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Current treatment strategies in managing side effects associated with domiciliary positive airway pressure (PAP) therapy for patients with sleep disordered breathing: A systematic review and meta-analysis

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ABSTRACT

Sleep disordered breathing is commonly treated with positive airway pressure therapy. Positive airway pressure therapy is delivered via a tight-fitting mask with common side effects including: leak, ineffective treatment, residual sleep disordered breathing, eye irritation, nasal congestion, pressure ulcers and poor concordance with therapy. This systematic review and meta-analysis aimed to identify the effectiveness of current treatment strategies for managing side effects associated with positive airway pressure therapy. Five databases were searched and 10,809 articles were screened, with 36 articles included in the review. Studies investigated: dressings, nasal spray/douche, chin straps, heated humidification and interfaces. No intervention either improved or detrimentally affected: positive airway pressure concordance, Epworth Sleepiness Score, residual apnoea hypopnea index or interface leak. The review was limited by study heterogeneity, particularly for outcome measures. Additionally, patient demographics were not reported, making it difficult to apply the findings to a broad clinical population. This review highlights the paucity of evidence supporting treatment strategies to manage side effects of positive airway pressure therapy.

1. Introduction

Sleep disordered breathing (SDB) is an umbrella term describing several conditions including obstructive sleep apnoea (OSA), complex sleep apnoea and chronic ventilatory failure. SDB is common, affecting an estimated 14% of the population, with this likely to increase [1]. SDB can be treated using positive airway pressure (PAP), either continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV). PAP is delivered via a tight-fitting interface attached to the patient's face with treatment effectiveness significantly influenced by interface fit. Patients often find the interface uncomfortable thus limiting concordance with treatment [2,3]. Pressure ulcers related to the interface are a documented side effect of PAP therapy [4] which can limit a patient's ability to concord with treatment. Patients are known to develop skin reactions such as dermatitis and have reported side effects of oronasal dryness, nasal congestion, sinus/ear pain, gastric bloating and eye irritation [5,6]. Interface leak has been found to cause ineffective ventilation [7,8], high residual apnoea hypopnea index (AHI) [9], persistent nocturnal desaturations [7] and ultimately failure of PAP therapy [10]. Concordance with PAP therapy is essential for treatment success, with four hours of nightly PAP use required for improvements in daytime sleepiness [11] and five hours of nightly use required for reduction in hypertension [12,13].

Individual studies investigating the effectiveness of management strategies report a variety of different techniques with varying success. There are currently no guidelines directing the management of PAP therapy side effects. Current available techniques are: dressings, nasal sprays/douches, creams/solutions, artificial saliva, chin straps, mask liners, heated humidification (HH) and different interfaces. A systematic review of these studies is warranted to inform clinicians and potentially formulate future guidance, especially given the increasing number of patients requiring PAP therapy.

2. Objectives

The aim of this systematic review was to identify the effectiveness of treatment strategies for managing side effects associated with PAP

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Abbreviations

AHI	Apnoea Hypopnea Index
APAP	Auto Positive Airway Pressure
BiPAP	Bilevel Positive Airway Pressure
CPAP	Continuous Positive Airway Pressure
EDS	Excessive Daytime Sleepiness
ESS	Epworth Sleepiness Score
HH	Heated Humidification/Heated Humidifier
NIV	Non-invasive Ventilation
OSA	Obstructive Sleep Apnoea
PSG	Polysomnography
RCT	Randomised Control Trial
RDI	Respiratory Disturbance Index
SWIFT	Sleepiness-Wakefulness Inability and Fatigue
S3NIV	S3 Non-invasive Ventilation

therapy interfaces in patients receiving domiciliary PAP therapy. The-systematic review aimed to.

1. Identify current treatment strategies used to minimise the following side effects associated with domiciliary PAP therapy interfaces:
   a. Interface leak
   b. Pressure ulcers and dermatitis
   c. Oronasal dryness and congestion
2. Determine the most effective treatment strategies for managing side effects of domiciliary PAP interfaces.
3. Determine the impact of treatment strategies for managing side effects of domiciliary PAP interfaces on:
   a. Residual AHI
   b. Epworth Sleepiness Score (ESS)
   c. PAP therapy compliance

3. Methods

This systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Protocols-2015 (PRISMA-P 2015) guidelines and the Cochrane handbook for Systematic Reviews of Interventions [14]. The project was prospectively registered to PROSPERO (registration number: CRD42021286437).

The following databases were searched from 1946 onwards: Allied and Complementary Medicine Database (AMED), Cochrane Central Register of Controlled Trials (CENTRAL), the Cumulative Index to the Nursing and Allied Literature (CINAHL; EBSCO host), EMBASE (via Ovid) 1946 and MEDLINE (via Ovid) 1946-. The search strategy was developed with a specialist librarian and piloted to ensure it was

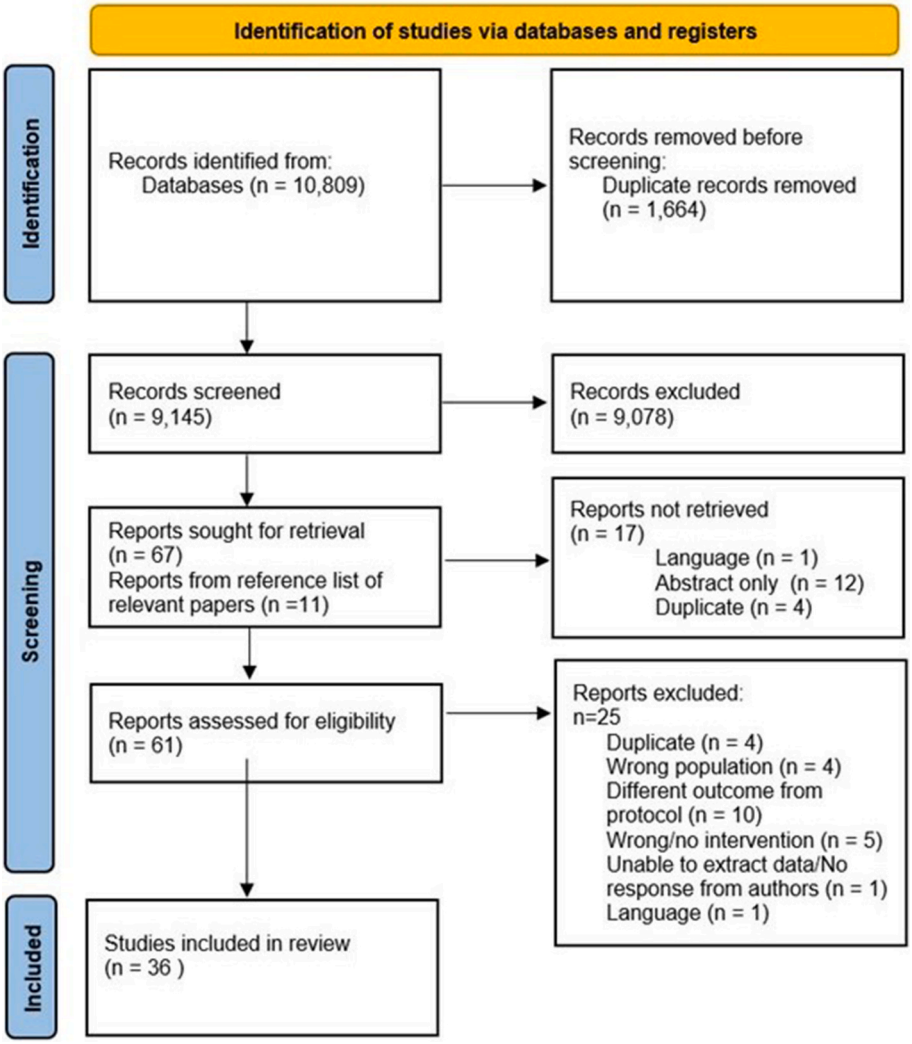

Fig. 1. PRISMA flow chart for included studies.

Table 1
Summary of studies included in the systematic review and meta-analysis.

Author (year), country	Study design	Format	Intervention	Population (n) Age Sex (%male)	Primary outcome
Bachour et al. (2004) [27], Finland	Observational	Consecutive patients with mouth leak and complaining of mouth dryness and nasal obstruction with CPAP	Chin strap	(15) Age: 53.7 ± 12.3 Sex: not reported	Total sleep time % mouth leak, one night polysomnography study
Bakker et al. (2012) [53], New Zealand	Pilot crossover randomised control trial (RCT)	Patients randomly selected from database with OSA (apnoea hypopnea index (AHI) > 30events/hr), aged >25 and established on continuous positive airway pressure (CPAP)	Nasal mask, under chin oronasal mask, standard oronasal	(12) Age: 48.8 (range 35–60) Sex: 92%	Difference in therapeutic pressure requirement, residual AHI and leak between nasal, standard oronasal, and under-chin oronasal masks
Beecroft et al. (2003) [39], Canada	Observational	Consecutive patients, diagnosed with obstructive sleep apnoea (OSA) (AHI>5 events/hr), naïve to CPAP	Nasal mask, oronasal mask, oracle mask	(72) Age: Nasal: 49.6 ± 10.2, Oronasal: 53.0 ± 19.0, Oracle: 53.1 ± 13.2 Sex: Nasal: 69.2%, Oronasal: 71.4%, Oracle: 73.1%	Adherence and satisfaction between interfaces
Blanco et al. (2018) [40], Argentina	Observational	Consecutive patients, CPAP concordant patients diagnosed with OSA >6months	Dreamwear nasal pillows "routine mask"	(55) Age: 65.2 ± 9.9 Sex: 67%	Patient satisfaction, therapeutic efficacy and compliance with nasal pillows
Boyer et al. (2019) [24], France	Cross over RCT	Consecutive patients diagnosed with severe OSA (AHI≥30 events/hr or AHI <30 events/hr with RDI >10 events/hr), naive to CPAP	Heated humidification (HH)	(40) Age: 62.4 ± 9.5 Sex 57.5%	CPAP concordance at 4 weeks
Callaghan and Trapp (1998) [18], UK	Observational	Convenience sample	Granuflex and spenco-dermal	(30) Age: control: 52 granuflex: 58 spenco dermal: 58 Sex: control 30% granuflex 30% spenco dermal 70%	Prevalence of pressure ulcer at 6 weeks post hospital discharge
Cheng et al. (2015) [54], Taiwan	RCT	Not reported	Customised interfaces	(40) Age: Customised group:50.9 ± 9.7 Standard 53.6 ± 11.5 Sex: 83%	AHI on treatment, end point not reported
Foellner et al. (2019) [41], Germany	Observational	Convenience, OSA patients (AHI>10 events/hr) reporting mouth dryness and mask leak. Combination of CPAP and bi-level positive airway pressure (BiPAP)	Oronasal mask, nasal mask, nasal mask plus oral shield	(29) Age: 59.5 (range 35–79) Sex: 58.6%	Mask leak and AHI after one night on therapy via polysomnography
Goh et al. (2019) [42], Singapore	Cross over RCT	Consecutive patients	Nasal mask, nasal pillows, oronasal mask	(85) Age: 45 ± 12 Sex: 83.5%	CPAP adherence at 1 month
Khanna (2003) [43], USA	RCT	Prospective patients with confirmed OSA (respiratory disturbance index (RDI) > 15 events/hr)	Oracle mask, nasal mask	(38) Age: Nasal: 50.9 ± 11.0 Oracle: 52.5 ± 1 Sex: Nasal 78.6% Oracle: 61.9%	CPAP concordance at 8 weeks
Koutsourekakis et al. (2010) [26], Greece	Cross over RCT	Consecutive patients with confirmed OSA (AHI >15 events/hr), not currently using HH and with symptomatic nasal obstruction	HH	(20) Age: HH1 (HH to sham) 61.5 (51.0–67.0) HH2 (sham to HH) 62.0 (48.8–68.5) Sex: 60%	Nasal inflammation at 3 weeks
Kreivi et al. (2010) [27], Finland	Observational	Consecutive patients with confirmed OSA (AHI >5 events/hr) and excessive daytime sleepiness referred to a sleep unit	HH	(536) Age: 55 ± 12 Sex: Not reported	CPAP adherence at 1year
La Mantia and Andaloro (2017) [19], Italy	RCT	Consecutive patients screened with confirmed OSA diagnosis (AHI ≥10events/hr) with symptomatic nasal obstruction	Hyaluronate plus CPAP, Saline plus CPAP, CPAP only	(102) Age: Hyaluronate 55.2 ± 10.7 Saline 56.03 ± 8.86 CPAP only 56.55 ±	Effects of Hyaluronate on nasal problems

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Table 1 (*continued*)

Author (year), country	Study design	Format	Intervention	Population (n) Age Sex (%male)	Primary outcome
				8.37 Sex: Not reported	
Lanza et al. (2018) [44], Italy	Retrospective observational	Retrospective review of all patients treated with CPAP between set time points at a sleep centre	Nasal pillows, Nasal mask	(144) Age: 68.14 ± 12.86 Sex: 76%	Long term effectiveness and adherence
Lebert et al. (2018) [45], Belgium	Prospective observational	Consecutive patients with confirmed moderate and severe OSA (AHI >15 events/hr)	Oronasal mask, Nasal mask	(72) Age: 55.8 ± 13 Sex: 69%	To identify factors of unintentional leakage
Li and Wang (2016) [28], China	RCT	Newly diagnosed OSA patients (AHI >15 events/hr) who preferred a cool sleeping environment (<20 °C)	HH	(40) Age: HH: 38 ± 15 non-HH: 39 ± 14 Sex: HH: 80% non-HH: 80%	Effects of HH during the winter
Mador et al. (2005) [23], USA	RCT	Newly diagnosed patients with OSA (AHI ≥10events/hr) with EDS, naive to CPAP	HH	(98) Age: HH: 59.9 ± 7.5 control: 57.1 ± 11.2 Sex: HH 96% Control: 98%	Whether the addition of HH at CPAP initiation provides superior outcomes
Massie et al. (1999) [29], New Zealand	Crossover RCT	Newly diagnosed OSA patients (RDI ≥10events/hr), aged 18 to 75 and naive to CPAP	HH and cold passover humidification	(38) Age: 44.1 ± 11 Sex: 79%	The effects of heated and cold passover humidification on symptoms and CPAP concordance
Massie et al. (2003) [46], New Zealand	Crossover RCT	Newly diagnosed OSA patients OSA (AHI ≥15 events/hr or AHI≥15events/hr plus EDS), aged 18 to 75 and naive to CPAP	Nasal mask, Nasal pillows	(39) Age: 48.7 ± 8.5 Sex: 82%	CPAP concordance, adverse effects, satisfaction with therapy, quality of life and residual AHI
Mortimore, Whittle and Douglas (1998) [52], Scotland	Crossover RCT	Consecutive patients newly diagnosed with OSA	Nasal mask, oronasal mask	(20) Age: 52 ± 3 Sex: Not reported	CPAP concordance and side effects between nasal and oronasal mask
Nava et al. (2008) [30], Italy	Pilot crossover RCT	Stable, hypercapnic patients naive to non-invasive ventilation (NIV)	HH, Heat moisture exchange	(14) Age: 62.8 ± 9.4 Sex: 50%	The clinical effects of HH and heat and moisture exchanger during long-term non-invasive mechanical ventilation in stable hypercapnic patients
Neill et al. (2003) [38], New Zealand	Crossover RCT	Patients with newly diagnosed OSA requiring CPAP	HH	(37) Age: 48.7 ± 13 Sex: 89%	The effect of HH on initial CPAP use, upper airway symptoms and daytime alertness
Nilius et al. (2016 [37]), Germany	RCT	Consecutive patients with OSA (AHI >10events/hr) naive to CPAP	HH	(72) Age: 52.3 (8.5) Sex: Not reported	To examine whether subjects with major nasal complaints are most likely to benefit from HH
Rakotonanahary et al. (2001) [31], France	Observational	Consecutive OSA patients (AHI >10events/hr)	Cold and heated humidification	(82) age: 54 ± 11 Sex: 86.5%	Define predictive factors for additional humidification in OSAS patients starting CPAP
Rowland et al. (2018) [22], Australia	Crossover RCT	Patients with moderate to severe OSA (AHI ≥44 or ≥ 30events/h with Epworth sleepiness score (ESS) > 10)	Nasal mask, nasal mask plus chinstrap, oronasal mask	(35) Age: 54.9 ± 13 Sex: 66%	Effects of interfaces on efficacy of treatment, CPAP adherence, overall leak and self-reported side effects, sleep quality, daytime sleepiness, mask comfort, and overall patient preference
Ruhle et al. (2011) [32], Germany	Crossover RCT	Patients aged 30 to 80 with OSA and no nasal symptoms	HH and HH plus heated tube	(44) Age: 51.5 ± 12.6 Sex: 88.6%	Whether HH improves nasopharyngeal side effects and sleep quality during initial treatment phase
Ryan et al. (2009) [20], Ireland	RCT	Consecutive OSA patients (AHI ≥10 events/hr) with excessive daytime sleepiness, naïve to CPAP	HH and topical steroids	(122) Age: Dry 48 ± 8, Fluticasone 48 ± 12, HH 50 ± 12 Sex: Dry 92%, Fluticasone 95%, HH 95%	Impact of HH or nasal topical steroids on concordance, nasal side effects, and quality of life
Ryan et al. (2011) [47], Ireland	Crossover RCT	Consecutive OSA patients (AHI ≥10 events/hr) with excessive daytime sleepiness, naïve to CPAP	Nasal pillows , Nasal mask	(21) Age: 49 ± 10 Sex: 90%	To compare nasal pillows to nasal masks in regards to concordance, side-effects, quality of life and sleepiness
Salgado et al. (2008) [34], Portugal	RCT	Consecutive patients with OSA	HH	(39) Age: With humidification 57.4 ± 9.2, without humidification 56.5 ± 10.7 Sex: HH 76%, without humidification 73%	Impact of HH on PAP concordance, comfort and side effects

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Table 1 (*continued*)

Author (year), country	Study design	Format	Intervention	Population (n) Age Sex (%male)	Primary outcome
Shirlaw et al. (2018) [51], Australia	Crossover RCT	Patients established on CPAP>18years	Nasal mask, oronasal nasal	(71) Age: 64 ± 10 Sex: 75%	Nasal masks compared with oronasal masks at 4 weeks
Soudorn et al. (2016) [33], Thailand	Crossover RCT	Patients referred to a sleep clinic, with moderate to severe OSA (AHI >15 events/hr)	HH	(20) Age: 48.9 ± 12.7 Sex: 70%	The effects of HH on CPAP adherence, nasopharyngeal symptoms, quality of life, and subjective sleepiness
Teo et al. (2011) [48], Australia	RCT	Patients referred to a sleep clinic, with moderate to severe OSA (RDI >15 events/hr) naïve to CPAP	Oronasal mask, Nasal mask	(24) Age: 51.3 ± 13.3 Sex 75%	Whether use of an oronasal mask requires higher pressures to maintain upper airway patency compared to nasal mask
Wiest et al. (2002) [35], Germany	Crossover RCT	Patients referred to a sleep clinic, with OSA (AHI >20 events/hr) and excessive daytime sleepiness naïve to CPAP	HH	(44) Age: 54.1 ± 9.7 Sex: 80%	Whether prophylactic HH improves patient comfort and acceptance
Worsnop et al. (2010) [25], Australia	RCT	Consecutive patients referred for OSA for nasal CPAP	HH	(54) Age: HH 55 ± 11, No HH 55 ± 12 Sex: HH 81%, No HH 76%	If the routine HH use reduces nasal symptoms and improves CPAP adherence
Yu et al. (2013) [36], China	RCT	Patients referred to a sleep clinic for CPAP, with OSA (AHI >15 events/hr) and excessive daytime sleepiness	HH	(52) Age: Without HH: 47.08 ± 7.36, HH: 46.5 ± 12.10 Sex: Without HH: 86% HH: 88%	The effects of HH during CPAP titration
Zhu et al. (2013) [49], Australia	Crossover RCT	Patients recruited from the ResMed Sleep Trials Registry, aged >18years and established on CPAP >6months	Nasal pillows , Nasal mask	(20) Age: 64.6 ± 9.5 Sex: 75%	Efficacy of nasal pillows compared with nasal masks at CPAP pressures ≥12cmH_2O

AHI: Apnoea Hypopnea Index, APAP: Auto Positive Airway Pressure, CPAP: Continuous Positive Airway Pressure, HH: Heated Humidifier/Humidification, NIV: Non-invasive Ventilation, OSA: Obstructive Sleep Apnoea, RCT: Randomised Control Trial. RDI: Respiratory Disturbance Index.
Footnote: Blanco et al. [40] compared nasal pillows to patients' "routine mask" but data were not presented in a way that could be utilised for pairwise comparison. Khanna et al. [43] investigated the Oracle interface compared to nasal interfaces this study was not included in the meta-analysis. Ethnicity: Not reported by any included studies.

inclusive of potential studies; trade names were used where appropriate (online supplement 1).

3.1. Inclusion and exclusion criteria

The following were included in the systematic review: 1) studies reporting treatment strategies to minimise side effects associated with domiciliary PAP therapy interfaces and their effectiveness (dressings, creams/solutions, mask liners, humidifiers, different interfaces, nasal sprays/douches, artificial saliva); 2) randomised controlled trials (RCT), prospective and retrospective observational studies including case-controlled studies, cohort studies and cross-sectional studies; and 3) studies including adult patients (>18years) receiving domiciliary PAP therapy. The following exclusion criteria were applied: 1) studies that were narrative reviews, non-research letters, abstracts, case reports, conference proceedings, theses and books; 2) systematic reviews and meta-analyses, literature reviews; 3) studies involving non-human subjects; and 4) studies not reported in English.

3.2. Outcomes

Studies were included where they measured at least one of: prevalence and grade of pressure ulcers, prevalence of dermatitis, interface leak (unintentional and overall leak), residual AHI/overnight desaturation index (ODI), concordance with treatment (hours/night and percentage of nights used >4 h), percentage of discontinuation of PAP therapy, inflammatory biomarkers and subjective measures such as ESS, Sleepiness-Wakefulness Inability & Fatigue Test (SWIFT), Severe Respiratory Insufficiency questionnaire, Visual Analogue Scale (VAS) (including pain scores) and S^3NIV.

3.3. Selection process

Two authors (SKM and ND) independently screened all article titles and abstracts identified for inclusion. Any disagreement was resolved with discussion. The articles were marked 'included' or 'excluded' in Rayyan QRCI [15]. Full texts were reviewed by two independent reviewers (SKM and ND) to assess eligibility for inclusion.

3.4. Data collection process

Using standardised forms following Cochrane Handbook guidelines [14], reviewers independently extracted data from eligible full text articles: demographic details, study characteristics and outcomes. Authors were contacted to resolve any uncertainties.

3.5. Risk of bias individual studies

Reviewers assessed the methodological quality of included studies and the risk of bias using the modified Newcastle-Ottawa Scale (NOS) for non-randomised studies [16] and the Cochrane Risk of Bias Tool (RoB 2) [14].

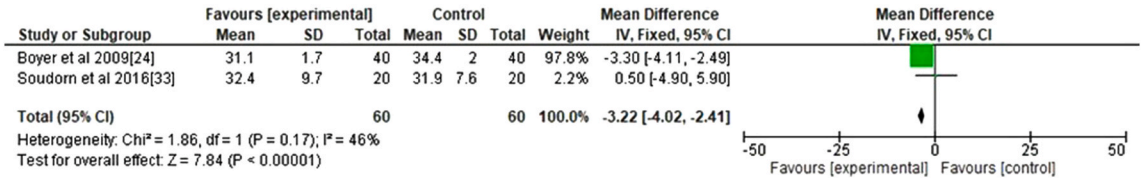

Fig. 2. Forest plot showing the association between HH and mask leak as measured by unintentional leak plus intentional leak.

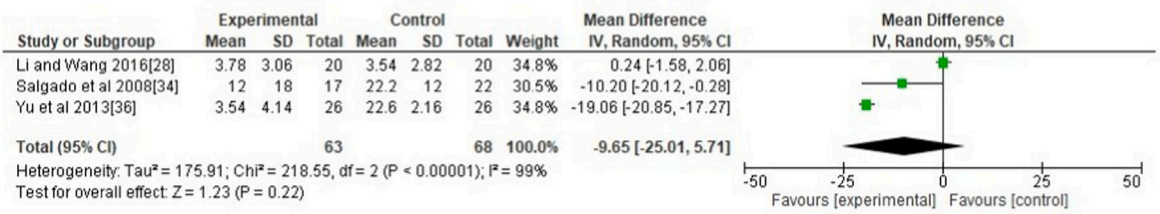

Fig. 3. Forest plot showing the association between HH and mask leak as measured by unintentional leak.

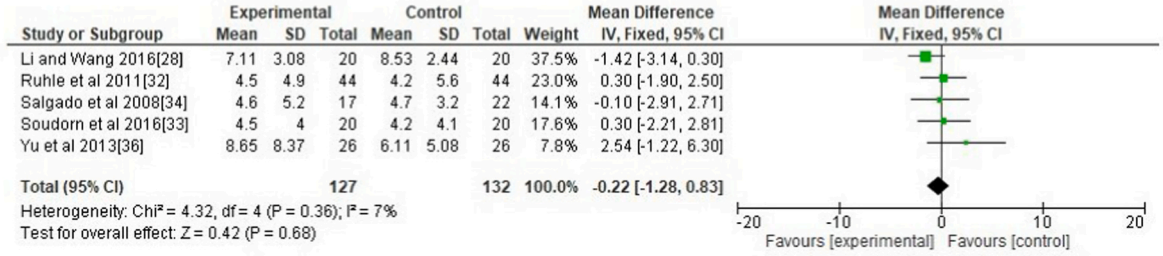

Fig. 4. Forest plot showing the association between HH and AHI.

3.6. Data synthesis

A narrative synthesis was provided using the "Cochrane consumers and communication review group: data synthesis and analysis" [17]. Studies were grouped by intervention and the outcome measure used.

Where there was sufficient homogeneity in study design and outcome measures, meta-analysis was conducted. An I^2 test was used to assess for heterogeneity between studies, which informed the use of random (I^2 >50%) or fixed (I^2 <50%) effects model for meta-analyses. Statistical analysis was performed with Review Manager (RevMan) Version 5.4.

4. Results

The initial search criteria generated 10,809 results, with 1664 duplicates immediately removed. After initial screening, 78 papers met the inclusion criteria for full text review. A further 42 papers were excluded after full text review, 36 papers were subsequently included in the final review (Fig. 1.). The majority of the studies included were RCTs (n = 27), eight were observational and one study was retrospective. An overview of the included studies is presented in Table 1.

4.1. Risk of bias assessment

Assessment of risk of bias using the NOS is detailed in online Supplement Table 2. There appeared to be low risk of selection bias across all studies and most undertook appropriate assessments of outcomes with adequate follow-up. The studies varied markedly in the comparability of cohorts, with either significant differences being reported between groups or limited detail offered regarding factors controlled.

Assessment of risk of bias for RCTs has been detailed in online Supplement Table 3. Some concerns relating to the randomisation process were evident for most studies, largely due to a lack of detail offered; however, across most there were no significant demographic differences between treatment groups. Given the interventional nature of the trials, blinding of participants was not always feasible but, where possible, this was attempted. Most did mention blinding of outcome assessors. Twenty-three of the 27 RCTs included all or nearly all the participants they had randomised (>90%) and were, therefore, at low risk of attrition bias. All trials reported the outcomes as stated in the methods and, therefore, were deemed low risk of bias.

4.2. Treatment interventions

4.2.1. Dressings

Only one study investigating the use of dressings was identified. Callaghan [18] conducted an observational cohort study of patients requiring NIV initiated during the acute phase and subsequently discharged home, and investigated two different dressings, Granuflex and Spenco-dermal, for preventing pressure ulcers. Granuflex was found to reduce prevalence of pressure ulcers at discharge (no dressing: 80%, Granuflex: 25%, Spenco-dermal: 62%). At six weeks post discharge, there was no difference in comfort scores (VAS Median (IQR)): no dressing: 6 (2–10), Granuflex: 7 (1–8), and Spenco-dermal: 6 (3–8). There was an increase in mean self-reported NIV use in both the Granuflex (12 hs) and the Spenco-dermal (11 hs) groups compared to those without dressings (9 hs).

Table 4
Summary of studies investigating different PAP interfaces.

Author (year)	Study design	n	Nasal n	Oronasal n	Pillows n	Other n	Duration	Apnoea hypopnea index AHI (events/hr) Mean (SD)	Sleepiness Epworth sleepiness score (ESS) Mean (SD)	Adherence (hrs/night) Mean (SD)
Bakker et al. (2012) [53]	Pilot Crossover randomised controlled trial (RCT)	12	12	Standard oronasal: 12 Under chin oronasal: 12	N/A	N/A	2 weeks	Nasal:0.60 (2.21) Under chin oronasal:1.95 (4.94) Oronasal:1.88 (3.43) p = 0.11	N/A	Nasal:6.46 (0.75) Under chin oronasal 6.71 (1.88) Oronasal mask 6.35 (2.93) p = 0.78
Beecroft et al. (2003) [39]	Observational	72	65	7	N/A	Oracle: 26	6 months	N/A	N/A	Nasal: 5.5 (1.8) Oronasal: 6.0 (not reported) Oracle: 4.8 (2.7) p = 0.423
Blanco et al. (2018) [40]	Observational	55	43	1	8	N/A	1 week	Routine mask: 3.38 (3.59) Dreamwear: 3.05 (2.7) p = 0.93	Routine mask: 6.9 (5.5) Nasal pillows: 4.7 (4.8) p = 0.01	Routine mask: 5.4 (1.8) Nasal pillows: 6.4 (1.3) p = 0.0042
Foellner et al. (2019) [41]	Observational	29	29	29	N/A	Nasal plus oral shield: 29	Single night	Nasal: 2.6 (2.3) Nasal plus mouth shield: 2.7 (2.6) Oronasal 8.5 (6.7)	N/A	N/A
Goh et al. (2018) [42]	Crossover RCT	85	85	85	85	N/A	1 month with each mask	Nasal: 4.0 (4.2) Pillows: 4.1 (3.3) Oronasal: 7.2 (5.2) p < 0.001	N/A	Nasal: 3.96 (2.26) Pillows: 3.48 (2.2) Oronasal: 3.26 (2.18) p < 0.001
Khanna (2003) [43]	RCT	38	17	N/A	N/A	Oracle: 21	8 weeks	N/A	N/A	Oracle 5.5 (2.6) Nasal 4.6 (2.5) p > 0.005
Lanza et al. (2018) [44]	Retrospective observational	144	42	N/A	102	N/A	1 year	Pillows: 0.7 (0.0, 9.0)*[a] Nasal: 1.1 (0.0, 9.5)* p = 0.172	Pillows: 4 (0, 14)* Nasal: 5 (0, 14)* p = 0.091	Pillows: 5.49 (1.84) Nasal: 5.31 (1.55) p = 0.787
Lebret et al. (2018) [45]	Prospective observational	72	58	14	N/A	N/A	Single night	Oronasal: 17.5 (8.7, 22.2)* Nasal: 10.3 (4.5, 16.7)* p = 0.19	N/A	N/A
Massie et al. (2003) [46]	Crossover RCT	38	39	N/A	39	N/A	3 weeks	Pillows: 10.2 (9.8) Nasal: 7.0 (7.7) p = 0.83	Pillows: 5.9 (3.4) Nasal: 6.4 (3.8) p = 0.84	Pillows: 5.61 (1.29) Nasal: 5.37 (1.55)
Mortimore, whittle and Douglas (1998) [52]	Crossover RCT	20	20	20	N/A	N/A	4 weeks	N/A	Nasal: 8.2 (2.9) Oronasal: 9.8 (0.9) p < 0.01	Nasal: 3 (0.4) Oronasal: 4.3 (0.5) p = 0.01
Rowland et al. (2018) [22]	Crossover RCT	35	35	34	N/A	Nasal mask plus chin strap: 35	12 weeks	Nasal: 4.0 (3.1) Nasal plus chinstrap: 4.2 (3.7) Oronasal: 2.1 (0.7) p = 0.001	Nasal: 6.6 (5.2) Nasal plus chinstrap: 6.0 (4.5) Oronasal: 6.9 (4.9) p = 0.177	Nasal: 4:14 (3:19) Nasal plus chinstrap: 4:43 (3:09) Oronasal: 4:26 (3:02) p = 0.177
Ryan et al. (2011) [47]	Crossover RCT	22	22	N/A	22	N/A	4 weeks	Pillows: 3.0 (2.9) Nasal: 2.6 (2.7) p = 0.509	Pillows: 8 (5) Nasal: 7 (5) p = 0.250	Pillows: 5.0 (1.7) Nasal: 5.1 (1.9) p = 0.701
Shirlaw et al. (2018) [51]	Crossover RCT	71	71	71	N/A	N/A	2 weeks	Nasal: 4.9 (2.6, 8.2)* Oronasal: 5.3 (5.3, 8.0)* p = 0.234	N/A	Nasal 7.3 (6.1, 8.2) Oronasal 7.3 (5.8, 8.1) p = 0.961
Teo et al. (2011) [48]	Crossover RCT	24	24	24	N/A	N/A	Single night	Nasal:13.3 (7.3) Oronasal: 17.6 (9.6) p = 0.02	N/A	N/A
Zhu et al. (2013) [49]	Crossover RCT	20	20	N/A	20	N/A	7 nights	Pillows: 1.9 (1.3) Nasal: 1.7 (1.1) p = 0.26	N/A	Pillows: 7.4 (1.4) Nasal: 7.2 (1.4) p = 0.22

AHI: Apnoea Hypopnea Index, ESS: Epworth Sleepiness Score, RCT: Randomised Control Trial.
[a] *Median(IQR)

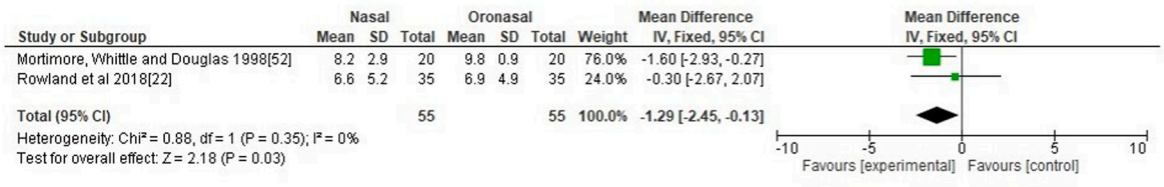

Fig. 5. Forest plot showing the pairwise comparison of the impact of nasal vs oronasal interfaces on ESS.

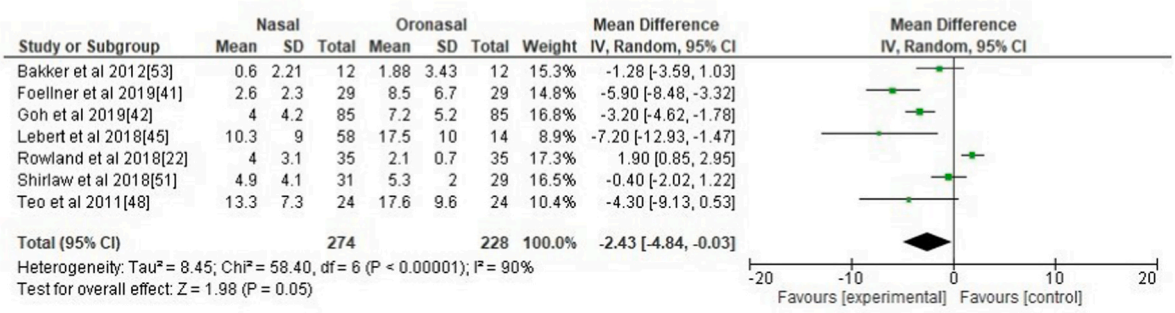

Fig. 6. Forest plot showing the pairwise comparison of the impact of nasal vs oronasal interface on AHI.

4.2.2. *Creams/solutions, artificial saliva and mask liners*

No studies were found investigating creams/solutions or mask liners in the management of pressure ulcers or dermatitis related to PAP therapy. Similarly, no studies were found investigating artificial salvia to manage oral dryness related to PAP use.

4.2.3. *Nasal sprays/douches*

Two studies [19,20] investigated use of nasal sprays and douches. La Mantia et al. [19] conducted an RCT investigating hyaluronan and saline in patients commencing CPAP therapy on nasal inflammation, ESS, AHI, mask leak and CPAP concordance. Nasal inflammation increased from baseline in all groups, but less so in the hyaluronan and saline groups ($p < 0.001$). There was no difference between groups in ESS ($p = 0.679$), AHI ($p = 0.726$) or mask leak ($p = 0.759$). A significant difference between the hyaluronan and CPAP alone group was reported in CPAP compliance rate (73.9% hyaluronan versus 71.6% CPAP alone; $p = 0.009$) and average duration of use (336.26 hyaluronan versus 319.3 mins CPAP only; $p = 0.004$), although this was not clinically meaningful.

Ryan et al. [20] compared the impact of heated humidification (HH) and topical nasal steroids to CPAP alone on CPAP concordance, ESS and nasal symptoms. No difference between groups was found in either hours/night used (Mean ± SD CPAP alone: 5.21 ± 1.66, fluticasone: 5.66 ± 1.68, HH: 5.21 ± 1.84; $p = 0.444$) or % of nights used (CPAP alone: 77 ± 25, fluticasone: 84 ± 19, HH: 76 ± 28; p not reported). Similarly, no difference in ESS was observed between groups (CPAP alone: 9 ± 5, fluticasone: 9 ± 5, HH: 8 ± 6; $p = 0.694$).

4.2.4. *Chin strap*

One study [21] investigated the addition of a chin strap with nasal masks when using CPAP therapy and reported a reduction in percentage of total sleep time with mouth leak (no chin strap: 42.9 ± 23.5 vs with chin strap: 23.6 ± 13.3 L/min; $p < 0.05$) and arousal index (no chin strap: 33.4 ± 18.6 vs with chin strap: 23.6 ± 9.3 event/hr; $p < 0.05$). One study compared nasal masks, nasal masks plus chin strap and oronasal masks [22]. They reported no difference in CPAP use (nasal mask 04:14 ± 03:19, nasal mask plus chin strap 04:43 ± 03:09, oronasal mask 04:26 ± 03:02 hh:mm; $p = 0.177$) or in ESS (nasal mask: 6.6 ± 5.2, nasal mask plus chin strap: 6.0 ± 4.5, oronasal mask: 6.9 ± 4.9; $p = 0.177$). The addition of a chin strap to the nasal mask did not reduce residual AHI (nasal mask: 4.0 ± 3.1 vs nasal mask plus chin strap: 4.2 ± 3.7; p not reported).

4.2.5. *Heated humidification (HH)*

A total of 17 studies investigated HH [20,23–38], which refers to the use of a chamber filled with water which sits on a warming plate, thus heating and humidifying air. One study [32] investigated the use of heated tubing with HH that aims to reduce the phenomenon of "rain out". Two studies [29,31] investigated cold/passover humidification, where air passes over water but is not heated before reaching the patient. All except one [30] investigated HH with CPAP therapy. Studies were heterogeneous in nature with varying primary endpoints (Table 1). Nilius et al. [37] defined the groups within their study as "high risk" or "low risk" of nasal symptoms, thus data were excluded from the meta-analysis.

One study investigated biomarkers [26] and reported reduction in nasal mucosal inflammatory markers with the addition of HH.

Concordance with PAP therapy was investigated by 12 studies [20,23–25,29–34,37,38]; however, there was a difference in reporting of concordance between studies. The internationally recognised method for reporting PAP therapy concordance is to report average hours used on nights used, and the percentage of nights used >4 h over the preceding 28 days. No studies reported on concordance as a percentage and 11 studies reported on concordance as hours worn on nights used with a mean difference of 0.22 h (95% confidence interval (CI) −0.09 to 0.54; $Z = 1.41$; $p = 0.16$) (Fig. S1).

ESS was measured in eight studies [23–25,29,33–35,38] with a mean difference of −0.08 (95% CI -0.69 to 0.53; $Z = 0.26$; $p = 0.79$) (Fig. S2).

A VAS to assess nasal/upper airway symptoms was used by seven studies [24,26–29,32,34]; however, different questions were posed, thus meta-analysis was not possible. Five studies [24,26–28,32] reported reduced nasal and upper airway symptoms associated with PAP therapy when HH was used.

Different manufacturers use different methods for reporting mask leak. Intentional leak is from the expiratory valve, which prevents rebreathing. Unintentional leak is leak from a poor fitting interface. Some manufacturers report unintentional plus intentional leak as an overall figure, whilst others report unintentional leak only. There is no consensus on thresholds for acceptable or high mask leak and no agreed minimally clinically important difference. Undertaking meta-analysis

for this outcome measure is therefore challenging. Two studies [24,33] reported leak measured as both intentional plus unintentional leak with a mean difference of −3.22 L/min (95% CI = −4.02 to −2.41; Z = 7.84; p < 0.00001) (Fig. 2.). Three studies [28,34,36] reported unintentional leak with a mean difference of −9.65 L/min (95% CI = −25.01 to 5.71; Z = 1.23; p = 0.22) (Fig. 3).

AHI was investigated by five studies [28,32–34,36] with a mean difference of −0.22 (95% CI -1.28 to 0.83; Z = 0.42; p = 0.68) (Fig. 4).

4.2.6. Interfaces

As per Table 4, 15 studies investigated the impact of different interfaces [22,39–52]. A pairwise comparison between interfaces was undertaken for each outcome measure.

As with the HH studies, there were differences between studies in the methods for reporting concordance. Meta-analyses were only possible for studies reporting average hours worn per night used. Six studies [22,39,42,51–53] compared nasal and oronasal masks investigating concordance with treatment, with no significant difference between the two groups (mean difference 0.14 h/night (95% CI −0.29 to 0.58) Z = 0.64; p = 0.52) (Fig. S3). Five studies [42,44,46,47,49] compared nasal and nasal pillows impact on PAP concordance and found no difference (mean difference −0.10 h(95% CI −0.39 to 0.18) Z = 0.72; p = 0.47) (Fig. S4). A pairwise comparison between oronasal and nasal pillows was not possible as only one study made this comparison [42].

ESS was assessed by two studies [22,52] comparing nasal and oronasal masks and found a greater improvement in favour of nasal interfaces (mean difference −1.29 (95% CI −2.45 to −0.13) Z = 2.18; p = 0.03) (Fig. 5). Three studies assessed ESS comparing nasal and nasal pillow interfaces and found no difference (mean difference 0.26 (95% CI −1.05 to 1.58) Z = 0.39; p = 0.69) (Fig. S5). A pairwise comparison between oronasal and nasal pillows was not possible as no studies made this comparison.

Two studies [22,48] considered the impact on patient symptoms measured via a VAS; however, they investigated different interfaces and meta-analysis was not possible.

Variations in methods for reporting leak previously described were similar in the interfaces. Three studies [45,51,53] compared nasal and oronasal masks and the impact on unintentional leak and found no difference (mean difference −0.09 L/min (95% CI −1.39 to 1.22) Z = 0.13; p = 0.90) (Fig. S6). No studies comparing nasal and nasal pillow interfaces or oronasal masks and nasal pillows were found.

Residual AHI was investigated by seven studies [22,41,42,45,48,51,53] comparing nasal and oronasal mask and found a lower residual AHI in favour of nasal masks (mean difference −2.43 (95% CI −4.84 to −0.03) Z = 1.98; p = 0.05) (Fig. 6). Five studies [42,44,46,47,49] comparing nasal masks and nasal pillows investigated impact on AHI and found no difference (mean difference −0.23 (95% CI −0.76 to 0.30) Z = 0.83; p = 0.40) (Fig. S7). Only one study [42] compared oronasal masks and nasal pillow interfaces and the impact on AHI.

4.2.7. Customised interface

Customised interfaces refer to the use of 3D printing to manufacture interfaces designed to be personal to the patient's facial features. One RCT [54] reported on the impact of a customised interface on AHI and mask leak and reported residual AHI as lower in the customised interface group (p < 0.001). No difference in mask leak (intentional plus unintentional) was reported (32.75 ± 18.56 customised vs 35.51 ± 47.76 L/min conventional; p = 0.137).

5. Discussion

This systematic review and meta-analysis have demonstrated there is robust data from a small set of studies that current interventions to manage side effects of PAP therapy do not impact on interface leak, residual AHI, PAP concordance or ESS [18–49,51–54]. Data were inconclusive, but there was an inference that HH can help manage oropharyngeal symptoms in those with oronasal symptoms and minimise nasal mucosal inflammation [26].

There are a paucity of studies investigating the impact of dressings, creams/solutions, mask liners, chin straps, artificial saliva and nasal sprays/douches. Whilst outside of the scope of this systematic review, the evidence base for prophylactic dressings in paediatric populations suggests dressings can reduce pressure ulcers [55]. Whilst medical grade creams are routinely recommended for prevention of pressure ulcers [56], in the case of PAP therapy, cream applied to the face could cause increased interface movement and increase friction, potentially increasing the risk of pressure ulcers [57].

Anecdotally, nasal sprays are commonly used to manage rhinitis associated with PAP therapy. However, the current evidence base does not support the routine use of nasal sprays in addressing PAP therapy side effects. Where patients have pre-existing rhinitis unrelated to PAP therapy, clinicians may consider nasal sprays more appropriate.

5.1. Heated humidification (HH)

Heated humidifiers can be used without detrimental impact on mask leak or AHI. Our meta-analysis indicated a reduction in overall (intentional plus unintentional) mask leak, although this was not clinically meaningful. The mechanism of improved mask leak is unclear; perhaps, if oronasal and pharyngeal symptoms are reduced with HH, there might be less mouth opening and thus improved mask fit. There are currently no methodologies for measuring mouth leak in the home setting and no authors to date have considered the impact of HH on mouth leak in a laboratory setting. This may be an important consideration in future studies. This impact of HH on mask leak and AHI has not been evaluated in meta-analyses before, making this a new finding. Additionally, clinicians may be reassured the addition of HH does not reduce the effectiveness of PAP therapy in controlling AHI.

In keeping with previous meta-analyses [58–60], HH did not increase PAP concordance or improve ESS. A minimum of 4 h/night of PAP use is required to achieve beneficial outcomes in terms of daytime sleepiness [61–64]. Whilst mean concordance was >4 h in all studies included, this is a crude measure of concordance which does not consider individual sleep duration. ESS was <10 both with and without HH and reduction in ESS <10 is not clinically meaningful. Whilst meta-analysis was not possible for patient comfort or biomarkers, the systematic review suggests a trend towards improved patient comfort and reduction in inflammatory markers in nasal mucosa. These results were also in keeping with previous systematic review and meta-analyses [58–60].

The routine use of HH remains a debated topic, with this and previous meta-analyses not supporting routine use. It may be appropriate to consider HH use on an individual patient basis, especially in the presence of nasal inflammation or high symptom burden.

5.2. Interfaces

Manufacturers are constantly developing new interfaces, resulting in limited quality evidence base to inform clinical practice. The decision guiding which interface to prescribe is multi-faceted and should ideally be a shared process between patient and clinician.

We found no difference between nasal, oronasal and nasal pillow masks for PAP concordance. This meta-analysis has demonstrated no difference between nasal, oronasal and nasal pillow masks for mask leak; this has not been assessed in previous meta-analyses, and so is a novel finding. There were conflicting results relating to impact of interface choice on CPAP concordance. Andrade et al. [65] reported lower concordance with oronasal masks. Patil et al. [60] reported no clinically significant difference in adherence between nasal pillows and nasal masks. However, they reported a clinically significant improvement in adherence when a nasal mask was used compared with oronasal mask. Chen et al. [66] conducted a network meta-analysis comparing

Practice points

- Whilst not detrimental, routine use of heated humidification does not appear to be of clinical benefit. Clinicians may consider the use of heated humidification in a select population with nasal symptoms.
- There is insufficient evidence supporting the preferential use of one interface type (nasal, oronasal, pillows) over another in optimising clinical outcomes.
- No routine interventions can be recommended to optimise home non-invasive ventilation therapy. Evidence in continuous positive airways pressure is unlikely to be translatable to non-invasive ventilation.

Research agenda

This review has demonstrated that there is the need for further research investigating:

- other available interventions in this growing field, including mask liners, nasal sprays and personalised mask interfaces.
- a more demographically representative population in order to identify effective interventions to optimise PAP therapy

The heterogeneity of the reported outcome measures highlights the need for consensus in future studies. Development of a Core Outcome Measures in Effectiveness Trials (COMET) set is recommended.

nasal masks, nasal pillows and oronasal masks, favouring nasal masks, with nasal pillow considered the second-best option and oronasal mask ranking third. It is unclear how these previous meta-analyses chose to define concordance with PAP therapy, which makes comparison with the presented results difficult.

In a pairwise comparison, our meta-analysis found a nasal mask performed better than both an oronasal mask and nasal pillows in reducing ESS. A meta-analysis [60] reported no meaningful difference in ESS between nasal pillows and nasal masks, nor between oronasal masks or nasal masks. Different inclusion criteria were applied resulting in discrepancies in included studies between this meta-analysis and the previous meta-analysis [60], which might explain the difference in results. Whilst our meta-analysis found a statistically significant difference in reducing ESS, the mean difference was not clinically meaningful, and ESS was <10 post-treatment in all included studies.

In a pairwise comparison, we found nasal masks performed better than oronasal masks in reducing AHI, with no difference between nasal masks and nasal pillows. This is in keeping with previous meta-analyses [60,65]. Patil et al. [60] report a higher residual AHI with oronasal masks compared to nasal masks, which they reported as not clinically meaningful. In a pairwise comparison in their network meta-analysis, Chen et al. [66] reported no difference between nasal pillows and nasal masks. They reported reduced residual AHI for both nasal masks versus oronasal masks and, nasal pillows versus oronasal masks. As with our results, whilst statistically significant, this higher residual AHI in oronasal masks did not reach clinically meaningful difference, with differences in AHI <4 events/hr. The network meta-analysis ranked nasal mask first for residual AHI, with nasal pillows second and oronasal mask third.

There is a paucity of evidence related to the efficacy of different interfaces in bi-level PAP therapy or NIV. A recent meta-analysis [67] pooled data from 8 RCTs with 290 individual patient data included, which aimed to compare the effects of nasal and oronasal masks on treatment efficacy and adherence in patients with COPD and obesity hypoventilation syndrome treated with home NIV. They reported that oronasal masks were most commonly used (86% of cases). However, they reported no difference in efficacy between nasal and oronasal masks, with gas exchange as a measure of treatment efficacy. They also reported no difference in adherence of NIV between nasal and oronasal masks.

5.3. Customised interfaces

Technological advances continue to enable personalised healthcare. Only one study investigating customised interfaces was eligible for inclusion, but other authors have investigated this possibility [68–72]. As only one study was included in this systematic review, caution with interpretation is required. Nonetheless, this appears to be a promising potential development.

5.4. Limitations

The heterogeneity of the included studies needs to be recognised when considering the implications of our meta-analysis. Different cut-off values for AHI were used when making a diagnosis of OSA, with some studies only including participants with moderate to severe OSA. The measurement method for outcome measures varied between studies; this was particularly true for mask leak and PAP concordance. An array of outcome measures were used for measuring excessive daytime sleepiness and our inclusion criteria only included studies which employed the ESS. The primary endpoint varied substantially between studies, with most studies of short duration (Median (IQR) duration of studies 4 weeks (1–4). This made drawing conclusions regarding the long-term benefits of potential interventions for managing PAP therapy side effects difficult. There are other approaches to managing the side effects of PAP therapy not included in the scope of this review, for example, the altering of PAP therapy prescriptions/settings. Nearly all studies investigated CPAP therapy and, whilst this is the most commonly deployed PAP therapy, clinicians should take caution in applying the results of this systematic review to other forms of PAP therapy, such as bi-level or NIV.

Concordance with PAP therapy is multifaceted and can be influenced by several factors. It was outside of the scope of this systematic review and meta-analysis to consider the societal, environmental or other factors which can impact patient concordance with PAP therapy. The scope of this systematic review was quantitative in nature and thus qualitative studies were excluded.

The demographics of the participants included in the studies were mostly male, aged 50 to 60. Whilst OSA is more common in males, the

lack of representation of females in the included studies means the results of this systematic review may not be generalisable to females. Caution should also be applied before assuming the results of this systematic review apply to younger and more elderly patients. Ethnicity was not reported in any of the included studies. Ethnicity could particularly impact upon studies investigating different interfaces, as different facial geometries could impact on appropriate PAP interfaces. The lack of reporting of ethnicity in the included studies makes it impossible to determine if the results of this systematic review apply to different ethnic groups.

5.5. Future research

This systematic review has demonstrated that there is a lack of consensus regarding which outcome measures should be prioritised when investigating the side-effects related to PAP therapy. The Core Outcome Measures in Effectiveness Trials (COMET) initiative aims to agree a standardised set of outcome measures in a specific area of healthcare. There is currently no COMET set for adults with sleep disordered breathing and this represents an important area to address which could be of significant benefit for future studies. Already completed COMET sets include measure of quality of life, efficacy and cost effectiveness. It is unclear from the current literature how commonly any of these interventions are utilised, what barriers or facilitators there might be, or how acceptable these interventions are to patients. Concordance with PAP therapy is multi-faceted and further research is needed on other influences, such as societal and environmental, as well as interventions that were outside of the scope of this systematic review. Studies that utilise qualitative methodologies are important for future research to ensure the voice of patients is incorporated into the evidence base.

As technology continues to enhance healthcare, personalised medicine may enable us to consider who is most at risk of developing side-effects to PAP therapy and prophylactically intervene. Similarly, personalised medicine may enable us to customise treatment for patients, such as with the use of customised interfaces.

6. Conclusion

This systematic review and meta-analysis reported on the evidence base for the management of side effects to PAP therapy. There is robust data from a small set of studies indicating that no current intervention either improves or detrimentally affects PAP concordance, ESS, residual AHI or interface leak. Oronasal interfaces may increase residual AHI, but not to a clinically meaningful level. There is a scarcity of studies investigating managing side effects to NIV, and this area of research should be prioritised considering the increasing number of patients receiving NIV. Development of a COMET set would be beneficial to the field with studies of longer duration and including participants representative of clinical populations as a priority. Clinicians should use current strategies to manage PAP side effects with personalised care for individual patients.

Declaration of competing interest

No direct COI to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smrv.2023.101850.

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