

Systematic review of clinical effectiveness of pressurised metered dose inhalers versus other hand held inhaler devices for delivering β_2 agonists bronchodilators in asthma

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Abstract

Objectives To determine the clinical effectiveness of pressurised metered dose inhalers compared with other hand held inhaler devices for delivering short acting β_2 agonists in stable asthma.

Design Systematic review of randomised controlled trials.

Data sources Cochrane Airways Group specialised trials database (which includes hand searching of 20 relevant journals), Medline, Embase, Cochrane controlled clinical trials register, pharmaceutical companies, and bibliographies of included trials.

Trials All trials in children or adults with stable asthma that compared the pressurised metered dose inhaler (with or without a spacer device) against any other hand held inhaler device containing the same β_2 agonist.

Results 84 randomised controlled trials were included. No differences were found between the pressurised metered dose inhaler and any other hand held inhaler device for lung function, blood pressure, symptoms, bronchial hyperreactivity, systemic bioavailability, inhaled steroid requirement, serum potassium concentration, and use of additional relief bronchodilators. In adults, pulse rate was lower in those using the pressurised metered dose inhaler compared with those using Turbohaler (standardised mean difference 0.44, 95% confidence interval 0.05 to 0.84); patients preferred the pressurised metered dose inhaler to the Rotahaler (relative risk 0.53, 95% confidence interval 0.36 to 0.78); hydrofluoroalkane pressurised metered dose inhalers reduced the requirement for rescue short course oral steroids (relative risk 0.67, 0.49 to 0.91).

Conclusions No evidence was found to show that alternative inhaler devices are more effective than standard pressurised metered dose inhalers for delivering acting β_2 agonist bronchodilators in asthma. Pressurised metered dose inhalers remain the most cost effective delivery devices.

Introduction

Inhalation of bronchodilators and corticosteroids is the mainstay of treatment for patients with asthma. Many inhaler devices and drug combinations are now available, and competing promotional claims can confuse both prescribers and patients. The costs of the drug used in specific devices differs greatly, and the annual cost to the NHS for asthma drugs is over £500m.¹ National and international guidelines are inconsistent in their recommendations for prescribing inhaler devices in different age groups.^{2,3} None is explicitly evidence based, and there has been no systematic review of published trials.

We conducted a systematic review to determine the clinical effectiveness of the standard chlorofluorocarbon containing pressurised metered dose inhaler compared with other hand held inhaler devices, including chlorofluorocarbon-free pressurised metered dose inhalers delivering short acting β_2 agonist bronchodilators in patients with stable asthma.

Methods

Identification and selection of trials

We identified trials published from 1966 to December 2000 by computerised searches of the Cochrane Airways Group trials database, which includes Medline, Embase, CINAHL, and hand searching of 20 relevant journals and proceedings of three respiratory societies, and reviews of the bibliographies of included trials (www.ncchta.org/execsumm/summ526.htm). We also independently searched the electronic databases (Medline, Embase, and CINAHL) and 17 online respiratory websites to decrease the chance of missing relevant trials. We included citations in any language. We also contacted the pharmaceutical companies that manufacture inhaled asthma drugs and searched the reference lists of trials included in this review for further studies.

The results of the computerised search were independently reviewed by two reviewers. Any potentially relevant articles were obtained in full. The full text of potentially relevant articles was reviewed

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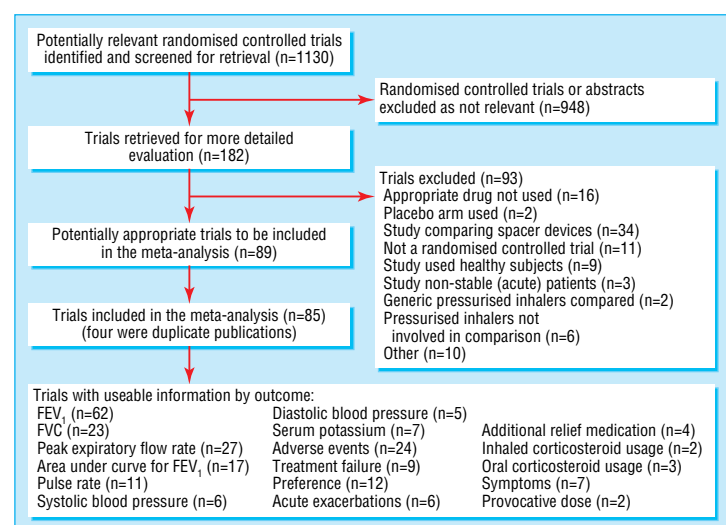


Fig 1 QUORUM trial flow results

independently by the two reviewers. Disagreement was resolved by third party adjudication.

Trial characteristics

We included only randomised controlled trials of short acting β_2 agonists. Trials could be laboratory, hospital, or community based. Trials were included if they compared clinical outcomes of a single drug delivered by standard pressurised metered dose inhalers (with or without a spacer device) against any other hand held device. Trials that compared different doses of inhaled drug and those that used challenge testing were also included. We included trials in both children and adults.

We looked at the following outcomes: lung function, quality of life measures, symptom scores, drugs for additional relief, steroid requirement, nocturnal awakening, acute exacerbation, days off work or school, treatment failure, patient compliance, patient preference, adverse effects, bronchial hyperreactivity, and systemic bioavailability. For trials using cumulative dosing schedules⁴⁻¹⁶ we used data that were generated after the administration of the last cumulative dose.

Data abstraction and assessment of validity

Two reviewers independently extracted details of each trial (intervention, duration, participants, design, quality, and outcome measures) directly into tables. Disagreement was resolved by consensus. We contacted the first authors of the included studies as necessary to provide additional information or data for their studies. We assessed internal validity of included trials using the Jadad¹⁷ and Cochrane scales.¹⁸

Analysis of data

We analysed the data using Review Manager (version 4.1.1) statistical software.¹⁸ For the meta-analysis, we used weighted mean differences for measures on the same scales (for example, forced expiratory volume in one second) or standardised mean differences for outcomes that used different scales (for example, symptoms).

The pressurised metered dose inhaler was compared with each of the different hand held inhaler devices. Each of these device comparisons was further separated into the different trial designs, duration, and

the method of reporting (mean absolute values, percentage change from baseline, and absolute change from baseline). Trials were analysed separately for children and adults.

Twenty trials that examined pulmonary function variables early (15-45 minutes) rather than late (hours) after administration of bronchodilator were reported separately. This is because the early and late effects of β_2 bronchodilators may be different, especially as these compounds have a short half life and short duration of effect.

We tested heterogeneity between trials using χ^2 tests. As long as statistical heterogeneity did not exist, we used a fixed effects model to calculate summary results and 95% confidence intervals. If heterogeneity occurred, we planned subgroup analyses beforehand to explore possible reasons for heterogeneity. These subgroups included quality of the trial, severity of asthma, type of β_2 bronchodilator, and use of spacer device with pressurised metered dose inhaler. Publication or selection bias was tested by preparing funnel plots.¹⁹

Results

The electronic search yielded 1130 citations: 40 references were found in Embase, Medline, CINAHL, and online respiratory journal databases, 1063 citations came from the Cochrane Airways Group register (fig 1). An additional 27 references were added from bibliographic searching of included trials. Of the 1130 abstracts, 181 trials were identified by two reviewers as potentially suitable for inclusion. On scanning the full text of these 181 trials, 92 were excluded (www.nccta.org/execsumm/summ526.htm). Disagreements over inclusion arose in five papers and were resolved after discussion with the third reviewer. Eighty nine papers provided 84 trials (see www.nccta.org/execsumm/summ526.htm for details) that were included in the review (with nine trials being duplicate publications of trials already included).^{4-16 20-86} Four of the included trials^{74 83-85} reported more than one trial in their paper or had additional independent trial arms that met our inclusion criteria and were therefore analysed as separate trials. We wrote to 78 authors of the 80 included trials for further information and received 34 replies.

Study characteristics

There were 45 single dose trials, 16 long term trials, and 17 cumulative dosing trials; 62 trials used a cross-over design and 10 a parallel design. Six trials used different or double dosing schedules and nine were challenge testing trials. Thirteen trials were in children. Some trials could be listed in more than one category.

The oldest included trial was published in 1977. The doses of β_2 agonist used in the included trials varied widely. In 64 trials of salbutamol, doses ranged from 100 μ g in single dose trials up to 4200 μ g in cumulative dose trials. In 15 trials of terbutaline doses ranged from 0.25 mg (single dose) to 4.0 mg (cumulative dose), and in five trials of fenoterol, single doses ranged from 200 μ g to 600 μ g.

Seventy one trials (with 67 references) were in adults^{4-16 23-62 73-86} and 13 in children.^{20-22 63-72} Most trials were in patients with mild to moderate asthma, as

Table 1 Non-significant outcomes in trials comparing pressurised metered dose inhaler with other inhaler devices

Trial design/Device	Non-significant outcomes (No of trials and reference Nos)
Crossover	
Turbohaler	FEV ₁ (6 ⁶ 9 ¹³ 41 ⁶⁰ 83 ¹), FVC (4 ⁶ 9 ¹³ 41 ¹), pulse rate (3 ⁴ 6 ⁹), AUC-FEV ₁ (1 ¹¹), blood pressure (1 ⁶), adverse effects (3 ⁴ 41 ⁴⁶), treatment failure (1 ⁴⁶), serum potassium (2 ⁶ 41 ¹)
Diskhaler	PEFR (1 ³⁹), adverse effects (1 ³⁹)
HFA-pressurised metered dose inhaler	FEV ₁ (5 ¹⁰ 14 ¹⁵ 54 ⁷⁴), FVC (3 ¹⁰ 14 ⁵⁴), adverse effects (2 ¹⁴ 74), AUC-FEV ₁ (2 ⁷⁴ 85), pulse rate (2 ¹⁰ 14), blood pressure (2 ¹⁰ 14), serum potassium (2 ¹⁰ 14)
Rotahaler	FEV ₁ (8 ⁵ 8 ¹² 16 ⁴⁰ 51 ⁶² 76 ¹), FVC (3 ¹⁶ 40 ⁶²), PEFR (4 ²⁶ 36 ³⁸ 62 ¹), AUC-FEV ₁ (2 ⁴⁰ 76), adverse effects (2 ³⁸ 76), exacerbations (1 ⁸)
Spiros	FEV ₁ (1 ⁸⁴), FVC (1 ⁸⁴), AUC-FEV ₁ (1 ⁸⁴), PEFR (1 ⁸⁴), pulse rate (1 ⁸⁴), blood pressure (1 ⁸⁴), serum potassium (1 ⁸⁴)
Spinhaler	FEV ₁ (1 ³¹), FVC (1 ³¹)
Easyhaler	FEV ₁ (4 ⁷ 59 ⁷⁹ 82 ¹), FVC (4 ⁹ 59 ⁷⁹ 82 ¹), PEFR (3 ⁵⁹ 79 ⁸²), AUC-FEV ₁ (2 ⁵⁹ 79 ¹), pulse rate (1 ⁷⁹), blood pressure (1 ⁷⁹), adverse effects (3 ⁷ 79 ⁸²)
Multidose powder inhaler	FEV ₁ (1 ⁸¹), AUC-FEV ₁ (1 ⁸¹), adverse effects (1 ⁸¹), preference (1 ⁸¹)
Clickhaler	FEV ₁ (1 ⁷⁷), adverse effects (1 ⁷⁷)
Gentlehaler	FEV ₁ (1 ⁴⁴), FVC (1 ⁴⁴), PEFR (1 ⁴⁴)
Autohaler	FEV ₁ (1 ⁶¹), FVC (1 ⁶¹), PEFR (1 ⁶¹)
Parallel	
Powder inhaler or HFA-pressurised metered dose inhaler	FEV ₁ (6 ²⁵ 27 ⁵⁰ 55 ⁷³ 80 ¹), FVC (2 ²⁷ 55), PEFR (3 ⁵⁰ 55 ⁵⁷), AUC-FEV ₁ (4 ²⁵ 73 ⁷⁸ 80 ¹), β_2 use (2 ⁵⁵ 57), symptoms scores (1 ⁵⁵), exacerbations (4 ²⁴ 57 ⁷⁸ 80 ¹), adverse effects (6 ²⁴ 50 ⁵⁵ 57 ⁷⁸ 80 ¹), preference (1 ⁴⁷), inhaled steroid requirement (1 ²⁵), pulse rate (1 ³⁰), treatment failure (4 ¹⁶ 25 ⁵⁰ 73 ¹)
Challenge	
Powder inhaler or HFA-pressurised metered dose inhaler	FEV ₁ (4 ²³ 43 ⁶⁴ 75 ¹), FVC (1 ⁴³), PD ₂₀ -FEV ₁ (2 ³² 81 ¹)
Different doses	
Powder inhaler or HFA-pressurised metered dose inhaler	FEV ₁ (5 ²⁸ 33 ⁴⁹ 52 ⁵⁵), PEFR (1 ⁵⁸), preference (1 ²⁶), symptoms (1 ³³)

FEV₁=forced expiratory volume in one second, FVC=forced vital capacity, AUC-FEV₁=area under curve for forced expiratory volume in one second, PEFR=peak expiratory flow rate, HFA=hydrofluoroalkane.

defined by a baseline forced expiratory volume in one second > 50% of predicted.

Data synthesis

Most of the trials were double blinded using double dummy technique and most had adequate concealment of allocation. All trials were of good methodological quality with a Cochrane score above B and Jadad score greater than 3. Four of the included trials were reported as abstracts with insufficient information for scoring.^{29 60 75 85}

Most trials reported continuous outcomes as mean values after giving bronchodilators. However, 10 trials reported the mean maximum values after bronchodilator.⁷³⁻⁸² We therefore did a sensitivity analysis (excluding these 10 trials) to find whether the results were different. In all cases, the results were not different with or without the inclusion of these trials.

For the 62 crossover trials, we had planned to use only the first arm data in our analysis. These data were reported by only 10 trials. However, with these 10 trials, we were able to use inverse variance pooling in order to test the effect of our software treating data from crossover trials as parallel data. The results were the same when comparing individual patient data with group means.

Thresholds for clinically important results of pulmonary function tests are often arbitrary. However, from the range of values that the trial researchers used, a guide would be 15-30 l/min or 7.5% to 20% for peak expiratory flow rate and 0.2 or 15% for forced expiratory volume in one second.

We found no significant differences in children or adults between the standard pressurised metered dose inhaler and any of the other 10 hand held inhaler

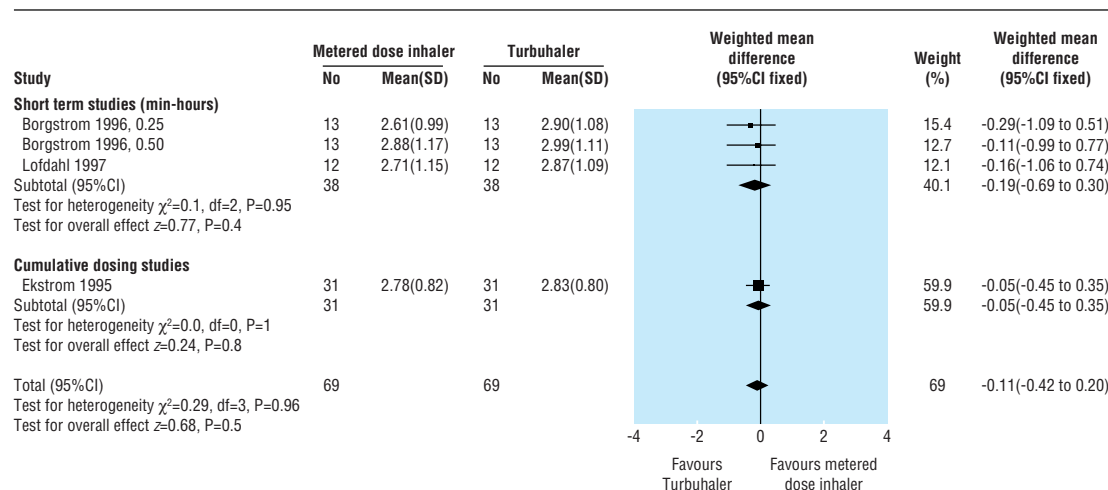
**Fig 2** Forced expiratory volume in one second values for patients in trials comparing pressurised metered dose inhalers with Turbohaler

Table 2 Significant outcomes found in more than one trial

Inhaler device	Outcome (favoured device)	No of trials and reference Nos	Type of trial (No of patients)	Effect size (95% CI)	P value
Adults					
Turbohaler	Pulse rate (higher with Turbohaler)	3 ^{4 6 9}	Cumulative dosing crossover (104)	SMD=0.44 (0.05 to 0.84)	0.03
Rotahaler	Patient preference (metered dose inhaler)	3 ^{26 35 38}	Crossover trials: 2 long term, 1 short term (156)	Odds ratio=3.10 (1.60 to 6.01)	0.0008
HFA-pressurised metered dose inhaler	Oral steroid requirement (lower with HFA inhaler)	3 ^{73 80}	Long term parallel trials (519)	Odds ratio=0.57 (0.37 to 0.88) NNT=9 (5.21 to 43.48)	0.01
Children					
Rotahaler	Patient preference (metered dose inhaler)	2 ^{65 70}	Long term trials: 1 parallel, 1 crossover (260)	Odds ratio=2.63 (1.56 to 4.44)	0.0003

SMD= standardised mean difference, HFA=hydrofluoroalkane, NNT=number needed to treat.

devices (Turbohaler, Diskhaler, hydrofluoroalkane pressurised metered dose inhaler, Rotahaler, Spiros, Easyhaler, multidose powder inhaler, Clickhaler, Gentlehaler, and Autohaler) for the following outcomes: forced expiratory volume in one second, forced vital capacity, peak expiratory flow rate, area under the curve for forced expiratory volume in one second, blood pressure, symptoms, bronchial hyperreactivity, systemic bioavailability, inhaled steroid requirement, serum potassium concentration, and use of additional relief bronchodilators (table 1). Figure 2 shows an example of the meta-analysis as Forrest plots. A complete set of Forrest plots is available on www.nchta.org/execsumm/summ526.htm. No data were available for quality of life, patient compliance, nocturnal awakening, and days off work or school.

Six of the trials that used a 2 to 1 or larger dosing schedule^{28 43 49 52 56 58} did not show significantly different results and did not provide results that were different from trials that used a 1 to 1 dosing schedule.

Tables 2 and 3 show all outcome measures that were significant in one or more trials ($P < 0.05$) and did not show any heterogeneity.

Five studies used spacer devices with the pressurised metered dose inhalers.^{21 32 33 52 71} There were no differences in the results of trials that used pressurised metered dose inhalers with and without spacer devices compared with alternative inhaler devices. However, this indirect subgroup comparison was not determined before the study and is therefore not a reliable method to assess the effectiveness of spacer devices.

Discussion

This large review of 84 trials and 14 outcome measures found no evidence that pressurised metered dose inhalers were any less effective than other inhaler

devices for administering short acting β_2 agonists. The number of trials that could be combined in the meta-analysis was limited by inconsistencies in measurement and reporting of outcomes. Publication bias is a threat to the validity of most systematic reviews. However, there was no evidence of funnel plot asymmetry in any of the comparisons (fig 3).

A pitfall of crossover trials, such as those included in this review, is that the effects of the first treatment can carry over into the second treatment period, leading to an underestimation of the real difference between treatments.⁸⁷ In the crossover trials included, treatment with short acting β_2 agonists did not seem to alter respiratory function (forced expiratory volume in one second) before treatment in the second arm, and if lung function differed by more than 10-15% from baseline values the patient was excluded from the trial or the second arm visit rescheduled.^{5 6 8 9 80} However, most trials included a washout period and patients were excluded if lung function differed by more than 10-15% from baseline.

Notable findings

Trials using 2 to 1 or greater dosing showed no clinical advantage over 1 to 1 dosing trials. Higher dosing schedules are often promoted by pharmaceutical companies to show clinical superiority of one inhaler device over another and to support prescribing recommendations. We found no evidence in support of these claims. A previous review of inhaler devices that considered the relation between clinical efficacy and lung deposition concluded that differences in drug deposition alone did not always explain corresponding differences in bronchodilatory responses among inhaler devices.⁸⁸

Three trials found a higher pulse rate in patients using Turbohaler than those using a pressurised

Table 3 Significant outcomes found in only one trial

Inhaler device	Outcome (favoured device)	Trial type (No of patients)	Effect size (95% CI)	P value
Adults				
Turbohaler	Preference (Turbohaler)	Long term parallel ⁴⁷ (258)	OR=2.83 (1.59 to 5.03)	<0.0006
Rotahaler	Pulse rate (Rotahaler)	Cumulative dosing crossover ¹⁶ (14)	WMD=-5.5 (-10.0 to -0.96)	0.02
Multidose powder inhaler	Preference (metered dose inhaler)	Short term crossover ⁸¹ (72)	OR=0.36 (0.14 to 0.93)	0.04
Spinhaler	FEV ₁ (metered dose inhaler)	Short term crossover ³¹ (40)	WMD=0.80 (0.01 to 0.16)	<0.05
Spinhaler	FVC (metered dose inhaler)	Short term crossover ³¹ (40)	WMD=0.26 (0.09 to 0.43)	0.002
Children				
Turbohaler	Preference (Turbohaler)	Long term crossover ⁶⁹ (114)	OR=3.27 (1.46 to 7.33)	0.004
Rotahaler	Peak expiratory flow (Rotahaler)	Long term crossover ⁶⁵ (86)	WMD=105.4 (59 to 150)	<0.0001
Rotahaler	Exacerbations (Rotahaler)	Long term parallel ⁷⁰ (204)	RR=0.52 (0.28 to 0.95)	0.034

OR=odds ratio, WMD=weighted mean difference, RR=relative risk.

metered dose inhaler.^{21 23 26} This would indicate greater systemic absorption with Turbohaler, although this did not translate into greater treatment effect.

Three trials found that adult patients preferred the pressurised metered dose inhaler to the Rotaler.^{26 35 38} One trial in children⁶⁹ and one in adults⁴⁷ showed that patients preferred the Turbohaler. One trial showed that patients preferred the pressurised metered dose inhaler to the multidose dry powder inhaler.⁸¹ These results should be viewed with caution because of the potential for bias regarding blinding of new inhaler devices in clinical trials.

Long term parallel trials have shown that regular daily use of hydrofluoroalkane pressurised metered dose inhalers may reduce the requirement for short course oral steroids.^{73 80} However, this result may be biased because of inadequate randomisation in one trial. Confirmation from further trials is required.

Further research

Although we did not find significant differences for most outcomes, the confidence intervals could include clinically important differences. Our comparison of population means cannot show such clinically important differences for individual patients from different inhaler devices. Small changes in physiological measures such as pulmonary function will not necessarily be important in themselves, but rather in the impact they have on the symptoms and quality of life of the patient.⁸⁹

Future trials should address the paucity of patient centred outcomes such as quality of life, adherence, nocturnal awakening, and days off work or school. Data on these outcomes were not available in this review. Further systematic reviews are needed to assess the effectiveness of pressurised metered dose inhalers with or without spacer devices and the effectiveness of training and education about use of inhaler devices.

Conclusion

We found no evidence that alternative inhaler devices are clinically more effective than pressurised metered dose inhaler for delivery of short acting β_2 bronchodilators. Therefore, pressurised metered dose inhaler or the cheapest inhaler device the patient can use adequately, should be prescribed as first line in all patients with stable asthma requiring short acting β_2 agonist bronchodilators.

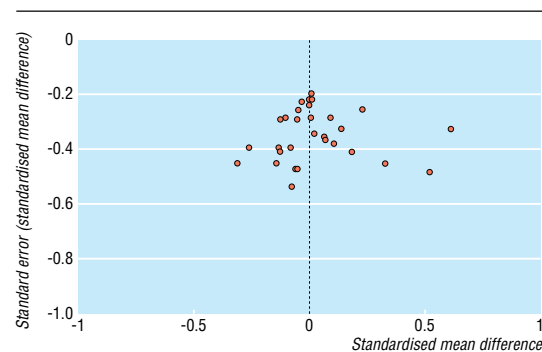


Fig 3 Example funnel plot for 31 trials (1290 participants) with data on forced expiratory flow volume in one second for pressurised metered dose inhaler and all other inhaler devices combined using standardised mean difference

What is already known on this topic

Many different inhaler devices are available for administration of short acting β_2 agonists in asthma

Current guidelines for their use are inconsistent and not evidence based

What this study adds

This systematic review found no evidence that alternative inhaler devices are more effective than pressurised metered dose inhalers for administering inhaled β_2 agonist bronchodilators

Pressurised metered dose inhalers (or the cheapest inhaler device) should be used as first line treatment in all patients with stable asthma who require β_2 agonists

This paper is based on a Cochrane review that is available in the Cochrane Library. As with all Cochrane reviews, the authors have committed to keep this review up to date.

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