

The risk of asthma exacerbation after reducing inhaled corticosteroids: a systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Asthma guidelines suggest reducing controller medications when asthma is stable.

Methods: The purpose of the study is to estimate the risk of asthma exacerbation in stable asthmatics who reduce inhaled corticosteroids (ICS) compared to those who maintain a stable ICS dose. We identified articles from a systematic review of English and non-English articles using MEDLINE, EMBASE, Web of Science, and CENTRAL (inception to May 25, 2013). We included randomized controlled trials (RCTs) with a stable asthma run-in period of 4 weeks or more, an intervention to reduce ICS, and a follow-up period of at least 3 months.

Results: The search strategy identified 2253 potential articles, of which 206 were reviewed at the full-text level and 6 met criteria for inclusion. The relative risk of an asthma exacerbation in individuals who reduced ICS compared to those who maintained the same ICS dose was 1.25 (95% CI 0.96, 1.62; $P = 0.10$; $I^2 = 0\%$) in studies with a mean follow-up of 22 weeks. Individuals who reduced ICS had a decreased% predicted FEV₁ of 0.87% (95% CI -1.58% , 3.33% ; $P = 0.49$, $I^2 = 58\%$) and a decreased mean morning peak expiratory flow of 9.57 l/min (95% CI 1.25, 17.90; $P = 0.02$; $I^2 = 74\%$) compared to those individuals who maintained a stable ICS dose.

Conclusions: Asthma exacerbations were statistically no more likely among individuals who reduced ICS compared to those who maintained their ICS dose, supporting current guidelines which recommend decreasing ICS by 50% after a period of asthma stability.

Asthma is one of the most common chronic diseases in the United States; nearly 14 million individuals are estimated to have an asthma attack each year (1). The National Asthma Education and Prevention Program's Expert Panel Report (EPR-3) published in 2007 includes a recommendation to consider stepping down asthma medications when asthma is

stable for 3 months, specifically suggesting a decrease of 25–50% in inhaled corticosteroid (ICS) dose (2). Authors of the Global Initiative for Asthma (GINA) guidelines similarly suggest a decrease in ICS by 50% if asthma is stable for 3 months (3). Both the EPR-3 and GINA recommendations for stepping down asthma medications are based on panel consensus expert opinion rather than high-level evidence (2, 3). Consequently, there is a need for better evidence to understand the risks and benefits of stepping down asthma medications in stable asthmatics.

Individuals and their healthcare providers must weigh the potential risks and benefits of stepping down asthma

Abbreviations

EPR-3, Expert Panel Report-3; FEV₁, forced expiratory volume in first second; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; LABA, long-acting β -agonist; PEF, peak expiratory flow; RCT, randomized controlled trial.

medication. Stepping down asthma medications may benefit individuals by limiting side-effects, reducing treatment burden, and saving on medication costs. These potential benefits are incompletely defined; however, recent research has reinforced the overall goal of using the least amount of medicine that controls symptoms and the risk of exacerbations (4). On the other hand, stepping down asthma medications may increase exacerbation risk or lead to loss of symptom control. Two previous systematic review and meta-analyses have addressed specific asthma medication step-down strategies and the risk they pose: stopping low-dose ICS (5) and going from combination treatment with ICS and long-acting β -agonist (LABA) to ICS alone (6). Reducing ICS is another commonly employed asthma step-down method that has not yet been subject to systematic review. The primary goal of this systematic review and meta-analysis is to evaluate the risk of asthma exacerbation after reducing ICS compared to maintaining a stable dose of ICS in individuals with stable asthma as measured in randomized controlled trials (RCTs). The secondary goal is to evaluate forced expiratory volume in the first second (FEV₁), morning peak expiratory flow (PEF), asthma symptoms, and asthma-specific quality of life in individuals who reduce ICS compared to those who maintain a stable dose ICS in RCTs.

Methods

Data sources and searches

This systematic review and meta-analysis is consistent with the elements of the 27-item PRISMA statement checklist (7). We performed a search to identify RCTs with the study intervention of reducing or maintaining a stable dose of ICS. The search was assisted by an expert medical librarian (PJE). We included studies that had 4 or more weeks of a run-in period on a stable dose of ICS to ensure a minimum period of asthma stability while part of the trial. We included studies with a period of 3 or more months following randomization to allow a reasonable time period for an asthma exacerbation to occur, which was the primary outcome we considered in our analysis. Using a 3-month follow-up period is supported by findings from one of the included studies with longer follow periods demonstrating that the majority of exacerbation events occurred in the first 3 months (8). There were no age restrictions. We excluded studies when the ICS was reduced, but another asthma controller was started in its place (e.g., LABA or leukotriene receptor antagonist). We excluded studies when the ICS was stopped altogether rather than reduced, as this risk estimate has been previously reported (5).

We performed a systematic review of English and non-English articles using Ovid MEDLINE, Ovid EMBASE, Ovid CENTRAL, and Web of Science (inception to May 25, 2013). Search terms included anti-asthmatic agents and numerous descriptors for reducing medications (e.g., step down, wean, withdraw, reduce). The detailed search strategy used for MEDLINE is detailed in Table S1. The MEDLINE search strategy was modified to accommodate the controlled

vocabulary for EMBASE and CENTRAL. Text words were used for Web of Science. In addition, we reviewed the reference sections of eligible studies and searched articles that had been cited by the eligible articles using Thomson Reuters Web of Science. We contacted several content experts and inquired about their knowledge of any studies that were not on our list of eligible studies or of any unpublished data pertinent to our research question. Finally, we searched the following clinical trial registries for studies: clinicaltrials.gov, clinicaltrialregister.eu, and anzctr.org.au.

Study selection

Two reviewers working independently determined the eligibility of each of the abstracts that resulted from executing the search strategy; the reviewers were not blinded to the author, institution, or journal of publication. The abstract reviewers decided if the abstract met criteria to advance to full-text review. Full-text manuscripts were obtained unless both reviewers determined that the abstract was ineligible for this study. For articles that could not be obtained in full text through the institution's interlibrary loan process and where disagreement existed between two reviewers about advancing to the full-text review stage, a third reviewer assessed the abstract for criteria to advance to the full-text review stage. If two of the three reviewers recommended a full-text review, additional efforts were made to obtain the full-text article. Full-text review was also performed in duplicate; disagreements about inclusion of full-text articles were harmonized by consensus. If consensus was not reached, arbitration by an additional content expert was arranged.

Data extraction and quality assessment

Data were extracted using a standardized form including the number of participants enrolled in each study arm, the study setting, ages of participants, dose and type of ICS used during run-in, the percentage that the ICS was reduced, the length of the run-in and follow-up periods, and the study funding. The number of individuals with an asthma exacerbation, lung function (PEF and FEV₁), asthma symptoms, and asthma-specific quality of life was abstracted. Data extraction was performed in duplicate by two independent reviewers. Disagreements were resolved by consensus. Attempts were also made to obtain additional study data on the outcomes of emergency department visits and hospitalizations for asthma. Authors were contacted if data were missing.

We assessed the following study characteristics to judge methodological quality of the included studies: how the randomization sequence was generated, how allocation was concealed, whether there were important imbalances in prognostic factors at baseline, which groups were blinded, and how missing outcome data were reported and analyzed. The risk of bias was assessed using the Cochrane Collaboration risk of bias tool (9) by two independent reviewers. Disagreements about risk of bias assessments were harmonized by consensus.

Data synthesis and analysis

We used a random-effects model to calculate the pooled relative risk (RR) of an individual experiencing at least one asthma exacerbation if they reduced ICS compared to if they continued a stable ICS dose. We selected a random-effects model due to anticipated heterogeneity in how the outcome of asthma exacerbation was defined. We recorded how asthma exacerbation was defined for each included study. We measured inconsistency using the I^2 test; higher I^2 scores suggest greater inconsistency. We used Review Manager 5.1 (Cochrane Collaboration) software to conduct the analyses.

Results

Our initial search strategy identified 1763 articles. Using the additional strategies of reviewing bibliographies, reviewing lists of works cited, searching clinical trial registries, and contacting experts, we identified an additional 533 unique citations. Of these 2253 citations, 206 met criteria for full-text review. Of the 206 full-text citations considered, 6 met criteria for inclusion (8, 10–14). The PRISMA template (7) for study selection is displayed in Fig. 1.

Select characteristics of the included studies are displayed in Table 1. Numbers of participants ranged from 14 to 259, with an average number of 148 participants per study. Two of the studies were performed in the United States, 1 in Canada, and 3 in Europe. Starting ICS dose varied between studies. The dose of ICS was reduced by 50% in 4 of the studies, by 76% in one study, and by 85% in the remaining study. Funding sources were mixed between government and pharmaceutical companies.

The definitions of asthma exacerbations used in the included studies are shown in Table 2. A healthcare utilization definition was used in all included studies; urgent visits, systemic corticosteroid, and increase use of rescue bronchodilators were the different asthma exacerbation criteria described. A decrease in PEF was used as a criterion for 3 of the included studies, and symptom-based criteria were used in 3 of the studies.

Quality assessment

The bias assessment, using the Cochrane Risk of Bias tool (9), found that most studies had either a low or unclear risk of bias (see Table S2). We did not identify a high risk of bias for any of the bias assessments of the included studies.

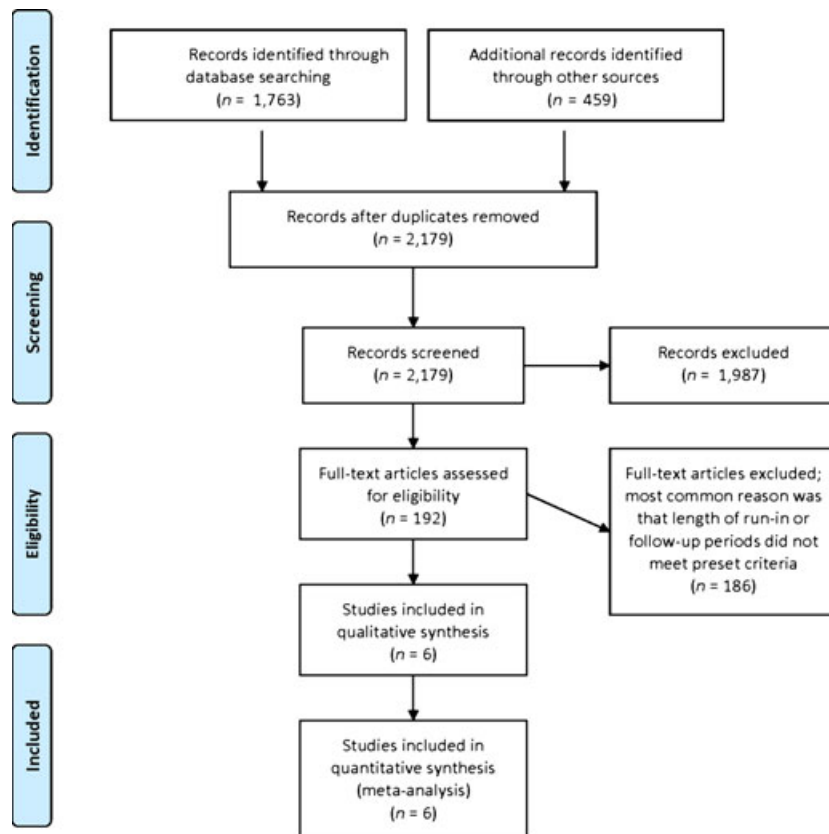


Figure 1 PRISMA flow diagram describing the steps of study selection (7).

Table 1 Characteristics of included studies

	N Control (continue ICS)	N Intervention (reduce ICS)	Setting	Trial location	Ages (years)	Inhaled cortico-steroid and daily dose used in run-in and treatment period	% ICS was Reduced	Run-in period (weeks)	Follow-up period (weeks)	Funding
Juniper 1991	8	6	Academic	Canada	>18	Budesonide 400–800 µg	50%	52	12	Pharmaceutical company; Canadian government
ZuWallack 1997	101	92	Academic/ Community	US	6–70	Flunisolide 1000 µg	50%	4	12	Pharmaceutical company
Visser 2001	28	27	Academic	Netherlands	6–10	Fluticasone propionate 200 µg	50%	8	26	Netherlands government; Pharmaceutical company
Hawkins 2003	129	130	Academic/ Community	UK	18–86	Beclomethasone 1000, 1500, or 2000 µg or Fluticasone propionate 500, 1000, 1500, or 2000 µg	50%	4	12	U.K government; Pharmaceutical company
Papi 2007	106	122	Academic	Italy, Austria, Spain, Poland	18–65	Beclomethasone 500 µg	76%	4	24	Pharmaceutical company
Martinez 2011	72	71	Clinical/Academic	US	6–18	Beclomethasone 80 µg	85%	4	44	US government; Pharmaceutical company

Overall analyses

Asthma exacerbations were statistically no more likely among individuals who reduced ICS compared to those who maintained their ICS dose 1.25 (95% CI 0.96, 1.62; $P = 0.10$; $I^2 = 0\%$; Fig. 2A). The pooled absolute risk difference for an asthma exacerbation was 0.02 (95% CI, -0.02 , 0.07 ; $P = 0.30$; $I^2 = 0\%$), with an event rate of 0.17 for individuals continuing ICS and 0.21 for those who discontinued ICS based on an average study length of 22 weeks.

Results for secondary outcomes of FEV₁, morning PEF, and asthma symptoms are shown in Fig. 2B–E. Individuals who reduced ICS had a mean decreased FEV₁% predicted of 0.87% (95% CI -1.58% , 3.33% ; $P = 0.49$, $I^2 = 58\%$) and a mean decreased morning PEF of 9.57 l/min (95% CI 1.25, 17.90; $P = 0.02$; $I^2 = 74\%$). The standardized mean increase in asthma symptoms among those who reduced ICS was 0.01 (95% CI, -0.26 , 0.28 ; $P = 0.93$; $I^2 = 70\%$), and the mean difference in asthma-specific quality of life was -0.05 (95% CI -0.30 , 0.21 ; $P = 0.73$; $I^2 = 38\%$).

To better assess the severity of asthma exacerbations within the selected studies, we considered whether individuals had emergency department or hospitalizations associated with asthma during the study periods. For 4 of the studies, no emergency department or hospitalizations were reported. In Hawkins et al. (13), there were 2 emergency department visits and 4 hospitalizations reported in the reduced group and 1 emergency department visit and 1 hospitalization in the stable ICS group. In Papi et al. (14), there were 3 severe exacerbations in the stable ICS group and none in the reduced group.

Discussion

Herein, we report a systematic review and meta-analysis of RCTs with the intervention of reducing ICS dose *vs* continuing a stable ICS dose. This is a common method of stepping down asthma medication with a poorly defined risk estimate. We were able to identify 6 studies that addressed this question and were unable to demonstrate an increased risk of asthma exacerbation in individuals who reduced ICS compared to those who maintained a stable dose. We found a statistically significant decrease in PEF in those who reduced ICS *vs* those who maintained a stable ICS dose, although the magnitude of this difference has questionable clinical relevance.

Compared to previous meta-analyses of asthma medication step-down risks, we found more (6) ($n = 5$) or fewer (5) ($n = 7$) studies to answer our research question. Despite identifying only 6 RCTs, however, we can have some reassurance that the relative risk of asthma exacerbation is likely lower than that for discontinuing ICS altogether. In addition, we only found evidence of severe exacerbations in 2 of the studies. Reducing ICS dose is the option for stepping down asthma medication that has the lowest risk of subsequent asthma exacerbation of the step-down choices studied in meta-analysis to date. Additional trials are needed to increase confidence in these estimates and strengthen our preliminary

Table 2 Asthma exacerbation definitions in included studies

	Health care utilization	Lung function	Symptoms
Juniper 1991	≥4 uses of bronchodilator per day for 2–3 consecutive days	Not specified	'A rapid deterioration in symptoms'
ZuWallack 1997	Oral steroids for asthma	Not specified	Not specified
Visser 2001	Oral steroids for asthma	Not specified	Not specified
Hawkins 2003	Physician visit to patient's home for asthma Physician office, ED, or Hospital visit for asthma Oral steroids for asthma	PEF < 70% was used to 'prompt' a visit to ER	Persistent symptoms despite bronchodilator use
Papi 2007	>8 puffs of rescue inhalers/day above baseline for 3 consecutive days Use of asthma medication outside of protocol (oral steroids)	PEF > 30% below baseline for 2 consecutive days	Not specified
Martinez 2011	Oral steroids for asthma	Not specified	Not specified

findings that reducing ICS is a favorable option for stepping down asthma medication.

We identified several limitations to this systematic review and meta-analysis. First, two of the selected studies (8, 14) had an intervention that used on-demand ICS as decided by patients in the reduce ICS group, which is different than a fixed dose reduction in the other 4 studies (including one of the studies that used a combined ICS-SABA inhaler). Despite this difference, we did not see significant heterogeneity for the main outcome measure ($I^2 = 0\%$ for asthma exacerbations). We performed a sensitivity analysis without these 2 studies and found similar results (RR=1.28, 95% CI 0.93, 1.76, $P = 0.14$, $I^2 = 0\%$). Stepping down to on-demand ICS is a promising approach that requires replication in additional trials (15). Second, we selected studies that included individuals who were stable on ICS for at least 4 weeks, whereas consensus expert opinion suggests at least 3 months (or 12 months) of stability prior to consideration of stepping down (2, 3). The length and seasonal timing of asthma stability may be an important factor in predicting successful asthma step down. We recommend that future studies enroll individuals for a run-in of at least 3–12 months to ensure asthma stability prior to the tested intervention. Third, asthma exacerbation was defined differently in each study. We therefore used a random-effects model and noted these different definitions for asthma exacerbation in Table 2. Authors attending a recent workshop have made specific recommendations for defining asthma exacerbations in trials; such standardized outcomes should be considered for future trials (16). In addition, we clarified 'severe exacerbations' as hospitalization or emergency department visits in the identified RCTs and reported only 11 such events identified from 2 studies. Fourth, the applicability of these findings may be limited for certain patient populations. Individuals <6 years old were not included in any of the trials that met criteria for this review. Three of the five RCTs were performed in North America and the other two in Europe; risk estimates may be different for other parts of the world. Fifth, differences between the use of HFA products in more recent studies

compared to non-HFA products in older studies could have influenced outcomes; however, we did not see any significant heterogeneity for our main outcome. Sixth, we identified studies that tested ICS dose reductions of 50–85% but did not identify any with smaller dose reductions, such as the 25% ICS dose reduction suggested as the lower range in the NAEPP-3 guidelines. A 25% ICS dose reduction is unlikely to pose a higher risk of asthma exacerbation than the risk we have estimated for a 50% or 85% dose reduction as reported in this meta-analysis. Finally, translating knowledge of the risks of asthma step down to clinical practice will likely require more than simple dissemination of this information. The current health system may be ill-equipped to help patients step down their medicines, in that the vast majority of visits to healthcare providers occur only when asthma symptoms are worsening (17).

Taken together, the results of this systematic review and meta-analysis suggest that reducing ICS may have lower risk of subsequent asthma exacerbations than previously studied step-down methods. These findings support the current guidelines that suggest a 25–50% ICS dose reduction be considered after 3 months of asthma stability. Optimally, these general practice guidelines would be tailored to an individual patient's anticipated asthma triggers such as upcoming allergy or viral seasons. The overall asthma management goal of using the least amount of medicine to control symptoms and limit exacerbations may be reached by careful and timely selection of asthma step-down choices.

Author contributions

Dr. Rank takes responsibility for the content of the manuscript, including the data and analysis. Dr. Hagan, Dr. Li, Ms. Erwin, and Dr. Rank made substantial contributions to conception and design of the study. Dr. Hagan, Dr. Samant, Dr. Volcheck, Dr. Li, Ms. Hagan, Ms. Erwin, and Dr. Rank were involved in data acquisition, analysis, and interpretation of the data. Dr. Rank wrote the first manuscript draft, and Dr. Hagan, Dr. Samant, Dr. Volcheck, Dr. Li,

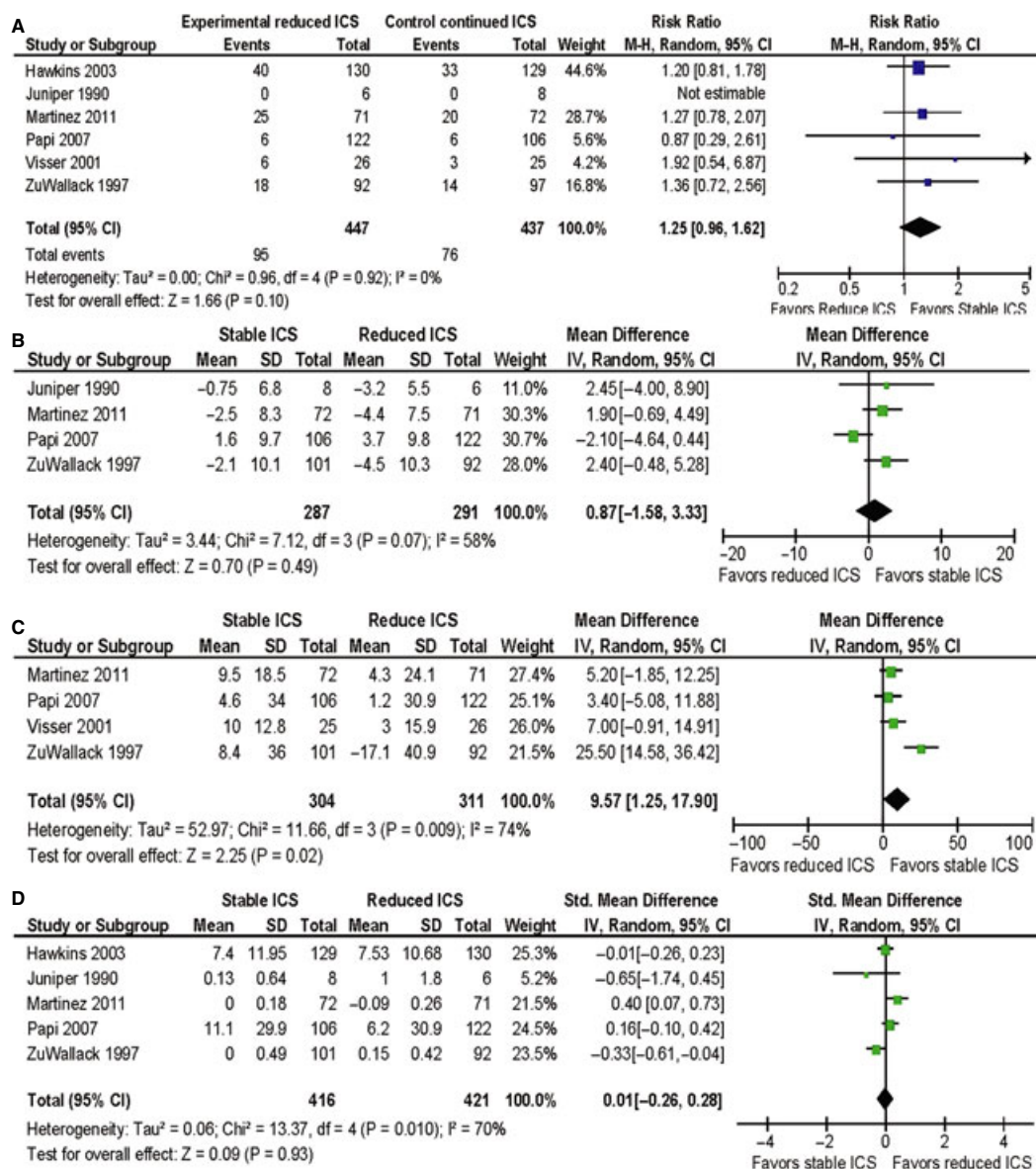


Figure 2 Asthma outcomes in individuals who reduce or maintain a stable inhaled corticosteroid dose (A) Relative risk ratio of asthma exacerbation in individuals who reduce or maintain stable inhaled corticosteroid dose; (B) Mean difference of % predicted FEV₁ in individuals who reduce or maintain stable inhaled corticosteroid dose; (C) Mean difference of peak expiratory flow (AM) in individuals

als who reduce or maintain stable inhaled corticosteroid dose; (D) Standardized mean difference in asthma symptoms in individuals who reduce or maintain stable inhaled corticosteroid dose (E) Asthma-specific quality of life in individuals who reduce or maintain stable inhaled corticosteroid dose.

Ms. Hagan, and Ms. Erwin each critically reviewed the manuscript. All authors have provided final approval of the manuscript.

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Conflicts of interest

None declared.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Database search terms.

Table S2. Risk of bias assessment.

References

1. National Institutes of Health. Factbook Fiscal Year 2011. Available at: <http://www.nhlbi.nih.gov/about/factbook/FactBook2011.pdf>. Last Accessed 24 May 2013.
2. National Heart Lung and Blood Institute. National Asthma Education and Prevention Program. Available at: <http://www.nhlbi.nih.gov/about/naep/>. Last Accessed 24 May 2013.
3. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2011 update. Available at: http://www.ginasthma.org/uploads/users/files/GINA_Report_2011.pdf. Last Accessed 24 May 2013.
4. Kelly HW, Sternberg AL, Lescher R, Fuhlbrigge AL, Williams P, Zeiger RS et al. Effect of inhaled glucocorticoids in childhood on adult height. *N Engl J Med* 2012;**367**:904–912.
5. Rank MA, Hagan JB, Park MA, Podjasek JC, Samant SA, Volcheck GV et al. The risk of asthma exacerbation after stopping low-dose inhaled corticosteroids: a systemic review and meta-analysis of randomized controlled trials. *J Allergy Clin Immunol* 2013;**131**:724–729.
6. Brozek JL, Kraft M, Krishnan JA, Cloutier MM, Lazarus SC, Li JT et al. Long-acting β_2 -agonist step-off in patients with controlled asthma. *Arch Int Med* 2012;**172**:1365–1375.
7. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;**339**:B2535.
8. Martinez FD, Chinchilli VM, Morgan WJ, Boehmer SJ, Lemanske RF Jr, Mauger DT et al. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomized, double-blind, placebo-controlled trial. *Lancet* 2011;**377**:650–657.
9. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available at: www.cochrane-handbook.org.
10. Juniper EF, Kline PA, Vanzieleghe MA, Hargreave FE. Reduction of budesonide after a year of increased use: a randomized controlled trial to evaluate whether improvements in airway responsiveness and clinical asthma are maintained. *J Allergy Clin Immunol* 1991;**87**:483–489.
11. ZuWallack RL, Rosen JP, Cohen L, Rachelefsky GS, Hong H Jr, Goldsobel AB et al. The effectiveness of once-daily dosing of inhaled flunisolide in maintaining asthma control. *J Allergy Clin Immunol* 1997;**99**:278–285.
12. Visser ML, Postma DS, Arends LR, de Vries TW, Duiverman EJ, Brand PL. One-year treatment with different dosing schedules of fluticasone propionate in childhood asthma. *Am J Respir Crit Care Med* 2001;**164**:2073–2077.
13. Hawkins G, McMahon AD, Twaddle S, Wood SF, Ford I, Thomson NC. Stepping down inhaled corticosteroids in asthma: a randomized controlled trial. *BMJ* 2003;**326**:1115.
14. Papi A, Canonica GW, Maestrelli P, Paggiaro P, Olivieri D, Pozzi E et al. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. *N Engl J Med* 2007;**356**:2040–2052.
15. Calhoun WJ, Ameredes BT, King TS, Icitovic N, Bleecker ER, Castro M et al. Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial. *JAMA* 2012;**308**:987–997.
16. Busse WW, Morgan WJ, Taggart V, Togias A. Standardizing asthma outcomes in clinical research: report of the asthma outcomes workshop. *J Allergy Clin Immunol* 2012;**129**:S1–S141.
17. Yawn BP, Wollan PC, Bertram SL, Lowe D, Butterfield JH, Bonde D et al. Asthma treatment in a population-based cohort: putting step-up and step-down treatment changes in context. *Mayo Clin Proc* 2007;**82**:414–421.

Table S1: Database search terms

	Search terms	# of articles
1	exp asthma/dt, th	45495
2	exp anti-asthmatic agents/ae, ad	21208
3	exp glucocorticoids/ad, ae	44612
4	(2 or 3) and (inhal*.mp. or administration, inhalation/ or "nebulizers and vaporizers"/)	9133
5	1 and 4	6031
6	(step* adj down).mp. or cessation/ or stop*.mp. or quit*.mp. or cease*.mp. or reduc*.mp. or eliminat*.mp. or taper*.mp. or wean*.mp. or withdraw*.mp. or discontinu*.mp. or rescue*.mp. or "on demand".mp. or "as needed".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	2843178
7	5 and 6	2129
8	7 and treatment failure/	24
9	disease progression/ or asymptom*.mp. or exacerbat*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	402646
10	Forced Expiratory Volume/ or exp Respiratory Function Tests/	57694
11	quality of life/	179400
12	(9 or 10 or 11) and 7	1239
13	12 and (double-blind method/ or random*.mp.) [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	693
14	clinical trial/ or exp controlled clinical trial/ or exp multicenter study/	811538
15	12 and 14	904
16	13 or 15	939

Table S2. Risk of bias assessment⁸

	Martinez 2011	Papi 2007	Hawkins 2003	Visser 2001	ZuWallack 1997	Juniper 1991
Random sequence generation	Low	Low	Low	Unclear	Unclear	Unclear
Allocation concealment	Low	Low	Low	Unclear	Unclear	Unclear
Blinding of participants and personnel	Low	Unclear	Unclear	Unclear	Low	Unclear
Blinding of outcome assessment	Low	Unclear	Low	Unclear	Low	Unclear
Incomplete outcome data	Unclear	Low	Low	Unclear	Low	Low
Selective reporting	Unclear	Low	Low	Low	Unclear	Low
Other bias	Unclear	Low	Low	Unclear	Low	Low