

Inhaler devices for the treatment of asthma and chronic obstructive airways disease (COPD)

J Wright, D Brocklebank, F Ram

The research evidence on the effectiveness of inhaler devices for the treatment of asthma and chronic obstructive pulmonary disease published in a recent issue of *Effective Health Care* is reviewed.

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This article summarises the research evidence presented in a recent issue of *Effective Health Care* on inhaler devices for the treatment of asthma and chronic obstructive airways disease (COPD).¹

BACKGROUND

Inhaled therapy delivering bronchodilator and corticosteroid drugs in various doses has become accepted as the mainstay of treatment for patients with asthma and chronic COPD.^{2,3} It allows low doses of medication to be delivered directly to the site of action in the airways, significantly reducing systemic side effects compared with oral therapy. The aim of inhaled therapy is to reverse and prevent airway inflammation and constriction and minimise symptoms. The two main categories of inhaled drugs are bronchodilators and corticosteroids. Bronchodilators (short and long acting β_2 agonists and antimuscarinic drugs) relieve symptoms of bronchoconstriction. Corticosteroids reduce airways inflammation to prevent symptoms of asthma.

A number of different inhalation devices are available. The pressurised metered dose inhaler (pMDI) is the most commonly used and cheapest device, which may also be used in conjunction with a spacer device. Newer chlorofluorocarbon (CFC)-free inhaler devices using hydrofluoroalkanes (HFAs) have also been developed. The drug is dissolved or suspended in the propellant under pressure. When activated, a valve system releases a metered volume of drug and propellant. Spacer chambers can be attached to pMDIs to make them easier to use.

Other devices include breath actuated pMDIs such as Autohaler and Easibreathe. They enable the patient to prime the inhaler which is then only actuated when the patient takes a breath, avoiding the need to coordinate actuation with breathing. Dry powder inhalers (DPI) such as Turbohaler, Diskhaler, Accuhaler and Clickhaler are also activated by inspiration by the patient. The powdered drug is dispersed into particles by the inspiration.

Nebulisers use oxygen, compressed air, or ultrasonic power to break up solutions or suspensions of medication into droplets for inhalation. The aerosol is administered by a mask or mouth-piece. However, nebulisers are more expensive

than pMDIs, require a power source, and need regular maintenance.

There is a confusing array of inhaler devices available for the treatment of asthma and COPD. The competing claims of pharmaceutical companies make it difficult for prescribers to choose the best device for different patients. This article summarises the current research evidence on the clinical and cost effectiveness of these pMDIs (with or without a spacer device) compared with other hand held inhaler devices. It updates the evidence from a number of systematic reviews carried out by the Cochrane Airways Group and funded by the NHS Health Technology Assessment Programme.⁴ The original reviews were used as supporting evidence for two technology appraisal guidance reports for the National Institute for Clinical Excellence^{5,6} and for forthcoming guidance from the British Thoracic Society. Details of the additional randomised controlled trials (RCTs) included in the update can be found in table 1.

RANGE AND COSTS OF DRUGS AND DEVICES

The annual cost to the NHS for asthma drugs is over £500 million.⁷ A large number of inhaler devices and drug/device combinations are commercially available. There are considerable differences in the costs of the same drug using different inhaler devices and of the drugs used in specific devices.⁸ The use of a specific inhaler device may limit prescribing choice to more expensive proprietary drugs. In addition, some inhaler and drug combinations are limited by commercial availability.

Clinical guidelines on the use of inhalers for asthma and COPD have been published from a number of sources.^{2,3,9,10} However, the recommendations for inhaler devices from these guidelines are either absent, vague, or inconsistent. Evidence based guidelines are currently being developed by the British Thoracic Society.

EFFECTIVENESS OF HAND HELD INHALER DEVICES FOR ASTHMA

Delivery of corticosteroids in stable asthma

Three studies in children comparing different devices failed to show significant differences in pulmonary function between the devices.^{11–13}

Three further studies in children were identified,^{14–16} but the heterogeneity of the original studies precluded any pooling of results. This remains the case with the addition of the new studies. Farmer *et al*¹⁴ studied 229 children with asthma aged 7–12 years and compared a CFC and

See end of article for authors' affiliations

Correspondence to:
Dr J Wright, Department of
Epidemiology and Public
Health, Bradford Hospitals
NHS Trust, Royal Infirmary,
Duckworth Lane, Bradford
BD9 6RJ, UK; john.wright@
bradfordhospitals.nhs.uk

Table 1 Additional randomised clinical trials included in the *Effective Health Care* update

Study	Methodology	Details	Results	Comments
Crompton ⁴⁰	<i>Design:</i> parallel open <i>Device:</i> pMDI+Nebuhaler v Turbuhaler <i>Drug:</i> budesonide <i>Dose:</i> "usual dose" <i>Duration:</i> 12 weeks	<i>Participants:</i> 72 asthmatics, mean age 47. Mean FEV ₁ % predicted, 68%. <i>Cochrane Quality:</i> B	4-point dysphonia score reported, FEV ₁ and FVC measured but only reported "no significant change in either group". Other non-clinical outcomes measured (laryngoscopy, voice analysis)	72 randomised, 64 completed and 51 "considered evaluable for per protocol analysis". Specifically designed to identify voice changes rather than asthma control.
Farmer ¹⁴	<i>Design:</i> Parallel, double blind <i>Device:</i> HFA v CFC Easibreath breath actuated pMDIs <i>Drug:</i> Beclomethasone <i>Dose:</i> 200 µg daily <i>Duration:</i> 12 weeks	<i>Participants:</i> 229 asthmatics aged 7–12, 199 supplied evaluable data. <i>Cochrane Quality:</i> B	No significant differences in diary card PEFR, FEV ₁ , symptom scores, adverse events, serum cortisol from 19% of the population	Authors' power calculation shows this to be underpowered to demonstrate equivalence
Goldin ⁴¹	<i>Design:</i> Parallel, double blind, double dummy <i>Device:</i> CFC v HFA pMDI <i>Drug:</i> Beclomethasone <i>Dose:</i> 200 µg daily <i>Duration:</i> 12 weeks	<i>Participants:</i> 34 asthmatics aged 19–56 years. Mean FEV ₁ 80% predicted <i>Cochrane Quality:</i> B	Diary card PEFR, symptom scores and beta-agonist use, FEV ₁ , methacholine challenge	Primary outcome was air trapping as measured by CT imaging. This is non-clinical and was not included in this analysis
Juniper ⁴² (see also Gross ⁷⁷)	<i>Design:</i> Parallel, single blind <i>Device:</i> HFA v CFC pMDIs <i>Drug:</i> Beclomethasone <i>Dose:</i> 400 µg v 800 µg daily <i>Duration:</i> 12 weeks	<i>Participants:</i> 347 moderate asthmatics (162 M, 185F), mean age 33 (3rd arm of 117 patients received HFA placebo) <i>Cochrane Quality:</i> B	Asthma quality of life questionnaire, daytime symptoms and sleep disturbance scores	Supplementary report of results to Gross. ⁷⁷
Pearlman ¹⁵	<i>Design:</i> Parallel, double blind <i>Device:</i> HFA v CFC pMDIs <i>Drug:</i> Triamcinolone <i>Dose:</i> 150, 300 and 600 mg daily, 6 arms <i>Duration:</i> 12 weeks	<i>Participants:</i> 473 children aged 6–13 years enrolled, 374 completed <i>Cochrane Quality:</i> B	% change FEV ₁ , change in β agonist use, FEF _{25–75%} , PEFR, night time wakening, symptom scores, adverse events	
Rufin ¹⁶	<i>Design:</i> Parallel, open trial <i>Device:</i> pMDI+spacer v Autohaler <i>Drug:</i> Beclomethasone <i>Dose:</i> 1000 µg daily <i>Duration:</i> 8 weeks	<i>Participants:</i> 127 asthmatic children 5–15 years old, mean age 11 <i>Cochrane Quality:</i> B	FEV ₁ , mid-flows, patient acceptability	
Stradling ³⁹	<i>Design:</i> Parallel, double blind, double dummy <i>Device:</i> pMDI+spacer v Clickhaler <i>Drug:</i> Beclomethasone <i>Dose:</i> "usual" dose <i>Duration:</i> 12 weeks	<i>Participants:</i> 240 asthmatics entered run in, 204 randomised. Mean age 50 years <i>Cochrane Quality:</i> B	PEFR (am, pm), daytime, night time symptom scores (FEV ₁ , FVC only reported "non-significant"), exacerbations, adverse events, serum cortisol	Unclear if ITT analysis used
Maladano-Alanis ⁷²	<i>Design:</i> 3 way parallel, open study <i>Device:</i> pMDI + Pulmona spacer v pMDI + Ellipse v Hudson nebuliser <i>Drug:</i> Salbutamol <i>Dose:</i> 200 v 200 µg v 150 µg/kg <i>Duration:</i> 6 hours	<i>Participants:</i> 63 asthmatic children aged 6–15 years. <i>Cochrane Quality:</i> B	FEV ₁ at 5, 20, 60 minutes and 2, 3, 4, 5, 6 hours. Reported equal at 1 hour (24% increased) but at 6 hours the nebuliser had decreased least (15.5 v 14.7 v 5.5%)	
Salzman ⁷¹	<i>Design:</i> Crossover, open trial <i>Device:</i> pMDI+spacer v Hudson Updraft II nebuliser at 6 l/min <i>Drug:</i> Metaproterenol <i>Dose:</i> 1.3 v 15 mg <i>Duration:</i> 2 × 1 day	<i>Participants:</i> 15 adult severe asthmatics, 18–47 years <i>Cochrane Quality:</i> B	Mean % increases in FEV ₁ , FVC, PEFR, MMFR, FEF _{25–75%}	

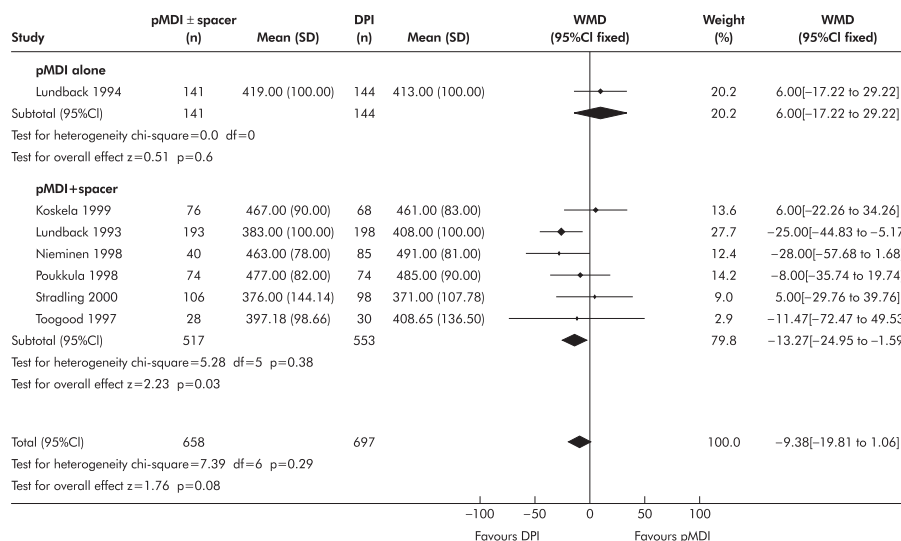


Figure 1 Absolute difference in FEV₁ between pMDI and dry powder inhaler (DPI) for the delivery of corticosteroids in stable asthma (Z statistic (2.23) indicates the level of significance for the overall result).

HFA Easibreathe (breath actuated inhaler) delivering beclomethasone dipropionate. No differences were found in diary card peak flow expiratory rate (PEFR), forced expiratory volume in 1 second (FEV₁), symptoms scores, adverse events, and serum cortisol levels from 19% of the population. Pearlman *et al*¹⁵ studied 473 children aged 6–13 years with asthma. Triamcinolone (not licensed in the UK) was given at 150, 300 and 600 µg daily by CFC and HFA pMDI devices. No clinically significant differences were found in β agonist use, forced expiratory mid flow (FEF_{25–75%}), PEFR, night-time waking, symptom scores, and adverse events. Rufin *et al*¹⁶ studied 127 5–15 year old children with asthma. Beclomethasone dipropionate was delivered 1000 µg daily via a pMDI plus large volume spacer versus an Autohaler (breath actuated inhaler). No clinically significant differences were found in FEV₁ and expiratory mid flow rates.

Twenty one studies in adults found no significant difference in measures of pulmonary function, symptom scores, exacerbation rates, and adverse effects such as hoarse voice, oral thrush, and effects on the hypothalamic-adrenal axis (serum cortisol) between a pMDI and a dry powder inhaler, hydrofluoroalkane pMDI, or breath actuated pMDI for the delivery of corticosteroids.^{17–38} Figure 1 shows the absolute difference in FEV₁ between pMDI and dry powder inhaler for the delivery of corticosteroids in stable asthma.^{21 22 32 33 35 36 39} Statistically significant differences were found for three outcomes for dry powder inhalers, but these were either within clinically equivalent limits or the differences were not apparent once baseline characteristics were taken into account.

Four further studies have since been identified.^{39–42} Juniper and Buist⁴² reported asthma related quality of life questionnaire scores from a previous study.³⁰ No significant differences were found between inhaler devices. In the study by Crompton *et al*⁴⁰ 51 patients with asthma were studied to evaluate the effect on voice changes rather than asthma control between pMDI+Nebuhaler vs Turbohaler for the delivery of budesonide. Clinical outcomes were also measured but no significant differences were found between the devices. Goldin *et al*⁴¹ studied 34 asthmatics taking beclomethasone 200 µg daily via a CFC or HFA pMDI. The primary outcome of the study was air trapping as measured by CT imaging. Other clinical outcomes were measured and no significant differences were found. Stradling *et al*³⁹ included 204 asthmatics taking beclomethasone at their “usual” dose via pMDI+spacer or Clickhaler. No significant differences were found.

The addition of data from these four studies to the original meta-analysis made no significant change to the results. For the delivery of inhaled steroids in stable asthma in children over 5 years and adults, pMDI (with or without spacer) is as effective as other hand held inhaler devices. There is no evidence to demonstrate differences in drug delivery between non-CFC pMDI and CFC pMDI at equivalent doses.

Delivery of short acting β₂ agonist bronchodilators in chronic asthma

A Cochrane review and meta-analysis of 84 RCTs found no differences between pMDI and 10 other hand held inhaler devices for lung function, blood pressure, symptoms, bronchial hyperreactivity, systemic bioavailability, inhaled steroid requirement, serum potassium, and use of additional relief bronchodilators.⁴³ In addition, no evidence was found to support claims that higher dosing schedules (2:1 or greater) had any clinical advantage over 1:1 dosing.

Regular use of HFA-pMDI containing salbutamol reduced the requirement for short courses of oral corticosteroids. These data were provided by three trials with a total of 519 patients (fig 2).^{44 45} However, the total number of exacerbations in these three trials was unchanged. The effect of HFA-pMDI on requirement for oral corticosteroid courses to treat acute exacerbations therefore needs to be confirmed.

Three trials in adults found a lower pulse rate in patients using pMDI than those using Turbohaler, suggesting greater

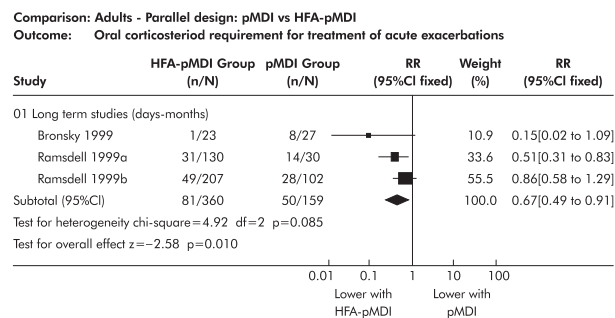


Figure 2 Short course oral corticosteroid requirement for acute exacerbations in adult patients with asthma. Data from three long term parallel design trials (represented as relative risk calculated using fixed effect model with 95% confidence intervals; Z statistic (2.58) indicates the level of significance for the overall result).

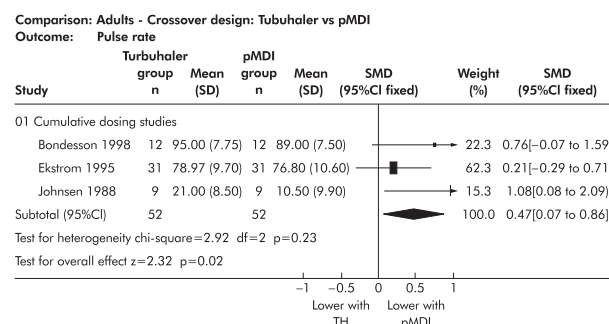


Figure 3 Mean (95% confidence interval) pulse rate (bpm) outcome from three cumulative dosing trials (Z statistic (2.71) indicates the level of significance for the overall result).

systemic absorption with the Turbuhaler device compared with the pMDI (fig 3).⁴⁶⁻⁴⁸

Three studies found that adult patients preferred pMDI to the less commonly used Rotahaler device (fig 4).⁴⁹⁻⁵¹ However, this result should be interpreted with caution because of the potential for bias due to lack of blinding.

For the delivery of inhaled short acting β_2 agonists in chronic asthma, pMDI (with or without spacer) is as effective as any other hand held inhaler device.

CLINICAL EFFECTIVENESS OF HAND HELD INHALER DEVICES FOR COPD

A Cochrane systematic review compared pMDI with other devices.⁵² No significant difference in clinical outcomes was found between dry powder devices and pMDI for delivery of β_2 agonists. A soft mist device for ipratropium (Respimat) was more effective than a pMDI in improving lung function but the data came from one small study. The dearth of published studies highlights a major gap in the research evidence for this important area.

EFFECTIVENESS OF NEBULISERS

Chronic asthma

Three studies in children totalling 51 participants compared different hand held inhaler devices with a nebuliser and found no evidence of clinical superiority of nebulisers over inhaler devices.⁵³⁻⁵⁵ Twenty three studies in adults showed clinical equivalence for inhaler devices and nebulisers for the main

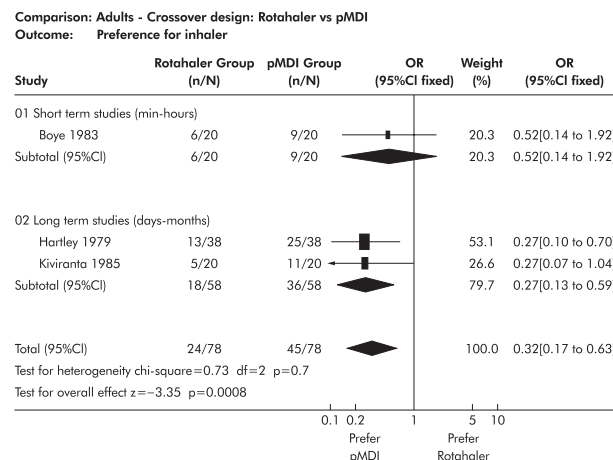


Figure 4 Inhaler device preference in adult patients with asthma. Data from one short term and two long term crossover design trials (represented as odds ratio calculated using fixed effect model with 95% confidence intervals; Z statistic (3.35) indicates the level of significance of the overall effect size).

pulmonary outcomes (FEV₁ and PEFr) and no evidence of significant difference in other outcomes.⁵⁶⁻⁶⁹

Figure 5 shows the standardised mean difference of FEV₁ between nebulisers and hand held inhaler devices for the delivery of β agonists in stable asthma.^{54 57-60 62 63 65-67 69-71}

Updated searching identified two further studies.^{71 72} Maldonado-Alanis *et al*⁷² evaluated the bronchodilator response of 63 children over 6 hours in a three way parallel study. The results were published as an abstract only and detailed statistical results were not shown. The initial bronchodilator response for salbutamol was similar between pMDI+Pulmona spacer, pMDI+Ellipse spacer (200 μ g from each) and a nebuliser (at a dose of 150 μ g/kg).

Salzman and Pyszczynski⁷¹ included 15 patients with severe stable asthma in a 2-day open crossover trial of metaproterenol 1.3 mg via pMDI+Aerochamber spacer device versus 15 mg via a nebuliser. No statistically significant differences in expiratory airflow were found between the delivery methods.

Acute asthma

A Cochrane systematic review of 16 trials comparing pMDI+spacer with nebulisers for the delivery of β_2 agonists for mild and moderate exacerbations of asthma found that clinical outcomes from pMDIs were at least equivalent to nebulisers and may have some advantages for children.⁷³ Children over 5 years and adults with mild and moderate exacerbations should be treated with pMDI+spacer with bronchodilator dose titration according to clinical response.

COPD

Thirteen trials have compared bronchodilator drugs delivered by inhaler devices compared with nebulisers for the treatment of patients with acute and stable COPD.^{66 74-85} There was considerable variation in settings and the drugs and delivery devices used, making comparisons difficult. However, a meta-analysis supported the findings of individual studies that there is no evidence to suggest clinical benefit of nebulisers over a standard pMDI with spacer, although a higher dose may be required.

INHALER TECHNIQUE

The effectiveness of inhaler devices depends on more than just the devices themselves. Patient technique is crucial to effective drug delivery and will depend on factors such as patient experience, education, physical ability, and effective teaching of technique.

A systematic review of RCTs and observational studies supports the anecdotal impression and prejudice that pMDI devices are not used as effectively as dry powder inhalers.⁴ The percentage of patients with correct technique (assessed by a scoring system of correct steps) was 43% compared with 55% for pMDI with spacer and 59% for dry powder inhalers. However, teaching had a positive effect and eliminates significant differences between devices by increasing the percentage of patients with correct technique to 63% for pMDI and 65% for dry powder inhalers.

Differences in effective patient technique therefore appear to owe more to the lack of teaching than to inherent differences in the devices themselves. All patients should receive appropriate instruction and guidance on effective technique when prescribed inhaler devices, and this should be regularly reinforced.

IMPLICATIONS

This article is based on systematic reviews that report average clinical effects from the trial results across drugs, doses, and devices. It may well be that, just as individual patients receive a dose tailored to their needs, they also require devices tailored to their individual needs. However, on the basis of the available evidence, there is no reason to expect alternative inhaler

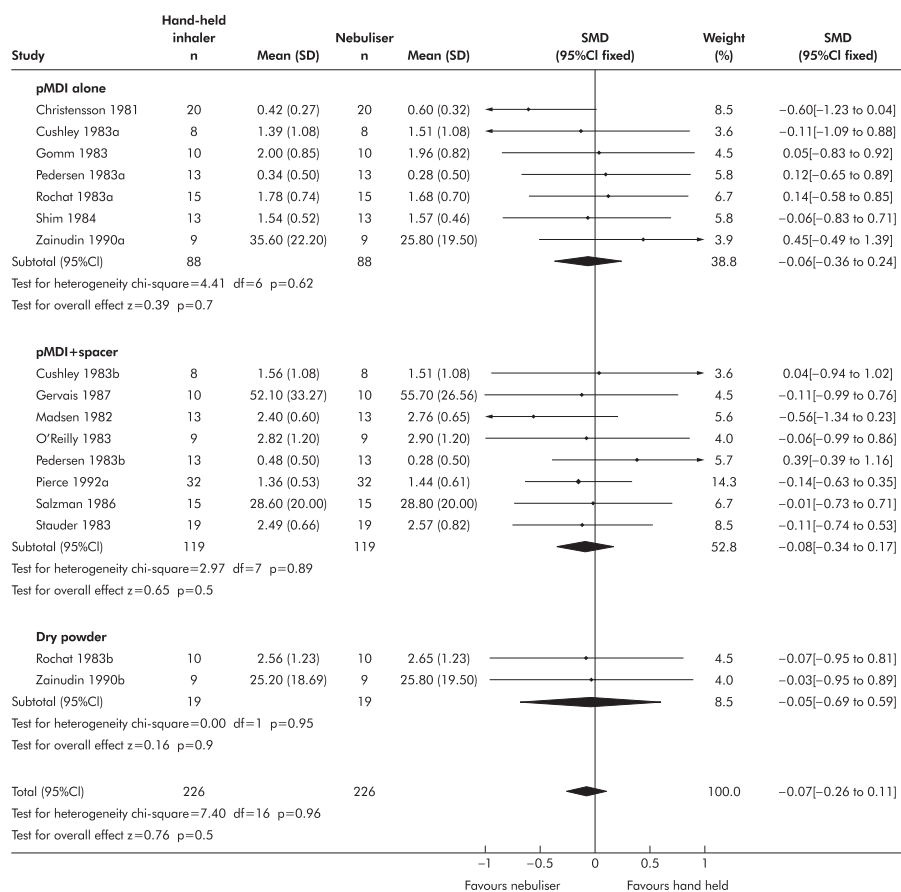


Figure 5 Standardised mean difference (SMD) of FEV₁ between nebulisers and hand held inhaler devices for the delivery of β agonists in stable asthma.

devices to be clinically more effective than pMDIs (with or without a spacer) for delivery of short acting β_2 bronchodilators or corticosteroids. pMDIs (with or without a spacer), or the cheapest inhaler device the patient can adequately use, should therefore be prescribed as first line in all adults and children with stable asthma or COPD requiring inhaled medication. More expensive devices such as dry powder inhalers should be reserved for patients who do not have the technique or coordination to use pMDIs effectively after appropriate teaching.

Further high quality RCTs are required to be able to make valid recommendations on the use of the various inhaler devices available for the treatment of asthma or COPD. This is of particular importance because of the phasing out of CFC propellants in pMDIs. Studies should be of sufficient duration to be clinically relevant and with medication doses that are clinically appropriate. They should be undertaken in real life community setting to ensure generalisability of results.

At present the introduction of a new device for the delivery of inhaled drugs needs far less rigorous testing than for a new drug by an old device. The licensing requirement is to demonstrate equivalence to an existing device. Equivalence is not the same as failing to detect a difference, and the design and powering of trials is specific and not without controversy. It may be that stricter controls are needed before approval

Given the chronic nature of asthma and COPD and their significant effects on morbidity, future trials should address the paucity of patient centred outcomes such as quality of life, adherence, nocturnal awakening, and days off work or school. In addition, adverse effects and systemic effects should be recorded more completely. If devices share equivalent effectiveness, then secondary factors such as adverse effects become much more significant.

The teaching of inhaler technique is another important area for future research. Studies should explore the effectiveness and frequency of patient education and consider interventions to improve it. In addition, studies of teaching of inhaler technique should measure health related outcomes as the relationship between inhaler technique and clinical outcome has not been established.

Authors' affiliations

J Wright, D Brocklebank, F Ram, Department of Epidemiology and Public Health, Bradford Hospitals NHS Trust, Royal Infirmary, Bradford BD9 6RJ, UK

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