	ND	NS	No effect estimates reported
	Yoshida et al, 2002 (67)	9.8	-0.2	$P < 0.05$	Inadequate reporting (crossover trial)
FEV₁ 1% predicted change from baseline					
	Helenius et al, 2004 (32)	-1.5	-1.3	NS	Inadequate reporting (crossover trial)
	Nakamura et al, 1998 (45)	Median: -3.5	Median: 1.1	NS	Data reported as medians
	Schäper et al, 2011 (53)	3.6	-0.3	NS overall	1st period of crossover
		5	-1.7		2nd period of crossover
Daytime symptoms change from baseline					
Scale: 0-3 (more symptoms)	Fish et al, 1997 (29)*	-	-	$P < 0.01$ (-1.4)	Expressed as weekly totals
Scale: 0-3 (more symptoms)	Green et al, 2006 (31)	-0.09 (-0.27 to 0.10)	-0.07 (-0.20 to 0.06)	NS	Inadequate reporting (crossover trial)
Scale: 5-35 (fewer symptoms)	Jayaram et al, 2005 (35)	-0.3	0.6	$P = 0.6$	Inadequate reporting (crossover trial)
Scale: 0-6 (more symptoms)	Löfdahl et al, 1999 (42)	0.07	0.12	NS	Inadequate reporting
Scale: 0.5-10 (more symptoms)	Minoguchi et al, 2002 (44)	-1.6	0	-	Inadequate reporting (crossover trial)
Scale: 0-3 (more symptoms)	Nathan et al, 1998 (46)*	-	-	$P < 0.01$ (-0.14)	"Adjusted" treatment effect
Scale: 0-3 (more symptoms)	Spector et al, 1994 (55)	-27%	-13%	$P \leq 0.01$	Reported as percentages
Scale: 0-4 (more symptoms)	Zeidler et al, 2006 (68)	-0.2	0.2	NS	Inadequate reporting (crossover trial)
SABA use (puffs/day) change from baseline					
	Awad et al, 2002 (21)	-14.3	-0.6	NS	Number of SABA tablets
	Cakmak et al, 2004 (26)	ND	ND	NS	No effect estimates reported
	Green et al, 2006 (31)	-0.6 (-1.14 to 0.06)	0.9 (-0.07 to 2.5)	NS	Inadequate reporting (crossover trial)
	Jayaram et al, 2005 (35)	-16	-9.4	NS	µg/d
	Nakamura et al, 1998 (45)	Median: 1.4	Median: 0.3	$P < 0.01$ (median: -1.4)	Data reported as medians
	Nathan et al, 1999 (47)	-1.79	0.1	$P < 0.05$	Patients with PEF $\geq 10\%$
		-0.75	-0.31	NS	Patients with PEF $< 10\%$
	Schäper et al, 2011 (53)*	ND	ND	$P < 0.05$	Inadequate reporting (crossover trial)
	Yoo et al, 2001 (66)	-5.36	0.28	-	Puffs/2 wk
Nocturnal awakenings (per week) change from baseline					
	Altman et al, 1998 (19)	-1.4 (-2.1 to -0.8)	0.8 (-1.4 to -0.1)	-	Number analyzed missing
	Dahlén et al, 2002 (28)	-0.18	-0.04	-	Number analyzed missing
	Nathan et al, 1999 (47)	-1	-0.23	$P < 0.05$	Patients with PEF $\geq 10\%$
		-0.7	-0.37	NS	Patients with PEF $< 10\%$
	Nathan et al, 2005 (48)	ND	ND	NS	No effect estimates reported
	Reid et al, 2008 (51)	0.2	0.7	-	Change in total awakenings
		-1.6	-1.1	-	Change in total awakenings
	Wise et al, 2009 (55)	-	-	NS	Patients with at least 1 awakening
		-	-	NS	Patients with at least 1 awakening

Continued on following page

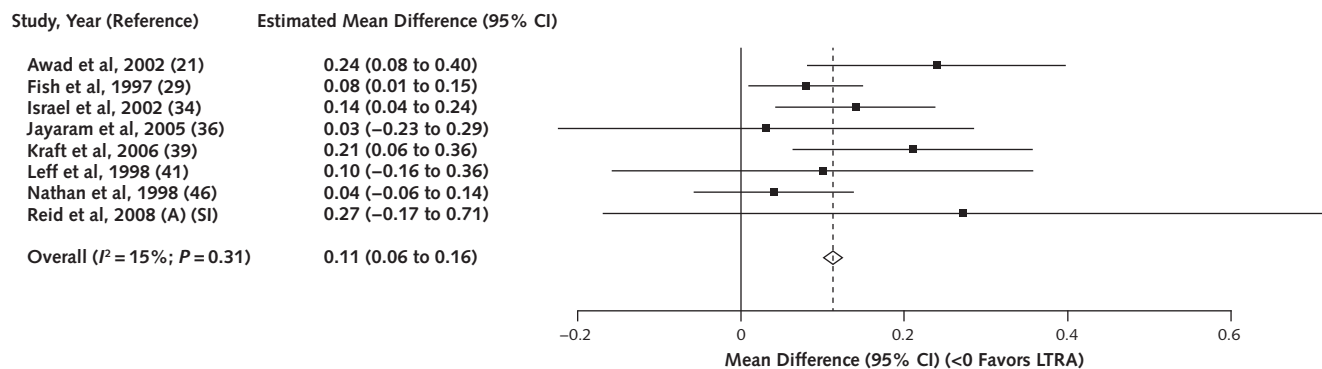
Appendix Table 5–Continued

Outcome Measure	Study, Year (Reference)	LTRA (95% CI)	Placebo (95% CI)	Reported P Value (Difference in Effects)	Reason for Exclusion
ASQL change from baseline					
Scale: 0–6 (better)	Altman et al, 1998 (19)	–	–	–	Pooled effect for all doses used in the trial (scale 0–6)
Scale: 1–7 (better)	Busse et al, 2001 (25)	ND	ND	–	No clinically meaningful difference for any AQLQ domain
Scale: 1–7 (better)	Green et al, 2006 (31)	0.2 (0 to 0.2)	0 (–0.2 to 0.3)	NS	Inadequate reporting (crossover trial)
Scale: ND	Spector et al, 2004 (56)	ND	ND	–	Significant improvement
Scale: 1–7 (better)	Zeidler et al, 2006 (68)	0.5	0.1	P = 0.04	Inadequate reporting (crossover trial)

AQLQ = asthma quality-of-life questionnaire; ASQL = asthma-specific quality of life; LTRA = leukotriene receptor antagonist; ND = no data; NS = not statistically significant; PEF = peak expiratory flow; SABA = short-acting β_2 -agonist.

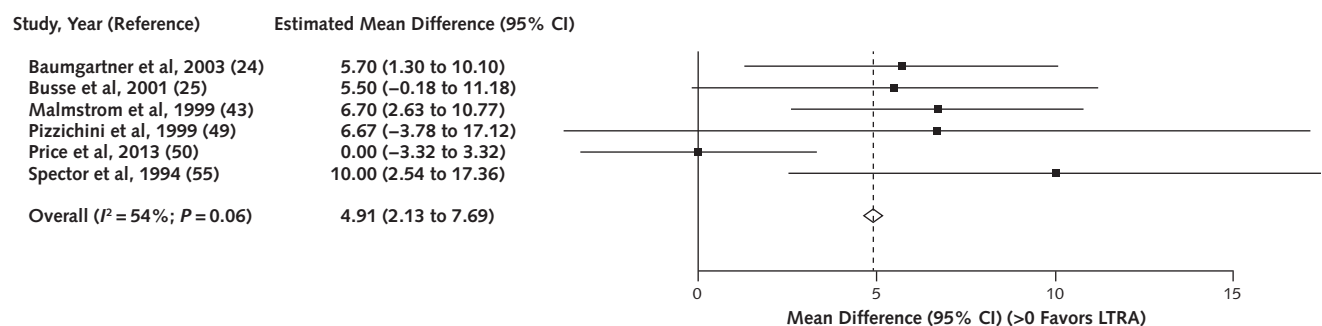
* Not meta-analyzed because final values and changes from baseline should not be combined as standardized mean differences.

Appendix Figure 1. Mean difference in change from baseline in FEV₁ in liters in trials of LTRA monotherapy.



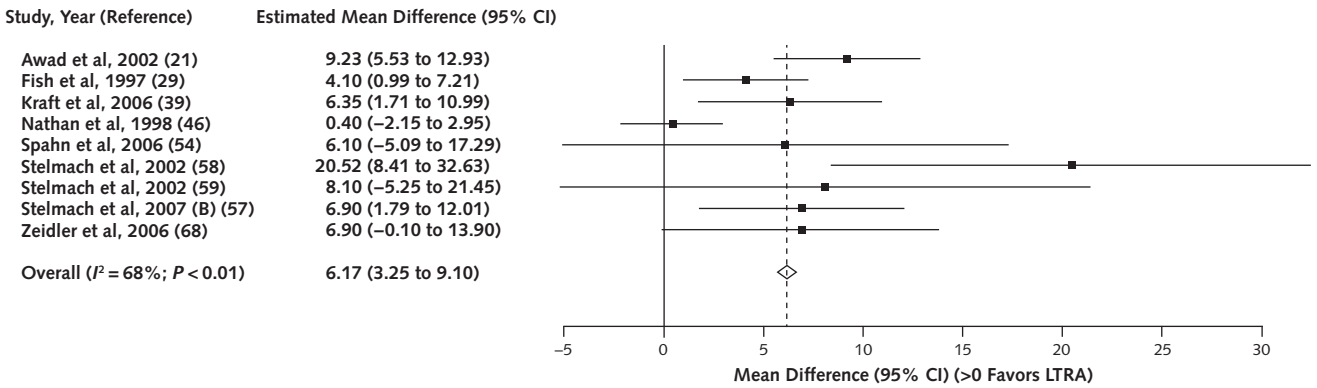
The center of the diamond (vertical dotted line) represents the pooled mean difference and its size the length of the 95% CI. Mean differences (squares) and 95% CIs (horizontal lines) for individual studies are also shown. The size of the squares is proportional to the weight of each study in the meta-analysis. LTRA = leukotriene-receptor antagonist.

Appendix Figure 2. Mean difference in percentage change from baseline in FEV₁ in trials of LTRA monotherapy.



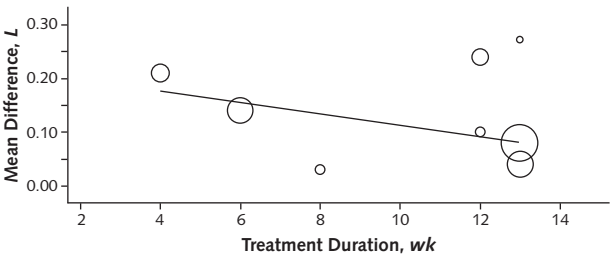
The center of the diamond (vertical dotted line) represents the pooled mean difference and its size the length of the 95% CI. Mean differences (squares) and 95% CIs (horizontal lines) for individual studies are also shown. The size of the squares is proportional to the weight of each study in the meta-analysis. LTRA = leukotriene-receptor antagonist.

Appendix Figure 3. Mean difference in change from baseline in percentage of predicted FEV₁ in trials of LTRA monotherapy.



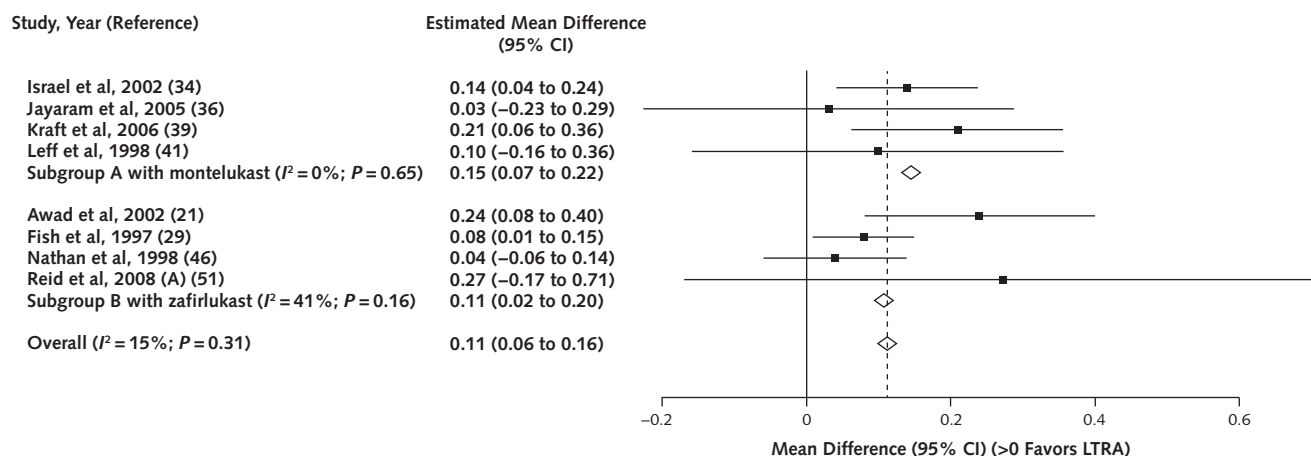
The center of the diamond (vertical dotted line) represents the pooled mean difference and its size the length of the 95% CI. Mean differences (squares) and 95% CIs (horizontal lines) for individual studies are also shown. The size of the squares is proportional to the weight of each study in the meta-analysis. LTRA = leukotriene-receptor antagonist.

Appendix Figure 4. Metaregression plot of mean difference in change from baseline in FEV₁ in liters by treatment duration.



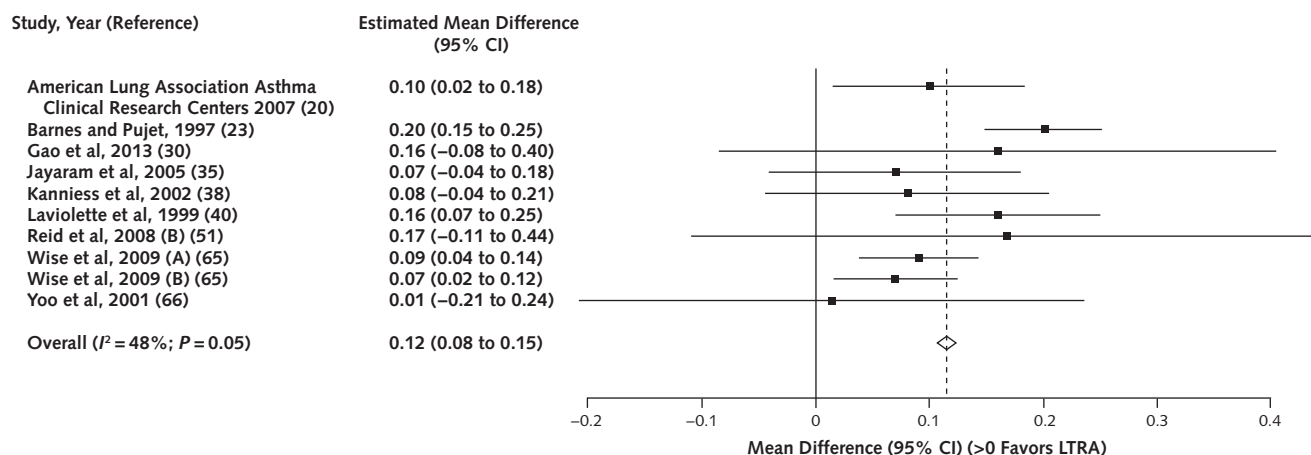
The line represents the change in mean difference. Circles represent studies included in the analysis, and their size is proportional to the weights assigned in metaregression. LTRA = leukotriene-receptor antagonist.

Appendix Figure 5. Mean difference in change from baseline in FEV₁ in liters by subgroups of LTRAs in trials of LTRA monotherapy.



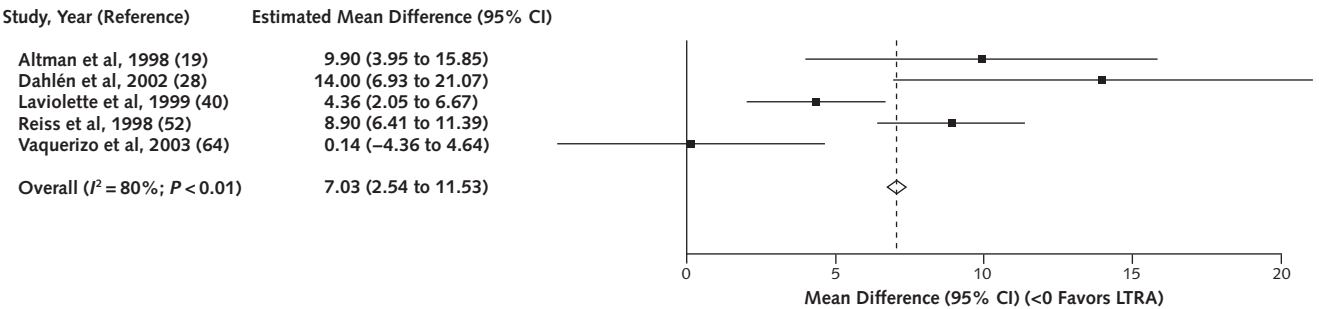
The center of the diamond (vertical dotted line) represents the pooled mean difference and its size the length of the 95% CI. Mean differences (squares) and 95% CIs (horizontal lines) for individual studies are also shown. The size of the squares is proportional to the weight of each study in the meta-analysis. LTRA = leukotriene-receptor antagonist.

Appendix Figure 6. Mean difference in change from baseline in FEV₁ in liters in trials of LTRAs as add-on therapy to ICSs.



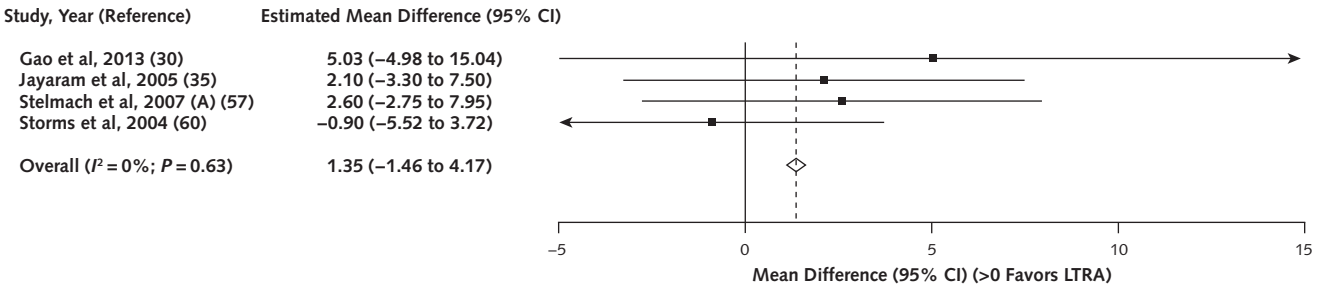
The center of the diamond (vertical dotted line) represents the pooled mean difference and its size the length of the 95% CI. Mean differences (squares) and 95% CIs (horizontal lines) for individual studies are also shown. The size of the squares is proportional to the weight of each study in the meta-analysis. ICS = inhaled corticosteroid; LTRA = leukotriene-receptor antagonist.

Appendix Figure 7. Mean difference in percentage change from baseline in FEV₁ in trials of LTRAs as add-on therapy to ICSs.



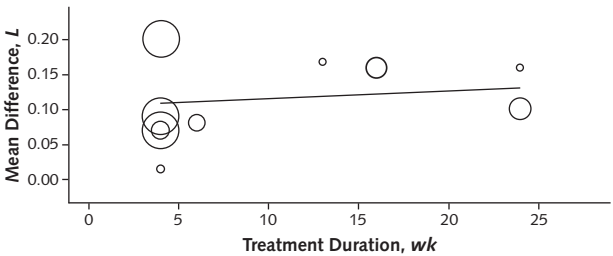
The center of the diamond (vertical dotted line) represents the pooled mean difference and its size the length of the 95% CI. Mean differences (squares) and 95% CIs (horizontal lines) for individual studies are also shown. The size of the squares is proportional to the weight of each study in the meta-analysis. ICS = inhaled corticosteroid; LTRA = leukotriene-receptor antagonist.

Appendix Figure 8. Mean difference in change from baseline in percentage of predicted FEV₁ in trials of LTRAs as add-on therapy to ICSs.



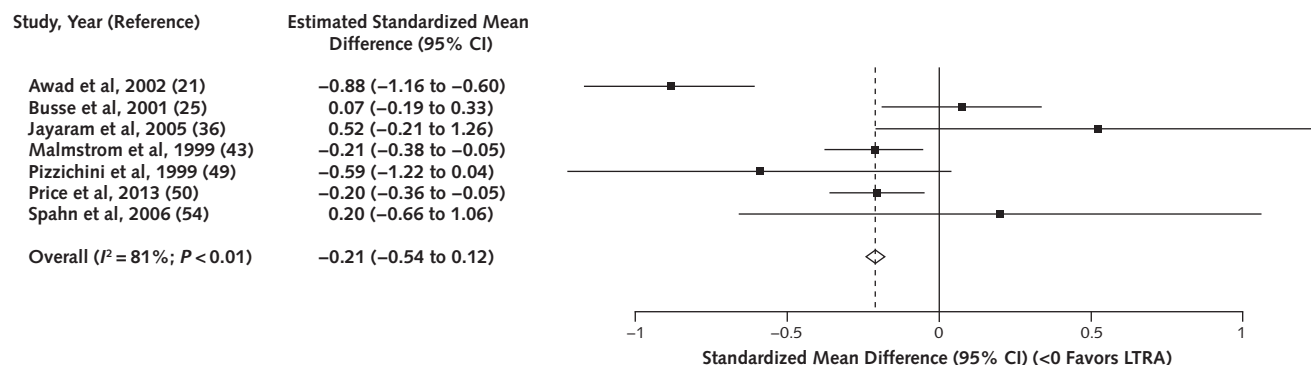
The center of the diamond (vertical dotted line) represents the pooled mean difference and its size the length of the 95% CI. Mean differences (squares) and 95% CIs (horizontal lines) for individual studies are also shown. The size of the squares is proportional to the weight of each study in the meta-analysis. ICS = inhaled corticosteroid; LTRA = leukotriene-receptor antagonist.

Appendix Figure 9. Mean difference in change from baseline in FEV₁ in liters by treatment duration in trials of LTRAs as add-on therapy to ICSs.



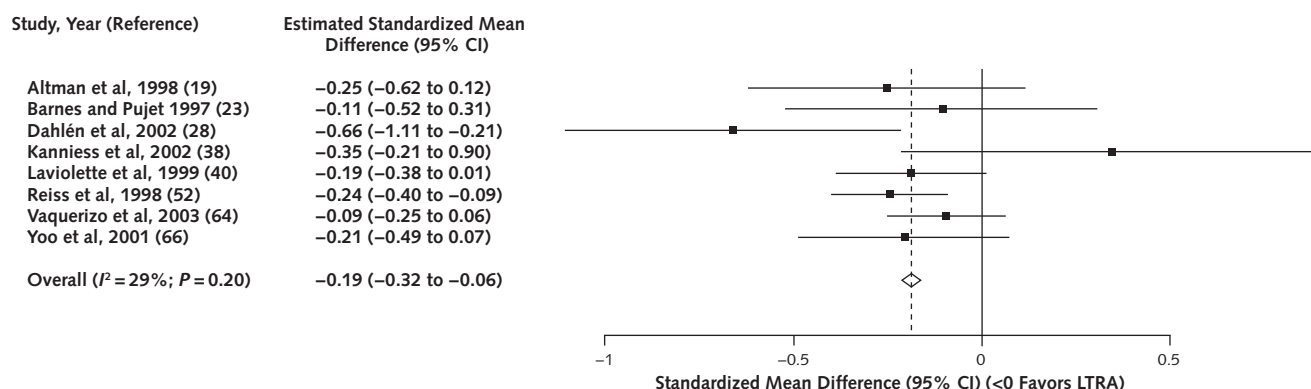
The center of the diamond (vertical dotted line) represents the pooled mean difference and its size the length of the 95% CI. Mean differences (squares) and 95% CIs (horizontal lines) for individual studies are also shown. The size of the squares is proportional to the weight of each study in the meta-analysis. ICS = inhaled corticosteroid; LTRA = leukotriene-receptor antagonist.

Appendix Figure 10. Standardized mean difference in change from baseline in daytime symptoms in trials of LTRA monotherapy.



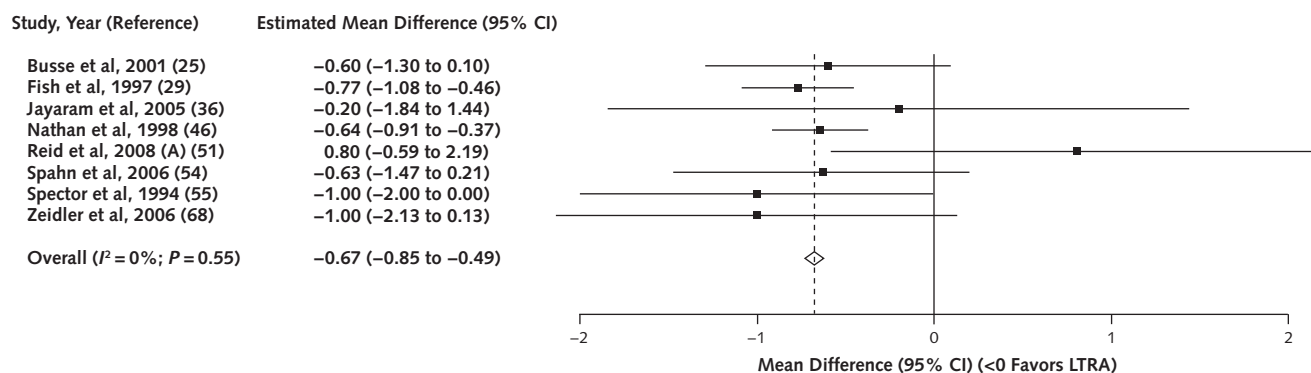
The center of the diamond (vertical dotted line) represents the standardized mean difference and its size the length of the 95% CI. Standardized mean differences (squares) and 95% CIs (horizontal lines) for individual studies are also shown. The size of the squares is proportional to the weight of each study in the meta-analysis. LTRA = leukotriene-receptor antagonist.

Appendix Figure 11. Standardized mean difference in change from baseline in daytime symptoms in trials of LTRAs as add-on therapy to ICSs.



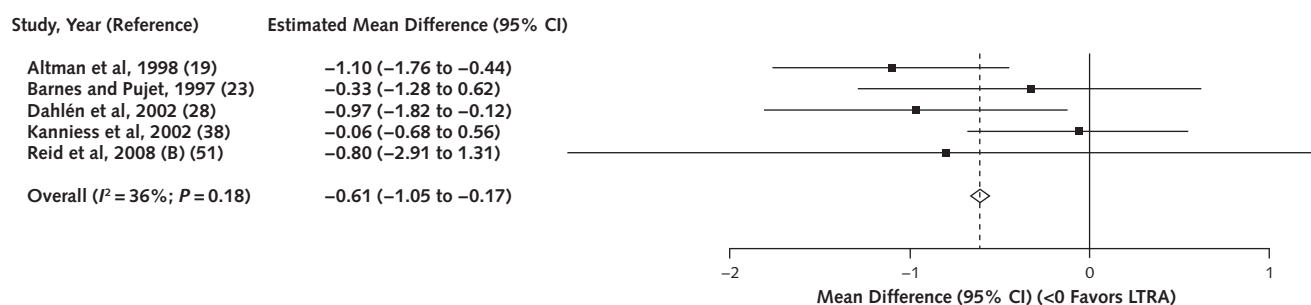
The center of the diamond (vertical dotted line) represents the standardized mean difference and its size the length of the 95% CI. Standardized mean differences (squares) and 95% CIs (horizontal lines) for individual studies are also shown. The size of the squares is proportional to the weight of each study in the meta-analysis. ICS = inhaled corticosteroid; LTRA = leukotriene-receptor antagonist.

Appendix Figure 12. Mean difference in change from baseline in SABA use in trials of LTRA monotherapy.



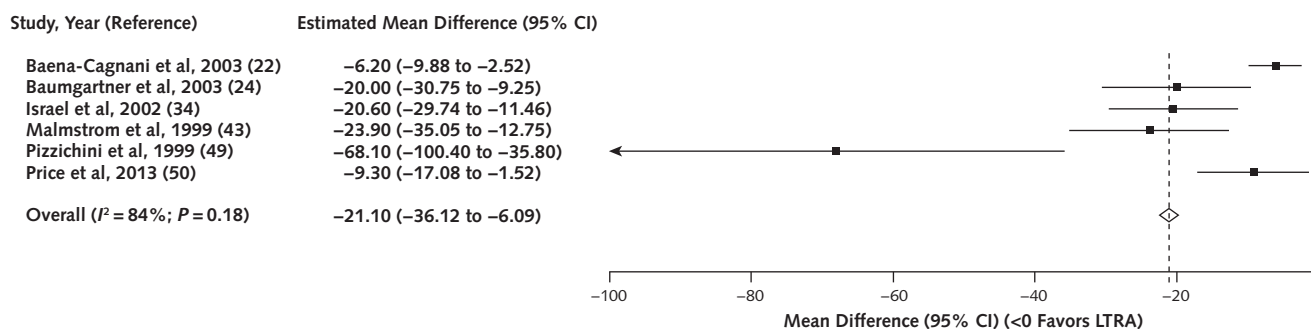
The center of the diamond (vertical dotted line) represents the pooled mean difference and its size the length of the 95% CI. Mean differences (squares) and 95% CIs (horizontal lines) for individual studies are also shown. The size of the squares is proportional to the weight of each study in the meta-analysis. LTRA = leukotriene-receptor antagonist; SABA = short-acting β_2 -agonist.

Appendix Figure 13. Mean difference in change from baseline in SABA use in trials of LTRAs as add-on therapy to ICSs.

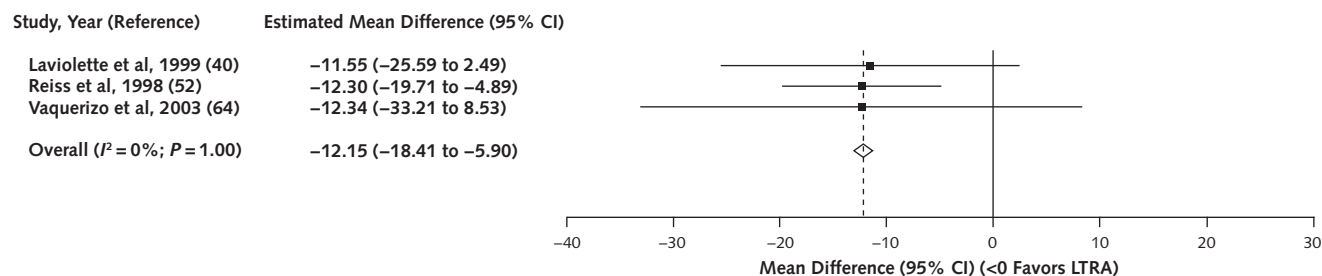


LTRA = leukotriene-receptor antagonist; SABA = short-acting β_2 -agonist.

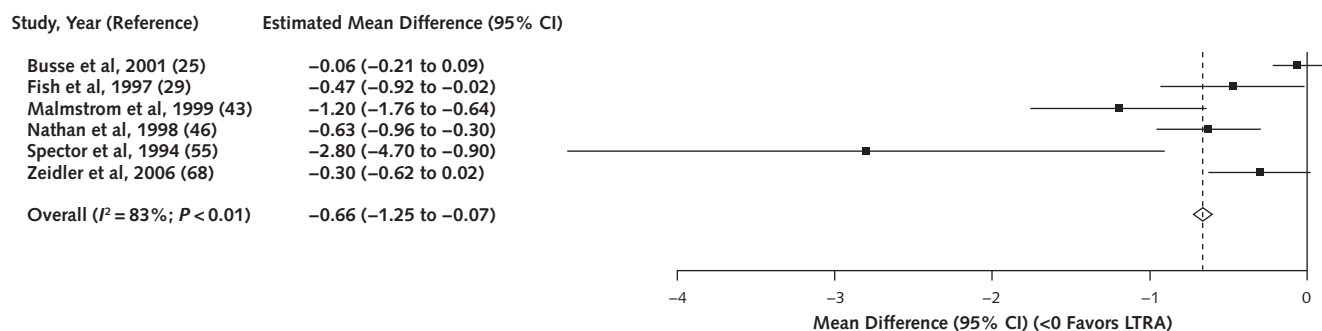
Appendix Figure 14. Mean difference in percentage change from baseline in SABA use in trials of LTRA monotherapy.



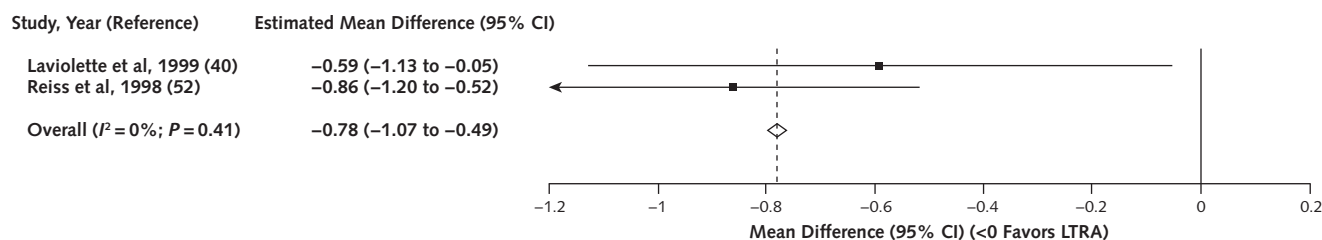
The center of the diamond (vertical dotted line) represents the pooled mean difference and its size the length of the 95% CI. Mean differences (squares) and 95% CIs (horizontal lines) for individual studies are also shown. The size of the squares is proportional to the weight of each study in the meta-analysis. LTRA = leukotriene-receptor antagonist; SABA = short-acting β_2 -agonist.

Appendix Figure 15. Mean difference in percentage change from baseline in SABA use in trials of LTRAs as add-on therapy to ICSs.

The center of the diamond (vertical dotted line) represents the pooled mean difference and its size the length of the 95% CI. Mean differences (squares) and 95% CIs (horizontal lines) for individual studies are also shown. The size of the squares is proportional to the weight of each study in the meta-analysis. ICS = inhaled corticosteroid; LTRA = leukotriene-receptor antagonist; SABA = short-acting β_2 -agonist.

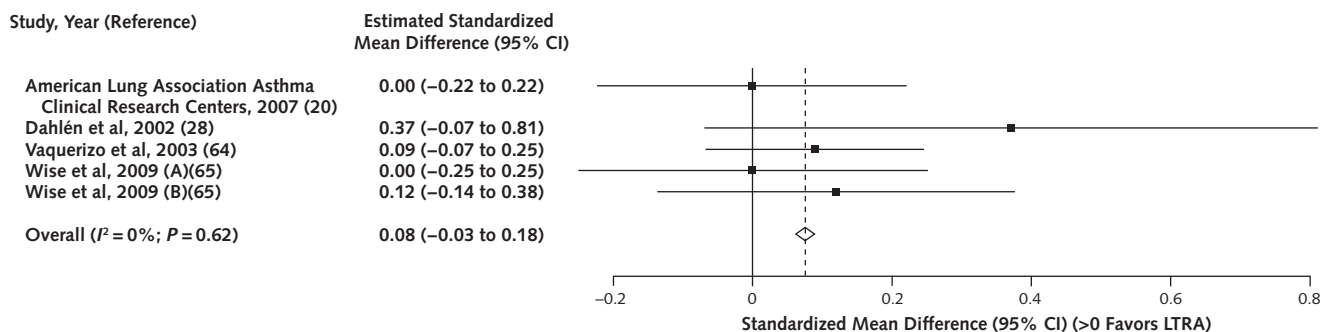
Appendix Figure 16. Mean difference in change from baseline in nocturnal awakenings per week in trials of LTRA monotherapy.

The center of the diamond (vertical dotted line) represents the pooled mean difference and its size the length of the 95% CI. Mean differences (squares) and 95% CIs (horizontal lines) for individual studies are also shown. The size of the squares is proportional to the weight of each study in the meta-analysis. LTRA = leukotriene-receptor antagonist.

Appendix Figure 17. Mean difference in change from baseline in nocturnal awakenings per week in trials of LTRAs as add-on therapy to ICSs.

The center of the diamond (vertical dotted line) represents the pooled mean difference and its size the length of the 95% CI. Mean differences (squares) and 95% CIs (horizontal lines) for individual studies are also shown. The size of the squares is proportional to the weight of each study in the meta-analysis. ICS = inhaled corticosteroid; LTRA = leukotriene-receptor antagonist.

Appendix Figure 18. Standardized mean difference in change from baseline in ASQL in trials of LTRAs as add-on therapy to ICSs.



The center of the diamond (vertical dotted line) represents the standardized mean difference and its size the length of the 95% CI. Mean differences (squares) and 95% CIs (horizontal lines) for individual studies are also shown. The size of the squares is proportional to the weight of each study in the meta-analysis. ASQL = asthma-specific quality of life; ICS = inhaled corticosteroid; LTRA = leukotriene-receptor antagonist.

Appendix Table 6. Sensitivity Analyses for Summary Effects of LTRAs Versus Placebo

Outcome Measure	LTRA Therapy	RCTs, n	Summary Effect (95% CI)*	Heterogeneity Assessed by I^2 , %
Exclusion of poor-quality studies				
FEV ₁ (L) change from baseline	Monotherapy	6	0.13 (0.06 to 0.19)	26
	Add-on to ICS	7†	0.12 (0.08 to 0.16)	55
FEV ₁ percentage change from baseline	Monotherapy	5	4.53 (1.18 to 7.88)	55
	Add-on to ICS	4	6.60 (0.77 to 12.42)	78
FEV ₁ % predicted change from baseline	Monotherapy	7	6.85 (2.90 to 10.80)	76
	Add-on to ICS	3	1.08 (–2.23 to 4.38)	0
Daytime symptoms change from baseline	Monotherapy	6	SMD: –0.20 (–0.61 to 0.21)	84
	Add-on to ICS	7	SMD: –0.18 (–0.34 to –0.01)	34
SABA use (puffs/day) change from baseline	Monotherapy	5	–0.65 (–0.88 to –0.41)	0
	Add-on to ICS	4	–0.61 (–1.12 to –0.10)	52
SABA use percentage change from baseline	Monotherapy	4	–26.03 (–49.20 to –2.85)	79
	Add-on to ICS	2	–11.80 (–23.44 to –0.15)	0
Nocturnal awakenings (per week) change from baseline	Monotherapy	3	–0.92 (–2.41 to 0.56)	88
	Add-on to ICS	1	–0.59 (–1.13 to –0.05)	NA
Exclusion of 1 crossover trial for each analysis				
FEV ₁ (L) change from baseline	Add-on to ICS	8†	0.12 (0.08 to 0.16)	51
FEV ₁ % predicted change from baseline	Monotherapy	8	6.25 (2.90 to 9.61)	72
	Add-on to ICS	3	1.08 (–2.23 to 4.38)	0
SABA use (puffs/day) change from baseline	Monotherapy	7	–0.64 (–0.96 to –0.32)	10
Nocturnal awakenings (per week) change from baseline	Monotherapy	5	–0.66 (–1.25 to –0.07)	87

ICS = inhaled corticosteroids; LTRA = leukotriene receptor antagonist; NA = not applicable; RCT = randomized, controlled trial; SABA = short-acting β_2 -agonist; SMD = standardized mean difference.

* Summary effects are provided as mean differences unless otherwise specified.

† 1 RCT included 2 independent comparisons of LTRA vs. placebo in different patients.

Appendix Table 7. AEs Reported in Included Trials

AE Study, Year (Reference)	Treatment Groups	Events, <i>n</i>	Patients With ≥1 Event, <i>n</i>	Total Patients, <i>n</i>	Reported <i>P</i> Value	Comments in Original Studies	
Abdominal pain							
Barnes and Pujet, 1997 (23)	Pranlukast		2	46	0.6	Led to withdrawal	
	Placebo		0	44			
Nathan et al, 1998 (46)	Zafirlukast		1	125			
	Placebo		0	132			
Vaquerizo et al, 2003 (64)	Montelukast/ICS		8	317			
	Placebo/ICS		6	308			
Yoo et al, 2001 (66)	Pranlukast	0		98			
	Placebo	1		99			
Back pain							
Fish et al, 1997 (29)	Zafirlukast		15	514			
	Placebo						
Nathan et al, 2005 (48)	Montelukast		8	248			
	Placebo						
Bronchitis							
Barnes and Pujet, 1997 (23)	Pranlukast		1	46	0.2		
	Placebo		2	44			
Laviolette et al, 1999 (40)	Montelukast/ICS		5	193			
	Placebo/ICS		4	200			
	Montelukast		7	201			
	Placebo		4	48			
Vaquerizo et al, 2003 (64)	Montelukast/ICS		5	317			
	Placebo/ICS		3	308			
Chest congestion							
Busse et al, 2001 (25)	Zafirlukast		6	111			
	Placebo		0	114			
Clinical AE							
Altman et al, 1998 (19)	Montelukast			57	NS	Headache, URTI most commonly observed	
	Placebo			58			
Israel et al, 2002 (34)	Montelukast			339	NS	Similar frequency, URTI, headache, sinusitis	
	Placebo			111			
Löfdahl et al, 1999 (42)						No significant differences between groups	
Minoguchi et al, 2002 (44)	Montelukast	26	13	27		Respiratory events most commonly observed	
	Placebo	30	15	28			
Nathan et al, 1999 (47)			64	96		<i>P</i> < 0.05 for pharyngitis	Pharyngitis and headache were common
			72	95			
Pizzichini et al, 1999 (49)	Montelukast			19	0.6	Few AE and similar frequencies	
	Placebo			21			
Tohda et al, 2002 (62)	Montelukast		6	89	0.6	Headache, stomachache, heartburn, diarrhea, constipation	
	Placebo		6	92			
Cough							
Barnes and Pujet, 1997 (23)	Pranlukast		0	46			
	Placebo		1	44			
Fish et al, 1997 (29)	Zafirlukast		16	514			
	Placebo		11	248			
Laviolette et al, 1999 (40)	Montelukast/ICS		8	193			
	Placebo/ICS		42	200			
	Montelukast		11	201			
	Placebo		3	48			
Diarrhea							
Barnes and Pujet, 1997 (23)	Pranlukast		2	46			
	Placebo		0	44			
Fish et al, 1997 (29)	Zafirlukast		14	514			
	Placebo		11	248			
Dyspepsia							
Nathan et al, 2005 (48)	Montelukast		11	282			
	Placebo		6	290			
Yoo et al, 2001 (66)	Pranlukast	1		98			
	Placebo	8		99			

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Appendix Table 7—Continued

AE Study, Year (Reference)	Treatment Groups	Events, <i>n</i>	Patients With ≥ 1 Event, <i>n</i>	Total Patients, <i>n</i>	Reported <i>P</i> Value	Comments in Original Studies
Dyspnea						
Barnes and Pujet, 1997 (23)	Pranlukast		2	46		
	Placebo		0	44		
Elevated ALT or AST						
Baumgartner et al, 2003 (24)	Montelukast		1	313		
	Placebo		0	103		
Dahlén et al, 2002 (28)	Montelukast		5	40		
	Placebo		7	40		
Fish et al, 1997 (29)	Zafirlukast		17	514	NS	
	Placebo		10	248		
Leff et al, 1998 (41)	Montelukast		1	54		More than 3 times the upper limit of normal
	Placebo		1	56		
Malmstrom et al, 1999 (43)	Montelukast		85	382		4 patients in each group had levels more than 3 times the upper limit of normal
	Placebo		56	254		
Nathan et al, 1998 (46)	Zafirlukast		2	231		
	Placebo		8	223		
Spector et al, 1994 (55)	Zafirlukast		3	67		
	Placebo		3	66		
Tohda et al, 2002 (62)	Montelukast		10	89		
	Placebo		8	92		
Yoo et al, 2001 (66)	Pranlukast	1		98		
	Placebo	2		99		
Epistaxis						
Nathan et al, 2005 (48)	Montelukast		6	282		
	Placebo		12	290		
Gastritis						
Awad et al, 2002 (21)	Zafirlukast	6		116		
	Placebo	2		99		
Spector et al, 1994 (55)	Zafirlukast		1	67		
	Placebo		4	66		
Headache						
Baena-Cagnani et al, 2003 (22)			11	311		
			11	302		
Barnes and Pujet, 1997 (23)			1	42		
			2	43		
Baumgartner et al, 2003 (24)			31	313		
			18	103		
Busse et al, 2001 (25)	Zafirlukast		2	111		
	Placebo		3	114		
Dahlén et al, 2002 (28)	Montelukast		0	40		Severe that led to withdrawal
	Placebo		1	40		
Fish et al, 1997 (29)	Zafirlukast		71	514		
	Placebo		28	248		
Laviolette et al, 1999 (40)	Montelukast/ICS		50	193		
	Placebo/ICS		42	200		
	Montelukast		52	201		
	Placebo		3	48		
Leff et al, 1998 (41)	Montelukast		11	54		
	Placebo		16	56		
Malmstrom et al, 1999 (43)	Montelukast		68	387		
	Placebo		40	257		
Nathan et al, 2005 (48)	Montelukast		40	282		
	Placebo		38	290		
Price et al, 2013 (50)	Montelukast		17	347	<0.05	
	Placebo		5	335		
Reiss et al, 1998 (52)	Montelukast		73	408		
	Placebo		57	273		
Spector et al, 1994 (55)	Zafirlukast		5	68		
	Placebo		8	70		
Vaquerizo et al, 2003 (64)	Montelukast		34	317	0.6	
	Placebo		29	308		
Wise et al, 2009 (65)	Montelukast		44	120		
	Placebo		34	121		
	Montelukast		35	119		
	Placebo		23	120		

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Appendix Table 7—Continued

AE Study, Year (Reference)	Treatment Groups	Events, <i>n</i>	Patients With ≥ 1 Event, <i>n</i>	Total Patients, <i>n</i>	Reported <i>P</i> Value	Comments in Original Studies
Yoo et al, 2001 (66)	Pranlukast Placebo	1 4		98 99		
Hepatitis						
Jayaram et al, 2005 (35)	Montelukast Placebo	1 0		14		Drug induced
Jayaram et al, 2005 (36)	Montelukast Placebo	1 0		19 22		Drug induced
Hypertonia						
Fish et al, 1997 (29)	Zafirlukast Placebo		15 8	514 248		
Nathan et al, 1998 (46)	Zafirlukast Placebo		1 0	125 132		Led to withdrawal
Influenza						
Fish et al, 1997 (29)	Zafirlukast Placebo		17 11	514 248		
Laviolette et al, 1999 (40)	Montelukast/ICS Placebo/ICS Montelukast Placebo		11 11 15 3	193 200 201 48		
Malmstrom et al, 1999 (43)	Montelukast Placebo		25 10	387 257		
Vaquerizo et al, 2003 (64)	Montelukast Placebo		38 34	317 308	0.7	
Laboratory AE						
Altman et al, 1998 (19)	Montelukast Placebo					More frequent in the placebo group
Israel et al, 2002 (34)	Montelukast Placebo		13 5	339 111	NS	
Löfdahl et al, 1999 (42)	Montelukast Placebo			113 113		No significant differences between groups
Minoguchi et al, 2002 (44)	Montelukast Placebo	5 6	4 5	27 28	NS	
Nathan et al, 1998 (46)	Montelukast Placebo		5 1	125 132		Increased bilirubin or alkaline phosphatase
Pizzichini et al, 1999 (49)	Montelukast Placebo					Infrequent and similar frequencies
Tohda et al, 2002 (62)	Montelukast Placebo		12 7	89 92	NS	Leukocytosis, increased levels of liver enzymes, glycosuria
Yoo et al, 2001 (66)	Pranlukast Placebo	2 1		98 99		Increased bilirubin
Myalgia						
Fish et al, 1997 (29)	Zafirlukast Placebo		19 9	514 248		
Nausea						
American Lung Association Asthma Clinical Research Centers, 2007 (20)	Montelukast Placebo		44 52	164 164		
Awad et al, 2002 (21)	Zafirlukast Placebo	5 1		116 99		
Laviolette et al, 1999 (40)	Montelukast/ICS Placebo/ICS Montelukast Placebo		5 11 12 0	193 200 201 48		
Yoo et al, 2001 (66)	Pranlukast Placebo	1 1		98 99		
Nervousness						
American Lung Association Asthma Clinical Research Centers, 2007 (20)	Montelukast Placebo		62 57	164 164		
Oropharyngeal candidiasis						
Busse et al, 2001 (25)	Zafirlukast Placebo		0 2	111 114		

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Appendix Table 7—Continued

AE Study, Year (Reference)	Treatment Groups	Events, <i>n</i>	Patients With ≥1 Event, <i>n</i>	Total Patients, <i>n</i>	Reported <i>P</i> Value	Comments in Original Studies
Pharyngitis						
Awad et al, 2002 (21)	Zafirlukast	2		116		
	Placebo	2		99		
Barnes and Pujet, 1997 (23)	Pranlukast		1	46		
	Placebo		0	44		
Fish et al, 1997 (29)	Zafirlukast		127	514		
	Placebo		53	248		
Laviolette et al, 1999 (40)	Montelukast/ICS		10	193		
	Placebo/ICS		16	200		
	Montelukast		12	201		
	Placebo		2	48		
Malmstrom et al, 1999 (43)	Montelukast		25	387		
	Placebo		11	257		
Nathan et al, 1998 (46)	Zafirlukast		43	231		
	Placebo		42	223		
Price et al, 2013 (50)	Montelukast		23	347	>0.05	
	Placebo		22	335		
Reiss et al, 1998 (52)	Montelukast		22	408		
	Placebo		29	273		
Spector et al, 1994 (55)	Zafirlukast		14	68		
	Placebo		16	70		
Vaquerizo et al, 2003 (64)	Montelukast		5	317	0.8	
	Placebo		4	308		
Rash/itching						
Barnes and Pujet, 1997 (23)	Pranlukast		1	46		
	Placebo		1	44		
Fish et al, 1997 (29)	Zafirlukast		16	514		
	Placebo		9	248		
Laviolette et al, 1999 (40)	Montelukast/ICS		1	193		
	Placebo/ICS		3	200		
	Montelukast		7	201		
	Placebo		3	48		
Yoo et al, 2001 (66)	Pranlukast	7		98		
	Placebo	4		99		
Respiratory disorder						
Barnes and Pujet, 1997 (23)	Pranlukast		3	46		
	Placebo		1	44		
Rhinitis						
Awad et al, 2002 (21)	Zafirlukast	1		116		
	Placebo	6		99		
Fish et al, 1997 (29)	Zafirlukast		16	514		
	Placebo		8	248		
Nathan et al, 1998 (46)	Zafirlukast		5	231		
	Placebo		8	223		
Spector et al, 1994 (55)	Zafirlukast		5	68		
	Placebo		1	70		
Vaquerizo et al, 2003 (64)	Montelukast		5	317	0.7	
	Placebo		6	308		
Sinusitis						
Busse et al, 2001 (25)	Zafirlukast		4	111		
	Placebo		4	114		
Fish et al, 1997 (29)	Zafirlukast		18	514		
	Placebo		12	248		
Laviolette et al, 1999 (40)	Montelukast/ICS		8	193		
	Placebo/ICS		9	200		
	Montelukast		12	201		
	Placebo		2	48		
Nathan et al, 1998 (46)	Zafirlukast		8	231		
	Placebo		13	223		
Reiss et al, 1998 (52)	Montelukast		31	408		
	Placebo		22	273		

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Appendix Table 7—Continued

AE Study, Year (Reference)	Treatment Groups	Events, <i>n</i>	Patients With ≥ 1 Event, <i>n</i>	Total Patients, <i>n</i>	Reported <i>P</i> Value	Comments in Original Studies
Sore throat						
Busse et al, 2001 (25)	Zafirlukast		3	111		
	Placebo		3	114		
Nathan et al, 2005 (48)	Montelukast		11	282		
	Placebo		9	290		
URTI						
Baumgartner et al, 2003 (24)	Montelukast		22	313		
	Placebo		7	103		
Laviolette et al, 1999 (40)	Montelukast/ICS		70	193		
	Placebo/ICS		79	200		
	Montelukast		72	201		
	Placebo		20	48		
Leff et al, 1998 (41)	Montelukast		12	54		
	Placebo		16	56		
Malmstrom et al, 1999 (43)	Montelukast		48	387		
	Placebo		28	357		
Price et al, 2013 (50)	Montelukast		8	347	>0.05	
	Placebo		7	335		
Reiss et al, 1998 (52)	Montelukast		129	408		
	Placebo		96	273		
Vaquerizo et al, 2003 (64)	Montelukast		17	317	0.5	
	Placebo		21	308		
Urinary tract infection						
Vaquerizo et al, 2003 (64)	Montelukast		6	317	0.7	
	Placebo		7	308		
Vomiting						
Awad et al, 2002 (21)	Zafirlukast		1	116		
	Placebo		0	99		

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ICS = inhaled corticosteroid; NS = not significant; URTI = upper respiratory tract infection.

Appendix Table 8. Withdrawals in Included Trials

Source	Treatment Groups	Withdrawals Due to Adverse Events, <i>n</i>	Withdrawals Due to Worsening Asthma/Exacerbation, <i>n</i>	Total Patients, <i>n</i>	Comments About Exacerbations
American Lung Association Asthma Clinical Research Centers, 2007 (20)	Montelukast Placebo	7 5		164 164	
Barnes and Pujet, 1997 (23)	Pranlukast Placebo		2 1	46 44	No definition of an exacerbation reported
Baumgartner et al, 2003 (24)	Montelukast Placebo	1 3		313 103	
Busse et al, 2001 (25)	Zafirlukast Placebo	1 1		111 114	
Capriles Hulett et al, 2014 (27)	Montelukast Placebo		5 18	46 42	Unclear definition of an exacerbation and no data on concomitant ICS use
Dahlén et al, 2002 (28)	Montelukast Placebo	0 1		40 40	
Fish et al, 1997 (29)	Zafirlukast Placebo	12 7	16 16	514 248	No definition of an exacerbation reported
Huang et al, 2003 (33)	Zafirlukast Placebo		3 4	20 18	Exacerbation that required emergency department visit
Kanniess et al, 2002 (38)	Montelukast Placebo		3 2	26 24	An exacerbation was defined as a decrease in PEF of >50% compared with values at entry, or an increase in daytime symptoms of three or more or in nighttime symptoms of two or more on >3 consecutive days
Laviolette et al, 1999 (40)	Montelukast/ICS Placebo/ICS Montelukast Placebo		2 8 23 7	193 200 201 48	
Leff et al, 1998 (41)	Montelukast Placebo	2 4		54 56	
Löfdahl et al, 1999 (42)	Montelukast Placebo	0 9	4 0	112 113	Exacerbation that required oral corticosteroids
Malmstrom et al, 1999 (43)	Montelukast Placebo	8 11			
Minoguchi et al, 2002 (44)	Montelukast Placebo		1 2	27 28	During washout period
Nakamura et al, 1998 (45)	Pranlukast Placebo	0 2		11 10	
Nathan et al, 1998 (46)	Zafirlukast Placebo	3 0	2 6	231 223	
Nathan et al, 1999 (47)	Zafirlukast Placebo		3 8	96 95	No definition of an exacerbation reported
Nathan et al, 2005 (48)	Montelukast Placebo		1 2	282 290	Exacerbation defined as any event that required treatment with asthma medications beyond study medications
Pizzichini et al, 1999 (49)	Montelukast Placebo	1 1	1 0	19 21	
Price et al, 2013 (50)	Montelukast Placebo	7 4		347 335	
Reiss et al, 1998 (52)	Montelukast Placebo		6 10	408 273	
Spahn et al, 2006 (54)	Montelukast Placebo		1 1	11 10	Required rescue prednisone
Spector et al, 1994 (55)	Zafirlukast Placebo		0 8	70 70	Treated with no specific treatment protocol
Stelmach et al, 2007 (57)	Montelukast Placebo Montelukast Placebo		0 0 0 2	29 29 29 29	No definition of an exacerbation reported
Strunk et al, 2008 (61)	Montelukast Placebo		0 3	19 19	Exacerbations required oral corticosteroids
Vaquerizo et al, 2003 (64)	Montelukast Placebo	3 5	3 3	317 308	
Wise et al, 2009 (A) (65)	Montelukast	2		120	
Wise et al, 2009 (B) (65)	Placebo Montelukast Placebo	2 2 2		121 120 121	

ICS = inhaled corticosteroid; PEF = peak expiratory flow.