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Ram FSF, Brocklebank DDM, Muers M, Wright JJ, Jones P

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[Intervention Review]

Pressurised metered-dose inhalers versus all other hand-held inhalers devices to deliver bronchodilators for chronic obstructive pulmonary disease

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ABSTRACT

Background

Bronchodilator therapy for COPD may be delivered by a number of different inhaler devices.

Objectives

To determine the efficacy of pressurised metered dose inhalers (pMDI) compared to any other handheld inhaler device for the delivery of bronchodilators in non-acute COPD.

Search methods

The Cochrane Collaboration, Asthma and Wheeze Randomised Controlled Clinical Trials register was searched for studies. The UK pharmaceutical companies who manufacture inhaled COPD medication were also contacted.

Selection criteria

Two reviewers independently reviewed the results of computerised search and any potentially relevant articles were obtained in full.

Data collection and analysis

One reviewer extracted details of each trial and a second reviewer checked all extracted data. Dichotomous outcomes such as exacerbation rate were assessed using relative risk, with 95% confidence interval (CI).

Main results

Fourteen studies appeared potentially relevant but only three studies (61 patients) met the entry criteria. Two studies compared a dry powder device (Turbuhaler or Rotahaler) with a pMDI for beta2-agonist delivery, and one (36 patients cross-over design) the Respimat (soft mist device for ipratropium) vs a pMDI. For the Turbuhaler and Rotahaler, none of the reported outcome measures were significantly different. The Rotahaler study used a high and low dose of medication with or without large volume spacer. The study using the Respimat showed significant increases in FEV1 when compared to a pMDI (difference in change from base line 70 ml, 95% CI 10, 130 ml). The effect on change in FVC was of similar size. There were no differences between these two devices for any other reported outcomes.

Although none of the included studies required prior patient ability to use any of the inhalers (and no study mentioned device training), it was assumed that all patients randomised into the study would have undergone training in use of the study inhalers and were capable of using those devices.

Authors' conclusions

In patients with stable COPD, pMDI produced similar outcomes to a dry powder device for delivering beta2-agonists, but the very small number of studies and included patients does not permit firm conclusions to be drawn. The soft mist device for ipratropium was more effective than a pMDI, but the data come from one small study. There need to be further well designed randomised controlled trials to define the role of inhaler devices using bronchodilators in stable COPD.

PLAIN LANGUAGE SUMMARY

Pressurised metered-dose inhalers versus all other hand-held inhalers devices to deliver bronchodilators for chronic obstructive pulmonary disease

This review involved the assessment of different inhaler devices for delivery of inhaled bronchodilators in stable chronic obstructive pulmonary disease (COPD). Studies included in this review involved pressurised metered dose inhalers (pMDI) being compared to any other handheld inhaler device containing bronchodilators. Only three randomised controlled trials met the inclusion criteria. Due to the very small number of studies included in this review, it is not possible to draw any conclusions on the use of inhaler devices containing bronchodilators in COPD. There need to be further well designed randomised controlled trials examining the role of bronchodilators in COPD.

BACKGROUND

Recently published guidelines for the investigation and management of chronic obstructive pulmonary disease (COPD) have emphasised the importance of bronchodilator therapy in this disease (ATS 1995, BTS 1997, ERS 1995). As opposed to asthma, achievable bronchodilatation or lung function reversibility is widely variable in COPD, with many patients showing (at least acutely) some degree of reversibility (Nisar 1990). This highlights the importance of optimising delivery systems that may prevent excessive use of inhaled medication (O'Driscoll 1997). The role of bronchodilators in this disease is for symptom relief however evidence suggest that bronchodilators do not affect prognosis (Anthonisen 1994) therefore this aspect of their effectiveness will not be considered in this review.

This review was confined to the assessment of different inhaler devices for the delivery of inhaled medication in COPD. Salbutamol is the most widely used bronchodilator in the UK however in the US ipratropium bromide is the frontline bronchodilator. This review proposes an analysis of choice of delivery system using either of these classes of agent.

OBJECTIVES

To determine the clinical effectiveness of pressurised metered dose inhalers (pMDI) with or without spacer device compared to any other handheld inhaler device for the delivery of bronchodilators (short acting beta-2 agonist or ipratropium bromide) in patients with stable COPD.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials were only considered. Studies were either laboratory or community based and were of any duration involving patients with non-acute COPD.

Types of participants

Studies were considered in patients who fitted internationally accepted criteria for the definition of COPD (e.g. ATS, BTS or ERS guidelines). Studies were also considered if they met a practical definition of chronic airflow obstruction in the appropriate clinical setting of older (> 30 years), usually (ex-) smoking patients having an FEV1 <70% and FEV1/FVC <70% of predicted or were diagnosed by a (respiratory) physician as having COPD. Whether or not patients were able to use a particular inhaler prior to study entry did not affect the inclusion of that study. It was understood that all patients would probably undergo training in use of the inhaler for the study.

Types of interventions

Studies were considered which described the use of pMDI (with or without spacer device) compared with any other hand-held inhaler for the delivery of the same bronchodilator. Co-intervention and or contamination (e.g. from crossover designs) which may have occurred were recorded where data was available.

Types of outcome measures

Primary outcomes

1. Physiological lung function measurements (e.g. FEV1, FVC, PEFR, FRC and TLC)
2. Validated quality of life measures (e.g. St George's or Chronic Respiratory Disease Questionnaire)

Secondary outcomes

1. Symptom scores
2. Use of additional relief medication
3. Use of inhaled or oral steroid requirement (maintenance, rescue)
4. Severity of disease
5. Days off work
6. Compliance
7. Patient preference
8. Side effects
9. Measures of systemic bioavailability
10. Subsidiary physiological measures (e.g. 6 or 12 minute walks and arterial blood gases)
11. Acute exacerbations (hospital admissions and unscheduled primary care attendance)

Search methods for identification of studies

The Cochrane Collaboration, Asthma and Wheeze Randomised Controlled Clinical Trials register was searched for studies as well as separate additional searches carried out on MEDLINE (1966-Dec 2000), EMBASE (1980-Dec 2000), CINAHL (1982-Dec 2000) and also on the CURRENT CONTENTS INDEX (1995-Dec 2000) as well as the SCIENCE CITATION INDEX (1995-Dec 2000). Citations were reviewed without language restriction.

All searches were conducted using the following search terms:

a) inhaler OR spacer* OR holding chamber OR volumatic OR neбуhaler OR aerochamber* OR fisonair OR extension OR spacing device OR inspirease OR accuhaler OR diskhaler OR turbohaler OR turbuhaler OR easibreathe OR autohaler OR rotahaler OR dry powder OR MDI OR DPI OR CFC-free OR HFA*

AND

b) salbutamol OR ventolin OR albuterol OR terbutaline OR bricanyl OR ipratropium OR atrovent OR oxitropium OR oxivent

The reference lists of all included studies and review articles were checked in order to identify any further relevant citations not captured by electronic and manual searches. Authors of included RCTs were contacted for any other unpublished studies and also if more data or clarification was required.

In addition, UK pharmaceutical companies who manufacture inhaled COPD medication were contacted in order to obtain details of any further published or unpublished studies.

Data collection and analysis

Selection of trials:

Two reviewers independently reviewed the results of computerised search based on study title, abstract and key words/MESH headings, any potentially relevant articles were obtained in full.

The full text of all potentially relevant articles were reviewed independently by the same two reviewers to assess each study according to previously written criteria. Written criteria included: (1) trials of a single bronchodilator (short-acting) delivered by a standard pMDI (with or without spacer) versus any other hand-held inhaler device in stable COPD, (2) randomised controlled trial, (3) patients with COPD diagnosed according to established internationally accepted guidelines (e.g. BTS, ATS, ERS) or by using a practical and objective definition of COPD & (4) laboratory or community based study of any duration involving one of the following drug: salbutamol OR ventolin OR albuterol OR terbutaline OR bricanyl OR ipratropium OR atrovent OR oxitropium OR oxivent.

Agreement between the two reviewers on inclusion of studies was complete. In all cases disagreements about inclusion of a study was resolved by consensus.

Selected studies subsequently excluded on methodological grounds were identified and the reason for exclusion recorded in 'Table of Excluded Studies'.

Quality assessment:

Methodological quality assessment was performed using the following methods. Firstly using the Cochrane approach for the assessment of allocation concealment all trials were scored according to the following grades:

Grade A: Adequate concealment
Grade B: Uncertain
Grade C: Clearly inadequate concealment
Grade D: Not used

In addition, each study was assessed using the 0-5 scale described by Jadad et al. (Jadad 1996) and summarised as follows:

- 1) Was the study described as randomised (1=yes; 0=no)?
- 2) Was the study described as double blind (1=yes; 0=no)?
- 3) Was there a description of withdrawals and dropouts (1=yes; 0=no)?
- 4) Was the method of randomisation well described and appropriate (1=yes; 0=no)?
- 5) Was the method of double blinding well described and appropriate (1=yes; 0=no)?
- 6) Deduct 1 point if methods for randomisation or blinding were inappropriate

Data extraction:

Details of each trial (e.g. intervention, duration, participants, design and outcome measures) were extracted and recorded in the table "Characteristics of included studies". First author of included studies were contacted to provide additional information or further data for the study.

Statistical considerations

Trials were combined for meta-analysis using Review Manager 4.1. Only trials with the same inhaler device being compared to the pMDI were combined, as different inhaler devices were kept

as separate comparisons. Fixed and or random effect models were used. Dichotomous outcomes such as exacerbation rate were assessed using relative risk (with 95% CI). However, most of the outcomes of interest in COPD are either continuous or categorical data such as the level of symptoms, which is usually treated as if it were continuous data. Data from each of the continuous outcomes were analysed as weighted mean differences (with 95% CI), or standardised mean differences if different scales were used.

If there were sufficient number of included studies sub-group analysis would have been carried out using: type of bronchodilator, age and disease severity. For each outcome measure, the null hypothesis that there is no heterogeneity between included RCTs was tested. Sensitivity tests were used to investigate any possible heterogeneity in the size of the measured response attributable to the sub-groups identified above and due to study quality. If sufficient studies were included, funnel plots would have been constructed for the outcome measures in order to test for possible publication bias.

RESULTS

Description of studies

Formgren 1994 (Formgren 1994a; Formgren 1994b)

Study design & Inclusion:

Randomised double-blind, double-dummy, crossover study. Study did not have a power calculation for either device superiority or equivalence and the authors did not state their intention but mentioned that the study was designed to compare the effects of lung function of terbutaline inhaled via a CFC pMDI and via Turbuhaler. A one week run-in period was used during which PEFR was measured 5 times a day and patients were included in the study if their diurnal PEF variation did not exceed 15%. Previous patient familiarisation with either the Turbuhaler or the pMDI was not mentioned as a requirement for study entry.

Patient characteristics:

15 hospitalised adult patients (4 women) in stable phase of their disease without recent exacerbations and medication unchanged in weeks. All patients were ex-smokers and upon admission all patients demonstrated a $\geq 15\%$ response in FVC and or a decrease in RV without increase ($< 15\%$) in FEV1 after inhalation of a beta-2 agonist (4 x 0.1 mg salbutamol or 4 x 0.25 mg terbutaline). COPD diagnoses was based on clinical history, X-ray, spirometry and body plethysmography after a run-in period of 1 week. Mean age 61 years (SD 9, range 44-72), mean % predicted FEV1=35.6% (range 23-48), mean disease duration 11.6 years (range 1-42). Mean basal FEV1 over the five study days for all patients did not vary greater outside 1.0 to 1.1 L.

Device: Turbuhaler vs. pMDI. A Turbuhaler is a dry powder inhaler containing no propellants or drug-carriers (e.g. lactose). It is primed by twisting twice the bottom half of the device and the patients breathes through the mouth piece with is located at the top of the inhaler. As a result of the patient breathing-in, medication is propelled through the length of the device and through the mouthpiece. The spiral effect of the internal structure of the device helps propel the medication through the device when the patients breathe through the mouth piece located at the top of the inhaler.

Drug & Dosing:

Terbutaline (1.0 mg = 2 doses of 0.5 mg) via Turbuhaler and placebo CFC pMDI (four doses); Terbutaline (1.0 mg = 4 doses of 0.5 mg) via CFC pMDI and placebo Turbuhaler (2 doses); Terbutaline (2.5 mg = 5 doses of 0.5 mg) via Turbuhaler and placebo CFC pMDI with Nebuhaler spacer (ten doses); Terbutaline (2.5 mg = 10 doses of 0.25 mg) via CFC pMDI with Nebuhaler and placebo Turbuhaler (five doses); placebo Turbuhaler (five doses) and placebo CFC pMDI with Nebuhaler (ten doses). The two different doses (1.0 mg & 2.5 mg) in this study were entered in RevMan as two references for ease of data entry.

Duration of study & measurements:

All treatments and measurements commenced at 0730 hours on each study day with an interval of at least 48 hours. On each study day, the patients underwent lung function measurements using body plethysmograph with registration of lung volumes before and after medication. Study measurements were made 10 minutes before and 5, 20 and 40 minutes after inhalation of test drug. Reported results included: FEV1, FVC, RV & SGaw. Results entered into the review were 40 minutes post bronchodilator. Treatment failures and adverse events were mentioned in study text. Data was reported at 40 minutes after study drug administration as absolute change from baseline.

[Iacono 2000](#)

Study design & Inclusion:

Randomised double blind, three-period crossover study. Interval of at least 2 days between treatment crossover. Study did report a power calculation for equivalence between Respimat and pMDI. A null hypothesis was proposed that FEV1 measured 45-245 minutes after the first inhalation dose would differ by more than 0.12 L between the two treatments. Thirty-six patients were required for an equivalence region of ± 0.12 L. Previous patient familiarisation with either the Respimat or the pMDI was not mentioned as a requirement for study entry.

Patient characteristics:

Thirty-six patients (7 women) presenting with stable COPD were recruited from outpatient chest clinic. COPD defined according to ATS 1987 criteria with no change in medication six weeks prior to screening visit, patient not on chronic oxygen therapy, oral corticosteroids, beta-blockers, antihistamines or cromolyn/nedocromil sodium. Stable use of inhaled corticosteroids was permitted. Patient baseline characteristics were, mean (SD): Age 52(6) years, FEV1 L 1.8(0.4), FVC L 3.0 (0.6), FEV1 % predicted 52.6(8.9), FVC% 72.1 (10.6), FEV1/FVC% 59.4 (7.7), FEV1 reversibility % 30.7 (7.7), smoking pack year history 49(15) and none of the patients were current smokers.

Device: Respimat vs. pMDI.

Respimat device is much like the standard pMDI in shape but it is a reusable, propellant-free, soft mist inhaler. The aerosol it produces has a narrow droplet size distribution, a high proportion of the dose in the fine particle fraction (mass median diameter < 5.8 μ m), and a particle velocity about one-fifth of that of the spray released from standard pMDI. This device was developed, as small particle size and low velocity are known to be important for optimal lung deposition ([Newman 1998](#)).

Drug & Dosing:

Patients received cumulative doses of ipratropium bromide for 1 + 1 + 2 + 4 + 8 puffs inhaled at 50 minute intervals from one

of the devices: Respimat 10 mcg/puff, Respimat 20 mcg/puff and pMDI 20 mcg/puff. For the purposes of this review, only the 20 mcg comparisons were used which had a total administered dose of 320 mcg. The treatment was open label between devices (Respimat vs pMDI) but was double-blinded for the two Respimat doses.

Duration of study & measurements:

180 minutes after the last dose of medication. Spirometry (FEV1, FVC) was performed before and 45, 60, 90, 120 & 180 min after the last dose of bronchodilator. Reported results included: adverse events, heart rate, blood pressure, QTc interval, RV & SGaw. All reported data were adjusted with baseline as covariant.

[Ikeda 1999](#) ([Ikeda 1999a](#); [Ikeda 1999b](#))

Study design & Inclusion:

Randomised double-blind, double-dummy, three-period crossover study. Interval between crossover ranged from 2 to 4 days. Study did not have a power calculation for either device superiority or equivalence and the authors did not state their intention but mentioned that the study was designed to compare the bronchodilator effects of salbutamol delivered via three devices (Rotahaler, pMDI, nebuliser). For the purposes of this review, only the Rotahaler and pMDI data were used. Previous patient familiarisation with either the Rotahaler or the pMDI was not mentioned as a requirement for study entry.

Patient characteristics:

10 male patients with stable COPD recruited from outpatient chest clinic. No exacerbation's of COPD during the preceding 3 months, no heart disease or other illness and no treatment with oral bronchodilators, theophylline and oral or inhaled corticosteroids during 4 weeks preceding the study. Baseline characteristics include, mean (SD): age 67(4) years, FEV1 L 1.56(0.32) = 60% predicted, smoking pack year history 52(21) and none of the patients were current smokers.

Device: Rotahaler vs. pMDI.

The Rotahaler device is a dry powder device, which requires to be loaded each time with a capsule that contains the medication and the carrier (lactose). The device needs to be taken apart in order to load the capsule which is then pierced and the medication is then breathed-in through the mouthpiece located at the top of the device. A rotor at the bottom of the device propels the drug through the device when a patient inhales. This is an old device now rarely used and has been superseded by newer devices. Unlike the pMDI this device does not have any propellants and therefore does not have the "cold feron" effect often felt with the pMDI. However, the Rotahaler device is reusable since only more capsules are required to be purchased.

Drug & Dosing:

Salbutamol 200 mcg and 1 mg via Rotahaler or pMDI with large volume (750 ml) spacer. Each treatment regime consisted of the administration of 5 capsules via Rotahaler and 10 puffs via the pMDI. The dose of 200 mcg via the Rotahaler was administered as one active 200 mcg capsule and 4 matching placebos, that of the 200 mcg via the pMDI was administered as 2 puffs of active (100 mcg /puff) drug and 8 puffs of placebo.

Duration of study & measurements:

Study measurements were done till 240 minutes after the last dose of study medication with spirometry performed before and 15, 30,

60, 90, 120 & 240 minutes post bronchodilator but only FEV1 max & AUC-FEV1 data were reported. Treatment failures and adverse events were also mentioned. Two doses used in study, therefore separated as two references for ease of data entry into RevMan. Data was reported as absolute mean value at the end of the study period. The 30 minute data was used, as it was the closest match to the data reported by another similar study (Formgren 1994).

Further details for the three included studies can be found in the table "Characteristics of included studies".

Risk of bias in included studies

The three included studies were of good quality designs with the Ikeda 1999 and [Iacono 2000](#) trials scoring an 'A' (for Cochrane quality) and the Formgren 1994 trial scoring a 'B'. All studies scored 5 when the Jadad scale was used, indicating that they were of high methodological quality.

Effects of interventions

From the search of the Cochrane Airways Group register, 1,565 abstracts were identified for possible inclusion in the review. Eight abstracts were selected by two reviewers as possibly being appropriate for inclusion in the review and six abstracts were obtained from bibliographies of retrieved articles. A total of 14 full text papers were retrieved for possible inclusion. After reading the full text of these 14 studies, nine were excluded as not appropriate, a further two were excluded on methodological grounds and the remaining three included in the review. Reasons for exclusion of the 11 studies are listed in the table for "Characteristics of excluded studies".

Data abstracted from the three included studies provided the following non-significant results.

Turbuhaler (containing terbutaline)

The following outcome measures were not statistically significant: FEV1, FVC, RV, SGaw, treatment failures and adverse effects.

Rotahaler (containing salbutamol)

The following outcome measures were not statistically significant: FEV1, AUC-FEV1, FVC, pulse rate, systolic blood pressure, diastolic blood pressure, treatment failures and adverse effects.

The outcome measures were not significantly different whether high or low doses of medication were used or whether a spacer device was used with the pMDI.

Respimat (containing ipratropium bromide)

One study ([Iacono 2000](#)) presented results as adjusted means, which showed that FEV1 and FVC were significantly greater with the use of Respimat inhaler device as opposed to the pMDI (without a spacer). There were no differences between the two devices in pulse rate and adverse events. Unfortunately, there were no other included studies, which used the Respimat device, so these results need to be confirmed by other similar RCT's.

Data were not available for the following outcome measures: quality of life measures, symptom scores, use of additional relief medication, use of inhaled or oral steroid requirement, severity of disease, days off work, compliance, patient preference, systemic bio-availability, subsidiary physiological measures (e.g. 6 or 12

minute walks, arterial blood gases) and acute exacerbations. In addition, there was insufficient number of included studies for subgroup analysis.

DISCUSSION

In patients with stable COPD, pMDI produced similar outcomes to a dry powder device for delivering beta2-agonists, but the very small number of studies and included patients does not permit firm conclusions to be drawn. The soft mist device for ipratropium was more effective than a pMDI, but the data come from one small study.

A comprehensive search strategy was developed for this review. Every effort was made to identify all of the relevant studies. No study was excluded due to language. While several attempts were made to identify unpublished work, it is still possible that some studies have been missed. However, the small number of eligible studies was not due to restricted selection criteria, but rather to the absence of identified RCTs evaluating inhaler devices (pMDI & DPI's) containing bronchodilators in COPD.

A common problem with conducting such a systematic review was that the included studies were designed as tests of the superiority of one device over another in which the null hypothesis was of equal efficacy. Such studies require fewer patients than those designed to test equivalence (null hypothesis than one device is superior to the other) and they also require pre-determined limits of equivalence as in [Iacono 2000](#) although this study was powered for superiority to test equivalence. Thus the three studies may have been underpowered. Failure to detect a difference should not necessarily imply equivalence as trials designed to compare efficacy increase the chances of type II error.

Another problem with such trials is that patients are usually selected on the basis of being able to use a pMDI as an inclusion criteria, therefore the results would favour pMDI use. In the three RCTs included in this review previous patient familiarisation with either the pMDI or the DPIs were not mentioned as a requirement for study entry. Therefore the limited results presented from these three RCTs can be applied to most patients with stable COPD. Although, adequate pMDI use was not a requirement for entry into the study, we should assume that all patients recruited into these three RCTs were taught to use both the pMDI and the DPIs prior to commencing the study.

AUTHORS' CONCLUSIONS

Implications for practice

In patients with stable COPD, the pMDI device produced similar outcomes to a dry powder device for delivering beta2-agonists, but the very small number of studies and included patients does not permit firm conclusions to be drawn. The soft mist device for ipratropium was more effective than a pMDI, but the data come from one small study.

Implications for research

There needs to be further randomised controlled trials examining the role of inhaler devices containing bronchodilators in COPD.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Formgren 1994a

Methods	Design: randomised double-blind, double- dummy, crossover, Latin square design. Device: Turbuhaler vs pMDI with Nebuhaler spacer for higher dose Drug: terbutaline Dose: 1.0 mg Duration: 40 minutes
Participants	15 hospitalised adult patients (4 women) in stable phase of their disease without recent exacerbations and medication unchanged in weeks. All patients were ex-smokers and upon admission all patients demonstrated a $\geq 15\%$ response in FVC and or a decrease in RV without increase ($< 15\%$) in FEV1 after inhalation of a beta-2 agonist (4 x 0.1 mg salbutamol or 4 x 0.25 mg terbutaline). COPD diagnoses was based on clinical history, X-ray, spirometry and body plethysmography after a run-in period of 1 week. Mean age 61 yrs (SD 9, range 44-72), mean %predicted FEV1=35.6% (range 23-48), mean disease duration 11.6 yrs (range 1-42). Mean basal FEV1 over the five study days for all patients did not vary greater outside 1.0 to 1.1 L.
Interventions	Four treatments regimes: Turbuhaler-terbutaline 1 mg; pMDI(CFC)-terbutaline (no spacer) 1 mg; Turbuhaler-terbutaline 2.5 mg & 2.5 mg pMDI(CFC)-terbutaline with Nebuhaler spacer 2.5 mg. A one week run-in period was used during which PEF was measured 5 times a day and patients were included in the study if their diurnal PEF variation did not exceed 15%. Interval of at least 48 hours between treatments. for washout. Study measurements were made before and 10 to 40 minutes after study drug administration.
Outcomes	FEV1, FVC, RV & sGaw. Results presented and entered into the review were 40 minutes post bronchodilator. Treatment failures and adverse events were mentioned in text.
Notes	Two different doses were used in study (separated by 48 hour washout), therefore separated as two references here for ease of data entry into RevMan.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	Information not available (Cochrane Grade B)

Formgren 1994b

Methods	Design: randomised double-blind, double- dummy, crossover, Latin square design. Device: Turbuhaler vs pMDI with Nebuhaler spacer for higher dose Drug: terbutaline Dose: 2.5 mg Duration: 40 minutes
Participants	15 hospitalised adult patients (4 women) in stable phase of their disease without recent exacerbations and medication unchanged in weeks. All patients were ex-smokers and upon admission all patients demonstrated a $\geq 15\%$ response in FVC and or a decrease in RV without increase ($< 15\%$) in FEV1 after inhalation of a beta-2 agonist (4 x 0.1 mg salbutamol or 4 x 0.25 mg terbutaline). COPD diagnoses was based on clinical history, X-ray, spirometry and body plethysmography after a run-in period of 1 week. Mean age 61 yrs (SD 9, range 44-72), mean %predicted FEV1=35.6% (range 23-48), mean disease duration 11.6 yrs (range 1-42). Mean basal FEV1 over the five study days for all patients did not vary greater outside 1.0 to 1.1 L.
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Outcomes	FEV1, FVC, RV & sGaw. Results presented and entered into the review were 40 minutes post bronchodilator. Treatment failures and adverse events were mentioned in text.
Notes	Two different doses were used in study (separated by 48 hour washout), therefore separated as two references here for ease of data entry into RevMan.
Risk of bias	
Bias	Authors' judgement Support for judgement
Allocation concealment?	Unclear risk Information not available (Cochrane Grade B)

Iacono 2000

Methods	Design: randomised 3-way crossover, design. Device: Respimat vs pMDI Drug: ipratropium bromide Dose: 320ug Duration: 180 minutes
Participants	36 patients (29M;7F) presenting with stable COPD recruited from outpatient chest clinic (COPD defined according to the ATS 1987 criteria). No change in pulmonary medication 6 weeks prior to screening visit, not on chronic oxygen therapy, oral corticosteroids, beta-blockers, antihistamines or cromolyn/nebdocromil sodium. Stable use of inhaled corticosteroids was permitted. Mean(SD): Age 52(6) yrs; FEV1 L 1.8(0.4); FEV1 % predicted 52.6(8.9); smoking pack year history 49(15) (range 20-80), with no current smokers. Mean FEV1 reversibility 60 min after 40ug ipratropium bromide via MDI was 30.7(7.7).
Interventions	Ipratropium bromide 320ug total dose administered. Using 20ug per puff for both the pMDI and RP (cumulative puffs were: 1 + 1 + 2 + 4 + 8 inhaled at 50 min intervals). There was also a third arm that used the RP administering a total cumulative dose of 160ug. Interval of at least 2 days between treatments.

Iacono 2000 (Continued)

Outcomes	Spirometry (FEV1, FVC) was performed before and 45, 60, 90, 120 & 180 min post bronchodilator. Adverse events and vital signs (pulse rate & blood pressure) also recorded. All reported data were adjusted with baseline as the covariant.
Notes	Author reply: allocation of treatment was randomised. Treatment was open label between devices (RP vs pMDI) but the third arm not used was double-blind (RP 160ug vs RP 320ug).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order of treatment group assignment (Cochrane Grade A)

Ikedo 1999a

Methods	Design: randomised double-blind, double- dummy, crossover, design. Device: Rotahaler vs pMDI with InspirEase spacer device (750ml) Drug: salbutamol Dose: 200ug Duration: 240 minutes
Participants	10 male patients with stable COPD recruited from outpatient chest clinic. No exacerbations in the last 3 months and no treatment with oral bronchodilators, theophylline and oral or inhaled corticosteroids during the preceding 4 weeks. Mean(SD): Age 67(4) yrs (range 62-73); FEV1 L 1.56(0.32) = 60% predicted (range 1.12-2.17); smoking pack year history 52(21) (range 20-100), with no current smokers.
Interventions	Salbutamol 0.2 mg and 1 mg via Rotahaler or pMDI (CFC)-salbutamol with InspirEase spacer. There were also nebuliser arms in the study. Interval of at least 2-4 days between treatments. Each treatment regime consisted of the administration of 5 capsules via Rotahaler, 10 puffs via the pMDI and approximately 2 ml solution via the nebuliser. The dose of 200 ug via the Rotahaler was administered as 1 active 200 ug capsule and 4 matching placebos, that of the 200 ug via the pMDI was administered as 2 puffs of active (100ug /puff) drug and 8 puffs of placebo.
Outcomes	Spirometry was performed before and 15, 30, 60, 90, 120 & 240 min post bronchodilator but only FEV1max & AUC-FEV1 reported. Treatment failures and adverse events mentioned.
Notes	Two doses used in study, therefore separated as two references for ease of data entry into RevMan. All medication and treatment sequence was coded in advance and the codes not revealed until all patients had completed the protocols. Author reply providing all requested information and data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order of treatment group assignment (Cochrane Grade A)

Ikedo 1999b

Methods	Design: randomised double-blind, double- dummy, crossover, design. Device: Rotahaler vs pMDI with InspirEase spacer device (750ml) Drug: salbutamol
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Ikeda 1999b (Continued)

Dose: 1000ug
Duration: 240 minutes

Participants	10 male patients with stable COPD recruited from outpatient chest clinic. No exacerbations in the last 3 months and no treatment with oral bronchodilators, theophylline and oral or inhaled corticosteroids during the preceding 4 weeks. Mean(SD): Age 67(4) yrs (range 62-73); FEV1 L 1.56(0.32) = 60% predicted (range 1.12-2.17); smoking pack year history 52(21) (range 20-100), with no current smokers.
Interventions	Salbutamol 0.2 mg and 1 mg via Rotahaler or pMDI (CFC)-salbutamol with InspirEase spacer. There were also nebuliser arms in the study. Interval of at least 2-4 days between treatments. Each treatment regime consisted of the administration of 5 capsules via Rotahaler, 10 puffs via the pMDI and approximately 2 ml solution via the nebuliser. The dose of 200 ug via the Rotahaler was administered as 1 active 200 ug capsule and 4 matching placebos, that of the 200 ug via the pMDI was administered as 2 puffs of active (100ug /puff) drug and 8 puffs of placebo.
Outcomes	Spirometry was performed before and 15, 30, 60, 90, 120 & 240 min post bronchodilator but only FEV1max & AUC-FEV1 reported. Treatment failures and adverse events mentioned.
Notes	Two doses used in study, therefore separated as two references for ease of data entry into RevMan. All medication and treatment sequence was coded in advance and the codes not revealed until all patients had completed the protocols. Author reply providing all requested information and data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	Study investigators were not aware as to order of treatment group assignment (Cochrane Grade A)

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bellamy 1981	Comparison was against a placebo aerosol inhaler.
Cushley 1983	Study compared: MDI vs MDI + spacer vs a mini-nebuliser
Gimeno 1988	Study includes patients with asthma, chronic bronchitis and emphysema. The author grouped all patients together and referred to them all as having COPD, no separate data was provided for each of the groups.
Harvey 1992	Patient allocation not randomised and patients not clearly diagnosed as having COPD.
Iversen 1999	Study compared terbutaline turbuhaler against placebo turbuhaler.
Larsen 1998	Study used a new type of micro-nebuliser (piezoelectric) device vs pMDI with both delivering 100ug per puff. Study also had mixed populations of subjects (Asthma = 39, COPD = 9).
Mutterlein 1990	Comparison of DPI vs DPI (no pMDI involved) using the Ingelheim M inhalator.
Petersen 1983	Author included mixed population (both asthmatic and COPD patients in study) and data not presented separately.
van der Palen 1995	Not a randomised controlled trial. Study set out to test the differences between inhaler techniques with 4 different devices (pMDI, Turbuhaler, Diskhaler & Rotahaler).

Study	Reason for exclusion
van der Palen 1998	Study compared DPI against DPI (Diskus/Accuhaler vs Turbuhaler). Study also had both asthma and COPD patients.
Wetterlin 1988	Not a RCT, a qualitative review on the working aspects of the Turbuhaler.

DATA AND ANALYSES

Comparison 1. Turbuhaler vs pMDI (absolute change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	2	60	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.06, 0.06]
1.1 Turbuhaler vs pMDI without spacer	1	30	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.07, 0.07]
1.2 Turbuhaler vs pMDI with spacer	1	30	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.14, 0.14]
2 FVC (L)	2	60	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.16, 0.27]
2.1 Turbuhaler vs pMDI without spacer	1	30	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.19, 0.39]
2.2 Turbuhaler vs pMDI with spacer	1	30	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.32, 0.32]
3 RV (L)	2	60	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.23, 0.64]
3.1 Turbuhaler vs pMDI without spacer	1	30	Mean Difference (IV, Fixed, 95% CI)	0.40 [-0.21, 1.01]
3.2 Turbuhaler vs pMDI with spacer	1	30	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.62, 0.62]
4 SGaw (kPa/L/s)	2	60	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.06, 0.13]
4.1 Turbuhaler vs pMDI without spacer	1	30	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.08, 0.16]
4.2 Turbuhaler vs pMDI with spacer	1	30	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.15, 0.19]
5 Treatment Failures/Drop outs	2	60	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.1 Turbuhaler vs pMDI without spacer	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 Turbuhaler vs pMDI with spacer	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Adverse Events	2	60	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.1 Turbuhaler vs pMDI without spacer	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Turbuhaler vs pMDI with spacer	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Turbuhaler vs pMDI (absolute change from baseline), Outcome 1 FEV1 (L).

Analysis 1.2. Comparison 1 Turbuhaler vs pMDI (absolute change from baseline), Outcome 2 FVC (L).

Analysis 1.3. Comparison 1 Turbuhaler vs pMDI (absolute change from baseline), Outcome 3 RV (L).

Analysis 1.4. Comparison 1 Turbuhaler vs pMDI (absolute change from baseline), Outcome 4 SGaw (kPa/L/s).

Analysis 1.5. Comparison 1 Turbuhaler vs pMDI (absolute change from baseline), Outcome 5 Treatment Failures/Drop outs.

Analysis 1.6. Comparison 1 Turbuhaler vs pMDI (absolute change from baseline), Outcome 6 Adverse Events.

Comparison 2. Rotahaler vs pMDI (mean absolute value)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L)	2	40	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.19, 0.25]
1.1 Rotahaler vs pMDI with spacer	2	40	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.19, 0.25]
2 AUC-FEV1 (L.min)	2	40	Mean Difference (IV, Fixed, 95% CI)	6.86 [-7.45, 21.17]
2.1 Rotahaler vs pMDI with spacer	2	40	Mean Difference (IV, Fixed, 95% CI)	6.86 [-7.45, 21.17]
3 FVC (L)	2	40	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.24, 0.34]
3.1 Rotahaler vs pMDI with spacer	2	40	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.24, 0.34]
4 Heart Rate (bpm)	2	40	Mean Difference (IV, Fixed, 95% CI)	0.38 [-7.81, 8.57]
4.1 Rotahaler vs pMDI with spacer	2	40	Mean Difference (IV, Fixed, 95% CI)	0.38 [-7.81, 8.57]
5 Systolic Pressure (mmHg)	2	40	Mean Difference (IV, Fixed, 95% CI)	2.60 [-3.97, 9.17]
5.1 Rotahaler vs pMDI with spacer	2	40	Mean Difference (IV, Fixed, 95% CI)	2.60 [-3.97, 9.17]
6 Diastolic Pressure (mmHg)	2	40	Mean Difference (IV, Fixed, 95% CI)	0.02 [-3.15, 3.20]
6.1 Rotahaler vs pMDI with spacer	2	40	Mean Difference (IV, Fixed, 95% CI)	0.02 [-3.15, 3.20]
7 Treatment Failures/Drop outs	2	40	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Rotahaler vs pMDI with spacer	2	40	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Adverse Events	2	40	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 7.32]
8.1 Rotahaler vs pMDI with spacer	2	40	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 7.32]

Analysis 2.1. Comparison 2 Rotahaler vs pMDI (mean absolute value), Outcome 1 FEV1 (L).

Analysis 2.2. Comparison 2 Rotahaler vs pMDI (mean absolute value), Outcome 2 AUC-FEV1 (L.min).

Analysis 2.3. Comparison 2 Rotahaler vs pMDI (mean absolute value), Outcome 3 FVC (L).

Analysis 2.4. Comparison 2 Rotahaler vs pMDI (mean absolute value), Outcome 4 Heart Rate (bpm).

Analysis 2.5. Comparison 2 Rotahaler vs pMDI (mean absolute value), Outcome 5 Systolic Pressure (mmHg).

Analysis 2.6. Comparison 2 Rotahaler vs pMDI (mean absolute value), Outcome 6 Diastolic Pressure (mmHg).

Analysis 2.7. Comparison 2 Rotahaler vs pMDI (mean absolute value), Outcome 7 Treatment Failures/Drop outs.

Analysis 2.8. Comparison 2 Rotahaler vs pMDI (mean absolute value), Outcome 8 Adverse Events.

Comparison 3. Respimat vs pMDI (absolute change from baseline)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L): absolute change from baseline	1	72	Mean Difference (IV, Fixed, 95% CI)	0.07 [0.01, 0.13]
1.1 Respimat vs pMDI without spacer	1	72	Mean Difference (IV, Fixed, 95% CI)	0.07 [0.01, 0.13]
2 FVC (L): absolute change from baseline	1	72	Mean Difference (IV, Fixed, 95% CI)	0.10 [0.08, 0.12]
2.1 Respimat vs pMDI without spacer	1	72	Mean Difference (IV, Fixed, 95% CI)	0.10 [0.08, 0.12]
3 Heart Rate (bpm): mean absolute value	1	76	Mean Difference (IV, Fixed, 95% CI)	1.18 [-2.92, 5.28]
3.1 Respimat vs pMDI without spacer	1	76	Mean Difference (IV, Fixed, 95% CI)	1.18 [-2.92, 5.28]
4 Adverse Events	1	74	Risk Ratio (M-H, Fixed, 95% CI)	3.69 [0.82, 16.62]
4.1 Respimat vs pMDI without spacer	1	74	Risk Ratio (M-H, Fixed, 95% CI)	3.69 [0.82, 16.62]

Analysis 3.1. Comparison 3 Respimat vs pMDI (absolute change from baseline), Outcome 1 FEV1 (L): absolute change from baseline.

Analysis 3.2. Comparison 3 RespiMat vs pMDI (absolute change from baseline), Outcome 2 FVC (L): absolute change from baseline.

Analysis 3.3. Comparison 3 RespiMat vs pMDI (absolute change from baseline), Outcome 3 Heart Rate (bpm): mean absolute value.

Analysis 3.4. Comparison 3 RespiMat vs pMDI (absolute change from baseline), Outcome 4 Adverse Events.

WHAT'S NEW

Date	Event	Description
18 August 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2000

Review first published: Issue 2, 2001

Date	Event	Description
25 November 2001	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Felix Ram (previous author) carried out all of the work involved in this review with help from the following people. David Brocklebank was involved in the duplicate screening of abstracts and full text papers for inclusion. John Wright was the third reviewer whose opinions were sort if disagreements persisted for study inclusion he also commented on draft versions. Martin Muers was involved in the early developmental stages of the review and also commented on the draft versions of the review. Paul Jones edited and revised many versions of the review before approval for the Cochrane library.

DECLARATIONS OF INTEREST

There are no known conflicts of interest.

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External sources

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INDEX TERMS

Medical Subject Headings (MeSH)

*Nebulizers and Vaporizers; Adrenergic Agonists [administration & dosage]; Bronchodilator Agents [*administration & dosage]; Pulmonary Disease, Chronic Obstructive [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans