Use of oscillatory positive expiratory pressure (OPEP) devices to augment sputum clearance in COPD: a systematic review and meta-analysis

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**ABSTRACT**

**Introduction**: Oscillating positive expiratory pressure (OPEP) devices are intended to facilitate sputum clearance in COPD, but there is uncertainty as to their place in treatment pathways. We aimed to review the existing literature to establish the evidence base for their use.

**Methods:** A systematic search of records up to March 2020 was performed on PubMed, CINAHL, Medline (Ovid), Cochrane, and Embase to retrieve clinical trials that evaluated the efficacy of OPEP devices in patients with COPD. Two independent reviewers retrieved the titles, abstracts, and full texts, and completed the data extraction.

**Results:** Following full text review of 77 articles, 8 (six randomised control trials and two crossover studies) were eligible for inclusion. Pooled analysis showed low grade evidence that the use of OPEP devices was associated with decreased COPD symptoms and exacerbations (odds ratio [95% CI], 0.37 [0.19 to 0.72]), and enhanced exercise capacity; 6 minute walk distance (mean difference [95% CI], 49.8m [14.2m to 85.5m]; p=0.009]). However, studies were mostly short term with the majority having a high risk of bias. The average acceptance, completion, and dropout rates were 82%, 91%, and 8%, respectively.

**Conclusion:** The use of OPEP devices can have a positive impact in COPD, but effect sizes are small and there is a need for further, higher quality studies to examine their long-term efficacy in COPD as well as to identify specific patient phenotypes that are more likely to respond.

**Word count:** 234

**Keywords:** Systematic review, meta-analysis, oscillatory positive expiratory pressure, chronic obstructive pulmonary disease, COPD

**Key messages**

* What is the key question?
  + Does the use of OPEP devices impact health-related quality of life and symptoms, exacerbations, lung function parameters, and exercise capacity, compared to usual care or alternative sputum clearance techniques in people with COPD?
* What is the bottom line?
  + Low grade evidence from mostly short-term studies suggests some benefit from the use of OPEP devices in COPD, but average effects are relatively small. At present insufficient information is available regarding their long-term effectiveness and value.
* Why read on?

This review systematically evaluates the evidence for the efficacy of OPEP devices in acute and stable COPD and highlights gaps in the evidence needed to guide their use.

**INTRODUCTION**

Productive cough due to mucus hypersecretion is a common feature in people with Chronic Obstructive Pulmonary Disease (COPD). Clearing mucus from the chest can be difficult, as lung hyperinflation, respiratory muscle dysfunction and premature airway collapse impede the ability to generate an effective cough.1-5 Cough with sputum production is a particular problem in COPD where there is co-existent bronchiectasis.6

When present, chronic cough is associated with worse quality of life.7 The inability to clear airway secretions contributes to lung damage and the systemic impact of COPD by increasing local inflammatory burden8 and the risk of respiratory exacerbations with their attendant consequences beyond the lung. Acute exacerbations of COPD (AECOPD) are a common cause of hospital admission and interventions that reduce their occurrence are needed. Airway clearance is therefore a potentially important goal for both individuals and the healthcare system.9

Therapeutic measures to enhance airway clearance include mucolytic drugs, and certain chest physiotherapy manoeuvres such as Airway Clearance Techniques (ACTs). 9 10 ACTs, particularly, can be augmented with the use of oscillating positive expiratory pressure (OPEP) devices for sputum clearance. OPEP devices are handheld airway clearance aids which operate on the principle that high-frequency oscillations during expiratory flow generate shear forces, which reduce the viscoelasticity of secretions and improve mucus transport.11-13 Furthermore, PEP during exhalation reduces airway collapsibility and facilitates collateral ventilation to maintain airway patency as well as facilitating the movement of secretions centrally for expectoration.10 14 Generally, OPEP devices incorporate an adjustable valve, which alters expiratory resistance and influences the amplitude and frequency of oscillations. Though all are based on the same principles, the design and operation of OPEP devices differs and so may yield different benefits.9 15-17

Although OPEP devices are intended to help with sputum clearance in COPD there is uncertainty about the indications for their use18, and they are still neglected in clinical guidelines for the management of COPD. Previous reviews of the use of OPEP devices show that they might contribute to reducing hospitalisation, improve short-term health status, and exercise tolerance, but these conclusions were based on a limited number of trials in a small number of participants.1819

United Kingdom (UK) prescribing data from 2013 to 2015 demonstrates very widespread prescription of mucolytic medications to treat patients with COPD, in whom sputum production was presumably identified as a major complication, but only a small number of patients were prescribed OPEP devices during the same period.18 Survey data show substantial uncertainty and variation in clinician views as to the indication for OPEP device use across a range of clinical scenarios, defined in terms of the extent of sputum production and exacerbation frequency.18

We therefore aimed to evaluate the available evidence regarding the effect of OPEP devices on outcomes including health-related quality of life (HRQoL) and symptoms of COPD, exacerbations of the disease, lung function, exercise capacity, antibiotic use, and hospital admission, as well as estimate the overall acceptance, completion, and dropout rates for clinical trials of OPEP devices in people with COPD to inform clinical practice and serve as a basis for designing further clinical trials in this area.

**METHODS**

This systematic review was registered on PROSPERO (CRD 42016041835). The Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guideline was used to complete this systematic review.

**Inclusion criteria**

* + 1. *Study type*: randomised controlled and randomised crossover clinical trials.
    2. *Population:* studies including individuals diagnosed with COPD (Defined as forced expiratory volume in 1 second (FEV1)/ forced vital capacity (FVC) ratio <70%, FEV1<80% predicted and any history of smoking). Studies could be either in stable patients or at the time of AECOPD
    3. *Type of intervention:* use of an OPEP device on its own or combined with another therapeutic intervention.
    4. *Type of outcome:* All reported primary and secondary outcomes of COPD were extracted.

**Exclusion criteria**

1. Trials not translated or published in English.
2. Studies that did not include COPD patients or included a mixed population.
3. Studies that did not describe the type or frequency of the treatment.
4. Studies that evaluated the effect of OPEP devices in a single session of treatment only.

(5) Studies that did not report the number of individuals who were approached for, consented to and completed the trial.

**Search strategy**

An electronic search of the following databases from earliest records to March 2020 was undertaken to identify and retrieve relevant articles: PubMed; CINAHL; MEDLINE (Ovid); Cochrane Library and Embase. Medical Subject Headings, subject headings, and/or keywords and combinations, used in all databases, were as follows: airway clearance device, airway clearance therapy; sputum clearance techniques, chest clearance techniques, Acapella, Aerobika, Flutter device, Lung Flute, positive expiratory pressure, positive expiratory pressure therapy, Oscillatory Positive Expiratory Pressure; OPEP; Chronic Obstructive Pulmonary Disease; Chronic Obstructive Lung Disease, and COPD. The search strategy was developed in collaboration with an expert health sciences librarian, to ensure the inclusion of appropriate and necessary keywords in the review. Keywords and subject terms were customised for each database. Full search strategy from all databases is provided in Appendix 1. Studies were defined as short-term if <12 weeks duration or long-term if >12 weeks.

**Search procedures**

The search was performed by the first author (SA), after which all articles were imported to EndNote version 7.8 and duplicates removed. All article titles and abstracts were screened by two reviewers (SA and RB). A third reviewer (NH) was available to resolve any disagreements. A manual search of the reference lists of relevant studies was undertaken to identify any potentially relevant articles that were missed by the database search but that might be suitable for inclusion in the review. A full-text review of all suitable articles was undertaken and any study that did not meet the inclusion criteria was excluded, with the reasons for exclusion recorded in Appendix 2.

**Data extraction**

A standardized Microsoft Excel spreadsheet was created for data extraction. We attempted to contact the corresponding authors of included studies to obtain missing data and complete the data extraction form. The form included information on acceptance, completion, and dropout rates, as well as patient characteristics, a description of the intervention and comparison groups and data on the outcomes of included studies. Data from the first evaluation and those from any subsequent follow-ups were extracted . The quality of studies was defined based on the Cochrane risk-of-bias assessment tool.20 Two independent reviewers (SA and RB) performed the quality assessment for the included studies. Any disagreement between the reviewers regarding study eligibility and quality assessment was resolved by discussion. A third reviewer (NH) was available to resolve any persisting disagreements.

**Data analysis**

The results synthesis focused on key outcomes of interest including HRQoL and symptoms of COPD, acute exacerbations of the disease, lung function parameters, exercise capacity, and antibiotic use, as well as acceptance, completion, and dropout rates. A meta-analysis was performed to estimate the pooled differences and 95% confidence intervals (CIs) in key outcomes between the OPEP group and the control group. The endpoint data after treatment exposure were used for analysis.21 22 A random-effects model was used to obtain a conservative estimate. Continuous data are expressed as the mean difference (Δ). Standardized mean difference (SMD) was used when the same outcome was assessed with different measures. Dichotomous data are expressed as odds ratios (OR). Heterogeneity among included studies was assessed using the I-square (I2) value. Publication bias was assessed with funnel plots for included studies. The statistical analyses were performed using the Cochrane Collaboration’s Review Manager Software (RevMan version 5.2.0).

The overall acceptance rate was defined as the total number of participants who consented to participate divided by the number of participants who were approached for participation in the trial. The completion rate was defined as the total number of participants who completed the trial divided by the number of participants who enrolled in the trial and the dropout rate as the total number of participants in each treatment arm who dropped out from the study divided by the number of participants who consented to participate in the study.23 Additional meta-analysis was preformed to estimate the pooled difference and 95% CI in acceptance, completion, and dropout rates between the OPEP and control groups. The estimation of rates weighted by the sample size in each study and data were pooled using random-effects models. All rates are expressed as proportions with 95% CIs. More information about the data analysis is provided in (Figure 1).

**RESULTS**

The search identified 1583 articles, 1351 after duplicates had been excluded, with a total of 77 articles retained for full-text review following title and abstract screening. Afterfull-text review, eight articles were eventually considered for the review as outlined in PRISMA flow diagram (Figure 2).

Six of the eight reports were randomised controlled parallel-group trials and two were crossover studies; the studies were published between 1996 and 2018. The eight included studies comprised a total of 381 patients with COPD, with sample sizes ranging from 15 to 120. Participant age (mean ± standard deviation) was 65 ± 7.4 years, and 61% were male. In total, 336 patients were recruited into trials of stable COPD, 45 during an acute exacerbation (AECOPD).24-30 Five studies were categorised as short term (<12 weeks), and three were categorised as long term, with duration up to 2 years. A range of comparisons were used including usual care (e.g. COPD medication regimen), Active Cycle of Breathing Technique (ACBT), Pulmonary Rehabilitation (PR), and sham devices.24-30 A summary of included studies is provided below in Table 1.

In the included studies, a range of different OPEP devices were used (e.g., Acapella [Smiths-Medical, Dublin, OH, USA], Flutter [Allergan, Inc., Dublin, Ireland], Aerobika [Monaghan Medical Corporation, Plattsburgh, NY, USA ], Lung Flute [Medical Acoustics, Buffalo, NY, USA], and RC-Cornet [Cegla Medical Technology, Montabaur, Germany]).

**Table 1:** A summary of included studies

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Author (Year)** | **Patient group**  **design** | **OPEP device** | **Treatment duration** | **Follow**  **up** | **Control** | **Results of OPEP group compared to corresponding groups** |
| Aggarwal (2010)24 | Hospitalised AECOPD  RCT | Flutter n=15 | 15-mins, 3x per day, for 5 days | Every day | **Control 1:**ACBT n=15  **Control 2:** pursed lip breathing n=15 | Flutter and ACBT had the same effect on lung function compared to pursed lip breathing (ΔPEFR; +30 L/min)  Flutter reduced hospital stay compared to ACBT and pursed lip breathing (3/5/5 days) |
| Cegla (2002)25 | Stable COPD FEV1 40±14%  RCT | RC-Cornet plus UC n=25 | >5-mins, 3x per day, for 2 years | Every 3 months | UC n=25 | RC-Cornet had the same effect as UC on lung function (ΔFVC%; predicted +2%)  RC-Cornet reduced antibiotic use compared to UC (12/25 vs 24/25)  RC-Cornet reduced exacerbations over 2 years compared to UC (5/25 vs 12/25)  RC-Cornet had the same effect as UC on hospital stays (17 vs 18 days). |
| McCarroll (2005)31 | Stable COPD with hypersecretion  RCT | Acapella plus PR n=12 | 10 - mins, 2x per week, for 8 weeks | Every 4 weeks | **Control 1:** UC n=11  **Control 2:** PR n=12 (2 sessions per week, for 8 weeks) | Acapella had the same effect as UC & PR on lung function (Δ FEV1 and PEFR; +0.28 L/min and +16 L/min)  Improvement in exercise capacity did not differ significantly between UC and PR (Δ6MWD; +44 m vs +54 m) |
| Nicolini (2018)26 | Stable COPD  FEV1=31±10%  RCT | Lung Flute plus UC n=40 | 30-mins, 2x per day, for 12 days and then 26 weeks follow up | Every 4 weeks | **Control 1:** Flutter n=40 (30-mins, 2x per day, for 12 days and then 26 weeks follow up)  **Control 2:** UC n=40 | Lung Flute and Flutter reduced exacerbations compared to UC (7/40 vs 9/40 vs 11/40)  Lung Flute and Flutter improved exercise capacity vs UC (Δ6MWD; +18.4 m/+11.5 m / -4.8 m)  Lung Flute, Flutter, and UC;no difference in cough or sputum clearance (Δ BCSS score; -3/ -3.1/-3.5)  Lung Flute and Flutter improved HRQoL compared to UC (Δ CAT score; -7.5/-6.4/-1.6)  Lung Flute and Flutter reduced dyspnoea compared to UC (ΔMMRC score; -0.6/-0.4/+0.1) |
| Sethi (2015)27 | Stable COPD with sputum production, FEV1 50±3%  RCT | Lung Flute plus UC  n=33 | 5-mins, 2x per day for 26 weeks | Every 8 weeks | UC  n=36 | Lung Flute reduced symptoms compared to UC (Δ CCQ score; -0.23 vs +0.01)  Lung Flute improved HRQoL compared to UC (ΔSGRQ score; -3.23 vs -1.85, p=0.03)  Lung Flute reduced exacerbations compared to UC (6/33 vs 14/36, p=0.03)  Lung Flute improved exercise capacity compared to UC (Δ6MWD; +7 m vs -42 m) |
| Svenningsen (2016)28 | Stable COPD- sputum producer vs non-sputum producer  FEV1 60±18%  RXT | Aerobika plus UC n=27 | 20-mins, 4x per day, for 3 weeks (one-week intervention, one-week washout, and one-week UC) | Not reported | UC | Aerobika improved lung function compared to UC (Δ FVC% predicted; +6%, p=0.005)  Aerobika improved HRQoL compared to UC (ΔSGRQ score; -9, p=0.01).  Aerobika improved sputum clearance compared to UC (ΔPEQ- ease-bringing-up-sputum; -1.2, p = 0.005)  Aerobika improved exercise capacity compared to UC (Δ 6MWD; +19 m, p = 0.04)  Aerobika improved regional ventilation compared to UC (Δ 3He MRI ventilation deficit percent; -1%). |
| Weiner*,* (1996)29 | Stable COPD  FEV1 35±8.5% predicted  RCT | Flutter n=10 | 10 mins, 4-8x per day for 3 months. | Not reported | Sham Flutter 10 mins, 4-8 times/day for 3 months. n=10 | Flutter and Sham Flutter no effect on lung function (ΔFVC% predicted +2% vs +2%)  Flutter improved exercise capacity vs Sham Flutter (Δ12-minute walk distance; +649 m vs +538 m) |
| Wolkove*,* (2004)30 | Stable COPD with sputum production and smoking history  FEV1 50±15%  RXT | Flutter plus UC n=15 | 10-mins, 4x per day, for 1 week | Every week | Sham Flutter 10-mins, 4x per day, for 1 week | Flutter improved lung function vs Sham Flutter (Δ FVC%; +24%, p=0.05)  Flutter improved exercise capacity vs Sham Flutter (Δ 6MWD; +10 m, p=0.05)  Flutter reduced dyspnoea vs Sham Flutter (Δ Borg scale; +1, p=0.05) |

Abbreviations: **Δ:** Data presented as mean difference in absolute values between groups; **x:** Sessions per day**; RXT:** Randomised crossover trial**; RCT**: Randomised control trial;  **N:** Number of participants**; OPEP**: Oscillatory Positive Expiratory Pressure; **ACBT:** Active Cycle of Breathing; **PR**: Pulmonary Rehabilitation; **I**: Intervention; **UC:** Usual Care; **C**: Control; **FVC**: Force Vital Capacity; **FEV1**: Forced Expiratory Volume in 1 second; **FEV1/FVC %:** FEV1/FVC ratio percentage; **PEFR:** Peak Expiratory Flow Rate; **SGRQ**: St. George’s Respiratory Questionnaire; **CCQ**: Clinical COPD Questionnaire; **FVC%:**predicted forced vital capacity; **mMRC**: Modified Medical Research Council; **6MWD:** Six-minutes Walking Distance; **MRI:** Magnetic Reasoning Imaging ; **BCSS**: The breathlessness, cough and sputum scale; **3He:** Hyperpolarized 3 Helium

**Use during AECOPD**

Only one study evaluated the impact of OPEP (Flutter) during hospitalisation for AECOPD.24 Aggarwal *et al*. performed an RCT of 45 patients with AECOPD, and found that use of the Flutter device, ACBT and pursed lip breathing were associated with no difference in peak expiratory flow rate (mean difference [95% CI], 6.91 L/min [-52.1 L/min to 65.9 L/min]). However, patients who used the Flutter spent less time than the usual care group (3 vs 5 days).24

**Stable COPD**

***HRQoL, symptoms and AECOPD***

The impact of OPEP devices on HRQoL and symptoms of COPD was assessed in three studies using disease-specific questionnaires (e.g. SGRQ [St. George's Respiratory Questionnaire] and CAT [COPD Assessment Test]).26-28 The meta-analysis for HRQoL is shown in Figure 4. Pooled analysis from two RCTs (n=137)26 27 showed that the use of an OPEP device (Lung Flute) improved HRQoL compared to routine care (SMD [95%], -1.11 [-1.52 to -0.70], p<0.001). Similarly, 3 weeks use of the Aerobika was associated with improvement in HRQoL assessed using the SGRQ compared to UC (mean ± standard deviation; Aerobika 38±12, UC 49±14; p=0.01). It was not possible to assess the effect of OPEP device on the separate SGRQ domains, which included activity, symptoms and influence because of incomplete data.28

***Number of exacerbations***

Figure 5 presents the study outcomes for number of exacerbation events.26 27 In the pooled analysis of three RCTs (n= 187) reporting data on exacerbation events during follow-up, the Lung Flute and RC-Cornet were effective for reducing exacerbations events after 6-months compared to routine care (OR [95% CI], 0.37 [0.19 to 0.72]; p = 0.003).26 27

***Antibiotic use***

Antibiotic use was measured in one long term study, which found that use of the RC-Cornet (twice a day) for 2 years significantly reduced the number of patients who took a course of antibiotics (13/25 vs. 24/25; OR [95% CI], 0.05 [0.01 to 0.38]; p=0.005).25

***Sputum clearance***

Only one study measured the sputum clearance outcome. 28A 3-week RXT found that use of the Aerobika device improved sputum clearance (assessed with the Patient Evaluation Questionnaire (PEQ)-ease-bringing-up-sputum) in COPD patients with sputum production compared to UC (mean difference ± standard deviation; Aerobika 2.70±1.10, UC 3.60 ±0.50; P=0.003).28 In this context, a reduced PEQ score indicates improved sputum clearance.28

***Lung function***

The impact of OPEP devices on measures of lung function was measured in six studies using a range of devices (RC-Cornet, Acapella, Flutter, and Aerobika). The studies used a range of parameters including forced expiratory volume in 1 second (FEV1), peak expiratory flow rate (PEFR), and predicted forced vital capacity (FVC%), and overall, the use of OPEP devices had no effect on lung function.24 25 28-31

***Exercise capacity***

Exercise capacity, assessed using six-minute walk distance (6MWD), was reported in six studies (Figure 6).26-31 Pooled analysis of four RCTs (n=181) demonstrated an improvement following use of OPEP (e.g., Acapella, Lung Flute, and Flutter) compared to the control group, with the mean effect exceeding the minimal clinical important difference (MCID) for the 6MWD32 (mean difference [95%CI], 49.8m [14.2m to 85.5m]; p=0.009).26 27 29 31 In contrast, data from two RXTs using OPEP (e.g., Aerobika and Flutter) did not demonstrate a significant improvement compared to usual care 28 30

***Acceptance, completion, and dropout rates***

The total number of patients with COPD approached to take part in the included studies was 463. Of these, 82 patients were deemed ineligible and were excluded. 339 participants were enrolled in the studies with intervention and control groups, of whom 177 were assigned to the intervention group, and 162 to the control group. Forty-two participants were enrolled in the crossover studies.

After randomisation, 350 participants completed their interventions, and 31 withdrew before the end of the study. Of these, the reasons for study withdrawal were ‘lost to follow-up’ (66%), exacerbations (16%), death (6%), back pain (6%), discomfort during MRI (3%), and unknown (3%). Overall, the unweighted average of acceptance, completion and dropout rates for all included studies were 82%, 91% and 6%, respectively. Additionally, we performed a meta-analysis to estimate the pooled difference in acceptance, completion, and dropout rates between the OPEP groups and the control group for all included studies (weighted by the sample size). The pooled analysis demonstrated significant differences in acceptance and completion, but not in the dropout rate between the OPEP and control groups (mean difference [95%CI], 63% [ 58% to 67%]; p<0.001, 58% [ 53% to 63%]; p<0.001, and 3% [1% to 6%]; p=0.21) respectively. Figures 7, 8 and 9

**Risk of bias and evidence quality assessment**

Using the Cochrane risk-of-bias assessment tool,20 the studies included showed considerable variation in the risk of bias, but most were limited by a lack of blinding and incomplete reporting of data (Figure 10). Funnel plot analysis (Figure 3) showed that all points were within the funnel, but an absence of smaller negative studies was consistent with some publication bias.

In addition small sample sizes limit the precision of estimates. Studies did not necessarily focus on patients with significant sputum production, limiting the directness of the evidence to the relevant COPD phenotype. Taken together therefore the evidence to support the use of OPEP devices in COPD is, by GRADE criteria, low.

**DISCUSSION**

In the context of COPD, improving sputum clearance and sputum production are desirable objectives, both in terms of day to day symptoms and HRQoL, and for reducing the risk of acute exacerbations. Our findings suggest that the use of OPEP devices has the potential to reduce COPD symptoms and exacerbations, reduce antibiotic use, and improve exercise capacity in people with COPD. Nevertheless, questions remain regarding the use of OPEP devices, including their general effectiveness, the relative effectiveness of different types of device, the best strategy for their use (regular, or as required), the threshold of symptoms at which adjunct devices should be recommended (as benefits are likely to be largest in those for whom sputum production is a major concern), longer term impacts and acceptability, as well as their value relative to other interventions. Some evidence supports the use of an OPEP device to reduce exacerbations. However, the effects observed were generally modest, results were based on a limited number of trials with considerable variation in the risk of bias, and most trials were short-term.

Although sputum production is an important symptom for patients, this is a relatively neglected area in COPD. The Global Initiative on Obstructive Lung Disease 201933 and joint American Thoracic Society/European Respiratory Society COPD guidelines34 do not make any reference to sputum clearance techniques (searched using the words ‘sputum’, ‘clearance’ and ‘physiotherapy’), although NICE COPD guidance (1.2.99) recommends that “If people have excessive sputum, they should be taught: how to use positive expiratory pressure devices and the active cycle of breathing techniques”35. The term “excessive” is not defined here and it is not clear if the use of OPEP might also benefit people with persistent but less severe symptoms of sputum production, not meeting this notional threshold.

In COPD, sputum clearance might be expected to reduce airflow obstruction and allow occluded lung units to be recruited.36 Included studies have shown contrasting results; however, one study reported a reasonable response in lung function parameters such as FEV1 and PEFR immediately after an OPEP session.37 Nonetheless, lung function parameters appear to be relatively insensitive to regular use of OPEP devices.

Meta-analysis of RCTs demonstrated improvements in 6MWD exceeding the MCID32 with longer term OPEP device use26 27 29 31, though results from cross-over studies were less compelling. 28 30As expected, patients with sputum production were more likely to improve than those without, 28 38 suggesting that patient stratification is needed to identify a responder phenotype, as with other interventions.

The included studies used a variety of devices; all demonstrated a reasonable acceptance and completion rate and OPEP device intervention trials seem generally acceptable among people with COPD. Regrettably, data comparing the effectiveness of OPEP devices are limited. Here, the largest improvements in COPD symptoms, exacerbation and HRQoL were seen with the use of the Acapella, Lung Flute and Aerobika devices. By contrast, fewer improvements were recorded for the Flutter. This may simply reflect study population recruited or other aspects of study design, but it could be due to device features such as the pattern of pressure waves the OPEP devices can produce or the usability of the device itself.39 Direct comparison studies are needed to establish whether factors such as the consistency of pressure amplitude and frequency or the level of resistance are important. Some devices, such as Acapella and Aerobika, have a valve for adjustable resistance while other OPEP devices do not. Taken together, these differences and similarities are factors which may influence device efficacy and optimal mechanical performance both between devices generally and in terms of variations between individual patient response or preference*.*40 41 42

In the included studies, COPD was described as either acute or stable. These brief descriptions of the disease are inadequate for determining the clinical phenotype in such a heterogeneous condition. Of the included studies, only one stratified participants into sputum producers or non-producers. Accordingly, we recommend that future studies stratify the COPD profile according to the amount of sputum produced as a step towards developing personalised approaches to COPD care. 9 43 In the included studies, most dropouts were for patient-related reasons; specifically, patients mostly discontinued OPEP trials because of exacerbations. Thus, attention must be paid to accommodate these when designing OPEP trials of COPD. Other factors should also be considered, such as the cognitive ability required to perform OPEP exercise adequately and the need for support and training to maintain correct use.

A number of lessons can be learned from this review. First, most of the clinical trials had varied data measurement and collection for specific outcomes such as cough, sputum production, dyspnoea and HRQoL. Second, most of the clinical trials failed to blind the patients and participants, as well as outcome assessors. Third, addressing missing data was not clearly discussed in the published studies. This is important because it introduces the risk of bias in trial outcomes, and consequently weakens the evidence regarding the effectiveness of OPEP devices for COPD. Unfortunately, the available clinical trials still do not provide sufficient information regarding the OPEP long-term effectiveness and value with COPD.

An additional contribution of this review is to inform future clinical study design regarding the acceptance, completion and dropout rates of OPEP device trials in COPD. Moreover, this review will also help researchers understand the reasons that prevent patients with COPD from completing OPEP therapy and provides evidence for the short-term use of OPEP in COPD management.

**Limitations**

There are several limitations that should be considered when interpreting the results of this review and should be addressed in future research. First, this meta-analysis excluded single-session studies and included only studies that evaluate the short-and-long impact of OPEP devices on key outcomes (e.g., HRQoL, exacerbations, and exercise capacity). However, the exclusion of single-session studies is not expected to have had an effect on the overall results of this review, as it is hard to evaluate the acute impact of a single-session of OPEP device on a prolonged outcome such as HRQoL. In addition, the meta-analysis included different study designs (e.g. RCTs and RXTs) with different quality levels. Furthermore, there were limited opportunities to pool results for key outcomes because of incomplete data. Future research needs to evaluate the impact of OPEP devices within different types of study designs (e.g. pre/post studies) as well as report the outcomes of interest using gold-standard measures.

**Conclusion**

The use of OPEP devices may have a positive impact on patients with COPD. However, well-designed clinical trials are needed to examine the long-term impact of OPEP devices in well-defined specific patient cohorts. Data should be collected using valid measures and questionnaires to allow for comparison between studies and direct comparisons between devices are needed.

**CONTRIBUTORS**

SA, NH, MP, SB and RB developed the idea and designed the study protocol. SA, RB, and NH designed and wrote the search strategy and the first protocol draft. SA, NH, RB, ASA and AMS planned the data extraction and statistical analysis. NH, MP, WB and SB provided critical insights. All authors have approved and contributed to the final written manuscript.

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**FIGURE LEGENDS**

Figure 1: Statistical methods for acceptance, completion, and dropout rates.

Figure 2: PRISMA Flow diagram showing studies related to the Oscillatory Positive Expiratory Pressure (OPEP) devices in COPD.

Figure 3: Funnel plot for detection of publication bias.

Figure 4: Forest plot comparing HRQoL measures (CAT and SGRQ) scores in OPEP interventions vs non-OPEP interventions.

Figure 5: Forest plot comparing exacerbation events six-months following the OPEP use (Lung Flute) vs usual care in stable COPD.

Figure 6: Forest plot comparing exercise capacity measured with 6MWD (in meters) in OPEP interventions vs non-OPEP interventions (RCTs data only).

Figure 7: Forest plot of pooled difference in acceptance rate in OPEP interventions vs non-OPEP interventions.

Figure 8: Forest plot of pooled difference in completion rate in OPEP interventions vs non-OPEP interventions.

Figure 9: Forest plot of pooled difference in dropout rate in OPEP interventions vs non-OPEP interventions.

Figure 10: Assessment of risk of bias for included studies.

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