Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature


Authors' objectives
To systematically review the clinical effectiveness and cost-effectiveness of inhaler devices in asthma and chronic obstructive pulmonary disease (COPD). The report consisted of seven systematic reviews investigating the following.

The relationship between in vitro characteristics of inhaler devices and clinical outcomes.

The delivery of corticosteroids in stable asthma.

The delivery of beta-agonist bronchodilators from the pressurised metered-dose inhaler (pMDI) versus other inhaler devices in stable asthma.

Beta-agonists for stable asthma: hand-held inhalers versus nebulisers.

Bronchodilators for stable and acute COPD: pMDI versus other hand-held inhalers.

Bronchodilators for stable and acute COPD: hand-held inhalers versus nebulisers.

The ability of individual patients to use the different inhaler devices.

Searching
The Cochrane Airways Group's Specialised Register of trials was searched for published evidence. This was supplemented by handsearches of 16 core journals in respiratory disease and 2 general medical journals (The Lancet and BMJ). Further attempts to identify relevant RCTs involved searching reference lists and the proceedings of relevant societies, and contacting study authors.

Study selection
Study designs of evaluations included in the review
Only RCTs were eligible for inclusion. The studies could be laboratory- or community-based. The trials had be a minimum of 4 weeks in duration for inclusion in review (a) (corticosteroids); any study duration was considered for the other reviews (b to e). To avoid confounding, studies were only included if they delivered the same single drug via both of the devices compared.

Specific interventions included in the review
The intervention was one of five different classes of drugs delivered by different inhaler devices. Trials that compared clinical outcomes of a single drug delivered by different inhaler devices were considered. The devices were a standard pMDI (with or without a spacer device) versus any hand-held device (reviews a, b and d), and a nebuliser versus any hand-held inhaler (reviews c and e). The five clinical reviews considered:

corticosteroids (beclometasone, budesonide and fluticasone) delivered by hand-held inhalers in stable asthma (review a);

beta-agonist bronchodilators delivered by pMDI versus other inhaler devices in stable asthma (review b);

beta-agonist bronchodilators delivered by nebuliser versus any hand-held inhaler in stable asthma (review c);

short-acting bronchodilators delivered by pMDI versus other hand-held inhaler devices in stable and acute COPD (review d);
short-acting bronchodilators delivered by nebuliser versus any hand-held inhaler in stable and acute COPD (review e).

Participants included in the review
Studies were included if they involved children aged 2 to 17 years inclusive and adults (from age 17) with chronic stable asthma (i.e. not during an exacerbation; reviews a, b and c) and patients with COPD in a stable or acute state (reviews d and e), all diagnosed by a clinician or according to internationally accepted criteria. Studies of children under 2 years old were specifically excluded due to the difficulty of diagnosing asthma against a less specific 'wheezing illness' in this age group.

Outcomes assessed in the review
The authors did not state any inclusion criteria relating to the outcomes. The outcomes measured in the selected randomised controlled trials (RCTs) included: peak expiratory flow rate (PEFR), peak inspiratory flow, maximum expiratory flow (MEF), MEF at 50%, volume of air expired in the first second of expiration (FEV1), maximum total volume of air expired from maximum capacity, maximum expiratory flow over 25 to 75% of expiration (FEV25-75%), maximum flow at 50% of expiration, symptoms and related scores, patient preference, St. George's Respiratory Questionnaire, dose of challenging drug required to cause a fall in FEV1 of 15 or 20%, exercise-induced asthma, heart rate, blood-pressure, volume of trapped gas, side-effects, specific airway conductance, vital capacity, change from baseline, flow at 30, 50 and 75 to 85%, and oscillatory resistance.

How were decisions on the relevance of primary studies made?
Two independent reviewers selected studies at both the title/abstract and full paper stages. Any disagreements were resolved by third-party adjudication.

Assessment of study quality
A quality assessment was performed using the Cochrane approach to assess allocation concealment. The trials were scored as either grade A (adequate concealment), grade B (uncertain), grade C (clearly inadequate concealment) or grade D (not used). The studies were ranked primarily by this grading and secondarily by study size. Two independent reviewers conducted the quality assessment.

Data extraction
Two independent reviewers extracted the data and resolved any disagreements by consensus. Data were extracted on the intervention, duration, participants, design, quality and outcome measures.

Methods of synthesis
How were the studies combined?
The studies in each section were combined in a meta-analysis with further discussion where needed. A narrative review was used where insufficient data were available or a meta-analysis was inappropriate.

The studies were combined in meta-analyses using a fixed-effect model where there was no statistically-significant heterogeneity between the results, and a random-effects model where heterogeneity was found. Where studies reported the same outcomes in the same units, the results were combined using the weighted mean difference. Where the units or measures differed between the studies, the results were combined using the standardised mean difference (SMD).

How were differences between studies investigated?
Heterogeneity between the study outcomes was investigated using the chi-squared statistic.

Results of the review
A total of 144 RCTs were included: 24 in review a, 87 in review b, 18 in review c, 2 in review d, and 13 in review e.

a. Effectiveness of MDIs for the delivery of corticosteroids in asthma.

The review of 3 trials in children and 21 trials in adults found no evidence to suggest clinical benefits of any other
inhaler device over a pMDI in corticosteroid delivery (SMD of FEV1 = -0.01, 95% confidence interval: -0.10, 0.09).

b. Effectiveness of MDIs for the delivery of beta-agonists in stable asthma.

Seven of the 11 included studies in children compared the 'Turbohaler' (dry powder inhaler; DPI) with the pMDI. One study found a significant treatment difference in PEFR, although there were differences in the patients' baseline characteristics. In adults, a review of 70 studies found no demonstrable difference in the clinical bronchodilator effect of short-acting beta-agonists delivered by the standard pMDI compared with that produced by any other DPI, hydrofluoroalkane pMDI, or the Autohaler device (a breath-actuated pMDI).

c. Effectiveness of nebulisers versus MDIs for the delivery of bronchodilators in stable asthma.

Three trials in children failed to demonstrate any evidence of clinical superiority of nebulisers over inhaler devices in bronchodilator delivery. A total of 23 studies in adults found equivalence for the main pulmonary outcomes, but no evidence of difference for the other outcomes.

d. Effectiveness of MDIs for the delivery of beta-agonists in COPD.

The 2 included studies failed to find any evidence of clinical difference in beta-agonist delivery.

e. Effectiveness of nebulisers versus MDIs for the delivery of bronchodilators in COPD.

Evidence from 14 trials demonstrated equivalence for the main outcomes of pulmonary function. There was no evidence of treatment difference in bronchodilator delivery for the other outcomes.

**Cost information**

An economic evaluation was carried out using the perspective of the National Health Service in England (UK). A decision analysis was used to estimate the relative cost-effectiveness of inhaler devices for the delivery of bronchodilator and corticosteroid inhaled therapy. Overall, there were no differences in patient outcomes among the devices. On the assumption that the devices were clinically equivalent, pMDIs were the most cost-effective devices for asthma treatment.

**Authors' conclusions**

The evidence from published literature showed there was no difference between nebulisers and alternative inhaler devices, compared with standard pMDIs with or without a spacer device, in terms of clinical effectiveness. The cost-effectiveness evidence favoured pMDIs (or the cheapest inhaler device) as first-line treatment for all patients with stable asthma, unless specific reasons were identified.

**CRD commentary**

This was a well-conducted review of the literature. The authors used appropriate inclusion criteria to select a range of studies, which were identified through extensive searches of the literature. At least two reviewers were employed in the study selection, extraction and quality assessment processes. The validity assessment was limited to grading studies on the basis of their attempts to conceal treatment allocation. Relevant details of the included studies (methods, participants, interventions, outcomes, etc.) were tabulated, and the approach to the synthesis was transparent and appropriate; heterogeneity between the study results, where present, was acknowledged. The authors' conclusions appear to follow from the evidence presented.

**Implications of the review for practice and research**

Practice: The authors stated that the evidence from published literature demonstrated no difference in clinical effectiveness between nebulisers and alternative inhaler devices, compared with standard pMDIs with or without a spacer device. The cost-effectiveness evidence therefore favoured pMDIs (or the cheapest inhaler device) as first-line treatment in all patients with stable asthma, unless other specific reasons were identified.
Research: The authors stated that further clinical trials are required to demonstrate any differences in the clinical effectiveness and cost-effectiveness of inhaler devices and nebulisers in comparison with pMDIs. These trials should be of sufficient statistical power and methodological rigour to demonstrate any clinical benefit. Trials should also be undertaken in community settings to ensure the generalisability of the results. The outcome measures should be more patient-centred and report adverse events in more detail. The reporting of trial data also requires improvement.

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