ORIGINAL RESEARCH

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

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2019-214360).

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Received 20 November 2019
Revised 10 June 2020
Accepted 16 June 2020

To cite: Alghamdi SM, Barker RE, Alsulayyim ASS, *et al*. *Thorax* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/thoraxjnl-2019-214360

ABSTRACT

Introduction Oscillating positive expiratory pressure (OPEP) devices are intended to facilitate sputum clearance in chronic obstructive pulmonary disease (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, eight (six randomised control trials and 2 cross-over 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 (OR 0.37, 95% CI 0.19 to 0.72), and enhanced exercise capacity; 6 min walk distance (mean difference (95% CI), 49.8 m (14.2 m to 85.5 m); p=0.009]). However, studies were mostly short term with the majority having a high risk of bias. The average acceptance, completion and drop-out rates were 82%, 91% and 8%, respectively.

Conclusion The use of OPEP devices can have a positive impact in COPD, but confidence in effect sizes is low 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.

PROSPERO registration number CRD 42016041835.

Key messages

What is the key question?

► Does the use of oscillating positive expiratory pressure (OPEP) devices impact health-related quality of life and symptoms, exacerbations, lung function parameters and exercise capacity, compared with usual care or alternative sputum clearance techniques in people with chronic obstructive pulmonary disease (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 coexistent 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 burden[8] 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

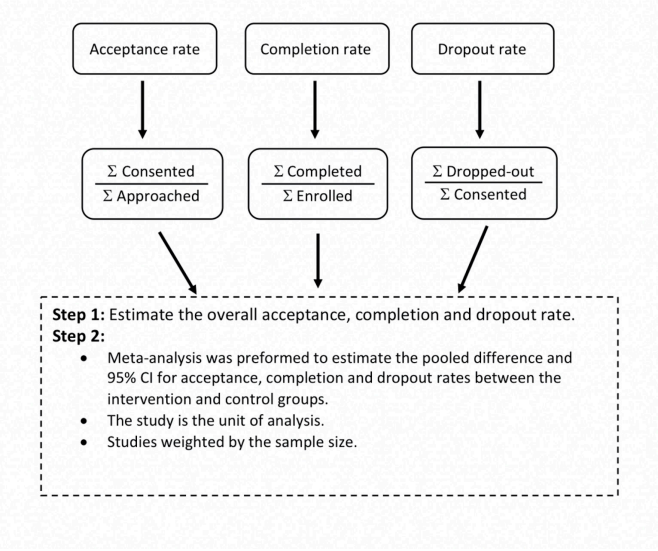

Figure 1 Statistical methods for acceptance, completion and drop-out rates.

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 use,[18] 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,

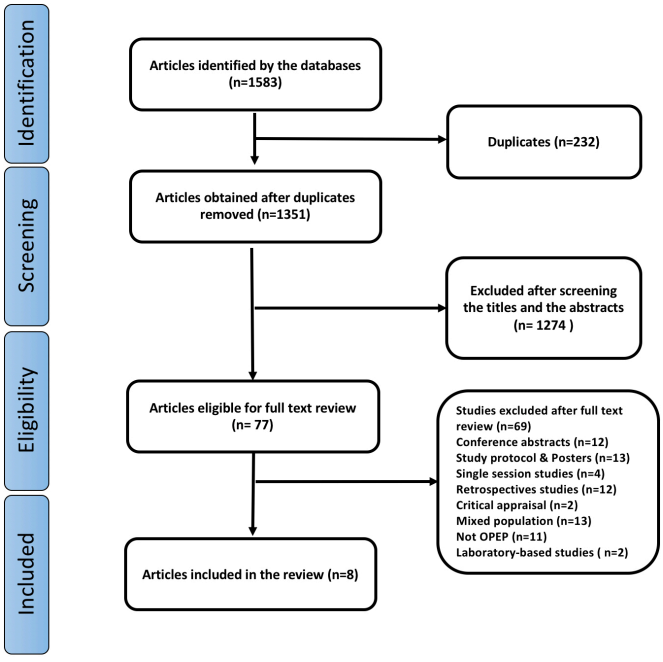

Figure 2 PRISMA flow diagram showing studies related to the oscillatory positive expiratory pressure (OPEP) devices in COPD. COPD, chronic obstructive pulmonary disease; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

but these conclusions were based on a limited number of trials in a small number of participants.[18 19]

UK prescribing data from 2013 to 2015 demonstrate 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 drop-out 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

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guideline was used to complete this systematic review.

Inclusion criteria

1. Study type: randomised controlled (RCT) and randomised cross-over (RXT) clinical trials.
2. Population: studies including individuals diagnosed with COPD (defined as forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio <70%, FEV_1 <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 patients with COPD 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

Table 1 A summary of included studies

Author (year)	Patient group design	OPEP device	Treatment duration	Follow-up	Control	Results of OPEP group compared with corresponding groups
Aggarwal (2010)[24]	Hospitalised AECOPD RCT	Flutter n=15	15 mins, 3 x 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 with pursed lip breathing (ΔPEFR; +30 L/min) Flutter reduced hospital stay compared with ACBT and pursed lip breathing (3/5/5 days).
Cegla (2002)[25]	Stable COPD FEV_1 40%±14% RCT	RC-Cornet plus UC n=25	>5 mins, 3 x 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 with UC (12/25 vs 24/25) RC-Cornet reduced exacerbations over 2 years compared with 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, 2 x 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 and PR on lung function (Δ FEV_1 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 FEV_1=31%±10% RCT	Lung Flute plus UC n=40	30 mins, 2 x per day, for 12 days and then 26 weeks follow-up	Every 4 weeks	**Control 1:** Flutter n=40 (30 mins, 2 x per day, for 12 days and then 26 weeks follow-up) **Control 2:** UC n=40	Lung Flute and Flutter reduced exacerbations compared with 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 with UC (Δ CAT score; −7.5/−6.4/−1.6) Lung Flute and Flutter reduced dyspnoea compared with UC (ΔMMRC score; −0.6/−0.4/+0.1).
Sethi (2015)[27]	Stable COPD with sputum production, FEV_1 50%±3% RCT	Lung Flute plus UC n=33	5 mins, 2 x per day for 26 weeks	Every 8 weeks	UC n=36	Lung Flute reduced symptoms compared with UC (Δ CCQ score; −0.23 vs +0.01) Lung Flute improved HRQoL compared with UC (ΔSGRQ score; −3.23 vs −1.85, p=0.03) Lung Flute reduced exacerbations compared with UC (6/33 vs 14/36, p=0.03) Lung Flute improved exercise capacity compared with UC (Δ6MWD;+7 m vs −42 m).
Svenningsen (2016)[28]	Stable COPD- sputum producer vs non-sputum producer FEV_1 60%±18% RXT	Aerobika plus UC n=27	20 mins, 4 x per day, for 3 weeks (1 week intervention, 1 week washout, and 1 week UC)	Not reported	UC	Aerobika improved lung function compared with UC (Δ FVC% predicted;+6%, p=0.005) Aerobika improved HRQoL compared with UC (ΔSGRQ score; −9, p=0.01). Aerobika improved sputum clearance compared with UC (ΔPEQ- ease-bringing-up-sputum; −1.2, p=0.005) Aerobika improved exercise capacity compared with UC (Δ 6MWD;+19 m, p=0.04) Aerobika improved regional ventilation compared with UC (Δ 3He MRI ventilation deficit percent; −1%).
Weiner, (1996)[29]	Stable COPD FEV_1 35%±8.5% predicted RCT	Flutter n=10	10 mins, 4–8 x 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).

Continued

Table 1 Continued

Author (year)	Patient group design	OPEP device	Treatment duration	Follow-up	Control	Results of OPEP group compared with corresponding groups
Wolkove, (2004)[30]	Stable COPD with sputum production and smoking history FEV_1 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).

Δ, data presented as mean difference in absolute values between groups; ACBT, active cycle of breathing technique; AECOPD, acute exacerbations of COPD; BCSS, Breathlessness, Cough and Sputum Scale; C, control; CAT, COPD assessment test; CCQ, Clinical COPD Questionnaire; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; 3He, hyperpolarised 3 helium; HRQoL, health-related quality of life; I, intervention; MMRC, Modified Medical Research Council; 6MWD, Six-minutes Walking Distance; OPEP, oscillatory positive expiratory pressure; PEFR, peak expiratory flow rate; PEQ, Patient Evaluation Questionnaire; PR, pulmonary rehabilitation; RCT, randomised controlled trial; RXT, randomised cross-over trial; SGRQ, St. George's Respiratory Questionnaire; UC, usual care.

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 online supplementary 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 (SMA), after which all articles were imported to EndNote version 7.8 and duplicates removed. All article titles and abstracts were screened by two reviewers (SMA and REB). A third reviewer (NSH) 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 online supplementary appendix 2.

Data extraction

A standardised 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 drop-out 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 (SMA and REB) 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 (NEH) 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 drop-out rates. A meta-analysis was performed to estimate the pooled differences and 95% 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). Standardised mean difference (SMD) was used when the same outcome was assessed with different measures. Dichotomous data are expressed as ORs. Heterogeneity among included studies was assessed using the I^2 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 V.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 drop-out 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

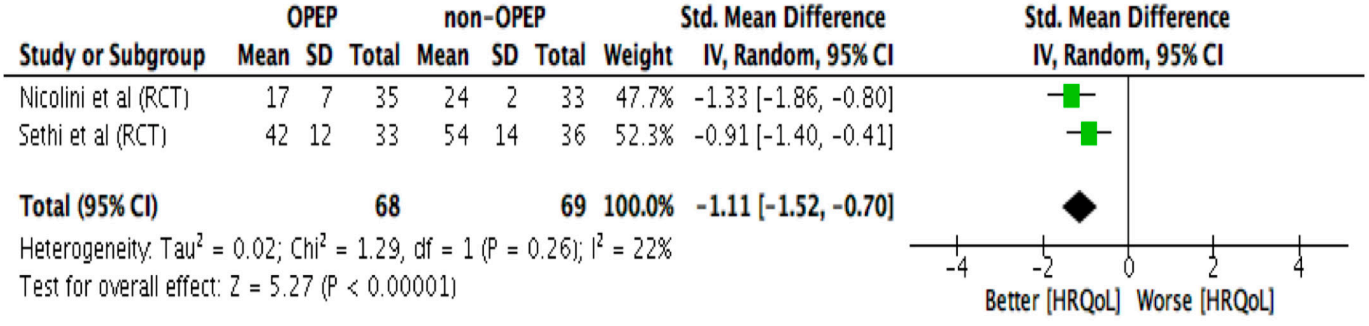

Figure 3 Forest plot comparing HRQoL measures (CAT and SGRQ) scores in OPEP interventions versus non-OPEP interventions. CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; HRQoL, health-related quality of life; OPEP, oscillating positive expiratory pressure; RCT, randomised controlled trial; SGRQ, St. George's Respiratory Questionnaire.

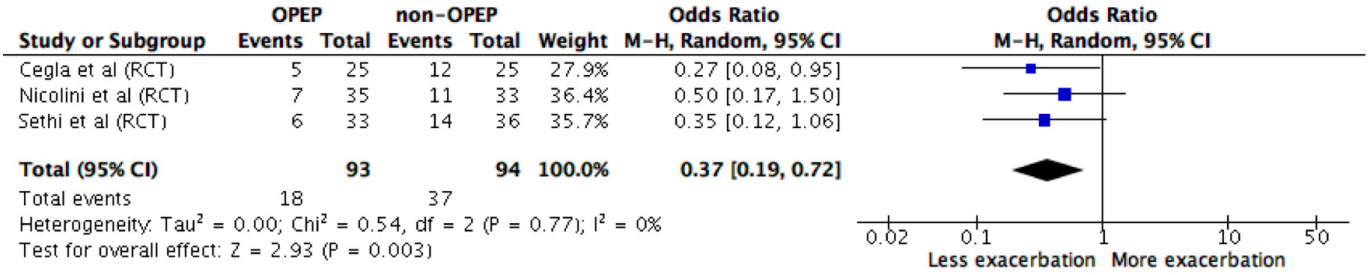

Figure 4 Forest plot comparing exacerbation events 6 months following the OPEP use (lung Flute) versus usual care in stable COPD. COPD, chronic obstructive pulmonary disease; M-H, Mantel-Haenszel; OPEP, oscillating positive expiratory pressure; RCT, randomised controlled trial.

acceptance, completion and drop-out 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. After full-text review, eight articles were eventually considered for the review as outlined in PRISMA flow diagram (figure 2).

Six of the eight reports were RCT parallel-group trials and two were cross-over 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±SD) was 65±7.4 years, and 61% were male. In total, 336 patients were recruited into trials of stable COPD, 45 during an 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 (UC) (eg, COPD medication regimen), active cycle of breathing technique (ACBT), pulmonary rehabilitation, 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 (eg, Acapella (Smiths-Medical, Dublin, Ohio, USA), Flutter (Allergan, Dublin, Ireland), Aerobika (Monaghan Medical, Plattsburgh, New York, USA), Lung Flute (Medical Acoustics, Buffalo, New York, USA) and RC-Cornet (Cegla Medical Technology, Montabaur, Germany)).

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 (PEFR) (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 UC 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 (eg, St. George's Respiratory Questionnaire (SGRQ) and COPD assessment test).[26–28] The meta-analysis for HRQoL is shown in figure 3. Pooled analysis from two RCTs (n=137)[26 27] showed that the use of an OPEP device (Lung Flute) improved HRQoL compared with routine care (SMD (95% CI), −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 with UC (mean±SD; 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 impact because of incomplete data.[28]

Number of exacerbations

Figure 4 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

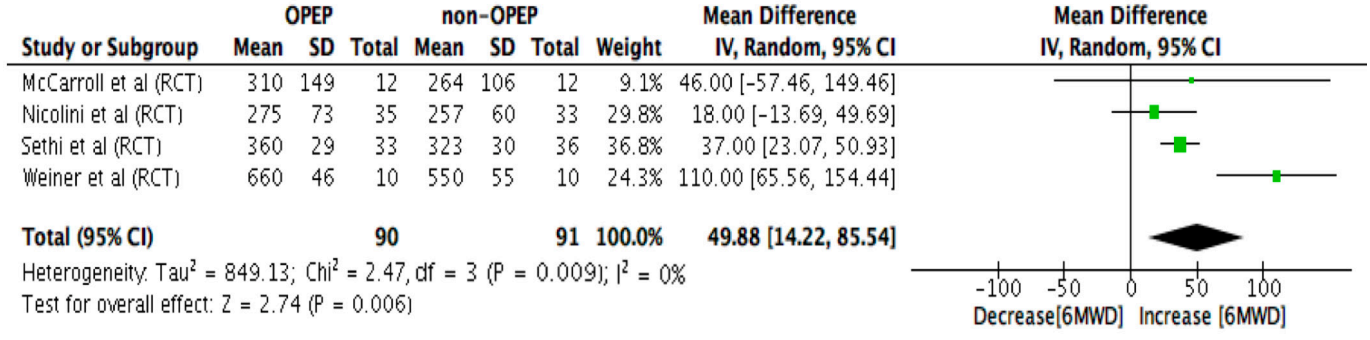

Figure 5 Forest plot comparing exercise capacity measured with 6MWD (in metres) in OPEP interventions versus non-OPEP interventions (RCTs data only). 6MWD, 6 min walk distance; IV, inverse variance; OPEP, oscillating positive expiratory pressure; RCT, randomised controlled trial.

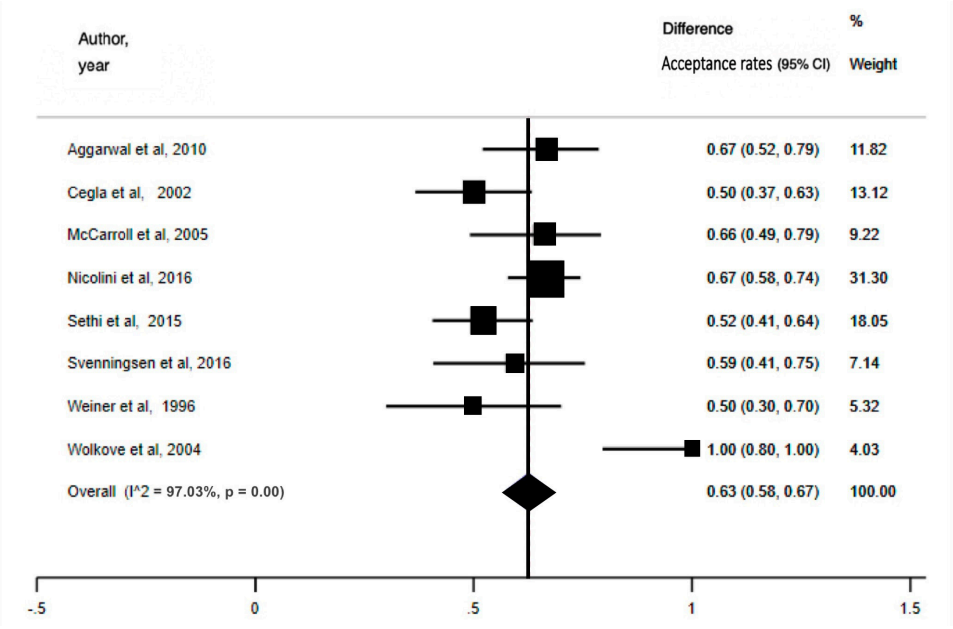

Figure 6 Forest plot of pooled difference in acceptance rate in OPEP interventions versus non-OPEP interventions. OPEP, oscillating positive expiratory pressure.

events after 6 months compared with routine care (OR 0.37, 95% CI 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 0.05, 95% CI 0.01 to 0.38; p=0.005).[25]

Sputum clearance

Only one study measured the sputum clearance outcome.[28]A 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 with UC (mean difference ±SD; 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 FEV_1, PEFR and predicted FVC%, and overall, the use of OPEP devices had no effect on lung function.[24 25 28–31]

Exercise capacity

Exercise capacity, assessed using 6 min walk distance (6MWD), was reported in six studies (figure 5).[26–31] Pooled analysis of four RCTs (n=181) demonstrated an improvement following use of OPEP (eg, Acapella, Lung Flute and Flutter) compared with the

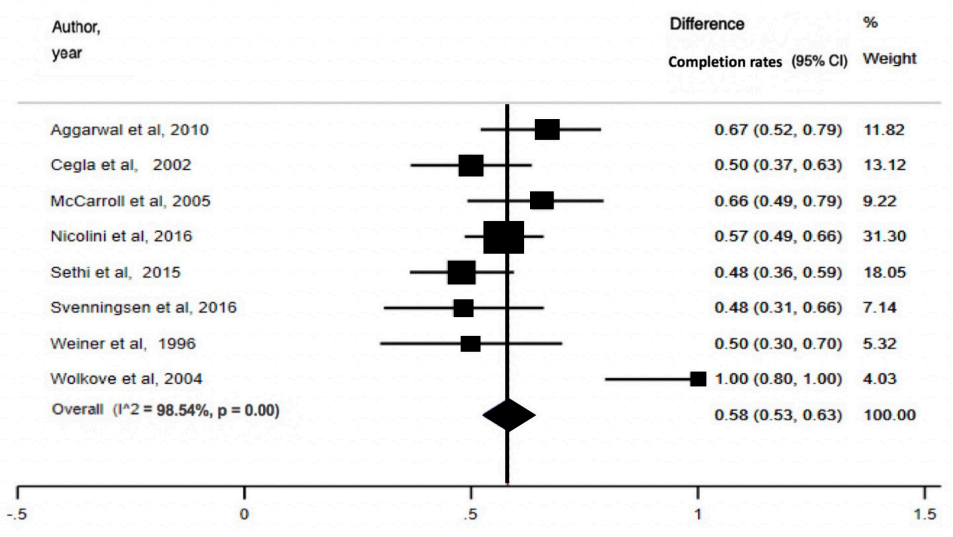

Figure 7 Forest plot of pooled difference in completion rate in OPEP interventions versus non-OPEP interventions. OPEP, oscillating positive expiratory pressure.

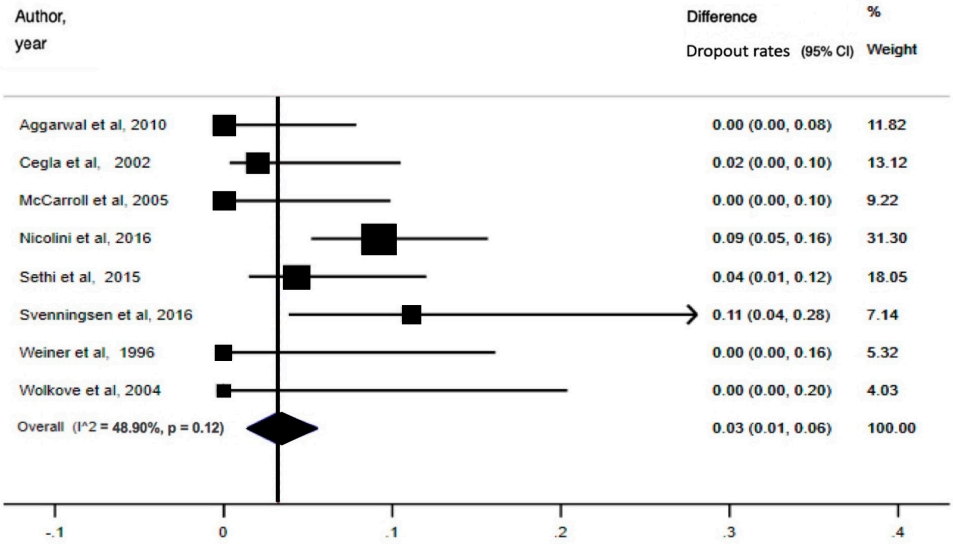

Figure 8 Forest plot of pooled difference in drop-out rate in OPEP interventions versus non-OPEP interventions. OPEP, oscillating positive expiratory pressure.

control group, with the mean effect exceeding the minimal clinical important difference (MCID) for the 6MWD[32] (mean difference (95% CI), 49.8 m (14.2 m to 85.5 m); p=0.009).[26 27 29 31] In contrast, data from two RXTs using OPEP (eg, Aerobika and Flutter) did not demonstrate a significant improvement compared with UC.[28 30]

Acceptance, completion and drop-out 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. A total of 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 cross-over 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 drop-out 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 drop-out 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 drop-out 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 6–8.

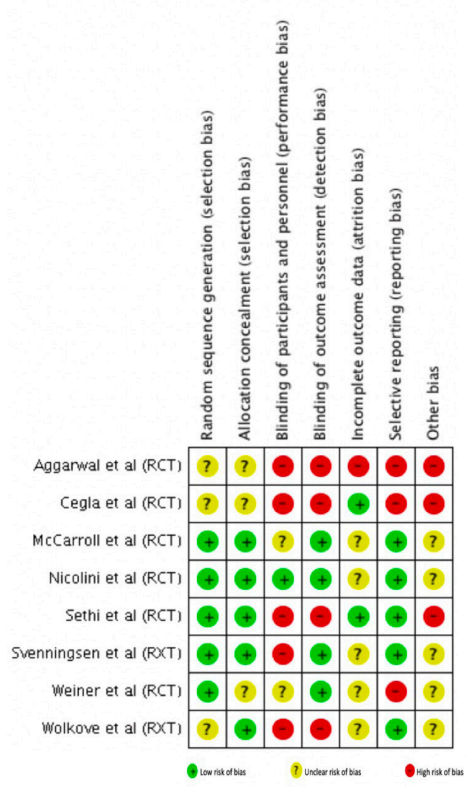

Figure 9 Assessment of risk of bias for included studies. RCT, randomised controlled trial; RXT, randomised cross-over trial.

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 9). Funnel plot analysis (figure 10) 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 Grading of Recommendations, Assessment, Development and Evaluations 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

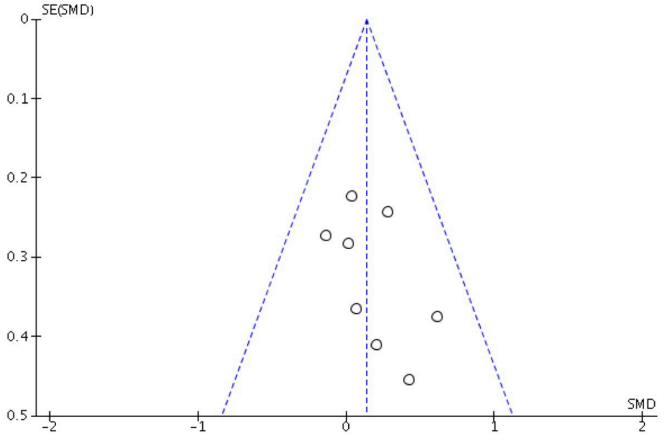

Figure 10 Funnel plot for detection of publication bias. SMD, standardised mean difference.

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.[33] 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 2019[34] and joint American Thoracic Society/European Respiratory Society COPD guidelines[35] do not make any reference to sputum clearance techniques (searched using the words 'sputum', 'clearance' and 'physiotherapy'), although National Institute for Health and Care Excellence (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 ACBTs'.[36] 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.[37] Included studies have shown contrasting results; however, one study reported a reasonable response in lung function parameters such as FEV_1 and PEFR immediately after an OPEP session.[38] 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 MCID[32] with longer-term OPEP device use,[26 27 29 31] though results from cross-over studies were less compelling.[28 30] As expected, patients with sputum production were more likely to improve than those without,[28 39] 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.[40] 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.[41–43]

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 44] In the included studies, most drop-outs 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 learnt 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 drop-out 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 (eg, 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 (eg, 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 (eg, 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.

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Contributors SMA, NSH, MIP, SSB and REB developed the idea and designed the study protocol. SMA, REB and NSH designed and wrote the search strategy and the first protocol draft. SMA, NSH, REB, ASSA and AMS planned the data extraction and statistical analysis. NSH, MIP, WASB and SSB provided critical insights. All authors have approved and contributed to the final written manuscript.

Funding The main author disclosed receipt of the following financial support for the research, authorship and/or publication of this article. This study was supported by a scholarship from Umm Al-Qura University in Saudi Arabia.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data generated or analysed during this study are included in this published article and its supplementary information files.

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