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Effective Health Care

Bulletin on the effectiveness of health service interventions for decision makers

This bulletin summarises the research evidence on the effectiveness of inhaler devices for the management of asthma and COPD.

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Inhaler devices for the management of asthma and COPD

- Asthma and chronic obstructive pulmonary disease (COPD) are common diseases of the airways and lungs that have a major impact on the health of the population. A key component of the management of these conditions involves the inhalation of medication.
- There is a confusing array of inhaler devices and drug/device combinations available and it can be difficult for a clinician to make informed prescribing decisions about all the possible permutations.
- Current evidence suggests that there is no difference in the effectiveness of nebulisers and alternative inhaler devices compared to standard pressurised metered-dose inhalers (pMDIs) with or without a spacer device.
- As both pMDIs and dry powder inhalers are cheaper than nebulisers, a stepped approach to treatment would seem justified. pMDIs (with or without a spacer), or the cheapest inhaler device the patient can use adequately, should be prescribed as first-line treatment in all adults and children with stable asthma or COPD.
- The effectiveness of inhaler devices depends on more than just the devices themselves. Teaching patients how to use devices appropriately can be crucial. All patients should receive appropriate instruction and guidance on effective technique when prescribed inhaler devices and this should be regularly reinforced.
- More expensive devices such as dry powder inhalers should be reserved for patients who are unable to use pMDIs effectively after receiving appropriate instruction.

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A. Background

Asthma and chronic obstructive pulmonary disease (COPD) are common diseases of the airways and lungs that have a major impact on the health of the population. Asthma severity ranges from intermittent mild symptoms such as coughs and wheezing to severe, life-threatening attacks which require immediate hospital treatment. COPD is a progressive condition in which the airways become narrower making it harder to breathe and eventually it leads to chronic disabling breathlessness.

The management of asthma and COPD involves a wide range of services including primary care, hospital inpatient and outpatient care, routine follow up, patient education and advice, emergency visits and prescribed drugs. The range of services used, combined with the level and intensity of use, means that the costs of health care are high.[1] In 2001, the total number of community dispensed prescriptions for inhaled therapy in England was around 33 million, with a net ingredient cost in excess of £442 million.[2]

B. Range and cost of drugs and devices

Inhaled therapy delivering bronchodilator and corticosteroid drugs in various doses is the mainstay of treatment for patients with asthma and COPD.[3,4] Inhaled therapy 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 to 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 the symptoms of asthma.

A number of different inhalation devices are available. The press-and-breathe pressurised metered dose inhaler (pMDI) was the first inhaler device, introduced in 1956. It contains chlorofluorocarbons (CFCs) as a propellant. This is the most commonly used and usually cheapest device which may also be used in conjunction with a variety of spacer devices.

With the implementation of the 1987 Montreal Protocol and phasing out of CFCs, newer CFC-free inhaler devices using ozone-friendly hydrofluoroalkanes (HFAs) have 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 (BA-pMDI) such as Autohaler® and Easibreathe®. They enable the patient to prime the inhaler which is then only activated 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 breath-activated 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 a mouthpiece. However, nebulisers are more expensive than pMDIs, require a power source and need regular maintenance.

In clinical practice, the fundamental principle is the use of the most clinical and cost effective drug, taking account of the ability of the patient to use the inhaler device effectively. However, there is a large and confusing array of inhaler devices and drug/device combinations available and it is difficult for a clinician to make informed prescribing decisions about all the possible combinations. There are also large differences in the costs of the same drug using different inhaler devices and of the drugs used in specific devices (see Table 1).[5]

Prescribing decisions should be based on the relative efficacy of different devices or drugs. However, in practice the use of a specific inhaler device may limit prescribing choice to more expensive proprietary drugs. In addition, some inhaler and drug combinations are not commercially available due to manufacturers' restrictions.

Clinical guidelines on the use of inhalers for asthma and COPD have been published.[3,4,6,7] However, the recommendations for inhaler devices from these guidelines are either absent, vague or inconsistent. Evidence-based guidelines are currently being prepared by the British Thoracic Society (BTS) and the Scottish Intercollegiate Guidelines Network (SIGN).[8]

This bulletin summarises the current research evidence on the clinical and cost effectiveness of pMDIs (with or without a spacer device) compared to other hand-held inhaler devices.

C. Nature of the evidence

This bulletin is based on evidence from several systematic reviews that have been funded by the NHS Health Technology Assessment

Table 1: Range and costs of drugs and devices[5]

Drug	Device type	Name	Company	Cost
Beclometasone dipropionate	pMDI	non-proprietary		£4.61*
		Becotide® 100	A&H	£5.78*
	pMDI (CFC-Free)	Qvar® 50	3M	£4.41*
	Dry powder	non-proprietary		£5.76*
		Asmabec Clickhaler®	Celltech	£5.91*
		Becodisks®	A&H	£10.17* (refill cost)†
		Becotide Rotahaler®		£8.04* (refill cost)†
	Breath actuated	Aerobec 100 Autohaler®	3M	£7.22*
		Beclozone Easi-breathe®	IVAX	£4.61*
	Breath actuated (CFC-free)	Qvar 50 Autohaler®	3M	£4.41*
Budesonide	pMDI	Pulmicort®	AstraZeneca	£5.32*
	Dry powder	non-proprietry (Cyclohaler)		£9.32*
		Pulmicort Turbohaler®	AstraZeneca	£10.36*
	Nebuliser solution	Pulmicort Respules®		£89.60*††
Fluticasone propionate	pMDI (CFC-free)	Flixotide Evohaler®	A&H	£5.46*
	Dry powder	Flixotide Accuhaler®		£8.96*
		Flixotide Diskhaler®		£12.23* (refill cost)
	Nebuliser solution	Flixotide Nebules®		£56.22*††
Salbutamol	pMDI	non-proprietary		£1.91**
	pMDI (CFC-Free)	non-proprietary		£1.90**
		Airomir®	3M	£1.97**
		Evohaler®	A&H	£2.30**
	Dry powder	non-proprietary		£5.05**
		As Cyclohaler		£4.28* (refill cost)
		Asmasal Clickhaler®	Celltech	£6.32**
		Ventodisks®	A&H	£5.26* (refill cost)
		Ventolin Accuhaler®		£8.33**
		Ventolin Rotahaler®		£4.76** (refill cost)
	Breath actuated	Aerolin Autohaler®	3M	£10.04**
		Salamol Easi-breathe®	IVAX	£6.30**
	Breath actuated (CFC-free)	Airomir Autohaler®	3M	£6.02**
		Salamol Easi-breathe®	IVAX	£6.30**
	Nebuliser solution	non-proprietary		£12.45**
		Ventolin Nebules®	A&H	£16.90**
Terbutaline sulphate	pMDI	Bricanyl®	AstraZeneca	£2.66**
	Dry powder	Bricanyl Turbohaler®		£6.30**
	Nebuliser solution	Bricanyl Respules®		£18.35**
		non-proprietary		£18.35**
Ipratropium bromide	pMDI	Atrovent®	Boehringer Ingelheim	£4.21**
	Dry powder	Atrovent Aerocaps®		£10.53** (refill cost)
	Breath actuated	Arrovent Autohaler®		£9.39**
	Nebuliser solution	Atrovent®		£32.40**
		non-proprietary		£30.10**
		Ipratropium Steri-Neb®	IVAX	£30.70**
		Respontin®	A&H	£27.25**
Oxitropium bromide	pMDI	Oxivent®	Boehringer Ingelheim	£6.69**
	Breath actuated	Oxivent Autohaler®		£15.72**

* Costs based on 28 days treatment with beclometasone dipropionate 200µg twice daily or equivalent. Assumes that fluticasone dipropionate is twice as potent and that qvar (beclometasone CFC-free) can be substituted at half the dose.[5]

** Costs based on 100 'reliefs' i.e. 200µg of salbutamol (two actuations of pMDI or one dry powder)[5]

† Becotide Becodisks® and Rotahaler® probably require twice the dose for equivalent efficacy and as such the higher cost figure would apply.

†† Nebulised doses may not be equivalent to the above assumptions as little information is available as to the equivalence of doses between hand-held inhalers and nebulisers (which in themselves are highly variable).

Table 2: Additional RCTs included in the bulletin

Study	Design	Participants	Results and Comments
Crompton[42] 2000	Design: Parallel open Device: pMDI+Nebuhaler® vs Turbuhaler® Drug: Budesonide Dose: usual dose Duration: 12 weeks Cochrane Quality: B (uncertain allocation concealment)	72 adult females with asthma, mean age 47. Mean FEV_1 % predicted, 68%	4-point dysphonia score reported: lower frequency: Nebuhaler® n=12/25, Turbuhaler® n=14/26 – not significant (ns) 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[15] 2000	Design: Parallel, double-blind Device: HFA vs CFC Easibreathe® breath-actuated pMDIs Drug: Beclomethasone Dose: 200µg daily Duration: 12 weeks Cochrane Quality: B	229 children with asthma aged 7–12 years Data for 199, 7 withdrawn during course of study, 22 excluded for protocol violations, 1 excluded from analysis as they had completed less than 10 weeks medication	No significant differences in: Diary card PEFR (mean morning change: HFA= +41 L/min, CFC= +34 L/min; mean evening change: HFA= +38 L/min, CFC= + 32 L/min), FEV_1 (mean change: HFA= +0.16 L, CFC= +0.13 L), symptoms scores (graphs only, adverse events, serum cortisol from 19% of the population (mean change: HFA= -4.6 nmol/24hrs, CFC= -28.5 nmol/24hrs) The authors' power calculation shows this to be under-powered to demonstrate equivalence
Goldin[43] 1999	Design: Parallel, double-blind, double dummy Device: CFC vs HFA pMDI Drug: Beclomethasone Dose: 200µg daily Duration: 12 weeks Cochrane Quality: B	34 adults with asthma aged 19–56 years. Mean FEV_1 80% predicted	Diary card PEFR (mean morning change: HFA= +25 L/min, CFC= +29 L/min – ns), symptom scores and beta-agonist use (mean change inhaler puffs: HFA= -0.69/d, CFC= -0.68/d – ns), FEV_1 (% change: HFA= -8.5 l, CFC= -9.6 L – ns) methacholine challenge: change in lung attenuation values (Hounsfield units) across all zones of interest showed significantly less air trapping with HFA than CFC (p< 0.001) The primary outcome of the study was air-trapping as measured by CT imaging
Juniper[40] (See also Gross[31]) 1999	Design: Parallel, single-blind Device: HFA vs CFC pMDIs Drug: Beclomethasone Dose: 400µg vs 800µg daily Duration: 12 weeks Cochrane Quality: B	347 adults with moderate asthma, 162M, 185F Mean age 33 (3rd arm of 117 patients received HFA-placebo)	Asthma Quality of Life Questionnaire (score change: HFA= +0.13, CFC= –0.3 – ns), day-time symptoms and sleep disturbance scores (results in Gross[31] equivalent asthma control at all time intervals over the 12 week period) A supplementary report of results to Gross[31]
Pearlman[16] 1999	Design: Parallel, double-blind Device: HFA vs CFC pMDIs Drug: Triamcinolone Dose: 150, 300 and 600µg daily, 6 arms Duration: 12 weeks Cochrane Quality: B	473 children with asthma aged 6-13 years enrolled, 374 completed	FEV_1 (% change: HFA 150-, 300-, 600-µg = +12.2, +21.4, +22 – p= 0.055; CFC 150-, 300-, 600-µg = +13.5, +19.4, +22.6 - p= 0.061 - no intergroup statistic), change in beta-agonist use (mean change inhaler puffs: HFA 150-, 300-, 600-µg = -2, -2.7, -3.6/d; CFC 150-, 300-, 600-µg = -2.2, -2.4, -3/d – ns HFA vs CFC), FEF25-75%, PEFR, night-time wakening, symptom scores, adverse events (% incidence: HFA= 77.8, CFC= 76.2)
Rufin[17] 2000	Design: Parallel, open trial Device: pMDI+spacer vs Autohaler® Drug: Beclomethasone Dose: 1000µg daily Duration: 8 weeks Cochrane Quality: B	127 children with asthma aged 5-15 years, mean age 11	FEV_1 (mean change: Autohaler®= +0.1 p= 0.0017; pMDI+spacer = +0.2 p= 0.0001; intergroup equivalence stated, but no statistic), mid-flows (intergroup equivalence stated, but no results or statistic), patient acceptability (easy to use: Autohaler® n=52/62 (85.2%), pMDI+spacer n=38/57 (57.6%) p= 0.002)
Stradling[41] 2000	Design: Parallel, double-blind, double dummy Device: pMDI+spacer vs Clickhaler® DPI Drug: Beclomethasone Dose: usual dose Duration: 12 weeks Cochrane Quality: B	240 adults with asthma entered run-in, 204 randomised. Mean age 50 years	PEFR am (mean change: DPI= +3.5 L/min, pMDI= +3 L/min – ns), pm (mean change: DPI= +1.7 L/min, pMDI= +1.4 L/min – ns) day-time,night-time symptom scores (FEV_1, FVC only reported non-significant), exacerbations (mild: DPI n=8, pMDI n=18, moderate: DPI n=3, pMDI n= 4), adverse events, serum cortisol Unclear if ITT analysis used
Maladano-Alanis[71] 1998	Design: 3 way parallel, open study Device: pMDI+Pulmona® spacer vs pMDI+Ellipse® vs Hudson® nebuliser Drug: Salbutamol Dose: 200 vs 200µg vs 150µg/kg Duration: 6 hours Cochrane Quality: B	63 children with asthma aged 6-15 years	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 vs 14.7 vs 5.5%)
Salzman[72] 1986	Design: Cross-over, open trial Device: pMDI+spacer vs Hudson Updraft II® (NEB) at 6 litres/min. Drug: Metaproterenol Dose: 1.3 vs 15mg Duration: 2 X 1 day Cochrane Quality: B	15 adults with severe asthma aged 18-47 years	Mean % increases in FEV_1 (pMDI= 28.6, NEB= 28.8 – ns), FVC (pMDI= 12, NEB= 15.8 – ns), PEFR (pMDI= 12, NEB= 15.8 – ns), MMFR (pMDI= 60.7, NEB= 55.3 – ns), FEF25-75% (result not given)

Programme,[1] and will be available on the Cochrane Library.[9] The reviews have been carried out by the Cochrane Airways Group and used as supporting evidence for two Technology Appraisal Guidance reports for the National Institute for Clinical Excellence.[10,11] They are also being used in the forthcoming guidelines from the BTS and SIGN.[8] These systematic reviews have been updated through further searching and identification of additional randomised controlled trials (RCTs). Using the original methodology (see Appendix),[7] the search strategy was repeated and the additional RCTs are detailed in Table 2 and discussed in the relevant sections. The different aspects of inhaler devices have been separated into the most clinically relevant comparisons.

D. Hand-held inhaler devices for asthma

D1. Delivery of corticosteroids in stable asthma (children) In the original review,[1] three RCTs in children comparing different devices failed to demonstrate statistically significant differences in pulmonary function between the devices.[12-14]

Three further studies in children have been identified (see Table 2).[15-17] The heterogeneity of the original RCTs precluded any pooling of results and this remains the case with the addition of the new studies. None of the three additional RCTs defined the severity of asthma in the children studied. The first RCT included 229 children with asthma aged 7–12 and compared a CFC and HFA Easibreathe® (breath-actuated inhaler) delivering beclometasone dipropionate over six weeks.[15] No statistically significant differences were found between groups in diary card peak expiratory flow rate (PEFR: measure of the maximum rate of airflow), FEV_1 (forced expiratory volume: measure of maximum volume of air that can be expelled in a given number of seconds), symptoms scores and adverse events.

The second RCT studied 473 children (6–13 years old) with asthma over 12 weeks.[16] Triamcinolone (not licensed in the UK) was given at 150, 300 and 600µg daily by CFC and HFA pMDI devices. No clinically significant differences were found in beta-agonist use, FEF 25-75% (forced expiratory flow: maximum expiratory flow over 25–75% of expiration), PEFR, night-time wakening, symptom scores and adverse events, between the groups.

The third RCT included 127 children (5–15 years old) with asthma over eight weeks.[17] Beclometasone dipropionate was delivered 1000µg daily via a pMDI plus large volume spacer versus an Autohaler® (breath-actuated inhaler). No clinically significant differences were found in FEV_1 and expiratory mid-flow rates, between the groups.

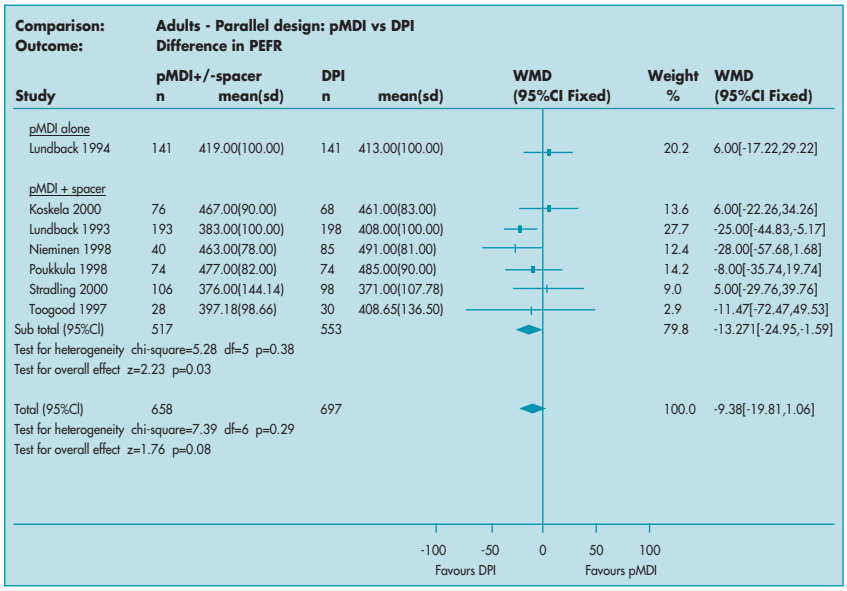

Figure 1 Difference in PEFR between pMDI and dry powder inhaler for the delivery of corticosteroids in stable asthma

Notes: The weighted mean difference (WMD) for each trial is indicated by a square box with the line through it representing the 95% confidence interval (CI). A WMD to the left of the vertical line favours DPI, those to the right favour pMDI. The solid diamond represents the pooled estimate of mean effect. A percentage weight (ie how much influence each trial has on the overall results of the meta-analysis) is allocated to each trial.
The z statistic indicates the level of significance for the overall result.

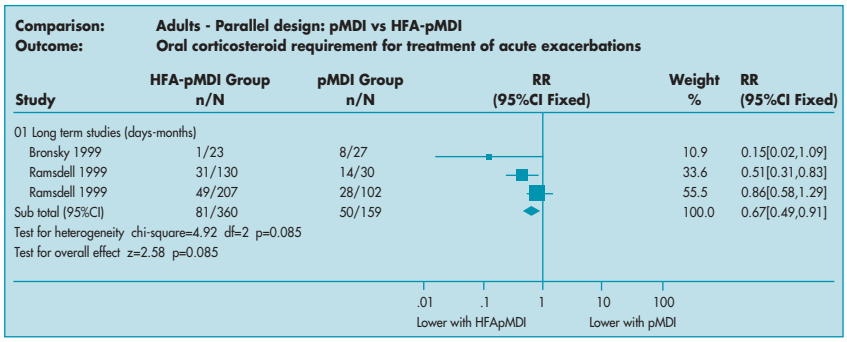

Figure 2 Short course oral corticosteroid requirement for acute exacerbations in adult patients with asthma

Notes: Data represented as relative risk calculated using a fixed effect model with 95% confidence intervals. Relative risk values left of the vertical line indicate lower requirement for oral corticosteroids when using HFA-pMDI and values on the right indicate lower requirement when using standard CFC-pMDI.

D2. Delivery of corticosteroids in stable asthma (adults) In the original review,[1] 21 studies in adults found no statistically 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.[18-39]

Whilst statistically significant differences were found for three outcomes for dry powder inhalers, these were either within clinically equivalent limits or the differences were not apparent once baseline characteristics were taken into account.

Figure 1 shows the difference in PEFR between pMDI (with and without spacer) and dry powder inhaler for the delivery of corticosteroids in stable asthma.

Four further RCTs have been identified (see Table 2).[40-43] One RCT[40] reports asthma related quality of life questionnaire scores from a previous study.[31] No significant differences were found between inhaler devices.

In the second RCT, 51 patients with asthma were included[42] to evaluate the effect upon voice changes rather than asthma control between pMDI plus Nebuhaler® versus Turbohaler® for the delivery of budesonide. Clinical outcomes were also measured but no statistically significant differences were found between devices.

The third RCT included 34 participants with asthma taking beclometasone 200µg daily via a CFC or HFA pMDI.[43] The primary outcome of the RCT was air-trapping as measured by CT (computed tomography) imaging. Other clinical outcomes were measured and no statistically significant differences were found between the devices.

The fourth RCT included 204 adults with asthma taking beclometasone at their 'usual' dose via pMDI+spacer or Clickhaler®.[41] No statistically significant differences were found between the devices. None of the four studies measured patient preference for device type. The addition of data from these four studies to the original meta-analysis did not change the results.

For the delivery of corticosteroids in stable asthma (in children and adults), pMDI (with or without spacer) is as effective as other hand-held inhaler devices. There is no evidence to demonstrate differences in the effectiveness of drug delivery between non-CFC pMDI and CFC pMDI at equivalent dosing.

D3. Delivery of short-acting β_2-agonist bronchodilators in chronic asthma Eighty-four RCTs were included in a Cochrane review[44] that was based on the original HTA review.[1] The review found no statistically significant differences between pMDI and 10 other hand-held inhaler devices for the following outcomes: lung function, blood pressure, bronchial hyper-reactivity, systemic bioavailability, inhaled steroid requirement, serum potassium and use of additional relief bronchodilators. In addition, there was no evidence to support claims that higher dosing schedules (2:1 or greater, comparator: pMDI) had any clinical advantage over 1:1 dosing.

Regular use of HFA-pMDI containing salbutamol significantly reduced the number of patients requiring short courses of oral corticosteroids to treat acute exacerbations (increases in the severity of symptoms). The data were provided by three trials with a total of 519 patients.[45,46] However, the incidence of acute exacerbations in these three trials was similar to pMDI. These results should be interpreted with caution as the effect of HFA-pMDI on requirement for oral corticosteroid courses needs to be confirmed in studies of higher methodological quality (Figure 2).

Three RCTs in adults found a higher pulse rate in patients using Turbohaler® than those using pMDI, suggesting greater systemic absorption with the Turbohaler® device.[47-49]

Three studies found that adult patients preferred pMDI to the less commonly used Rotahaler® device.[50-52] However, this result should be interpreted with caution because it is unclear if any of the RCTs utilised adequate methods of allocation concealment (process by which clinicians and participants are unaware of upcoming treatment assignments).

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.

E. Hand-held inhaler devices for COPD

A Cochrane review[53] that was based on the original HTA review[1] compared pMDI to other devices. No significant difference in clinical outcomes was demonstrated between dry powder devices and pMDI for delivery of β_2-agonists. A soft mist device for ipratropium (Respimat – not licensed in the UK) was more effective than a pMDI in improving lung function but the data come from one small RCT. The dearth of published studies highlights a major gap in the research evidence for this important area.

F. Nebulisers for asthma

F1. Chronic asthma. In the original review,[1] three studies in children (n=51) compared a variety of doses of beta-agonists through different hand-held inhaler devices with a

nebuliser.[54-56] There was no evidence of clinical superiority of nebulisers over inhaler devices. Again in the original review,[1] 23 RCTs in adults demonstrated clinical equivalence for inhaler devices and nebulisers for the main pulmonary outcomes (FEV_1 and PEFR) and no evidence of significant differences in other outcomes.[57-70]

Update searching identified two further studies.[71,72] Results for the first RCT (n=63) were published as an abstract only and detailed statistical results were not shown.[71] The initial bronchodilator response for salbutamol was similar between pMDI plus Pulmona® spacer, pMDI plus Ellipse® spacer (200µg from each) and a nebuliser (at a dose of 150µg/kg).

The other RCT included 15 people with severe stable asthma in a two-day, open cross-over trial of metaproterenol 1.3 mg via pMDI plus Aerochamber® spacer device versus 15 mg via a nebuliser.[72] No statistically significant differences were found between the delivery methods in the usual laboratory measurements of expiratory air-flow.

F2. Acute asthma. An updated Cochrane review of 21 RCTs comparing pMDI plus spacer to 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 five years and adults with mild and moderate exacerbations should be treated with pMDI plus spacer with broncholdilator dose titration according to clinical response.

G. Nebulisers for COPD

In the original review,[1] 13 RCTs compared bronchodilator drugs delivered by inhaler devices to nebulisers for the treatment of patients with acute and stable COPD.[67,74-85] Overall, the methodological quality of included studies was poor. In addition, there was considerable variation in settings and the drugs and delivery devices used, making comparisons difficult.

There was no evidence to suggest clinical benefit of nebulisers over a standard pMDI with spacer, although a higher dose may be required. No additional studies were identified by update searching.

H. 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 be influenced by factors such as patient experience, education, physical ability and effective teaching of technique.

The findings of the original review suggest that pMDI devices are not used as effectively as dry powder inhalers.[1] The percentage of patients with correct technique (assessed by a scoring system of correct steps) was 43% compared to 55% for pMDI with spacer and 59% for dry powder inhalers. However, teaching had a positive effect and eliminated statistically significant differences between the 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 are likely to be due to lack of teaching. Therefore all patients should receive appropriate instruction and guidance on effective technique when prescribed inhaler devices and this should be regularly reinforced.

I. Implications

- Current evidence suggests that there is no difference in the effectiveness of nebulisers and alternative inhaler devices compared to standard pressurised metered-dose inhaler (pMDI) with or without a spacer device.
- The 28-day cost of pMDIs is lower than dry powder inhalers and other inhaler devices (see Table 1). Both pMDIs and dry powder inhalers are cheaper than nebulisers. As there are no significant differences in patient outcomes, a stepped approach to treatment would seem justified. pMDIs (with or without a spacer), or the cheapest inhaler device the patient can use adequately, should be prescribed as first-line treatment 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 are unable to use pMDIs effectively after appropriate instruction.
- Further high quality RCTs are required to demonstrate any differences in the effectiveness of inhaler devices and nebulisers compared with 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 settings to ensure generalisability of results, recruiting patients who are not pre-selected on the basis of good inhaler technique, adherence and motivation.
- Given the chronic nature of asthma and COPD and their significant effects on morbidity, future trials should address 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 are equally effective then secondary factors such as adverse effects become much more important. Studies of sufficient duration are required to compare the risk of long-term systemic effects of inhaled steroids from different devices.

- The teaching of inhaler technique is another important area for future research. Good quality studies should explore the clinical and cost effectiveness of patient education and consider practical interventions to improve patient technique in everyday clinical settings. Additionally, studies of teaching of inhaler technique should measure health-related outcomes, as the relationship between inhaler technique and clinical outcome has not yet been established.

Appendix on Research Methods

This bulletin is based on evidence from a number of systematic reviews carried out by the Cochrane Airways Group and funded by the NHS Health Technology Assessment Programme.[1] The original reviews have been updated through further searching and identification of additional RCTs. Methods involved systematic searching of the Cochrane Airways Group Register of Trials, electronic databases and bibliographies for RCTs and systematic reviews. Pharmaceutical companies and experts in the field were contacted for further information. Full details of the search strategy are available elsewhere.[1]

Trials were eligible for inclusion that compared clinical outcomes of a single drug delivered by different inhaler devices. Trials that met inclusion criteria were appraised and data extraction undertaken by one reviewer and checked by a second reviewer, with any discrepancies being resolved through discussion.

Quality assessment was performed and included an assessment of allocation concealment and was carried out independently by two reviewers. All trials were classified using the following principles:

Grade A: adequate concealment

Grade B: uncertain

Grade C: clearly inadequate concealment

Grade D: not used

Data were combined using meta-analysis with further discussion as needed. Where insufficient data were available or meta-analysis was inappropriate, narrative review was used. Full details of the review methodology are available elsewhere.[1]

References

1. Department of Health. Prescription Cost Analysis 2001. [Accessed November 2002] Available from: http://www.doh.gov.uk/stats.pca2001.pdf
2. Brocklebank D, Ram F, Wright J, et al. Comparison of effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a review of the literature. *Health Technol Assess* 2001;5.
3. British Thoracic Society, National Asthma Campaign, Royal College of Physicians. The British guidelines on asthma management: 1995 review and position statement. *Thorax* 1997;52(Suppl. 1):S1-S20.
4. The COPD Guidelines Group of the Standards of Care Committee of the BTS. BTS guidelines for the management of chronic obstructive pulmonary disease. *Thorax* 1997;52(Suppl. 5):S1-S28.
5. British Medical Association, Royal Pharmaceutical Society of Great Britain. *British National Formulary* (44). London: British Medical Association, Royal Pharmaceutical Society of Great Britain, 2002.
6. Inhaler devices for asthma. *Drug Ther Bull* 2000;38:9-13.
7. National Heart Lung and Blood Institute. *Guidelines for inhaler devices.* National Heart, Lung and Blood Institute; 2002. [cited October 2002]. Available from: http://www.nhlbi.nih.gov/guidelines/asthma/index.htm
8. British Thoracic Society. *British Thoracic Society: guidelines in preparation.* 2002. [cited October 2002]. Available from: http://www.brit-thoracic.org.uk
9. *The Cochrane Library.* Oxford: Update Software; 2002.
10. National Institute for Clinical Excellence. *Guidance on the use of inhaler systems (devices) in children under the age of 5 years with chronic asthma.* London: National Institute for Clinical Excellence, 2000.
11. National Institute for Clinical Excellence. *Inhaler devices for routine treatment of chronic asthma in older children (aged 5-15 years).* London: National Institute for Clinical Excellence, 2002.
12. Adler L, Clarke I, and members of the PANDA 3 clinical study group. Efficacy and safety of beclomethasone dipropionte (BDP) delivered via a novel dry powder inhaler (Clickhaler) in paediatric patients with asthma. *Thorax* 1997;52:A57.
13. Agertoft L, Pederson S. Importance of the inhalation device on the effect of budesonide. *Arch Dis Child* 1993;69:130-3.
14. Edmunds A, McKenzie S, Tooley M, et al. A clinical comparison of beclomethasone dipropionate delivered by pressurised aerosol and as a powder from a Rotahaler. *Arch Dis Child* 1979;54:233-5.

15. Farmer I, Middle M, Savic J, et al. Therapeutic equivalence of inhaled beclomethasone dipropionate with CFC and non-CFC (HFA 134a) propellants: Both delivered via the Easibreathe(TM) inhaler for the treatment of paediatric asthma. *Respir Med* 2000;94:57-63

16. Pearlman D, Kane R, Banjeri D. Comparative dose-ranging study of triamcinolone acetonide inhalation aerosol using propellants hydrofluoroalkane 134a or P-12 in children with chronic asthma. *Curr Ther Res Clin Exp* 1999;60:595-606.

17. Rufin P, Iniguez J, Calvayrac P, et al. Comparison of the efficacy, tolerance and acceptability of beclomethasone dipropionate delivered by Prolair Autohaler(TM) versus a standard aerosol doser linked to a spacer device in children. *J Pediatr Pueric* 2000;13:105-10.

18. Drepaul B, Payler D, Qualtrough J, et al. Becotide or Becodisks? A controlled study in general practice. *Clin Trials J* 1989;26:335-44.

19. Milanowski J, Qualtrough J, Perrin V. Inhaled beclomethasone (BDP) with non-CFC propellant (HFA 134a) is equivalent to BDP-CFC for the treatment of asthma. *Respir Med* 1999;93:245-51.

20. Vidgren M, Arppe J, Vidgren P, et al. Pulmonary deposition and clinical response of 99mTc-labelled salbutamol delivered from a novel multiple dose powder inhaler. *Pharm Res* 1994;11:1320-4.

21. Busse W, Brazinsky S, Jacobson K, et al. Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. *J Allergy Clin Immunol* 1999;104:1215-22.

22. Lundback B, Alexander M, Day J, et al. Evaluation of fluticasone propionate (500 mcrog day-1) administered either as a dry powder via a Diskhaler (R) or pressurized inhaler and compared with beclomethasone diprionate (1000 microg day-1) administered by pressurized inhaler. *Respir Med* 1993;87:609-20.

23. Nieminen M, Vidgren P, Kokkarinen J, et al. A new beclomethasone dipropionate multidose inhaler in the treatment of bronchial asthma. *Respiration* 1998;65:275-81.

24. Chatterjee S, Butler A. Beclomethasone in asthma: a comparison of two methods of administration. *Br J Dis Chest* 1980;74:175-9.

25. Lal S, Malhotra S, Gribben M, et al. Beclomethasone dipropionate aerosol compared with dry powder in the treatment of asthma. *Clin Allergy* 1980;10:259-62.

26. Engel T, Heinig H, Malling H, et al. Clinical comparison of inhaled budesonide delivered either via pressurised metered dose inhaler or Turbuhaler. *Allergy* 1989;44:220-5.

27. Nieminen M, Lahdensuo A. Inhalation treatment with budesonide in asthma. A comparison of Turbuhaler and metered dose inhalation with Nebuhaler. *Acta Ther* 1995;21: 179-92.

28. Dahl R, Ringdal N, Ward S, et al. Equivalence of asthma control with new CFC-free formulation HFA-134a beclomethasone dipropionate and CFC-beclomethasone dipropionate. *Br J Clin Pract* 1997;51:11-15.

29. Demedts M, Cohen R, Hawkinson R. Switch to non-CFC inhaled corticosteroids: a comparative efficacy study of HFA-BDP and CFC-BDP metered-dose inhalers. *Int J Clin Pract* 1999;53:331-8.

30. Davies R, Stampone P, O'Connor B. Hydrofluoroalkane-134a beclomethasone dipropionate extrafine aerosol provides equivalent asthma control to chlorofluorocarbon beclomethasone dipropionate at approximately half the total daily dose. *Respir Med* 1998;92 Supp A:23-31.

31. Gross G, Thompson P, Chervinsky P, et al. Hydrofluoroalkane-134a beclomethasone dipropionate, 400ug is as effective as chlorofluorocarbon beclomethasone dipropionate, 800ug for the treatment of moderate asthma. *Chest* 1999;115:343-51.

32. Carmichael J, Duncan D, Crompton G. Beclomethasone dipropionate dry-powder inhalation compared with conventional aerosol in chronic asthma. *BMJ* 1978;2:657-8.

33. Koskela T, Hedman J, Ekroos H, et al. Equivalence of two steroid-containing inhalers: Easyhaler multidose powder inhaler compared with conventional aerosol with large volume spacer. *Respiration* 2000;67:194-202.

34. Lundback B, Dahl R, De Jonghe M, et al. A comparison of fluticasone propionate when delivered by either the metered-dose inhaler or the Diskhaler in the treatment of mild-to-moderate asthma. *Eur J Clin Res* 1994;5:11-19.

35. Morrison Smith J, Gwynn C. A clinical comparison of aerosol and powder administration of beclomethasone dipropionate in asthma. *Clin Allergy* 1978;8: 479-81.

36. Poukkula A, Alanko K, Kilpio K, et al. Comparison of a multidose powder inhaler containing beclomethasone dipropionate (BDP) with a BDP metered dose inhaler with spacer in the

treatment of asthmatic patients. *Clin Drug Invest* 1998;16:101-10.

37. Toogood J, White F, Baskerville J, et al. Comparison of the antiasthmatic, oropharyngeal and systemic glucocorticoid effects of budesonide administered through a pressurized aerosol plus spacer or the Turbuhaler dry powder inhaler. *J Allergy Immunol* 1997;99:186-93.

38. Jenkins M. Clinical evaluation of CFC-free metered dose inhalers. *J Aerosol Med* 1995;8:S41-S7.

39. Agertoft L, Pedersen S. Influence of spacer device on drug delivery to young children with asthma. *Arch Dis Child* 1994;71:217-9.

40. Juniper E, Buist A. Health-related quality of life in moderate asthma: 400 microg hydrofluoroalkane beclomethasone dipropionate vs 800 microg chlorofluorocarbon beclomethasone dipropionate. *Chest* 1999;116:1297-303.

41. Stradling J, Pearson M, Morice A, et al. Efficacy and safety of a novel beclomethasone dipropionate dry powder inhaler (Clickhaler) for the treatment of adult asthma. Amsterdam Clinical Study Group. *J Asthma* 2000;37:183-90.

42. Crompton G, Sanderson R, Dewar M, et al. Comparison of Pulmicort pMDI plusNebuhaler and Pulmicort Turbuhaler in asthmatic patients with dysphonia. *Respir Med* 2000;94:448-53.

43. Goldin J, Tashkin D, Kleerup E, et al. Comparative effects of hydrofluoroalkane and chlorofluorocarbon beclomethasone dipropionate inhalation on small airways: Assessment with functional helical thin-section computed tomography. *J Allergy Clin Immunol* 1999;104:S258-S67.

44. Ram F, Brocklebank D, White J, et al. Pressurised metered dose inhalers versus all other hand-held inhaler devices to deliver beta-2 agonist bronchodilators for non-acute asthma (Cochrane Review). *The Cochrane Library.* Issue 2 2002 Oxford: Update Software.

45. Bronsky E, Ekholm B, Kliner N, et al. Switching patients with asthma from chlorofluorocarbon (CFC) albuterol to hydrofluoroalkane-134a(HFA) albuterol. *J Asthma* 1999;36: 107-14.

46. Ramsdell J, Klinger N, Ekholm B, et al. Safety of long-term treatment with HFA albuterol. *Chest* 1999;115:945-51.

47. Bondesson E, Friberg K, Soliman S, et al. Safety and efficacy of a high cumulative dose of salbutamol inhaled via turbuhaler or via a pressurized metered-dose inhaler in patients with asthma. *Respir Med* 1998;92:325-30.

48. Ekstrom T, Andersson A, Skedinger M, et al. Dose potency relationship of terbutaline inhaled via turbuhaler or via a pressurized metered dose inhaler. *Ann Allergy Asthma Immunol* 1995;74:328-32.

49. Johnsen C, Weeke E. Turbuhaler: a new device for dry powder terbutaline inhalation. *Allergy* 1988;43:393-5.

50. Boye K. A comparison of fenoterol powder capsules and fenoterol metered dose spray in bronchial asthma. *Eur J Respir Dis* 1983;64(Suppl. 130):9-11.

51. Hartley J, Nogrady S, Seaton A. Long-term comparison of salbutamol powder with salbutamol aerosol in asthmatic out-patients. *Br J Dis Chest* 1979;73:271-6.

52. Kiviranta K. Fenoterol inhalation powder and aerosol in the treatment of asthma. *Allergy* 1985;40:305-7.

53. Ram F, Brocklebank D, Muers M, et al. Pressurised metered-dose inhalers versus all other hand-held inhaler devices to deliver bronchodilators for chronic obstructive pulmonary disease (Cochrane Review). *The Cochrane Library.* Issue 2 2002, Oxford: Update Software.

54. Blackhall M. A dose response study of inhaled terbutaline administered via nebuhaler or nebuliser to asthmatic children. *Eur J Respir Dis* 1987;71:96-101.

55. Grimwood K, Johnson-Barrett J, Taylor B. Salbutamol: tablets, inhalational powder or nebuliser? *BMJ* 1981;282:105-6.

56. Pierce R, McDonald C, Landau L, et al. Nebuhaler versus wet aerosol for domiciliary bronchodilator therapy (Adults). *Med J Aust* 1992;156:771-4.

57. Cissik J, Bode F, Smith J. Double-blind crossover study of five bronchodilator medications and two delivery methods in stable asthma. *Chest* 1986;90:489-93.

58. Zainudin B, Biddiscombe M, Tolfree S, et al. Comparison of bronchodilator responses and deposition patterns of salbutamol inhaled from a pressurized metered dose inhaler, as a dry powder and as a nebulised solution. *Thorax* 1990;45:469-73.

59. Christensson P, Arborelius M, Lilja B. Salbutamol inhalation in chronic asthma bronchiole: dose aerosol vs jet nebulizer. *Chest* 1981;79:416-9.

60. Gervais A, Begin P. Bronchodilatation with a metered-dose inhaler plus an extension, using tidal breathing vs jet nebulisation. *Chest* 1987;92:822-4.

61. Gomm S, Keaney N, Hunt L, et al. Dose-response comparison of ipratromium bromide from metered- dose inhaler and by jet nebulisation. *Thorax* 1983;38: 297-301.

62. Laursen L, Munch E, Weeke E, et al. Comparison of a 750 ml spacer and a nebulizer in domiciliary treatment of severe chronic asthma with terbutaline. *Eur J Respir Dis* 1983;64:498-503.

63. Madsen E, Bundgaard A, Hidinger K. Cumulative dose-response study comparing terbutaline pressurized aerosol administered via a pearshaped spacer and terbutaline in a nebulized solution. *Eur J Clin Pharmacol* 1982;23:27-30.

64. O'Reilly J, Buchanan D, Sudlow M. Pressurized aerosol with conical spacer is an effective alternative to nebuliser in chronic stable asthma. *BMJ* 1983;286:1548.

65. Prior J, Nowell R, Cochrane G. High-dose inhaled terbutaline in the management of chronic severe asthma: comparison of wet nebulisation and tube-spacer delivery. *Thorax* 1982;37:300-3.

66. Rochat T, Vonwil A, Bachofen H. Die inhalation von beta-stimulatoren: Wirkungsvergleich zwischen sechs vershiedenen inhalationsgeraten.(Inhalation of beta-stimulantors: comparative effects of six different inhalation devices.). *Schweiz Med Wochenschr* 1983;113:314-9.

67. Shim C, Williams H. Effect of bronchodilator therapy administered by canister versus jet nebulizer. *J Allergy Clin Immunol* 1984;73:387-90.

68. Stauder J, Hidinger K. Terbutaline aerosol from a metered dose inhaler with a 750-ml spacer or as a nebulized solution. *Respiration* 1983;44:237-40.

69. Watanabe S, Turner W, Renzetti A, et al. Bronchodilator effects of nebulized fenoterol. A comparison with isoproterenol. *Chest* 1981;80:292-9.

70. Pedersen J, Bundgaard A. Comparative efficacy of different methods of nebulising terbutaline. *European J Clin Pharmacol* 1983;25:739-42.

71. Maldonado-Alanis M, Ortega-Cisneros M, Linares-Zapien J, et al. Albuterol by nebulizer versus albuterol meter dose inhaler (MDI) with "Pulmona" spacer and MDI with "Ellipse" spacer. *Ann Allergy Asthma Immunol* 1998;80:131.

72. Salzman G, Pyszczynski D. A comparison of two delivery methods for aerosolized metaproterenol sulfate. *J Asthma* 1986;23:297-301.

73. Cates C, Rowe B. Holding chambers versus nebulisers for bega-agonist treatment of acute asthma (Cochrane Review). *The Cochrane Library*. Issue 2 2002, Oxford: Update Software.

74. Ikeda A, Nishimura K, Koyama H, et al. Comparison of the bronchodilator effects of salbutamol delivered via a metered-dose inhaler with spacer, a dry powder inhaler, and a jet nebulizer in patients with chronic obstructive pulmonary disease. *Respiration* 1999;66: 119-23.

75. Wetterlin K. Turbuhaler: a new powder inhaler for administration of drugs to the airways. *Pharmacol Res* 1998;5:506-8.

76. Berry R, Shinto R, Wong F, et al. Nebulizer vs spacer for broncodilator delivery in patients hospitalised for acute exacerbations of COPD. *Chest* 1989;96:1241-6.

77. Gross N, Petty T, Friedman M, et al. Dose response to ipratropium as a nebulized solution in patients with chronic obstructive pulmonary disease. A three-centre study. *Am Rev Respir Dis* 1989;139:1188-91.

78. Hansen N. Terbutaline powder inhalation from Bricanyl Turbuhaler compared to terbutaline as nebulizer solution in severe chronic airways obstruction. *Eur Respir J* 1989;2:716-20.

79. Hansen N, Evald T, Ibsen T. Terbutaline inhalations by the Turbuhaler as replacement for domiciliary nebulizer therapy in severe chronic obstructive pulmonary disease. *Respir Med* 1994;88:267-71.

80. Hansen N, Andersen P. Salbutamol powder inhaled from the diskhaler compared to salbutamol as nebulizer solution in severe chronic airways obstruction. *Respir Med* 1995;89:175-9.

81. Higgins R, Cookson W, Chadwick G. Changes in blood gas levels after Nebuhaler and nebulizer administration of terbutaline in severe chronic airway obstruction. *Bull Eur Physiopathol Respir* 1987;23:261-4.

82. Jenkins S, Heaton R, Fulton T, et al. Comparison of domiciliary nebulized salbutamol and salbutamol from a m etered-dose inhaler in stable chronic airflow limitation. *Chest* 1987;91:804-7.

83. Maguire G, de Lorenzo L, Brown R. Comparison of a hand-held nebulizer with a metered dose inhaler-spacer combination in acute obstructive pulmonary disease. *Chest* 1991;100:1300-5.

84. Mestitz H, Copland J, McDonald C. Comparison of outpatient nebulized vs metered dose inhaler terbutaline in chronic airflow obstruction. *Chest* 1989;96:1237-40.

85. Turner J, Corkery K, Eckman D, et al. Equivalence of continuous flow nebulizer and metered-dose inhaler with reservoir bag for treatment of acute airflow obstruction. *Chest* 1988;93: 476-81.

Effective Health Care

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