Establishing an evidence base to improve sleep disorder medicine and home ventilation programs that treat patients with chronic obstructive pulmonary disease

by

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is a disabling disease associated with high health care utilization. Patients with sleep-related breathing disorders (SRBD) or chronic hypercapnic respiratory failure (CHRF) in addition to COPD have improved health outcomes if they become established on positive airway pressure (PAP) therapy. Here, evidence regarding success becoming established on PAP therapy in patients with COPD is summarized and novel barriers to use of this therapy were explored.

Methods: A systematic review and meta-analysis of available literature quantified the acceptance of and adherence with non-invasive PAP therapy in patients with COPD when prescribed for long-term use at home. Concurrently, a prospective cohort study was conducted to assess barriers to use of PAP therapy in patients with a SRBD and COPD compared to controls with obstructive sleep apnea (OSA).

General Conclusions: After a systematic assessment and synthesis of data from 86 studies, qualitative and quantitative syntheses were performed. Acceptance of PAP therapy in patients with COPD was high, with the proportion of patients who declined or discontinued PAP therapy within one year of prescription was only 14% (95% CI 10-20%). Adherence to newly prescribed PAP therapy was reported in both continuous and dichotomous measures, with participants achieving a median pooled usage of 6.24 hours/day (95% CI 5.80-6.69 h/day). Among included studies, pooled summary estimates had significant heterogeneity. Among studies, the heterogeneity in acceptance and adherence were partially explained by indication for therapy. Clinical variables that were identified as being important to explore heterogeneity in acceptance and adherence were often not reported in detail such as timing of initial follow-up and types of

health care providers involved in care. More patients with CHRF secondary to COPD discontinued therapy within one year; however, of those who accepted therapy, use per day was longer when PAP therapy was prescribed for CHRF secondary to COPD than for patients with COPD and a SRBD. Within studies, variables affecting heterogeneity for uptake and use of PAP therapy were sporadically reported and rarely comprehensively assessed.

Pilot data from a prospective cohort study using survey methodology in Albertans explores the acceptance and adherence with PAP therapy in patients with COPD and a SRBD compared to controls with OSA matched for age and body mass index. Twenty-one of 28 recruited patients with COPD and a SRBD and 12 of 26 controls had completed the study at the time of thesis preparation. Of these, the proportion of participants who were able to both accept and adhere to PAP therapy were 65% of the patients with COPD and 33% of matched controls. The adherence to PAP therapy at 6 weeks was 6.02 hours/day in patients with COPD vs 4.62 hours/day in matched controls. A preliminary descriptive analysis of the characteristics of patients successful in accepting and adhering to PAP therapy for both groups is summarized.

Conclusion: The majority of patients with COPD prescribed PAP therapy successfully accept and adhere to therapy; however, significant heterogeneity was observed among studies. The studies within this research program both synthesize available evidence and generate novel data to inform program structure and policy development. Dissemination of these results in peer-reviewed literature has been accomplished and will continue following the thesis defense. Finally, these data will be used to impact local and national policies for the implementation of PAP therapy to increase the probability of success with PAP therapy in patients with COPD.

Preface

This thesis is an original work by Dr. Cheryl Laratta. The research projects, of which this thesis is a part, received research ethics approval from the University of Alberta Health Research Ethics Board. The systematic review and the prospective cohort study were collaborative works.

The proposed study that received granting from the Medicine Strategic Clinical Network, Respiratory subsection, entitled, "Prevalence and treatment status of obstructive sleep apnea in patients presenting to the Emergency Department with an exacerbation of COPD," was not pursued due to restrictions recruiting patients from the Emergency Department (ED) during the pandemic (Ethics Reference ID: Pro00100459, operational approval not sought during COVID-19 pandemic).

The systematic review is a collaborative work. Contributors to the study protocol include Dr. Rachel Jen. Additional contributors to the execution of the systematic review include Dr. Linn E. Moore (LM), Scott W. Kirkland (SK). Dr. Nana Owusu Essel contributed statistical support.

The prospective cohort study is also a collaborative work. Contributors to this work include Dr. Irvin Mayers, Dr. Brian McNab for patient recruitment and research staff support. Geoffrey Charm and Pradhee Bastola provided assistance with data acquisition.

Dedication

To my grandfather, Mr. Patrick J. Lane.

Acknowledgements

The opportunity to develop this program of research has been a privilege. Prior to sharing this thesis, I would first like to thank the professional and personal support that has allowed this work. First, the significant professional growth opportunities that I have been afforded is due to sage advice and mentorship provided by my supervisor, Dr. Brian Rowe, Professor in the Department of Emergency Medicine and School of Public Health, University of Alberta. Similarly, I credit the dedicated feedback from my supervisory committee, Dr. Sachin Pendharkar, Associate Professor, Departments of Medicine and Community Health Sciences, University of Calgary, and Dr. Joanna MacLean, Associate Professor, Department of Pediatrics, University of Alberta. Their willingness to supervise this subspecialty research has required patience, time and the development of local infrastructure. Throughout this process, their mentorship has had a profound impact on my professional growth. Beyond my supervisory team, mentorship and academic support was kindly and consistently provided by Dr. Brian McNab, Dr. Irvin Mayers, Dr. Giovanni Ferrara and my colleagues at the University of Alberta.

Secondly, I am greatly appreciative of the funding granted by the Respiratory Section, Medicine Strategic Clinical Network, Alberta Health Services whose investment in me as an early investigator provided the seed grant funding that supported the prospective survey study.

Lastly, to perform this research alongside my professional career was only possible due to my incredible family. I am inspired by our children, Jason and Sophia, who are a daily source of light and laughter, questioning and testing hypotheses. Our parents and sisters have shared this journey with love, kind words and helping hands. Most importantly, I credit this work to my husband, Peter Laratta, whose unwavering love and encouragement has kept the dreams alive.

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Abbreviations

AASM	American Academy of Sleep Medicine
ABG	Arterial blood gas
AHCIP	Alberta Health Care Insurance Pan
AHI	Apnea-hypopnea index
ASV	Adaptive servoventilation
BMI	Body mass index
BPAP	Bilevel positive airway pressure
CAT	COPD Assessment Test
CBT-I	Cognitive behavioural therapy for insomnia
CENTRAL	Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials
CHRF	Chronic hypercapnic respiratory failure
CI	Confidence interval
CPAP	Continuous positive airway pressure
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CSA	Central sleep apnea
CT	Chest tomography

CXR	Chest radiograph
ECOPD	Exacerbations of COPD
ED	Emergency department
EPAP	Expired positive airway pressure
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HCO3	Bicarbonate
HI-NIV	High intensity non-invasive ventilation
HSAT	Home sleep apnea testing
HMV	Home mechanical ventilation
ICD-9-CA	International Classification of Diseases and Related Health Problems
ICS	Inhaled corticosteroid
IPAP	Inspired positive airway pressure
IQR	Interquartile range
LABA	Long-acting beta agonist
LAMA	Long-acting muscarinic antagonist
LI NIV	Low intensity non-invasive ventilation
LLN	Lower limit of normal

MeSH	Medical Subject Headings
MRC	Medical Research Council
NIV	Non-invasive ventilation
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnea
PCO_2	Partial pressure of carbon dioxide
$PaCO_2$	Partial pressure of arterial carbon dioxide
PAP	Positive airway pressure
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
PCV	Pressure control ventilation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
PROSPERO	International Prospective Register of Systematic Reviews
PSV	Pressure support ventilation
PSG	Polysomnography
RCT	Randomized control trial
RDI	Respiratory disturbance index
REI	Respiratory event index
REM	Rapid eye movement
REML	Restricted maximum-likelihood estimator

RevMan	Review Manager Software
RRT	Registered respiratory therapist
SABA	Short-acting beta agonist
SAMA	Short-acting muscarinic antagonist
SD	Standard deviation
SRBD	Sleep-related breathing disorder
$TcCO_2$	Transcutaneous carbon dioxide
VAPS	Volume assured pressure support

Chapter 1: Evidence-based innovation to improve the management of patients with COPD prescribed positive airway pressure therapy: Background and study rationale.

1.1 Chronic obstructive pulmonary disease: An overview

1.1.1 Epidemiology

Chronic obstructive pulmonary disease (COPD) is a syndrome of chronic respiratory symptoms including cough, sputum production, dyspnea or wheeze associated with fixed airflow obstruction on spirometry that is not attributed to an alternative cause[1]. Chest imaging often suggests structural pulmonary abnormalities of large or small airways disease with or without emphysema[1]. The prevalence of COPD is high, affecting an estimated 10.3% of the world's population[2]. Of persons who achieve normal lung function by early adulthood, the disease generally affects those age ≥40 years old[3]. In the CanCOLD study, up to 16.2% of non-institutionalized adults in Canada met criteria for COPD[4]. Chronic obstructive pulmonary disease is more prevalent in males (13.4%) than females (7.8%)[5]. Social determinants of health impact the disease prevalence, with a higher prevalence of COPD in those with a lower socio-economic status[6]. Health care utilization is common in patients with COPD, with 86 hospitalizations for COPD per 100,000 people/year in Canada[7]. Admissions to hospital for COPD exacerbations (ECOPD) represent the second most common reason for admission in Canada and length of stays can be prolonged[8]. Canadian age and sex-standardized rates of COPD admissions continue to increase[9]. One in 20 Canadians with COPD who are

hospitalized qualify as “high users” and have ≥3 hospitalizations and ≥30 days spent in hospital per year[10]. With such a high burden from disease, it is not surprising that COPD is a leading cause of disability and death worldwide[11, 12]. Patients with COPD have frequent non-respiratory co-morbidities such as cardiovascular disease, obesity, mental health conditions, osteoporosis and GERD[1] as well as respiratory co-morbidities such as lung cancer, sinonasal disease, obstructive sleep apnea (OSA), bronchiectasis, or asthma[13]. Comorbidities are associated with increasing ECOPD and decreasing health-related quality of life[14]. There is also emerging evidence that suggests other factors may also influence health outcomes, including frailty[15].

1.1.2 Pathophysiology

The pulmonary manifestations of COPD are the result of destruction of lung tissue in susceptible individuals through chronic inflammation secondary to recurrent infection and the direct effects of tobacco smoking, environmental pollutants, fumes/gases/vapors within work environments or smoke from biomass fuel combustion indoors[3]. A genetic predisposition to COPD occurs in individuals with alpha-1 anti-trypsin deficiency[16] and is suspected to be a factor in families that have clustering of COPD[17, 18]. While the majority of patients with COPD develop the syndrome in adulthood, 4-12% of the general population are predisposed to developing COPD by not achieving their predicted peak lung function by early adulthood due to health events in early childhood or barriers to healthy lung development[19, 20]. By association, these patients also have increased risk of adverse health outcomes in future years[21].

Exacerbations of COPD are driven by a variety of triggers and are deleterious to long-term health of patients with COPD by accelerating lung function decline over time[22]. Known

triggers of ECOPD include environmental exposures, such as air pollution[23] or infections[24]. Eosinophilic airway inflammation and seasonal trends in ECOPD are also known to occur[24].

1.1.3 Diagnosis

The diagnostic criteria for COPD are based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, termed the 2024 GOLD Report, and require a combination of history and examination findings, simple and advanced radiographic imaging and evidence of fixed airflow obstruction on spirometry. A post-bronchodilator forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) ratio (aka: FEV_1/FVC ratio) of <0.7 is the threshold criteria for airflow obstruction in the 2024 GOLD Report. Causes of fixed airflow obstruction other than COPD include asthma, bronchiectasis, and less common causes of respiratory bronchiolitis, so the FEV_1/FVC ratio is only one component of the diagnostic criteria. Once fixed airflow obstruction is documented to be from COPD, the FEV_1 determines severity of airflow limitation and is a clinically important measure associated with health outcomes and mortality[25]. In the 2024 GOLD Report, the severity grades are as follows in patients with FEV_1/FVC <0.7:

- GOLD 1 – mild: FEV_1 ≥80% predicted;
- GOLD 2 – moderate: 50% ≤ FEV_1 <80% predicted;
- GOLD 3 – severe: 30% ≤ FEV_1 <50% predicted;
- GOLD 4 – very severe: FEV_1 <30% predicted.

Additional clinical tools are commonly used to assess symptom burden and health-related quality of life in patients with COPD. These includes the Medical Research Council (MRC) dyspnea scale which rates dyspnea on exertion on a scale 1-5 and is a method to categorize disability[26].

The COPD Assessment Test (CAT) is a questionnaire measure representing the impact of COPD on health-related quality of life, where <10 is low impact, 10-20 medium impact, 21-30 high impact, and >30 very high impact, with 40 being the maximum score[27, 28].

The definition of ECOPD has evolved recently with the updated Rome Proposal, where ECOPD is defined as a worsening of specific cardinal symptoms of COPD within a 14 day period accompanied by increased work of breathing and/or tachycardia and associated with local and systemic inflammation[29]. The severity of an ECOPD was historically determined by the need for health care resource allocation. While widely used, this historical definition has important limitations[30]. The 2024 GOLD Report defines the severity of ECOPD as the following[25]:

- Mild: Managed with short-acting bronchodilators only;
- Moderate: Managed with short-acting bronchodilators, oral corticosteroids and/or antibiotic therapy;
- Severe: Management included a visit to the emergency department (ED) or a hospitalization.

1.1.4 Treatment

Interventions for COPD are intended to reduce symptoms, improve health-related quality of life, reduce ECOPD, reduce health care utilization and/or prolong survival. These interventions include the following guideline-based strategies[25, 31-33]:

1) *Prevention:* Smoking cessation counselling and treatment using best practices, vaccination against respiratory viruses and *Streptococcus pneumonia;*
2) *Education and supportive care:* Education targeted towards prevention of hospitalization; long-term oxygen therapy for those who qualify for funding; pulmonary rehabilitation for patients with recent ECOPD or functional impairment;

3) *Rapid access to health care specialists:* Case management including implementation and use of written COPD action plans;
4) *Optimized pharmacologic management:* Guideline-based pharmacologic treatment of COPD[32] that may include use of long-acting β-agonists (LABA), long-acting muscarinic antagonists (LAMA), inhaled corticosteroids (ICS), reliever inhalers (short-acting β-agonists [SABA] and short-acting muscarinic antagonists [SAMA]), and other pharmacotherapies such as macrolide antibiotics, phosphodiesterase-4 inhibitors, methylxanthines, mucolytic agents, or alpha-1-antitrypsin augmentation therapy;
5) *Optimized procedural management*: Lung volume reduction surgery, endoscopic lung volume reduction and/or lung transplantation for highly selected patients;
6) *Airway support:* Positive airway pressure (PAP) therapy for patients with chronic hypercapnic respiratory failure (CHRF) secondary to COPD or OSA.

1.2 Obstructive sleep apnea and chronic hypercapnic respiratory failure in patients with COPD: an overview

1.2.1 Epidemiology

The most recent 2024 GOLD Report recommends that PAP therapy be prescribed to patients who have either CHRF or OSA. While patients with CHRF secondary to COPD or patients with SRBD such as hypoventilation or OSA are often separately defined for the purposes of research, they often overlap in clinical practice.

Obstructive sleep apnea is characterized by recurrent episodes of transient narrowing or closure of the upper airway leading to arousals from sleep or desaturations. There is a wide variation in the estimated prevalence of comorbid COPD and OSA in part due to differing characteristics of

the study populations, ranging from 7.6% to 55.7% of patients initially diagnosed with OSA; and 2.9% to 65.9% of patients initially diagnosed as COPD[34]. In general, OSA co-exists with COPD in an estimated 1.0-3.6% of Canadians[35]. Patients with both OSA and COPD experience worse health outcomes when compared to patients with COPD alone, such as an increased number of hospitalizations in the preceding year[36, 37], longer length of stay in hospital[38] and increased risk of readmission to hospital[39-41]. These patients also have increased mortality compared to patients with COPD who do not have OSA[39]. Hospitalizations for cardiovascular or cerebrovascular disease are also increased in these patients when compared to those with severe OSA or patients with COPD in isolation[42].

Patients with COPD and health care utilization are commonly hypercapnic. Observational studies suggest that the prevalence of compensated hypercapnic respiratory failure is estimated as 52.7%, in patients hospitalized with COPD[43]. There is a still higher prevalence in patients with COPD and recurrent hospitalizations[43]. When prospectively assessed, patients with COPD and CHRF have a high mortality[44, 45], with the median survival in Yang *et al* of 5.0 years, with respiratory failure being a frequent cause of death[45].

1.2.2. Pathophysiology

Many clinical variables affect the prevalence and severity of OSA in patients with COPD. Risk factors for OSA in the general population include older age, obesity, male sex, and postmenopausal females; however, there are a variety of predisposing conditions or associated diseases[46]. Additionally, some medications or substances may increase the risk of OSA such as alcohol[47]; whereas others, such as opioids[48], have demonstrated conflicting results in epidemiologic studies. Body mass index (BMI) in patients with COPD is an important risk factor for OSA, even when at the upper limits of normal[49]. In patients with COPD, the presence of

peripheral edema or smoking increases the risk of OSA; whereas, the state of being hyperinflated with air trapping or experiencing a shorter duration of rapid eye movement (REM) sleep decrease the risk of having OSA[50]. Research assessing the impact of alcohol on the AHI in patients with COPD and OSA was insufficient to result in generalizable conclusions[47, 51]. Opioids are commonly prescribed with palliative intent in patients with COPD, with an observational study associating use of opioids with adverse events [52]; however, opioid use has not been evaluated specifically as to the impact on the prevalence of OSA in this patient population[53]. These clinical factors impact physiologic mechanisms that affect upper airway patency, namely pharyngeal dilator function, anatomic structures surrounding the upper airway, the stability of ventilatory control, and the arousal threshold, all which can vary among individuals[54].

The co-existence of these two conditions affects how OSA and COPD impact sleep and health. Patients with COPD and OSA have lower oxygen saturations and greater oxygen desaturations on sleep diagnostic testing when compared to people with OSA who do not have COPD[35]. Sleep quality on questionnaires is lower in patients with COPD and OSA when compared to patients with COPD alone[55]. Patients with COPD and OSA have higher pulmonary artery pressures on echocardiography[56], and a higher prevalence of heart failure and coronary artery disease[57] when compared with patients with COPD who do not have OSA.

The presence of less common types of SRBDs such as central sleep apnea (CSA) contribute to heterogeneity of the diagnosis and treatment of OSA in patients with COPD. In patients with COPD, the types of CSA that may co-exist include CSA secondary to opioids, CSA secondary to an underlying disease such as cerebrovascular disease, or Cheyne-Stokes breathing. Each type of CSA has different mechanistic considerations; however, generally reflect a decrease or

variability in the drive to breathe rather than a narrowing or collapse of the upper airway leading to decreased airflow. The implications of CSA in addition to OSA, CHRF and COPD are not well understood and are an area requiring further study.

Hypercapnic respiratory failure is defined by the presence of an elevated level of partial pressure of carbon dioxide ($PaCO_2$) in the arterial blood. The elevation in $PaCO_2$ may be transient, such as with ECOPD, or chronic. The cause of a chronic elevation in $PaCO_2$ may be due to brainstem respiratory suppression, neurologic disease within the central nervous system, peripheral neuropathies, diseases or substances that affect the neural-neural junction or neuromuscular junction, myopathies, obesity, chest wall disease or chest wall injuries, pleural disease, pulmonary vascular disease, COPD or end-stage ventilatory failure from other pulmonary diseases[58]. Mechanisms specific to pulmonary disease from advanced COPD that contribute to chronic hypercapnia include decreased minute ventilation and ventilation-perfusion mismatch leading to increased dead space ventilation, decreased respiratory drive from the central nervous system, altered respiratory system mechanics, and increased ventilatory demand[59]. Chronic hypercapnic respiratory failure in patients with COPD is often multifactorial including causes such as obesity[50], advanced COPD[60], and use of opioids[61, 62]. The physiological mechanisms that underlie the need for airway support in COPD can vary markedly, resulting in a diverse and heterogenous cohort of patients that require PAP therapy.

1.2.3. Diagnosis

In patients with COPD, the diagnoses of CHRF and/or OSA are assessed with sleep diagnostic testing, an arterial blood gas, spirometry and anthropometrics, in addition to a comprehensive clinical assessment. Sleep diagnostic testing assesses for OSA by confirming the number of

narrowings (hypopneas) or collapses (apneas) of the upper airway during sleep. Several types of sleep diagnostic testing may be used:

- Level I: Attended polysomnography (PSG, gold standard);
- Level II: Unattended polysomnography (rarely used clinically, more often in research settings);
- Level III: Home sleep apnea testing (3-4 channels of data);
- Level IV: Overnight oximetry (1-2 channels of data).

The appropriateness of the type of sleep diagnostic testing requested depends on the pre-test probability of OSA, the differential for the SRBD, the severity of COPD and the severity of co-morbidities[46, 63].

The criteria to score and report on sleep diagnostic testing is outlined in the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events[64]. For OSA, the number of obstructive hypopneas or apneas/hour of either total sleep time or total recording time determines disease severity. On PSG, this ratio is the apnea-hypopnea index (AHI) or, less commonly reported, the respiratory disturbance index (RDI). Other measures obtained from sleep diagnostic testing, such as respiratory event index (REI) or oxygen desaturation index (ODI), are surrogates of the AHI and are obtained using ambulatory sleep diagnostic testing[64]. Disease severity for OSA is similarly defined by various resources[65, 66]; however, for the purposes of this thesis, will be defined as per the AASM clinical practice guidelines, with the AHI, REI or ODI substituted for the RDI where appropriate[67]:

- Mild: RDI ≥5 and <15 events/hr;
- Moderate RDI ≥ 15 and ≤30 events/hr;

- Severe: RDI >30 events/hr.

Hypercapnic respiratory failure may be diagnosed on sleep diagnostic testing, such as with transcutaneous carbon dioxide ($TcCO_2$); however, is mostly commonly assessed by documenting an elevation of the $PaCO_2$ to ≥45 mmHg[58] with an arterial blood gas (ABG) or capillary blood gas (capillary PCO_2). Chronic hypercapnia is present if the hypercapnia persists 2-4 weeks after the resolution of an ECOPD or when measured at the patient's medical baseline[33]. Sleep-related hypoventilation on PSG may occur even when eucapnia is present on an ABG. Sleep-related hypoventilation is defined as a rise in transcutaneous carbon dioxide ($TcCO_2$) by >10 mmHg to a value >50 mmHg for ≥10 min or an increase in $TcCO_2$ to >55 mmHg for ≥10 min on PSG[64].

1.2.4 Treatment

In patients with COPD, treatment of OSA or CHRF when diagnosed at the patient's medical baseline is first addressed with education and addressing the underlying cause. Strategies may include optimizing the pharmacologic and procedural management of COPD, reducing weight in the setting of obesity, and minimizing opioids. Alongside these interventions, treatment with long-term PAP therapy is recommended. PAP therapy may be provided as one of the following modalities:

- Continuous positive airway pressure (CPAP): application of a fixed airway pressure (6-20 cmH2O) through a mask interface, with or without humidity.
- Non-invasive ventilation (NIV): application of an inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP), usually with a minimum pressure difference (pressure support) of 4 cmH2O (bilevel positive airway pressure, BPAP). Maximum inspiratory pressures vary between devices and prescribers. A backup

rate may be applied. Additional modes are available on some ventilators are more varied, including volume control, pressure control or adaptive modes that vary the IPAP and/or EPAP breath to breath to target a minute ventilation or other physiologic measure.

In patients with OSA, CPAP reduces sleepiness, improves health-related quality of life, and improves hypertension control[68]. In patients with COPD and OSA, a systematic review of observational studies suggests additional benefits including fewer ECOPD, fewer COPD-related hospitalizations and lower mortality based upon data from 5 cohort studies, notably including a comparison population of patients who did not accept or adhere to CPAP[69]. More recently, an administrative study that linked physician billing claims with cloud-based user data demonstrated that adherence to PAP therapy in patients with COPD and OSA was associated with less frequent all-cause hospitalizations and ED visits, fewer exacerbations of COPD requiring hospitalization, and lower health care costs than patients who were nonadherent with PAP therapy[70].

For treatment of CHRF secondary to COPD, a systematic review of RCTs suggests that NIV results in short-term improvement in health-related quality of life and an improved survival[71]. When instituted for persistent hypercapnia after an exacerbation of COPD, NIV for CHRF may prolong admission-free survival[71]. Observational studies suggest that treatment of CHRF associated with COPD may also decrease health insurance expenditures, if initiated shortly after the diagnosis[72].

1.3 Implementation of PAP therapy in sleep disorders programs

While PAP therapy is a guideline recommendation for patients with COPD and CHRF or OSA, there is limited knowledge surrounding how it should be successfully implemented. A recent

review of home mechanical ventilation (HMV) programs worldwide reported 133 centers had HMV programs[73]; however, COPD was not a diagnosis for which ventilation was being provided in HMV centres in Canada. An observational study using an Ontario sample suggested that COPD was the primary indication for NIV in 18.8% of patients funded through a provincial assistive device program[74]; however, as this was not captured in the HMV program survey, it may be that the management of these patients is not occurring within HMV programs. The use of NIV for COPD is increasing over time, although NIV prescription remains low in Canada compared to European countries where the majority of reported HMV programs are based[73].

While many studies have assessed PAP therapy in patients with COPD, there has been little published work to date to collate knowledge about program structures that have success in implementation of PAP therapy in this population. Even within a single region, the timing, assessment and care pathways to use of NIV in patients with COPD is quite variable in clinical practice[75]. Management of patients with COPD with CHRF and frequent hospitalizations does not often result in outpatient use of home NIV[43]. In the national survey on HMV programs in Canada, barriers to use of HMV were insufficient funding for home caregivers/equipment/supplies, access to caregivers, and negotiating public funding for care[76]; however, barriers to use of PAP therapy otherwise are not well understood.

1.4 Summary and Future Directions

Given the limited available evidence to inform program development for the provision of PAP therapy in patients with COPD, it seems that there are only two options that patients have, which is “to sink or to swim” with PAP therapy after the initial prescription. ‘Life jackets’ may be provided through local experience and innovation; however, the lack of an evidence-based approach to this issue is problematic. The studies undertaken in this thesis will inform an

evidence-based approach to the design and implementation of programs that prescribe and support patients with COPD who require airway support with PAP therapy.

The program of research is presented as a chapter-based thesis. Chapter 2 is a systematic review of existing literature related to acceptance of and adherence with PAP therapy in patients with COPD. Chapter 3 explores pilot data from a prospective cohort study to assess barriers to success with therapy. In Chapter 4, the groundwork that was instituted to assess health care outcomes related to the use of PAP therapy in patients with a SRBD and COPD will be reviewed. In Chapter 5, the current state of the projects and program of research will be summarized. By the end of this document, it is my intention to convey the importance of the work that is nearing completion from these projects. Moreover, I intend to highlight the significant infrastructure for research that has been implemented through this work that will form the foundation of a program of research in PAP adherence and airways disease in the future.

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Chapter 2: Success initiating and using long-term non-invasive positive airway pressure therapy in patients with COPD: a systematic review and meta-analysis

2.1 Abstract

Introduction: Non-invasive positive airway pressure (PAP) therapy is an effective, albeit complex, intervention for obstructive sleep apnea (OSA) and chronic hypercapnic respiratory failure (CHRF) in patients with chronic obstructive pulmonary disease (COPD). Systematic review methods were used to summarize acceptance of and adherence with long-term PAP therapy.

Methods: Eight databases and the grey literature were searched. Study arms were assessed according to a predefined protocol (PROSPERO CRD42021259262). Acceptance and adherence (hours of use/day) were pooled with inverse variance weighted random effects meta-analyses using Freeman–Tukey-transformed values and quantile estimation of medians, respectively. Meta-regression using backward elimination explored heterogeneity.

Results: Of the 86 included studies, 56 arms from 51 studies contributed data to the summary estimates for acceptance and 77 arms from 60 studies contributed data to adherence. PAP therapy was discontinued on average in 14% (95% CI 10–20) of cases, often within 6 weeks of initiation among studies reporting repeated measures. The pooled median adherence was 6.24 hours/day (95% CI 5.80–6.69) in 66 arms reporting this specific measure. There was sporadic reporting of barriers to use other than device intolerance. Meta-regression found lower acceptance ($p=0.03$) and longer use/day ($p<0.01$) when PAP therapy was prescribed for CHRF due to COPD versus OSA.

Conclusions: Patients with COPD can achieve success with PAP therapy; however, significant heterogeneity was found among studies, partly explained by indication for use. Comprehensive reporting on barriers to use is needed to explore variability in PAP acceptance and adherence.

2.2 Introduction

Positive airway pressure (PAP) therapy is a complex long-term therapy that improves health outcomes in select groups of patients with chronic obstructive pulmonary disease (COPD). Studies evaluating the benefits of PAP therapy in patients with COPD have included indications such as severity of COPD, high health care utilization, chronic hypercapnic respiratory failure (CHRF) secondary to COPD, or co-morbid sleep-related breathing disorders (SRBD) such as hypoventilation or obstructive sleep apnea (OSA). When used for CHRF secondary to COPD, a systematic review of RCTs demonstrated that NIV improved short-term health-related quality of life and increased survival, with improved admission-free survival noted in those who had chronic and persistent hypercapnia after an exacerbation of COPD (ECOPD)[1]. When used for OSA co-morbid with COPD, administrative studies[2-4] and a systematic review of observational studies[5] suggest reduced ECOPD, reduced hospitalizations for ECOPD and increased survival when compared to patients who did not tolerate or adhere to therapy. There have been fewer randomized control trials (RCTs) in patients with COPD and OSA given the known benefits of treating OSA with PAP therapy[6]. Zheng *et al* demonstrated that in patients with OSA with CHRF and COPD, both continuous positive airway pressure (CPAP) and non-invasive ventilation (NIV) reduced sleepiness, improved sleep quality and improved neurocognitive function[7]. Hypercapnia was improved to a greater degree with NIV[7]. Through pilot data, Patout *et al* demonstrated that NIV in patients with COPD, OSA and CHRF had similar outcomes after randomization to a titration with polysomnography (PSG) or

transcutaneous oxi-capnometry monitoring and a titration led by a specialized nurse from an inpatient hospital unit[8].

While there is benefit to treating these patients, there has been variability in the implementation of PAP therapy even within similar health regions[9]. Success establishing use of PAP therapy in patients with COPD is an imperative; however, uptake and barriers to use of PAP therapy in patients with COPD is not well known. This systematic review will explore what is known about acceptance of and adherence with PAP therapy in patients with COPD. Acceptance of and adherence with PAP therapy are summarized descriptively, including descriptive summary of any variable within included studies that is associated with acceptance or adherence. A linear meta-regression explores heterogeneity in the pooled summary estimates. The limitations of the available literature are summarized.

2.3 Methods

2.3.1 Study Design

This study was exempt from the need for ethics as it relies upon reports shared with an academic audience. The methods were developed based upon methodological frameworks outlined in the Cochrane Handbook of Systematic Reviews[10]. The protocol was registered on July 13, 2021 in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42021259262)[11] after confirming that no similar systematic reviews had been registered, and updated on April 17, 2023, while piloting the selection process (see Appendix 1). A detailed protocol was published July 3, 2023 (see Appendix 2)[12]. The results are reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) 2020 statement[13].

2.3.2 Eligibility Criteria

2.3.2.1 Study Design

Primary research studies reporting on randomized interventional trials or observational studies were included.

2.3.2.2 Types of Participants

Studies of adults (age ≥18 years) with COPD newly prescribed PAP therapy for long-term use at home were included. Studies where >20% of the COPD cohort had neuromuscular or comorbid lung diseases were excluded. For studies of patients with chronic lung disease where <80% of included participants had isolated COPD, the studies were only included if the data for the population with COPD were reported separately.

2.3.2.3 Exposures

PAP therapy was defined as the provision of non-invasive positive pressure through a mask for >7 days at home. The types of PAP therapy were often denoted as CPAP, NIV or mixed modalities (both CPAP and NIV). While PAP therapy was often used nocturnally, studies that allowed daytime use were included. Treatment provided with fixed pressure or auto-adjusting machines were included within CPAP. Controlled and supported modes of non-invasive positive pressure ventilation through a mask interface were reported as NIV, such as bilevel positive airway pressure (BPAP), pressure support ventilation (PSV), pressure-controlled ventilation (PCV), volume-controlled ventilation (VCV), volume assured pressure support (VAPS) or adaptive servoventilation (ASV). Studies including patients with invasive ventilation through tracheostomy were excluded, as were studies that had a significant proportion of patients being re-started on PAP therapy. Sham PAP interventions were excluded from the primary but included as a variable in the secondary outcome assessment.

2.3.2.4 Comparator

Not applicable.

2.3.2.5 Outcomes

Two primary outcomes were assessed: acceptance of and adherence with PAP therapy. The secondary outcome was to summarize variables associated with acceptance of or adherence with PAP therapy.

Acceptance of PAP therapy was defined as the proportion who declined or discontinued therapy within one year of being prescribed therapy (aka: "new starts"). Studies that had loss to follow-up of ≥5% of the study population were excluded from contributing data to acceptance to avoid introducing bias, although were retained for adherence estimates. For studies that reported repeated measures, the closest acceptance to 1 year that did not exceed this was used in the pooled summary estimate. Measures of acceptance either prior to study enrollment or beyond one year were not included from the summary effect estimate as this could represent persistence with therapy beyond one year which may be impacted by changes in disease severity, weight, medications or other factors. Studies that pre-specified acceptance (e.g., had to have a follow-up under a CPAP designation) were excluded to avoid introducing bias.

Adherence to PAP therapy was determined by device counter or machine download. Studies including diaries or self-report were excluded. In studies with repeated measures, the closest adherence to one year that did not exceed it was used in the pooled summary estimate. Studies that selected for adherent patients were excluded unless patient selection prior to that exclusion criteria being applied were reported and could be selectively included in the review. For cross-over trials, the adherence data was included if measures were provided after a trial of one PAP therapy setting/mode prior to transitioning to another.

2.3.3 Literature search

A search was executed by an expert searcher/health librarian (SC) on the following databases: PROSPERO, OVID Medline, OVID EMBASE, Wiley Cochrane Library (CDSR and Central), EBSCO CINAHL, APA PsychInfo, Proquest Dissertations and Theses Global and SCOPUS using controlled vocabulary (e.g., MeSH, Emtree, etc.) and key words representing the concepts “COPD" and "CPAP" and "patient adherence”. Pediatric studies were excluded. No other language or publication limits were applied. Databases were searched from inception to August 18, 2022. Detailed search strategies are available (see S1, Appendix 3).

The grey literature search was executed (CL). Forward and reverse citation checks of the included articles were completed. The publication lists for the last author on the included studies were reviewed. Indexes of conference abstracts were hand searched from the American Thoracic Society, Canadian Thoracic Society, European Respiratory Society, American College of Chest Physicians, Associated Professional Sleep Societies, Canadian Sleep Society, and the World Sleep Society for the past 5 years (2018-2023). A Google Scholar search was conducted. Corresponding authors were not contacted as this was not anticipated to add significant value to the search given the extent of relevant literature available.

2.3.4 Study selection

Search results had duplicates removed. The title screen was completed by a single author (CL) as the number of citations retrieved was >1000. After piloting the inclusion/exclusion criteria, studies were included that did not have demographics reported for all participants contributing data. Screening of studies was performed independently and in duplicate (CL, LM), with a title and abstract screen followed by a full text review with reasons for exclusion documented. The

grey literature search was conducted (CL) followed by a full text review (CL, LM). Discrepancies were discussed and consensus achieved.

2.3.5 Data extraction

Data extracted included study design, funding, conflicts of interest, inclusion and exclusion criteria, study setting, PAP therapy implementation, follow-up details, and the composition of the multidisciplinary team (SK), details on indication for therapy and PAP therapy type (CL). Details including demographics, proportion without demographics, anthropometric measures, lung function, hypercapnia, sleep diagnostic testing, deaths and losses to follow-up, timing, definition, and measure of the primary outcome measures of acceptance and adherence were extracted by one reviewer and confirmed by the second (CL, SK). Discrepancies were discussed and consensus achieved. Studies with discrete groups with different categorization within the pre-specified clinically relevant co-variates, or for whom the primary outcomes were reported on different study populations, were separated into arms within the study, labeled A-D and synthesized separately as per the study protocol (see Appendix 2. Section: Methods; Eligibility Criteria; Exposures; page 4/12)[12].

2.3.6 Quality rating

The Newcastle Ottawa Scale for cohort studies[14] was adapted to allow for an evaluation of selection bias and comparability to other cohort studies based upon the reporting and characterization of the indication for PAP therapy (selection) and characterization of patients using demographics (age, sex) and spirometry (FEV_1) (comparability) (see S2, Appendix 3). Quality assessment of RCTs and randomized crossover studies was completed with the Cochrane risk-of-bias tool version 2.0 for randomized trials[15]. The risk of bias assessment was then piloted and subsequently applied independently and in duplicate to the included studies (CL,

LM) separately for acceptance and adherence. Discrepancies between assessments were resolved through discussion and consensus.

2.3.7 Data Management

Results of the searches were exported to Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia. Accessed at www.covidence.org). Screening by title, abstract and full text review and reasons for exclusion were documented in Covidence. Excel documented the data extraction and risk of bias assessment.

2.3.8 Analysis

Both narrative and quantitative synthesis of the data was undertaken. Statistical analyses were completed using Stata statistical software (StataCorp. 2023. *Stata Statistical Software: Release 18.* College Station, TX: StataCorp LLC) or R statistical software (v4.3.3, R Core Team 2024). For the quantitative synthesis of acceptance, the proportion that discontinued therapy often neared zero; therefore, with or without stratification, the data underwent a variance stabilizing transformation (Freeman-Tukey double arscine transformation)[16], following which variance was estimated and an inverse-variance weighted random effects meta-analysis of proportions with the restricted maximum-likelihood estimator (REML) was applied. A weighted proportion was calculated, and the standard error of the weighted proportion used to derive a confidence interval (CI). The data was then back transformed for ease of interpretation and reported as a mean pooled proportion with 95% CI.

For the quantitative synthesis of adherence, any means were converted to medians using the Confidence Distribution method, and a medians-based approach to the meta-analysis using quantile estimation was applied to generate a weighted summary estimate[17]. For stratified

analyses, a Z-statistic was applied. Results are reported as a pooled median adherence with a 95% CI.

Stratification of the meta-analysis as well as multivariable linear random effects meta-regression with pre-specified co-variates was undertaken to explore heterogeneity of the pooled summary estimates for acceptance and adherence. The following variables were defined (see S3, Appendix 3) and explored through meta-analysis with the first five listed co-variates specified *a priori* to be also explored in the meta-regression: indication for PAP therapy, hypercapnia, severity of COPD, type of PAP therapy, pressure intensity of NIV, obesity, medical stability at the time of initiation PAP therapy, timing of initial follow-up, having home visits during follow-up, age, sex and time. As the indication for therapy was often narrative and relevant details not reported, this was designated post-hoc according to the category that was appropriate for at least 70% of the cohort.

The following tests for outliers and influential studies were completed: Funnel plot-based methods and the leave-one-out analysis. A sensitivity analysis was used to assess the robustness of the results given the inclusion of various study designs, and publication rigour.

2.4 Results

2.4.1 Study Flow

The database search identified 2200 citations. After exclusion of duplicates, 1801 citations were reviewed for inclusion. The title screen resulted in the removal of 544 citations. Of the 1257 citations remaining, 1069 were excluded during title and abstract screen. A full text review was performed on 188 citations, following which 45 were determined to be relevant for inclusion, with the reasons for exclusion documented (Figure 2.1). The grey literature search resulted in a further 195 citations undergoing full text review. Of these, 41 citations were deemed eligible for

inclusion and the reasons for exclusion documented in figure 2.1. Two citations were not possible to obtain an accurate translation and were excluded for no data in the available translated abstracts. Figure 2.1 is an adapted PRISMA diagram summarizing the study selection flow.

2.4.2 Study Characteristics

Characteristics of the 86 included studies with 109 arms of data are summarized in Table 2.1. Sources of data were 77 published journal articles, 10 abstracts[18-27], and one thesis report[28]. Study design was observational other than 22 RCTs[8, 28-48], and five randomized cross-over trials[49-53]. Fourteen studies were multicentre[35-37, 39, 41, 43, 46, 48, 50, 52, 54-57]. Multiple arms within studies were due to variation in the populations for which acceptance or adherence were reported[8, 31, 34, 36, 45, 58], variation in the indication for therapy[20, 56, 59, 60], location of the titration of PAP therapy[8, 24], mode/settings of NIV provided[30, 44, 47, 61], or the support provided after the PAP prescription[34, 42, 62]. Where reported, the sources of the participants were clinical research units, hospitals, respirology clinics, home ventilation programs, PSG laboratories or respiratory homecare companies. One study sourced patients from a cloud-based system for PAP adherence[57]. A minority of included studies had an objective specific to acceptance or adherence[23, 26, 28, 30, 32-34, 44, 57, 61-71].

When synthesizing clinically important variables among the included studies, limitations in reporting were evident. There was limited reporting of BMI[33, 40, 42, 56, 72-75], and only 37 studies routinely completed sleep-diagnostic testing. Demographics were available for 91.2% of participants; however, were missing predominantly in patients who did not accept or adhere to therapy. The proportion of included patients with past exacerbations or long-term oxygen therapy use was infrequently reported and inconsistently defined. Titrations were performed in

hospitals, ventilation units or by PSG, with rare titrations within a home environment[29, 31]. There was limited reporting of the support available to patients after PAP therapy initiation. Beyond respirologists, follow-up after PAP therapy initiation was documented to involve nurses[31, 32, 34, 37, 38, 41, 43, 46, 52, 54, 60, 65, 68, 69, 76], nurse practitioners[46, 65, 77], respiratory therapists[22, 52, 56, 59, 61, 62, 66, 69, 76], technicians or technologists[60, 65], psychologist[34, 37, 65], physical therapist[65], or a speech therapist[65]. The involvement of other physicians than pulmonologists or ventilation/sleep specialists was infrequent[22].

2.4.3 Acceptance of PAP therapy

Sixty-nine arms from 61 studies, involving 3512 patients, contained data that could be extracted for acceptance. The definitions for lack of acceptance with therapy varied (see Table 2.2), with the label discontinuing therapy applied where not otherwise specified. Acceptance prior to research participation was reported in four prospective studies as the number of participants that declined to be titrated on CPAP[58] or declined to be enrolled in a study with NIV due to a historical intolerance of PAP therapy at the time of approaching or enrollment[8, 34, 36]. Eight studies only reported acceptance estimates for >1 year[18, 22, 54, 75, 76, 78-80], where the estimates represent both acceptance to therapy and persistence with therapy beyond one year. In 56 arms from 51 studies, acceptance within one year was reported, involving 2717 participants with a median sample size of 24 (IQR: 14, 54). Summary estimates of average pooled proportion of patients with COPD who declined or discontinued PAP therapy within one year was 14% (95% CI 10-20%), with significant heterogeneity among studies.

Five prospective studies had exceedingly detailed reporting of the reasons for declining to be recruited into their studies on PAP therapy in patients with COPD, and included a question as to how many patients who were eligible for recruitment declined to be recruited due to the need to

use PAP therapy. Among these five studies reporting this measure, the proportion of people who declined to participate in prospective research studies due to NIV in the study protocol was an estimated pooled proportion of 7% (95% CI 3-12%). This measure was not reported by most prospective studies, where these patients would have likely been recorded as having simply declined to participate.

The proportion of participants who did not persist with PAP therapy, as documented by acceptance estimates for study periods >12 months was 8% (95% CI 2-16%). Given heterogeneity in the time of reporting on the primary outcome after the initial prescription, time was evaluated post-hoc as a potential explanatory variable of the heterogeneity in the summary effect estimate. Acceptance of PAP therapy within one year of the initial prescription was not dependent on the time at which the proportion of patients who declined or discontinued therapy was reported within one year of the initial prescription. This was true whether time that the measure was reported against acceptance was evaluated as either a continuous (See Figure 2.2b), or a categorical variable (see S4, Figure A1, Appendix 3).

Meta-regression of the five key clinical subgroups identified indication for therapy as the only co-variate that accounted for some of the heterogeneity among the 56 arms of the 51 studies that contributed data to the pooled summary estimate. When backward elimination methods were used, the meta-regression suggests that fewer patients declined or discontinued therapy when the indication for treatment with PAP therapy was a SRBD rather than CHRF secondary to COPD (β -0.33, 95% CI -0.64 to -0.01, p=0.04). In the fully adjusted model without backward elimination, no single co-variate explained the heterogeneity in the pooled summary estimate for the proportion of patients that declined or discontinued therapy. The pooled summary estimate for the proportion of patients that decline or discontinue PAP therapy within one year in patients

with CHRF secondary to COPD was 18% (95% CI 12-25%), and in patients with COPD and a SRBD was 6% (95% CI 0-16%). For detailed results of the meta-regression(see S4, Table A1, Appendix 3).

Thirteen arms reported repeated measures of acceptance, including measures at the time of initiation of PAP therapy to additional measures that ranged from 6 weeks to 6 months[30, 31, 33, 50, 65, 81] with three groups having their second measure at 12 months[68, 73, 74] and three studies having reporting time of ~2 years[82], 3 years[64], or >5 years[83]. Five studies with follow-up extending to at least 6 months reported that patients often declined or discontinued therapy at time of initiation or within 6 weeks[64, 68, 73, 81, 82], with a final one demonstrating this but at 3 months as that was the earliest measure reported[74].

2.4.4 Adherence with PAP Therapy

Seventy-seven arms from 60 studies, involving 10992 patients, contributed data to adherence. The median sample size was 31 (IQR: 15, 58). Adherence was frequently defined as a continuous measure defined as hours of use/day; however, when adherence was reported as a proportion, definitions varied (see Table 2.2). Often, adherence was reported as both a continuous measure and a proportion[8, 19, 29, 35, 37, 40, 41, 43, 46, 47, 52, 58, 59, 61, 62, 67-69, 77, 84, 85]. Infrequently, adherence was reported only as a proportion[18, 24, 26, 48, 57, 58, 66, 86-88]. Adherence was reported as hours/day in 66 arms of 51 studies, involving 2838 participants with a median sample size of 20 (IQR: 11, 47). The median pooled adherence was 6.24 hours/day (95% CI 5.80-6.69), with significant heterogeneity among studies (see Figure 2.2a). Adherence measures reported at 3-6 months were significantly greater and less heterogeneous compared to within 1 month or ≥12 months (see Figure 2.2b); however, adherence was not associated with time as a continuous measure (see S4, Figure A2, Appendix

3). Exploration of the pooled results of adherence estimates by pre-specified co-variates demonstrated departure of the summary effect estimates when stratified by indication for therapy, BMI and type of PAP therapy. A detailed summary of the adherence estimates when the results were stratified by pre-specified co-variates are summarized (see S4, Table A2 and Figure A3, Appendix 3).

To explore heterogeneity among studies, meta-regression was used, with 66 arms from 51 studies contributing median hour of use/day as the dependent variable. With use of the backward elimination method, use of PAP therapy was shorter when the indication for therapy was COPD with a SRBD rather than CHRF secondary to COPD (β -1.46, 95% CI -2.45 to -0.47, p=0<01). In the fully adjusted model, this association was not significant. The "other" category for indication for PAP therapy was significantly associated with a shorter adherence with therapy in both the fully adjusted model (β -1.98, 95% CI -3.75 to -0.21, p=0.03), and the final model obtained by backward elimination (β -1.66, 95% CI -2.71 to -0.62, p<0.01). The pooled median use of PAP therapy for patients with CHRF secondary to COPD was 6.96 h/day (95% CI 6.44 – 7.47) and in patients with COPD and a SRBD, the pooled median use of PAP therapy was 5.51 h/day (95% CI 4.93-6.10), which was significantly different (p<0.01). For studies with an indication in the "other" category, the pooled median use of PAP therapy was 5.22 hours/day (95% CI 4.01-6.44), which was not compared to the other groups for clinical significance as these studies either did not have a clearly defined indication or had indications for therapy that fell outside of OSA or CHRF, such as eucapnic COPD, high health care utilization, or mixed indications. Detailed results of the meta-regression are available (see S4, Table A3, Appendix 3).

Seven studies reported repeated measures of adherence[31, 34, 36-38, 61, 84]. From detailed reporting in several studies, the number of individuals contributing adherence data at any given

follow-up interval varied[36, 38]. For some studies, repeated measures of adherence were stable over time[31, 37, 38, 84], whereas others reported an increase in or achievement of adherence between six weeks and three months, followed by stability[36, 61], or reported an increase in adherence between three months and one year[34].

2.4.5 Sources of heterogeneity within studies

The reasons for declining, discontinuing or being non-adherent with PAP therapy were sporadically reported, and predominantly reported as device intolerance, without a structured assessment of other reasons. An effect direction plot[89, 90] summarizes the available literature and the specific variables explored (see Figure 2.4). The effect direction plot demonstrates that there have been many variables assessed in the available literature for an association with acceptance or adherence; however, much of the evidence was in variables associated with disease severity for OSA, CHRF or COPD, or was related to device intolerance. The available evidence is restricted to only a few categories of possible variables that affect adherence to chronic medical therapies outlined in the World Health Organization framework. Barriers to use were reported in narrative form or t-test, with only rare evidence of adjusting for confounders through multivariate or logistic regression. Few studies were designed to evaluate aspects of PAP therapy implementation and the impact on adherence, as follows. Related to implementation of NIV, there was a favorable association between adherence and the use of a call center and telemedicine[62], high intensity NIV (HI-NIV) compared to low intensity NIV (LI-NIV)[30], and the use of cognitive-behavioural therapy for insomnia (CBT-I) delivered by a psychologist at the time of NIV adaptation at home[34], with no difference observed between implementation of NIV during ECOPD compared to during a period of medical stability[71] or after ambulatory initiation of NIV compared to in-hospital initiation of NIV[31].

2.4.6 Tests of outliers and influential studies

Funnel plot asymmetry was present visually for both acceptance and adherence and publication bias is likely present. The funnel plot asymmetry was quantified by the Rank correlation test and the Egger test for both acceptance and adherence. For adherence, a small sample size effect existed. The leave-one-out summary of medians did not suggest that any one study significantly impacted the results for acceptance or adherence.

2.4.7 Sensitivity analysis

The study results were not impacted by a sensitivity analysis performed to evaluate whether the results varied if a fixed or random effects model was used, RCTs compared to other study designs, or whether the publication was a poster compared to a published article or thesis.

2.4.8 Study Quality

Of the 62 observational studies included in this systematic review, 59 did not have a comparison arm which was anticipated. For acceptance of therapy, 22/44 of the included observational studies were of good quality, 11 were of fair quality and 11 were of poor quality. For adherence to therapy, 21/38 of the observational studies were of good quality, 6 were of fair quality and 11 were of poor quality. For a summary of the scores and overall quality of included studies, see Figure 2.5. Detailed accounting of the risk of bias scoring are available (see S4, Figure A25, Appendix 3).

For both primary outcomes, quality scores for studies that were ranked as poor quality were commonly due to a lack of clarity in the indication for therapy as this impacted the selection of the cohort, if the demographics and a measure of COPD severity were not provided for study participants that did not tolerate PAP therapy (5.2% of patients in the included studies), or if prior PAP use was not explicitly excluded, as this decreased comparability and introduced

selection bias. Several studies received high quality scores but reported acceptance of 100% and minimal losses to follow-up. Given that the primary objective of these studies was not to report acceptance or compliance, it is possible that the study reporting did not include relevant selection bias. For adherence, multiple measures of adherence were obtained with only a single measure reported also resulted in a lower quality score. Adherence data for patients that died or were lost to follow-up during the study were also inconsistently reported. The timing of the adherence measure was at times inferred as when similar clinical data were obtained in follow-up if the timing was not explicitly reported. Where unclear, the median/mean follow-up of patients was used as the timing of the compliance measure. In several studies, the timing of follow-up was unclear[19, 22-24], preventing the use of several in the sample size weight bubble plot analysis where adherence in hours of use/day was plotted against time[19, 23].

2.5 Discussion

In order to experience health benefits of PAP therapy, patients with COPD must be able to use the therapy as prescribed. This systematic review examined the acceptance of and adherence to PAP therapy among patients with COPD using a registered protocol employing a comprehensive search strategy to avoid publication bias, a study selection process designed to mitigate selection bias and sophisticated analytic strategies. This systematic review is the first to synthesize acceptance and adherence data for PAP therapy in adult patients with COPD irrespective of indication or mode of therapy. By doing so, a broader lens can be applied to the entire scope of literature available to better understand heterogeneity in success implementing PAP therapy in this population. While indication for therapy is an important consideration that may impact acceptance and adherence, it is important to consider other variables that may impact these measures. This systematic review was designed to summarize the knowledge available

surrounding known variables that impact acceptance and adherence. A notable finding of this systematic review is that there have been limited investigations into programmatic features that may explain some of the heterogeneity in the acceptance and adherence estimates. This research also highlights that there is incomplete reporting of variables that may be important in acceptance and adherence such as health system supports, timing of follow-up, types of providers involved in follow-up, and systematic assessments of more varied variables than disease specific parameters and device intolerance.

Overall, acceptance of PAP therapy within one year of initiation was high in patients with COPD. There was notable variation among studies in the proportion of patients declining or discontinuing PAP therapy within one year. Most people who declined or discontinued therapy did so at the time of recommendation or within 6 weeks. Acceptance did not vary substantially over time. Studies with repeated measures and a follow-up of at least 6 months also demonstrated that the majority of patients declined or discontinued therapy within 6 weeks of initiation. Meta-regression demonstrated that more patients who were prescribed treatment for CHRF secondary to COPD declined or discontinued therapy than did patients with COPD prescribed PAP therapy for a SRBD. While indication for therapy may impact this, other potential reasons for this observation for which there was insufficient reporting include differences in symptom burden, device tolerance, program structure, social or financial supports. This systematic review highlights several clinically relevant aspects of program structures that have not been reported comprehensively in the literature to date.

Adherence to PAP therapy was high in patients with COPD prescribed PAP therapy, with significant variation in the adherence among studies. Adherence at 3-6 months demonstrated more homogeneity than closer to the time of initiation or at 12 months of use. Studies with

repeated measures had varying time intervals within one year to achieve adherence, but then generally documented stability in use (hours/day) after achieving a mean/median use >4 h/day. Despite having a lower acceptance, meta-regression suggests that patients with CHRF secondary to COPD have a longer duration of use/day than patients with COPD and a SRBD. This finding is supported by an individual patient data meta-analysis that analyzed data for 118 patients with COPD who were randomized to NIV in a RCT, all deemed high quality in design, with mean use of 6.7±2.2 hours/day[91]. Studies with a mixed or varied indication for use, as summarized in the "other indication" category, also had a lower use in hours/day than patients with CHRF secondary to COPD. Possible reasons for this could include a more heterogeneous population, as the indication for therapy may have varied between study participants, variation in other factors such as adherence to other therapies, as often these patients had high health care utilization, less support within programs, as many study designs in this category were not RCTs.

Clinically relevant variables that impact the success implementing PAP therapy were infrequently reported. Details such as types of health care providers involved in follow-up, timing of follow-up after PAP therapy prescription, titration details and settings provided, virtual or in-person assessments, tools for assessing barriers to adherence were infrequently reported. In the studies that did report these details, use of multidisciplinary teams including respiratory therapists and nurses was common. Some evidence exists for titration of PAP therapy in an ambulatory setting compared to a monitored setting such as a HMV unit, hospital ward, or PSG laboratory. Where reported, barriers to use were commonly reported for variables of disease severity or device intolerance; however, limited data is available in other possible categories suggesting that a broad approach to characterizing barriers to use of PAP therapy has not been applied.

Limitations of this review include that acceptance and adherence to PAP therapy were not the primary outcome of included studies and often were not reported in detail. Despite diverse definitions being used, particularly for adherence, many studies did report acceptance and mean hours/day of use. Loss to follow-up and deaths for these measures may not be accurately reported as acceptance and adherence were often only briefly mentioned in the included studies. As studies with significant losses to follow-up were excluded from contributing to acceptance, this primarily impacts adherence in this review. Stanchina *et al* report that death during the study period was associated with low adherence[67], highlighting how not reporting acceptance or adherence for this population may introduce bias in the summary estimate. Despite efforts to limit selection bias, some studies required that patients attend a follow-up appointment after a pre-specified period of time or have a complete dataset (including machine download) for retrospective studies, which may introduce bias. Acceptance estimates may also be impacted by rare reporting of declining to use PAP therapy prior to research involvement, which may result in prospective studies underestimating how many decline or discontinue therapy by up to 20%. Finally, key demographics may not be represented in the available literature as 8.2% of the included patients were not characterized, and these were predominantly those who declined or did not adhere to therapy.

Notwithstanding the limitations above, this systematic review and meta-analysis demonstrate that patients with COPD are often successful with accepting and adhering to use of PAP therapy. Novel findings include that a high acceptance and adherence is observed in both patients with OSA and COPD in addition to patients with CHRF secondary to COPD. Novel findings also including identifying that patients with CHRF secondary to COPD decline or discontinue PAP therapy more frequently than patients with COPD and a SRBD. The high heterogeneity observed

among studies was also notable. As many included studies were reported from subspecialty centres such as sleep programs or HMV programs, the acceptance and adherence observed may not be seen in different settings. Variables associated with PAP acceptance and adherence were not systematically assessed or reported in any of the studies included in this review. Few studies have been completed to inform strategies for implementation of PAP therapy in programs that manage patients with COPD and whom do not achieve reported acceptance and adherence. Sporadically reported variables that represent barriers to use of PAP therapy spanned the categories of the World Health Organization framework for barriers to adherence to chronic therapies. Detailed reporting and further work is required in order to better understand how to ensure patients who may benefit from therapy have the best possible chance of success with use. Table A3 contains tabulated documentation of some of the limitations in reporting of acceptance and adherence and potential ways to address these for future trials (see S4, Appendix 3).

2.6 Conclusion

Approximately seven out of eight patients with COPD prescribed PAP therapy successfully initiate treatment and achieve a clinically meaningful daily use. Significant heterogeneity was identified among studies for both acceptance and adherence, only some of which was explained by the indication for therapy. Barriers to use of PAP therapy that contribute to the observed heterogeneity were not routinely assessed and were only sporadically reported. Detailed reporting of program structure and teams that achieved high acceptance and adherence would be beneficial to aid in program design for programs where the acceptance and adherence is not as robust for patients newly prescribed therapy. Further work dedicated to exploring barriers to use of PAP therapy in patients with COPD would lead to a greater understanding of how to support patients with COPD when they are initiating PAP therapy.

2.7 Acknowledgements

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2.8 Tables

Table 2.1 Summary of included studies.

First author (year) [ref]	Country	Study Design	Sample size for acceptance or adherence	FEV_1 (% unless otherwise specified)	BMI (kg/m^2)	AHI (events/hr)	$PaCO_2$ or capillary PCO_2 (mmHg)	CPAP or NIV	Outcome measure included	
									Acceptance	Adherence
Indication: Chronic hypercapnic respiratory failure (CHRF) secondary to COPD										
Bleksley (2017)[17]	UK	Retrospective cohort	150	NR	NR	NR	NR	NIV	Yes	Yes
Bräunlich (2015)[92]	Germany	Prospective cohort	11	29.7 (NR)	<30	NR	53.7 (NR)	NIV	Yes	No
Bräunlich (2019)[49]	Germany Multicentre	Randomized cross-over	82	NR	23.1 (4.8)	NR	56.5 (5.4)	NIV	Yes	No
Budweiser (2005)[83]	Germany	Retrospective cohort	46	29 (8.2)	26.5 (4.8)	NR	55.9 (7.3)	NIV	No	Yes
Budweiser (2007)[77]	Germany	Prospective cohort	188	31 (9.6)	27.2 (6.9)	NR	56.3 (9.3)	NIV	Yes	Yes
Budweiser (2007)*[80]	Germany	Prospective cohort	140	28.3 (8.9)	25.4 (6.6)	NR	60.9 (9.5)	NIV	Yes	Yes
Casanova (2000)[36]	Spain Multicentre	RCT	26	0.82L (0.23)	25 (4)	3 (1.5)	50.7 (7.9)	NIV	Yes	Yes
Cherian (2021)[24] B	Canada	Retrospective cohort	61	25.8 (12)	NR	NR	60.6 (11.7)	NIV	No	Yes
Cheung (2010)[37]	Hong Kong	RCT	23	28.1 (8.5)	19.2 (3.6)	<10	57.75 (7.5)	NIV	Yes	Yes

Clini (1998)[63]	Italy	Prospective cohort	49	31 (9)	23 (3)	NR	51.8 (4.5)	NIV	Yes	No
Clini (2002)[47]	Italy and France Multicentre	Prospective cohort	43	27 (8)	26 (5)	<10	54 (4.5)	NIV	No	Yes
Criner (1999)[64]	USA	Prospective cohort	20	0.71 L (0.1)	NR	NR	70 (3)	NIV	Yes	No
Dreher (2010)[29] A	Germany	RCT	9	0.97 L (0.46)	<30	NR	54.975 (.075)	NIV	Yes	Yes
Dreher (2010)[29] B	Germany	RCT	8	0.64 L (0.11)	NR	NR	54.975 (.075)	NIV	Yes	Yes
Dreher (2015)[93]	Germany	Prospective cohort	20	31.4 (17.1)	28.7 (8)	NR	51 (46.5, 62.8)	NIV	Yes	No
Duiverman (2008)[38]	Netherlands	RCT	37	0.83L (.36)	27.1 (6.4)	<10	55.5 (7.5)	NIV	Yes	Yes
Duiverman (2011)[31]	Netherlands	RCT	31	<50	27.2 (5.1)	<10	NR ()	NIV	No	Yes
Duiverman (2017)[48]	Netherlands	Randomized cross-over	14	34 (9)	25.2 (5.8)	Excluded OSA	52.5 (18.75)	NIV	Yes	No
Duiverman (2020)[30] A	Netherlands	RCT	33	<50	24.9 (6)	NR	NR	NIV	Yes	Yes
Duiverman (2020)[30] B	Netherlands	RCT	34	N<50	25.7 (4.1)	NR	NR ()	NIV	Yes	Yes

Duiverman (2020)[30] C	Netherlands	RCT	86	<50	25.3 (5.1)	NR	NR ()	NIV	Yes	Yes
Elliott (1992)[73]	UK	Prospective cohort	12	0.60L (0.25)	NR	NR	57.75 (1.26)	NIV	Yes	No
Freitas (2021)[84]	Portugal	Before-after studies	81	34.3 (13.1)	NR	NR	57 (8)	NIV	Yes	Yes
Gadsby (2020)[19] A	Australia	Retrospective cohort	11	25	<30 ()	NR	58.8 ()	NIV	No	Yes
Garrod 2000[39]	UK	RCT	23	33.2 (7.96)	NR ()	NR	44.2 (6.68)	NIV	Yes	Yes
Janssens (2003)[53]	Switzerland Multicentre	Prospective cohort	58	29 (14)	25 (7)	NR	50 (6)	NIV	Yes	Yes
Jones (1998)[79]	UK	Prospective cohort	11	TBC	TBC	NR	TBC	NIV	Yes	No
Köhnlein (2014)[40]	Germany & Austria Multicentre	RCT	102	26 (11)	24.8 (5.8)	NR	58.5 (6)	NIV	Yes	Yes
Marino (1991)[81]	USA	Prospective cohort	8	NR	NR	NR	NR	NIV	Yes	No
Marsden (2012)[20]	UK	Retrospective cohort	38	30.4 (14.1)	27.5 (6.1)	NR	59.925 (8.86890 0000000 002)	NIV	No	Yes
McEvoy (2009)[42]	Australia Multicentre	RCT	72	25 (95% CI 22.4-2.76)	25.5 (95% CI	≤20	52.6 (95% CI	NIV	No	Yes

					24.3-26.7)		51.0-54.2)			
Meecham Jones (1995)[50]	UK	Randomized cross-over	18	31.8 (8.8)	25.3 (4.1)	NR	55.8 (3.6)	NIV	Yes	Yes
Murphy (2012)[32]	UK	RCT	12	34 (10.2)	NR	NR	63.2 (13.1)	NIV	Yes	No
Murphy (2017)[35] A	UK Mulitcentre	RCT	57	24 (8.6)	21.5 (IQR 18.8-24.5)	NR	59 (7)	NIV	Yes	Yes
Murphy (2017)[35] B	UK Multicentre	RCT	2021	24 (8.6)	21.5 (IQR 18.8-24.5)	NR	59 (7)	NIV	Yes	No
Márquez-Martín (2014)[41] A	Spain	RCT	15	35	NR	NR	51 (NR)	NIV	Yes	Yes
Márquez-Martín (2014)[41] B	Spain	RCT	15	28	NR	NR	50 (NR)	NIV	Yes	Yes
Nickol (2008)[59] B	UK	Prospective cohort	10	29 (13)	30 (6)	NR	NR	NIV	No	Yes

Oscroft (2010)[70]	UK	Retrospective cohort	35	0.59 L (.24)	26.9 (6)	<5	66 (9.75)	NIV	Yes	Yes
Oscroft (2014)[43] A	UK	RCT	20	29.4 (11)	25.9 (7.5)	≤10	58.8 (6)	NIV	No	Yes
Oscroft (2014)[43] B	UK	RCT	20	26 (9.6)	29 (6.7)	≤10	61.50 (8.25)	NIV	No	Yes
Patout (2020) [55]	UK & France Multicentre	Prospective cohort	305	NR	NR	NR	NR	NIV	No	Yes
Perrin (1997)[94]	France	Prospective cohort	14	0.75L (0.18)	NR	<5	58.5 (5.25)	NIV	Yes	Yes
Schönhofer (2001)[95]	Germany	Prospective cohort	13	0.85 L (0.32)	27.7 (2.8)	<5	60 (7.5)	NIV	Yes	Yes
Schönhofer (2006)[71]	UK	Prospective cohort	25	0.85 L (0.2)	22.5 (4.7)	NR	55.2 (5.2)	NIV	Yes	Yes
Schucher (1999)[96]	Germany	Retrospective cohort	54	0.8L (0.3)	25 (7)	NR	57 (9)	NIV	Yes	No
Simonds (1995)[74]	UK	Prospective cohort	33	0.58 L (0.3)	NR	NR	62.2 (13.5)	NIV	Yes	No
Struik (2014)[45]	Netherlands Multicentre	RCT	101	25.6 (7.8)	24.6 (5.4)	NR	59.25 (9)	NIV	Yes	Yes
Strumpf (1991)[51]	USA Multicentre	Randomized cross-over	19	0.56L (0.03)	NR	Excluded OSA	49 (2)	NIV	Yes	Yes
Suraj (2018)[72]	India	Prospective cohort	120	41.4 (2.1)	NR	NR	49.6 (3.2)	NIV	Yes	No

Tsolaki (2008)[97]	Greece	Prospective cohort	49	34.9 (10.7)	29.2 (4.9)	<10	54.7 (4.5)	NIV	Yes	No
Windisch (2002)[98]	Germany	Prospective cohort	14	0.97L (.43)	28.4 (7.2)	NR	59.5 (8.4)	NIV	Yes	Yes
Zhou (2017)[34]	China Multicentre	RCT	57	23.34 (7.48)	19.4 (3.1)	NR	57.78 (2.88)	NIV	Yes	Yes
Sleep-related breathing disorder and COPD										
Baiamonte (2018)[62]	Italy	Retrospective cohort	80	75.4 (19.8)	34.3 (5.8)	37.1 (19.7)	42.9 (5.4)	CPAP	Yes	No
Cherian (2021)[24] A	Canada	Retrospective cohort	206	45.8 (17.4)	NR	NR	58.6 (11.8)	NIV	No	Yes
de Miguel (2002)[99]	Spain	Before-after studies	55	58.8 (NR)	35.8 (NR)	37.3 (26.1)	47.7	CPAP	Yes	No
Economou (2018)[57] A	Greece	Prospective cohort	38	1.78 (0.52)	35.4 (8.6)	50.7 (31.7)	NR	CPAP	No	Yes
Economou (2018)[57] B	Greece	Prospective cohort	N/A						Yes	No
Gadsby (2020)[19] B	Australia	Retrospective cohort	39	41	NR	NR	67.6	NIV	No	Yes
Horvath (2021)[60] C	Switzerland	Retrospective cohort	34	NR	>30	NR	NR	NIV	No	Yes

Horvath (2021)[60] D	Switzerland	Retrospective cohort	34	NR	>30	NR	NR	NIV	No	Yes
Jaoude (2014)[58] A	USA	Retrospective cohort	104	1.7 L (0.5)	36.4 (8.7)	35.2 (29.2)	51.6 (4.3)	CPAP	No	Yes
Jaoude (2014)[58] B	USA	Retrospective cohort	167	2.1 L (0.56)	34.7 (6.8)	29.2 (23.8)	37 (2.7)	CPAP	No	Yes
Jaoude (2019)[100]	USA	Retrospective cohort	184	2.1 L (0.9)	35.3 (7.8)	30.2 (23.2)	NR	CPAP	No	Yes
Jolly 2021[68]	France	Prospective cohort	66	34 (27.4-49)	26.3 (21.8-31.3)	13 (7-26.8) ()	50.25 (45.8-55.3)	NIV	No	Yes
Konikkara (2016)[85]	USA	Retrospective cohort	24	NR	40.2 (7.4)	28.4 (33.6)	NR	Both	No	Yes
Le Bouar (2018)[25] B	NR	Retrospective cohort	6	NR	NR	NR	NR	NIV	No	Yes
Leger (1994)[75]	France	Prospective cohort	50	NR	NR	NR	53 (9)	NIV	Yes	No
Loachimescu (2020)[65]	USA	Prospective cohort	404	0.754	29.3	NR	NR	Both	No	Yes
Machado (2010)[54]	Brazil Multicentre	Prospective cohort	95	0.415 (12.2)	34 (7)	43.2 (12.5)	45.9 (6.2)	CPAP	Yes	No

Mansfield (1999)[87]	Australia	Prospective cohort	14	0.95L (0.12)	34.8 (4.2)	13.3 (7.9)	55.2 (5.9)	CPAP	No	Yes
Marin (2010)[82]	Spain	Prospective cohort	468	56 (16)	30.6 (6.2)	34.5 (12.5)	NR ()	Both	Yes	No
Nickol (2008)[59] A	UK	Prospective cohort	9	42 (16)	39 (8)	()	53.25 (5.25)	NIV	No	Yes
Nowinksi (2007)[101]	Poland	Before-after studies	9	2.2 L (0.6)	39 (5.2)	59.5 (26.5)	44.7 (6.2)	CPAP	Yes	No
O'Brien (2005)[76]	USA	Retrospective cohort	76	54.38 (2.61)	35.45 (1.06)	28.59 (4.23)	NR	CPAP	No	Yes
Patout (2019)[8] A	UK	RCT	7	0.314 (12.3)	35.5 (4)	>5 or 4% ODI >7.5	52.725 (3)	NIV	Yes	Yes
Patout (2019)[8] B	UK	RCT	7	28.7 (18.8)	38.9 (7)	>5 or 4% ODI >7.5	54.975 (7.5)	NIV	Yes	Yes
Patout (2019)[8] C	UK	RCT	42	30.1 (15.3)	37.2 (5.7)	>5 or 4% ODI >7.5	53.85 (5.85)	NIV	Yes	No
Stanchina (2013)[66]	USA	Retrospective cohort	227	56.7 (NR)	37 (NR)	33.2 (NR)	NR	CPAP	Yes	Yes
Sterling (2022)[56]	USA	Retrospective cohort	6810	NR	NR	NR	NR	Both	No	Yes

Theerakittikul (2014)[69]	USA	Retrospective cohort	46	58.5 (17.4)	34.1 (6)	36.8 (26.1)	NR	Both	Yes	No
Tondo (2022)[86]	Italy	Retrospective cohort	105	67.4 (18.45)	32.17 (6.74)	42.21 (22.91)	39.99 (4.87)	Both	Yes	Yes
Wang (2015)[102]	China	Prospective cohort	47	46.4 (41.4, 54.4)	31.4 (2.1)	34 (24.4,43.7)	40.5 (3.73, 42.8)	CPAP	Yes	No
Zheng (2022)[46] A	Australia	RCT	16	45 (19.8)	45 (7.8)	57 (34)	57 (8)	NIV	No	Yes
Zheng (2022)[46] B	Australia	RCT	16	51 (17.5)	40 (5.8)	61 (37)	52 (5.6)	CPAP	Yes	Yes
Combined or other indication										
Bhatt (2013)[28]	USA	RCT	15	30.3 (7)	24.8 (2.8)	NR	42.4 (5.6)	NIV	Yes	Yes
Elabd (2021)[18]	USA	Retrospective cohort	57	NR	35 (25.2, 41.5)	NR	66 (57, 70.1)	NIV	No	Yes
Horvath (2021)[60] A	Switzerland	Retrospective cohort	22	NR	<30	NR	NR	NIV	No	Yes
Horvath (2021)[60] B	Switzerland	Retrospective cohort	22	NR	<30	NR	NR	NIV	No	Yes

Le Bouar (2018)[25] A	NR	Retrospective cohort	12	NR	NR	NR	NR	NIV	No	Yes
Leonard (2021)[61] A	USA	Prospective cohort	10	NR	32 (IQR 13.6)	NR	NR	NIV	Yes	Yes
Leonard (2021)[61] B	USA	Prospective cohort	10	NR	NR	NR	NR	NIV	Yes	Yes
McDowell (2021)[103]	UK	Retrospective cohort	42	40 (15.45)	29.23 (10.71)	NR	NR	NIV	Yes	No
Mezzanotte (1994)[104]	USA	Prospective cohort	8	1.1L (0.08)	NR	5.5 (2.1)	36.5 (1.8)	CPAP	Yes	Yes
Pahnke (1997)[105]	Unclear	Retrospective cohort	40	NR	NR	NR	NR	NIV	Yes	No
Qasim (2019)[21]	USA	Retrospective cohort	14	NR	TBC	NR	68 (53-109)	NIV	Yes	No
Ramalho (2019)[22]	NR	Retrospective cohort	37	NR	27 (8)	NR	NR	NIV	No	Yes
Ramsay (2018)[27]	UK	RCT	16	NR	NR	NR	NR	NIV	No	Yes
Russo (2022)[26]	NR	Observational	24	NR	NR	NR	NR	NIV	No	Yes
Sin (2007)[44] A	Canada	RCT	23	31.5 (14.9)	27.2 (6.7)	<20	44.2 (10.1)	NIV	Yes	No

Sin (2007)[44] B	Canada	RCT	11	37.6 (17.7)	28.2 (7.2)	<20	45.2 (13.5)	NIV	No	Yes
Sivasothy 1998[78]	UK	Retrospective cohort	26	27 (14.6)	TBC	NR	TBC	NIV	Yes	Yes
Tai 2018[23] A	Canada	Retrospective cohort	24	NR	NR	NR	71.55 (NR)	NIV	No	Yes
Tai 2018[23] B	Canada	Retrospective cohort	15	NR	NR	NR	63.5 (NR)	NIV	No	Yes
Theunisse 2021[67]	Netherlands	Prospective cohort	48	31.8 (11.5)	25.7 (5.7)	NR	51.75 (11.25)	NIV	Yes	Yes
Volpato 2022[33] A	Italy	RCT	45	49.74 (29.48)	30.06 (8.96)	NR	50.04 (10.86)	NIV	No	Yes
Volpato 2022[33] B	Italy	RCT	45	51.74 (25.51)	28.85 (6.76)	NR	45.57 (8.95)	NIV	No	Yes
Volpato 2022[33] C	Italy	RCT	108	50.71 (27.01)	29.45 (7.91)	NR	47.86 (10.16)	NIV	Yes	No
Windisch 2005[52]	Germany	Randomized cross-over	9	0.80 L (0.22)	29 (4.7)	NR	NR	NIV	Yes	No

Legend: FEV_1: forced expiratory volume in one second; BMI: body mass index; $PaCO_2$: partial concentration of carbon dioxide in the arterial blood; capillary PCO_2: partial concentration of carbon dioxide in the capillary blood; RCT: randomized controlled trial; NR: not reported; TBC: to be calculated; NIV: non-invasive ventilation; CPAP: continuous positive airway pressure; *Differentiates a second study labeled Budweiser 2007.

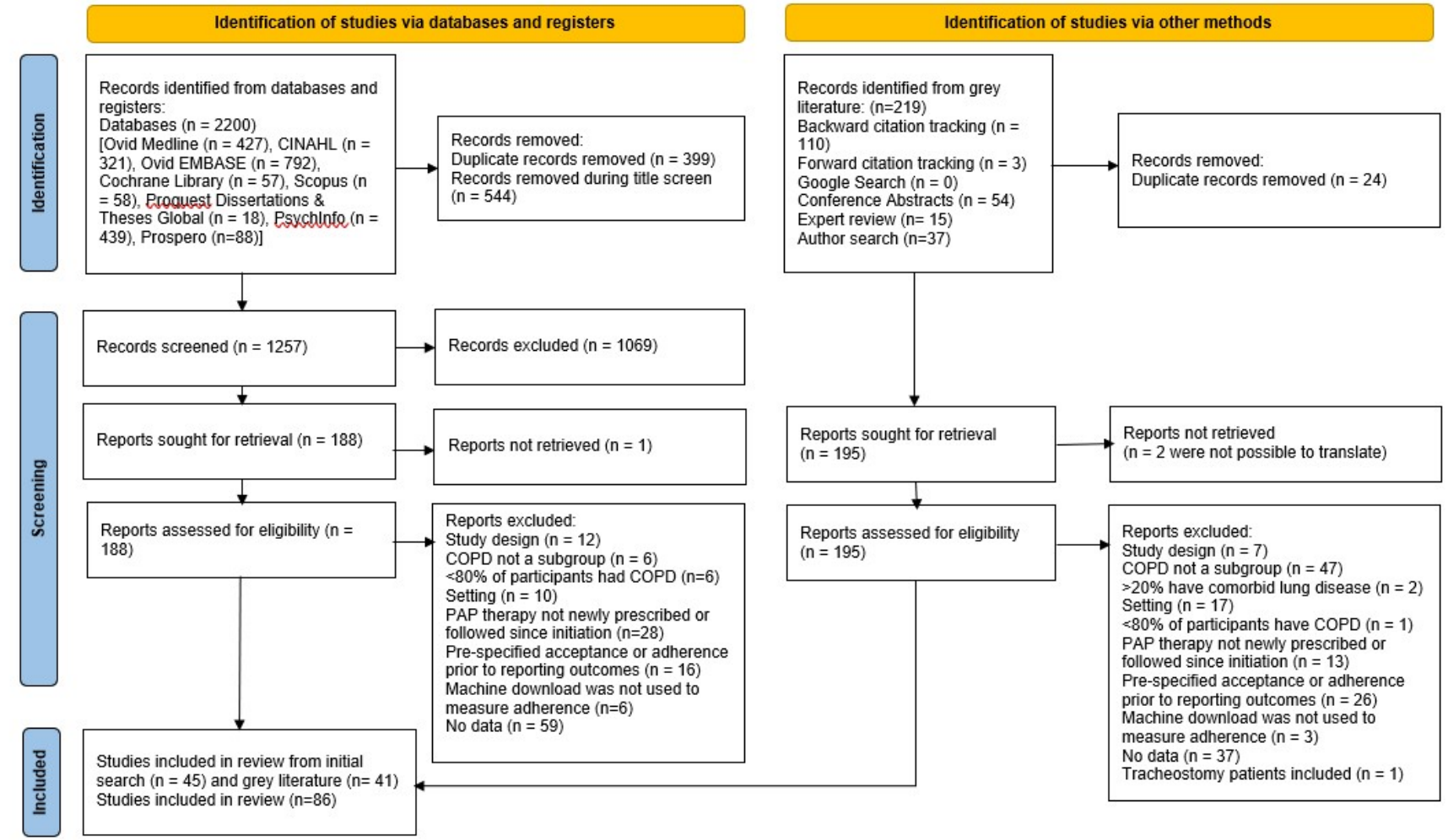
Table 2.2: Definitions of acceptance and adherence in the included studies.

Acceptance	Study References
• Declined PAP therapy	[8, 30, 33, 35, 44, 54, 57, 66, 72, 82, 96, 101]
• Intolerant or declined from the outset	[80]
• Did not accept therapy	[95]
• Rejected PAP therapy	[77, 86, 104]
• Voluntarily stopped because of PAP therapy	[75, 81]
• Did not endure ventilation	[67]
• Discontinued PAP therapy	[17, 21, 28, 29, 32, 34-38, 40, 41, 46, 48-52, 62, 64, 69-72, 74, 78-81, 91, 92, 94, 97, 100, 102, 103]
• Withdrawn from the study due to compliance/PAP use	[39, 73, 82]
• Interruptions for non-compliance	[53]
• Not adherent and lost to follow-up	[30]
• Not adherent and discontinued therapy	[84]
• Refused or could not use for more than a predefined threshold of adherence during the titration	[8, 63]
• Stopped PAP therapy at night and only used it during the day	[93]
• Dropped out of study with reasons provided	[45]
Adherence	
• Number or proportion of days used	[28, 30, 31, 60-62, 84]
• Hours of use on days used	[61]
• Hours of use per day	[8, 18-20, 22, 24, 26-31, 33-46, 50, 51, 53, 55, 58-61, 66-68, 70, 71, 76-78,

	80, 83, 84, 93, 94, 97, 99, 103]
• Hours of use per day on days used	[66]
• Threshold proportion of days used for >4 hours (80% or 70% threshold)	[60, 65, 85]
• Proportion of days with >4 hours of use	[8, 17, 28, 61, 66]
• Threshold proportion of hours of use per day (6, 5, 4, 3.5, 3 hours)	[17, 28, 34, 36, 39, 40, 42, 45-47, 53, 57, 58, 67, 68, 76, 83, 87]
• PAP usage for ≥4h/night on ≥70% of nights in a 30 day period within a 90 day timeframe in ≥1/8 consecutive 90 day time frames from device setup or ≥8/8 consecutive 90 day time frames	[56]
• Able to sleep through the night at two weeks	[51]
• Compliance not otherwise specified	[18, 23, 25, 86]

2.9 Figures

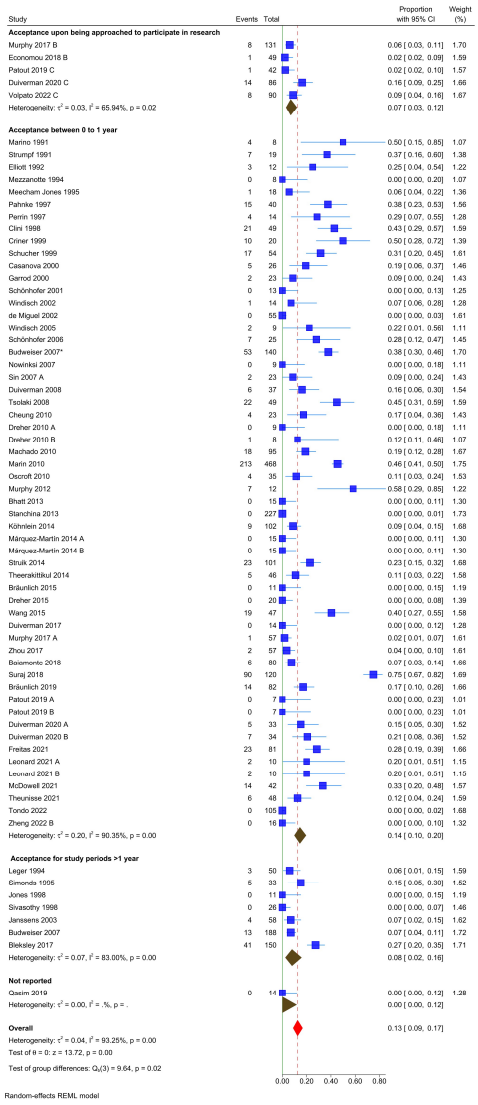
Figure 2.1: Flowchart of the included and excluded studies for the systematic review.



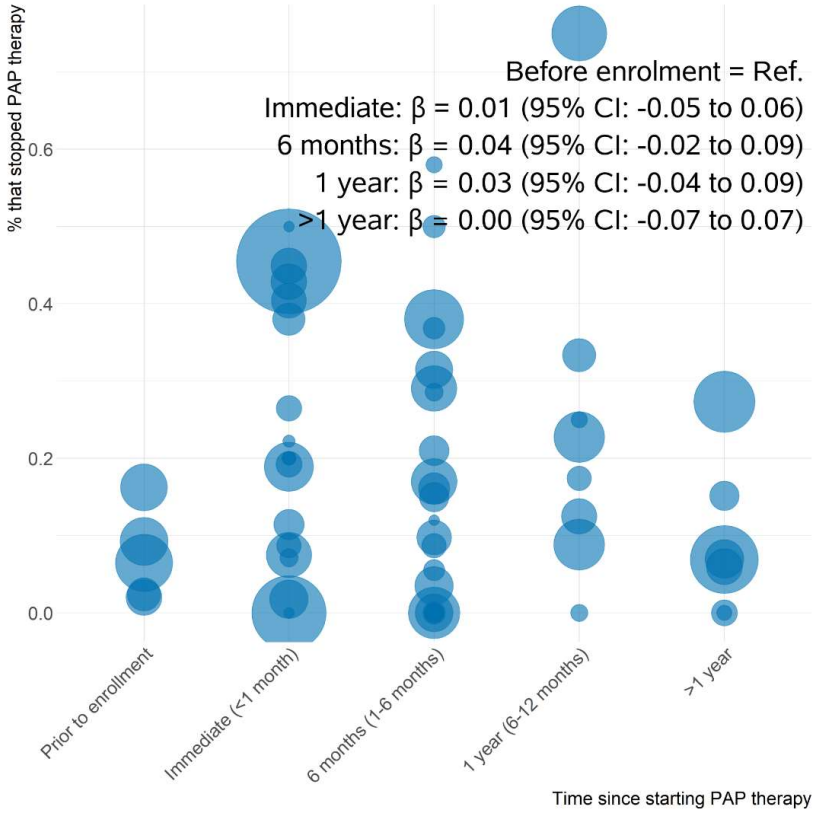
Adapted from the PRISMA 2020 statement template

Figure 2.2: a. Forest plot of summary estimates of acceptance of PAP therapy. b. Sample-size weighted bubble plot of acceptance over time.

a.



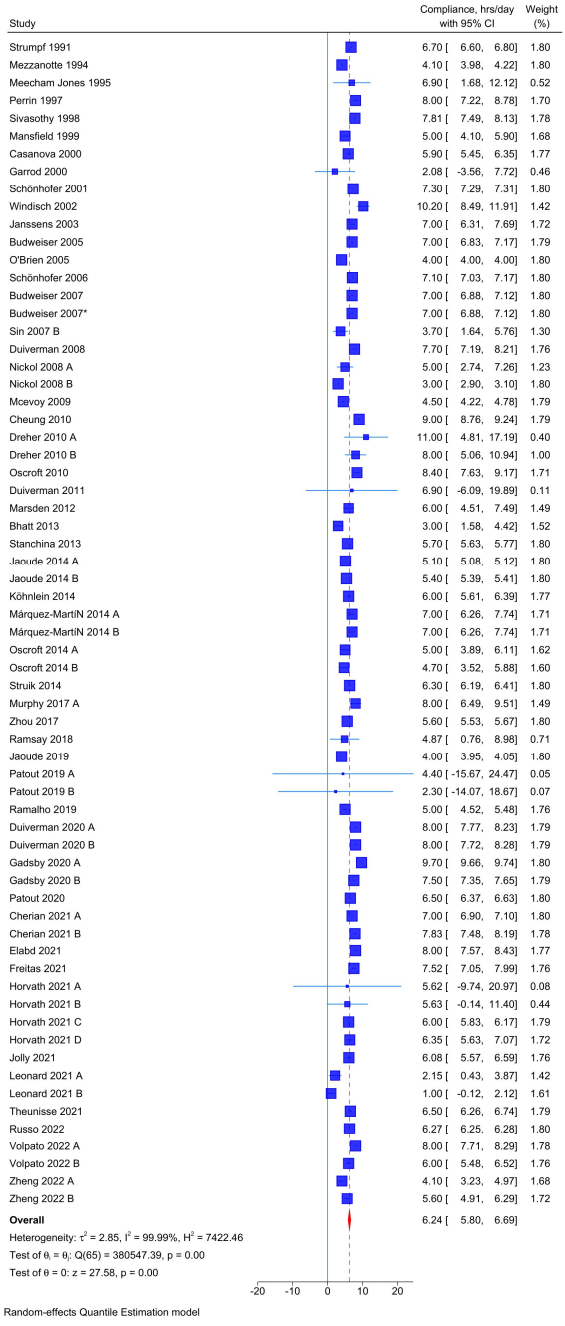
b.



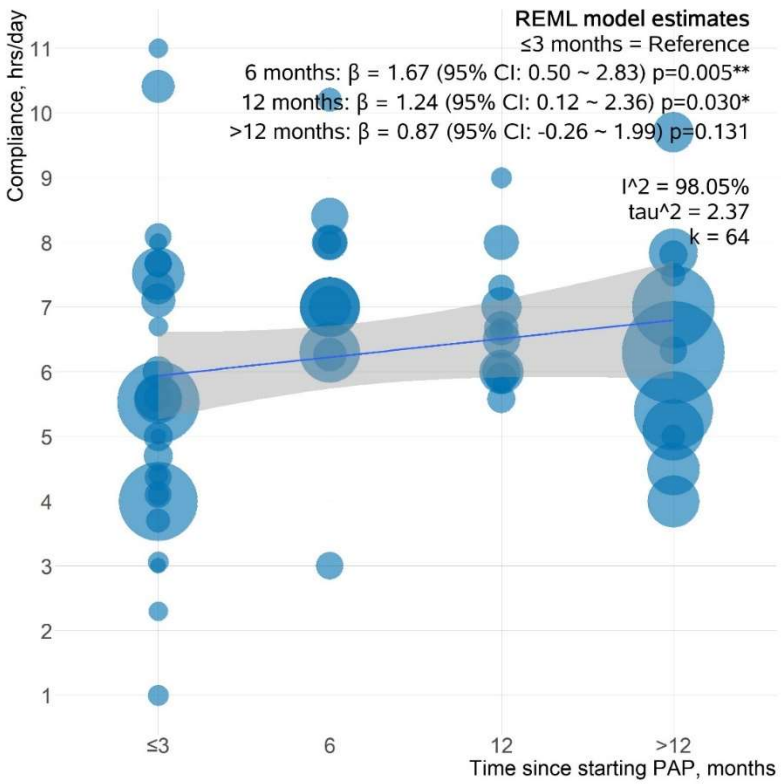
Legend: a. Forest plot of summary estimates of acceptance using a stratified inverse-variance weighted random effects meta-analysis with the restricted maximum-likelihood (REML) estimator. b. Sample size-weighted bubble plot of proportion of study participants that declined or discontinued PAP therapy over time at which the measure was reported. If multiple measures were reported, the measure closest to but not exceeding one year was included. The size of the circle is proportional to the sample size in the study.

Figure 2.3: a. Forest plot of summary estimates of adherence. b. Graphical representation of weighted sample estimates of acceptance per duration of follow-up.

a.


Study
Compliance, hrs/day with 95% CI
Weight (%)
Strumpf 1991 6.70 [6.60, 6.80] 1.80
Mezzanotte 1994 4.10 [3.98, 4.22] 1.80
Meecham Jones 1995 6.90 [1.68, 12.12] 0.52
Perrin 1997 8.00 [7.22, 8.78] 1.70
Sivasothy 1998 7.81 [7.49, 8.13] 1.78
Mansfield 1999 5.00 [4.10, 5.90] 1.68
Casanova 2000 5.90 [5.45, 6.35] 1.77
Garrod 2000 2.08 [-3.56, 7.72] 0.46
Schönhofer 2001 7.30 [7.29, 7.31] 1.80
Windisch 2002 10.20 [8.49, 11.91] 1.42
Janssens 2003 7.00 [6.31, 7.69] 1.72
Budweiser 2005 7.00 [6.83, 7.17] 1.79
O'Brien 2005 4.00 [4.00, 4.00] 1.80
Schönhofer 2006 7.10 [7.03, 7.17] 1.80
Budweiser 2007 7.00 [6.88, 7.12] 1.80
Budweiser 2007* 7.00 [6.88, 7.12] 1.80
Sin 2007 B 3.70 [1.64, 5.76] 1.30
Duiverman 2008 7.70 [7.19, 8.21] 1.76
Nickol 2008 A 5.00 [2.74, 7.26] 1.23
Nickol 2008 B 3.00 [2.90, 3.10] 1.80
Mcevoy 2009 4.50 [4.22, 4.78] 1.79
Cheung 2010 9.00 [8.76, 9.24] 1.79
Dreher 2010 A 11.00 [4.81, 17.19] 0.40
Dreher 2010 B 8.00 [5.06, 10.94] 1.00
Oscroft 2010 8.40 [7.63, 9.17] 1.71
Duiverman 2011 6.90 [-6.09, 19.89] 0.11
Marsden 2012 6.00 [4.51, 7.49] 1.49
Bhatt 2013 3.00 [1.58, 4.42] 1.52
Stanchina 2013 5.70 [5.63, 5.77] 1.80
Jaoude 2014 A 5.10 [5.08, 5.12] 1.80
Jaoude 2014 B 5.40 [5.39, 5.41] 1.80
Köhnlein 2014 6.00 [5.61, 6.39] 1.77
Márquez-MartiN 2014 A 7.00 [6.26, 7.74] 1.71
Márquez-MartiN 2014 B 7.00 [6.26, 7.74] 1.71
Oscroft 2014 A 5.00 [3.89, 6.11] 1.62
Oscroft 2014 B 4.70 [3.52, 5.88] 1.60
Struik 2014 6.30 [6.19, 6.41] 1.80
Murphy 2017 A 8.00 [6.49, 9.51] 1.49
Zhou 2017 5.60 [5.53, 5.67] 1.80
Ramsay 2018 4.87 [0.76, 8.98] 0.71
Jaoude 2019 4.00 [3.95, 4.05] 1.80
Patout 2019 A 4.40 [-15.67, 24.47] 0.05
Patout 2019 B 2.30 [-14.07, 18.67] 0.07
Ramalho 2019 5.00 [4.52, 5.48] 1.76
Duiverman 2020 A 8.00 [7.77, 8.23] 1.79
Duiverman 2020 B 8.00 [7.72, 8.28] 1.79
Gadsby 2020 A 9.70 [9.66, 9.74] 1.80
Gadsby 2020 B 7.50 [7.35, 7.65] 1.79
Patout 2020 6.50 [6.37, 6.63] 1.80
Cherian 2021 A 7.00 [6.90, 7.10] 1.80
Cherian 2021 B 7.83 [7.48, 8.19] 1.78
Elabd 2021 8.00 [7.57, 8.43] 1.77
Freitas 2021 7.52 [7.05, 7.99] 1.76
Horvath 2021 A 5.62 [-9.74, 20.97] 0.08
Horvath 2021 B 5.63 [-0.14, 11.40] 0.44
Horvath 2021 C 6.00 [5.83, 6.17] 1.79
Horvath 2021 D 6.35 [5.63, 7.07] 1.72
Jolly 2021 6.08 [5.57, 6.59] 1.76
Leonard 2021 A 2.15 [0.43, 3.87] 1.42
Leonard 2021 B 1.00 [-0.12, 2.12] 1.61
Theunisse 2021 6.50 [6.26, 6.74] 1.79
Russo 2022 6.27 [6.25, 6.28] 1.80
Volpato 2022 A 8.00 [7.71, 8.29] 1.78
Volpato 2022 B 6.00 [5.48, 6.52] 1.76
Zheng 2022 A 4.10 [3.23, 4.97] 1.68
Zheng 2022 B 5.60 [4.91, 6.29] 1.72
Overall 6.24 [5.80, 6.69]
Heterogeneity: τ^2 = 2.85, I^2 = 99.99%, H^2 = 7422.46
Test of $\theta_i = \theta_j$: Q(65) = 380547.39, p = 0.00
Test of θ = 0: z = 27.58, p = 0.00
-20
-10
0
10
20
Random-effects Quantile Estimation model

b.



Legend: a. Forest plot of summary estimates of adherence using a pooled inverse-variance weighted random effects meta-analysis of median adherence using quantile estimation. b. Sample size weighted bubble plot of adherence to PAP therapy with the interval of time at which the measure was reported. If multiple measures were reported, the measure closest to one year was included in this figure. The size of the circle is proportional to the sample size in the study.

Figure 2.4: Effect direction plot of the variables associated with acceptance of or adherence with PAP therapy, organized within the World Health Organization framework.

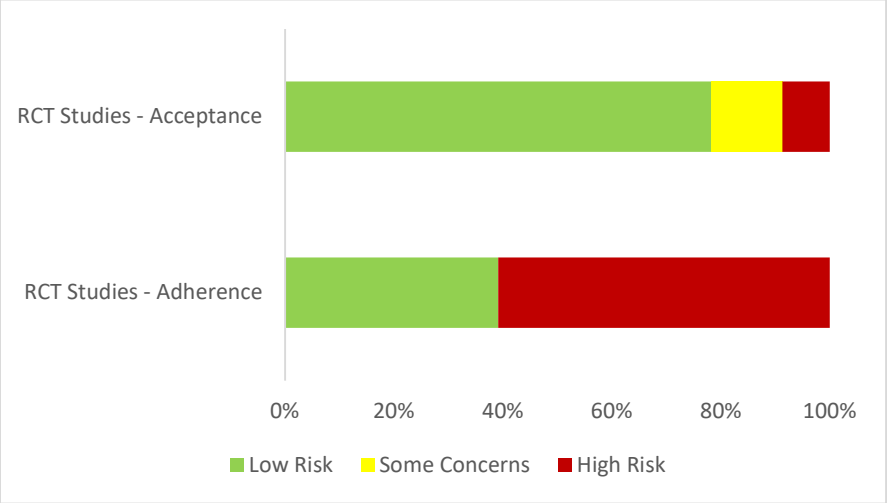
Author Year [ref]	Study design	Acceptance	Adherence	Variable
Exposure: Factors associated with disease severity for COPD, CHRF or SRBD				
Bräunlich 2019[49]	Randomized crossover trial	▼		disease-related reasons
Clini 1998[63]	Prospective cohort	▼		physician recommendation
Duiverman 2008[38]	RCT	▼		lung function
Gadsby 2020[19]	Retrospective cohort		▼	high BMI
Gadsby 2020[19]	Retrospective cohort		▼	presence of OSA
Garrod 2000[39]	RCT		▼	upper airway symptoms
Jaoude 2019[99]	Retrospective cohort		◄►	presence of an ECOPD
Murphy 2012[32]	RCT	▼		physician recommendation
Theunisse 2021[67]	Prospective cohort		◄►	hypercapnia vs eucapnia
Exposure: Factors associated with PAP therapy implementation, delivery or support				
Baiamonte 2018[62]	Retrospective cohort	▼		device intolerance
Bleksley 2017[17]	Retrospective cohort	▼		device intolerance
Bräunlich 2019[49]	Randomized crossover trial	▼		device intolerance
Budweiser 2007*[80]	Prospective cohort	▼		device intolerance
Casanova 2000[36]	RCT	▼		device intolerance
Cheung 2010[37]	RCT	◄►		LI-NIV vs sham PAP
Cheung 2010[37]	RCT	▼		device intolerance
Clini 1998[63]	Prospective cohort	▼		device intolerance
Dreher 2010[29] A & B	RCT	▲		HI-NIV vs LI-NIV
Dreher 2010[29] A & B	RCT	▼		device intolerance
Duiverman 2008[38]	RCT	▼		device intolerance
Duiverman 2020[30] A & B	RCT		◄►	telemedicine
Elliott 1992[73]	Prospective cohort	▼		device intolerance
Elliott 1992[73]	Prospective cohort	▼		sleep disturbance
Garrod 2000[39]	RCT		▼	disturbance to spouse

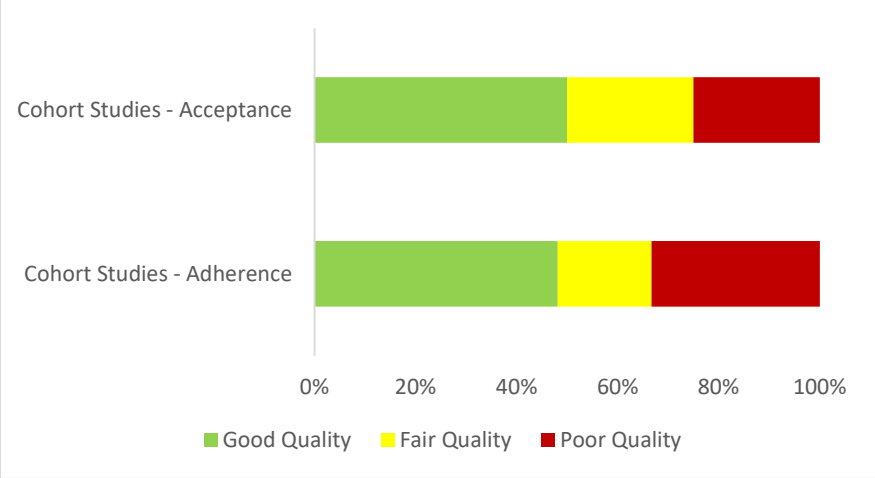
Garrod 2000[39]	RCT	▼	inability to sleep due to noise
Köhnlein 2014[40]	RCT	▼	device intolerance
Leonard 2021[61]	Prospective cohort	▲	call center/telemedicine vs routine care
Machado 2010[54]	Prospective cohort	▼	device intolerance
Marino 1991[81]	Prospective cohort	▼	device intolerance
Meecham Jones 1995[50]	Randomized crossover trial	▼	device intolerance
Murphy 2012[32]	RCT	▼	device intolerance
Murphy 2012[32]	RCT	▼	claustrophobia
Murphy 2017[35] A	RCT	▼	device intolerance
Oscroft 2010[70]	Retrospective cohort	▼	device intolerance
Oscroft 2010[70]	Retrospective cohort	◄►	initiated after an ECOPD vs stable state
Patout 2019[55] A & B	RCT	◄►	respiratory monitor titration vs PSG titration
Perrin 1997[93]	Prospective cohort	▼	device intolerance
Perrin 1997[93]	Prospective cohort	▼	sleep disturbance
Qasim 2019[21]	Retrospective cohort	▼	device intolerance
Schonhofer 2006[71]	Prospective cohort	▼	device intolerance
Simonds 1995[74]	Prospective cohort	▼	device intolerance
Sin 2007[44] B	RCT	◄►	NIV vs sham PAP
Sivasothy 1998[78]	Retrospective cohort	▼	device intolerance
Struik 2014[45]	RCT	▼	device intolerance
Strumpf 1991[51]	Randomized crossover trial	▼	device intolerance
Strumpf 1991[51]	Randomized crossover trial	▼	sleep disturbance
Strumpf 1991[51]	Randomized crossover trial	▼	anxiety associated with ventilator use
Theerakittikul 2014[69]	Retrospective cohort	▼	device intolerance
Volpato 2022[33] A & B	RCT	▲	CBT-I vs standard care

Volpato 2022[33] C	RCT	▼	device intolerance
Wang 2015[101]	Prospective cohort	▼	device intolerance
Windisch 2002[97]	Prospective cohort	▼	device intolerance
Windisch 2005[52]	Randomized crossover trial	▼	device intolerance
Zhou 2017[34]	RCT	▼	device intolerance
Social or economic factors			
Garrod 2000[39]	RCT	▼	finances
Machado 2010[54]	Prospective cohort	▼	lack of insurance
Suraj 2018[72]	Prospective cohort	▼	social
Wang 2015[101]	Prospective cohort	▼	finances
Patient-related factors			
Köhnlein 2014[40]	RCT	▼	perception of uselessness
Struik 2014[45]	RCT	▼	lack of motivation
Zhou 2017[34]	RCT	▼	perception of uselessness
Health system or societal factors			
Cheung 2010[37]	RCT	▼	caregiver could not cope with treatment
Research-specific factors			
Bräunlich 2019[49]	Randomized crossover trial	▼	study-related reasons

Legend: * differentiates Budweiser 2007 from a different publication with the same author and year. RCT: randomized controlled trial; BMI: body mass index; OSA: obstructive sleep apnea; HI-NIV: high intensity non-invasive ventilation; LI-NIV: low intensity non-invasive ventilation; CBT-I: cognitive behavioural therapy for insomnia. Upward arrow means a positive impact on outcome; sideways arrow means no difference; downwards arrow means negative association with outcome. Large arrow ▲ means that the size of the study population with COPD prescribed PAP therapy is >300 (no studies met this criteria); medium arrow ▲ 50-300; small arrow ▲ <50. Risk of bias denoted by cell colour: green means low risk of bias; yellow means some concerns; red means high risk of bias.

Figure 2.5: Risk of bias for acceptance and adherence for the included studies. a. Risk of bias as assessed with the adapted NOS for cohort studies. b. Risk of bias as assessed with the Cochrane RoB v.2.





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Chapter 3: Characteristics of patients with COPD and a sleep-related breathing disorder who struggle to adhere to newly prescribed PAP therapy: pilot data from a prospective cohort.

3.1 Abstract

Introduction: Chronic obstructive pulmonary disease (COPD) is a common and disabling disease. In patients with COPD, both obstructive sleep apnea (OSA) and chronic hypercapnic respiratory failure (CHRF) are associated with high health care utilization. Continuous positive airway pressure (CPAP) or non-invasive ventilation (NIV) treat these conditions; however, some patients fail to successfully initiate and sustain therapy.

Methods: A prospective cohort study was conducted to describe factors associated with successful initiation of CPAP or NIV in consecutive patients diagnosed with COPD and undergoing polysomnography (PSG) for either OSA or CHRF. Patients, matched for age and body mass index (BMI), without significant lung disease and with OSA on PSG were recruited as controls. Telephone surveys were conducted before and after therapy. Medical records were reviewed for comorbidities, spirometry, PSG results and machine downloads.

Results: Twenty-eight patients with COPD (43% GOLD 3 or 4) and 26 controls were enrolled, of a similar age (64±8 years), sex (45% male), BMI (37.4±9.1 kg/m^2), working status, education, bed partner and companionship status. Patients with COPD were more frequently frail (68% vs 32%, p=0.01), on home oxygen (35% vs 4%, p<0.01), and there was a non-significant trend towards being more frequently prescribed NIV (36% vs. 12%, p=0.06) than controls. Twenty-one patients with COPD and 12 controls have completed the study (17 vs 7 accepting therapy).

Of those initiating therapy with CPAP/NIV at home, use was 6.0 h/day and 76% used therapy for >4 hours/day in the COPD group compared to the control group where use was 4.6 h/day and 43% used therapy > 4 hours/day. Thirteen of 21 (62%) patients with COPD and 4/12 (33%) controls both accepted therapy and used CPAP/NIV >4 hours/day (p=0.16). A logistic regression model adjusting for sex and COPD failed to demonstrate that modality (NIV or CPAP) accounted for success initiating therapy (OR 0.9; 95% CI: 0.2-4.4).

Conclusion: Patients with COPD are often successful initiating and sustaining PAP therapy. The mode of PAP therapy provided did not account for success with therapy after controlling for COPD. Further recruitment is required to explore additional barriers to use of CPAP or NIV in patients with COPD.

3.2 Introduction

Chronic obstructive pulmonary disease (COPD) is a systemic condition defined by the presence of fixed airflow limitation on pulmonary function testing accompanied by symptoms of dyspnea, cough, sputum production or wheeze[1]. Significant disability is associated with the diagnosis[2], and there is often a gradual decline of health-related quality of life as the disease progresses[3]. Patients with COPD often require Emergency Department (ED) access and hospitalization more than patients without COPD matched for age and sex[4], with the highest resource utilization occurring in patients with advanced disease who experience frequent exacerbations[5]. Interventions that increase health-related quality of life and decrease health care utilization are urgently needed.

Positive airway pressure (PAP) therapy is a treatment recommended to improve health outcomes in certain populations of patients with COPD[6]. When prescribed for the most common sleep-related breathing disorder (SRBD), obstructive sleep apnea (OSA), observational studies suggest that adherence to PAP therapy decreases COPD-related health care utilization[7-9] and increases survival[10, 11]. A systematic review of randomized controlled trials (RCTs) suggests that non-invasive ventilation (NIV) for CHRF in patients with COPD improves health-related quality of life and increases survival[12].

For PAP therapy to have an impact on health and health outcomes, it must be tolerated and used regularly[13]. Despite the benefits of PAP therapy, a systematic review suggests that while many patients with COPD accept and adhere to therapy, there is significant heterogeneity among studies for which the reasons are not well understood (see Chapter 2). The World Health Organization has identified non-adherence with therapies to be a key impediment to achieving

the benefits of medical interventions to date[14]. Despite this, there has not been a lot of dedicated work to better understand barriers to acceptance and adherence of these therapies.

In this study, we seek to better understand barriers to success initiating or sustaining use of newly prescribed PAP therapy in patients with COPD. To accomplish this, a prospective cohort study was conducted evaluating the acceptance of and adherence with newly prescribed PAP therapy in patients with COPD and a SRBD compared to controls matched by age and body mass index (BMI). The null hypothesis is that patients with COPD and SRBD will have similar PAP acceptance and adherence to age- and BMI-matched controls. The alternative hypothesis is that patients with COPD and SRBD will have higher acceptance and adherence of PAP compared to age and BMI-matched controls.

3.3 Methods

3.3.1 Setting

The study was conducted at a single tertiary care centre at the University of Alberta Hospital Sleep Disorders Laboratory in Edmonton, Alberta, *Canada*. Edmonton is the provincial capital of Alberta, has a population of ~1 million, and is located on Treaty 6 Territory, which is the traditional home and meeting ground to many First Nations and Métis people. The catchment area for the sleep laboratory includes Central and Northern Alberta, the Northwest Territories and Nunavut. More than 1500 PSG are completed each year. Referral for PSG can be made either by a respirologist or a sleep subspecialist.

3.3.2 Patient population

Consecutive adults (age ≥ 18 years old) who underwent PSG since June 2021 and who consented to contact for research were recruited into a prospective telephone survey study. The exposure group included patients with a Respirologist-confirmed diagnosis of COPD, airflow obstruction

on spirometry and a SRBD, either obesity and sleep-related hypoventilation/CHRF or OSA and sleep-related hypoventilation/CHRF. The control group were patients with OSA with or without obesity and CHRF prescribed PAP therapy, matched for age and BMI. Exclusion criteria were use of PAP therapy for ≥4 weeks in the past, current use of PAP therapy at the time of the intake survey, history of significant chronic lung disease other than COPD, neuromuscular disease including diaphragmatic paralysis, non-English speaking where a family member was not available by telephone to translate, dementia or physical impairment that prevented participation by telephone, use of a PAP machine that did not have a remote connection available to obtain a machine download, or those who declined to participate. Patients were excluded from the control group if they were diagnosed with central sleep apnea.

3.3.3 Investigations

Polysomnography was performed as either a diagnostic study with or without an associated treatment study on a separate night, or a split-night study, which consists of a diagnostic study (~120 minutes of sleep, and ideally including REM sleep) followed immediately by a titration study within the same night. Obstructive sleep apnea was defined as either an apnea-hypopnea index (AHI) ≥5 events/hr associated with symptoms and/or relevant cardiovascular or cerebrovascular comorbidity or an AHI ≥15 events/hr[15]. Chronic hypercapnic respiratory failure was defined as having a partial pressure of carbon dioxide ($PaCO_2$) ≥45 mmHg and was generally associated with obesity or OSA in the study population. Arterial blood gases were not routinely available for the study population. Sleep-related hypoventilation was defined as a 10 mmHg rise in transcutaneous carbon dioxide ($TcCO_2$) concentrations to a value >50 mmHg lasting ≥10 min or a sustained elevation in the $TcCO_2$ to ≥55 mmHg lasting at least 10 min[16] and was routinely available on the patients in this study.

3.3.4 PAP Titration

During titration studies, continuous positive airway pressure (CPAP) was titrated from approximately 6 cmH_2O to a maximum of 18-20 cmH_2O to achieve a target AHI <10 events/hr and SpO_2 ≥90%. To achieve this, CPAP pressure was increased by 2 cmH_2O increments every 5 minutes. If these physiologic targets were not achieved, NIV was titrated using bilevel positive airway pressure spontaneous/timed (BPAP S/T). The titrations are performed without supplemental oxygen unless for safety or if despite high NIV settings, the hemoglobin oxygen pulsed saturation (SpO_2) was <85% for 5 min during the titration. All patients were initiated on therapy in their home after receiving study results. The home initiation of PAP therapy is supported by respiratory homecare companies (private businesses that provide PAP equipment), a respirologist who prescribes the therapy and the patient's primary care provider. A subset of the patients were followed by a tertiary care sleep disorders program, through which registered respiratory therapists provide additional support.

3.3.5 Policy Issues

Funding availability for PAP therapy may influence responses to some of the survey questions about barriers to accessing treatment. Within Alberta, funding is available for NIV if a titration study during PSG demonstrated that CPAP did not decrease the AHI to <10 events/hr or markedly improve gas exchange in patients with obesity. For patients with an FEV_1<50%, NIV funding is only available for patients with a SRBD. For patients in Alberta prescribed CPAP, funding is not available except through private insurance or for specific populations if specific criteria are met on PSG and during an ambulatory trial of therapy, such as low-income seniors, patients qualifying as having a severe handicap, patients on work-related disability, or patients qualifying for the Non-Insured Health Benefits Program in Canada.

3.3.6 Survey development

The two telephone surveys were developed using a modified Delphi technique to determine the content. The survey was initially developed with literature review and expert opinion, then distributed for feedback from sleep specialists, respirologists and a methodologist from 4 institutions and 3 provinces. Input from 6/14 sampled experts was achieved and feedback consisted of Likert scale (1-5) responses and open-ended comments. Consensus was achieved after 2 rounds. The Edmonton Frail Scale – Acute Care (EFS-AC)[17] was added after the Delphi survey as a novel variable to explore. Secondly, a pilot of the surveys was performed on 5 patients diagnosed with COPD and OSA on CPAP therapy, with revisions made to improve clarity and an additional question was added. The intake survey assessed non-respiratory sleep disorders, sleepiness, frailty, pre-treatment expectancies, social determinants of health, companionship status and baseline pulmonary symptoms. The intake survey was performed prior to starting PAP therapy and included the COPD Assessment Test (CAT)[18], EFS-AC[17], Epworth Sleepiness Scale (ESS)[19], Self-efficacy Measure for Sleep Apnea (SEMSA)[20], Global Assessment of Sleep Questionnaire (GSAQ)[21] and 10 questions designed by the research team. The post-treatment survey reassesses pulmonary symptoms, sleepiness and explores device-related side effects and barriers to use of a social or financial nature and was performed 1-2 months after PAP therapy was started or at 6 months if the PAP prescription had not been filled. The second survey was composed of the ESS[19], CAT[18], Side Effects to CPAP Treatment Inventory (SECI)[22], MRC breathlessness scale[23] and 17 questions designed by the research team.

3.3.7 Study procedures

Consecutive patients who underwent PSG since June 2021 were approached. After enrolling 10 participants into the exposure group, recruitment for controls began. The intake telephone survey was administered prior to starting PAP therapy and a second follow-up survey was conducted approximately 1-2 months after starting PAP therapy, or at 6 months if PAP therapy had not been started by that time and was not imminent. A chart review was undertaken to characterize objective measures such as sleep study findings, pulmonary function testing, arterial blood gas or bicarbonate levels, comorbidities, medications and health care utilization. Subsequently, a machine download with PAP settings, duration of time used, and effectiveness was obtained from the respiratory homecare company in the community. The 30-day machine download was requested at the time of the second survey and was obtained for most patients 4-6 weeks after starting PAP therapy. A directed acyclic graph is available (see Appendix 4).

3.3.8 Sample Size Estimate

Airways disease was present in approximately 20% of patients who attended the sleep laboratory during the recruitment period. Assumptions were that of those who are diagnosed with a SRBD, the majority would be offered PAP therapy (95%), approximately 20% would not accept therapy[24-26], and approximately 60% of these patients would be adherent with PAP therapy and use their device for >4 hours/day[26-28]. As a result, a convenience sample size of 50 patients in the exposure and 50 patients in the control groups were targeted. To date, just over half of the target recruitment has been completed. Partial study results are presented to complete the requirements of the MSc thesis in the School of Public Health.

3.3.9 Outcomes

The primary outcome was the proportion that both accepted and adhered to newly prescribed PAP therapy in patients with COPD (achieved mean use >4 hours/day within 1-6 months of being prescribed therapy) compared to controls. The secondary outcome was to characterize these sample populations on variables that may be or are known to be associated with PAP acceptance or adherence using surveys developed based upon literature review and expert opinion.

3.3.10 Statistical analysis

Electronic consent and data were distributed, collected by and managed using Research Electronic Data Capture (REDCap) electronic data capture tools hosted at the University of Alberta[29, 30].

Study findings were summarized descriptively given the small sample size with mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. The normal distribution of variables was assessed using visual inspection of a histogram and Q-q plots followed by application of the Shapiro-Wilk Test for appropriate distributions. For normally distributed continuous variables, a t-test was used to assess clinically important comparisons. For non-normally distributed data, non-parametric testing with the Mann-Whitney U test was applied. For dichotomous variables, a Chi square statistic with Yates continuity correction or the Fishers exact test was used to assess clinically important comparisons. Logistic regression was used to evaluate whether NIV therapy was associated with acceptance or adherence after controlling for potential confounders. Stata was used for the statistical analysis (StataCorp. 2023. *Stata Statistical Software: Release 18*. College Station, TX: StataCorp LLC).

3.3.10 Ethics

Research ethics board approvals were obtained from the University of Alberta Research Ethics Monitoring Board (Pro00107920). Administrative approvals and a Data Sharing Agreement were obtained from Alberta Health Services. Electronic consent was obtained for study enrollment.

3.4 Results

As of September 1, 2023, 28 patients with COPD and 26 controls were enrolled, with the reasons for exclusion outlined in Figure 3.1. Of these, 33 have completed the study. Overall, the enrolled patients were similar based upon age (64 ± 8 years), BMI (37.4±9.1 kg/m^2) and sex (45% male). Two patients in the control group had attempted PAP therapy previously, one for 4 weeks one year previously, and another for <4 weeks 25 years prior. One patient in the COPD group had previously tried CPAP for <4 weeks.

Of the patients with COPD, 26 patients had OSA and two patients had sleep-related hypoventilation without OSA. Patient characteristics are outlined in Table 1. As expected, patients with COPD and control groups differed on characteristics associated with COPD. Current smoking was more frequent in patients with COPD than controls, although this factor did not reach statistical significance (44% vs 15%, p=0.07). Patients with COPD had a lower forced expiratory volume in one second (FEV_1) (52.3 ± 21.0% vs 91.6 ± 16.1%, p<0.01; 43% had GOLD 3 or 4 disease) and more frequently were prescribed home oxygen (36% vs 4%, p<0.01). After COPD was removed as a variable, the modified Charlson Comorbidity Index (CCI) was higher in patients with COPD (p=0.02), with COPD. The severity of OSA was similar between the exposure and control groups (AHI 22.4 events/h (IQR 9.0, 62.8) vs. 29.2 events/h (IQR 18.5, 45.6) events/hr), respectively. Patients with COPD were frequently titrated on NIV during PSG (p=0.06) and often required oxygen during the PSG titration (43% vs 19%, p=0.08)

(see Figure 3.2); however, neither result was statistically significant. Both groups were similar based upon working status, education, bed partner and companionship status.

Success achieving >4 hours/day of PAP therapy use within 1-6 months of the initial prescription is known in the 33 patients who have completed the study, with 13/21 (62%) patients with COPD and 4/12 (33%) controls having both accepted therapy and used CPAP/NIV >4 hours/day within 6 months of the prescription (relative risk 1.52, 95% CI 0.88-2.67, p=0.16). Of those who were not successful, two patients in the COPD and SRBD group and four patients in the control group did not accept PAP therapy. The machine downloads for patients in the COPD and SRBD group who reached study completion were obtained at a median of 47 days (IQR: 30, 104 days), measuring 6.0 h/day (IQR: 4.8, 7.1 h/day, n=17). In the control group, the machine downloads were obtained at a median of 36 days (IQR: 30, 43 days) measuring 4.6 h/day (IQR: 2.6, 6.8 h/day, n=7). Given that three patients who did not accept therapy were lost to follow-up for the second survey (two patients in the COPD and SRBD group and one in the control group), patients lost to follow-up for whom acceptance and compliance data were not available were classified as patients who were unsuccessful initiating therapy.

As part of an exploratory analysis, the patients were characterized for variables known to be associated with PAP adherence in patients with OSA with the addition of frailty.

A descriptive analysis was conducted to characterize the patients included in the study for themes that may be relevant to success initiating and sustaining therapy. Patients with COPD and an indication for PAP therapy had significant co-morbidity with a higher CCI score. Despite this, they have frequent reporting of having important people in their life supporting them in their use of PAP therapy. Similar proportions of patients with COPD and controls report having a bed partner or being in a long-term relationship. Figure 3.2 summarizes variables that relate to sleep

diagnostic testing, frailty and comorbidity stratified by success initiating and sustaining PAP therapy. From a financial perspective, three patients in the study that were lost to follow-up for the second survey reported that a lack of funding was the reason to decline PAP therapy at home. Patients with COPD less frequently had medical coverage for PAP therapy.

Device factors assessed by the SECI questionnaire are summarized in Figure 3.3, which demonstrates that the most frequently reported side effects that caused some, great or very great problems with PAP use in patients with COPD were related to sinonasal symptoms, dry throat, increased awakenings, uncomfortable pressure from the mask, mask leak, noise, difficulty exhaling or anxiety during treatment. Three of the patients with COPD who required home oxygen reported having difficulty transitioning between the PAP therapy with oxygen to home oxygen by nasal cannula, which is a novel barrier to treatment volunteered by study participants. The pre-treatment expectancies assessed by the SEMSA questionnaire are summarized in Figure 3.4 with similar results for both patients with COPD and controls.

Finally, questions designed to assess the potential bidirectionality of pulmonary symptoms and use of PAP therapy are summarized in Table 3.2. Both patients with COPD and controls report an impact of PAP therapy on symptoms of cough, shortness of breath, chest tightness and sputum production, with the most improvement after starting PAP therapy being for cough and shortness of breath in patients with COPD. Approximately 25% of the patients with COPD reported a worsening in one of these symptom domains with use of PAP therapy. Within the control group, this was also described. One control patient who experienced a worsening in cough, sputum production and chest tightness with PAP therapy reported symptoms of panic or anxiety while wearing the mask as a precipitant of the symptoms.

Limited quantitative synthesis was possible given the low sample size recruited and having completed the study at the time of the pilot data being presented. Only one variable was possible to explore as to whether it was associated with adherence. As there was no difference between groups as to the presence or absence of COPD, a logistic regression model was developed with the categorical dependent variable being success achieving adherence to therapy to see if the ventilatory modality may be associated with overall acceptance and adherence. Having NIV as the initial ventilatory modality prescribed did not increase the odds of success initiating or maintaining PAP therapy within 6 months of the initial prescription when compared to CPAP (OR = 0.9; 95% CI: 0.2-4.4) after adjusting for sex and presence of COPD. Given that the population was matched based upon age and BMI, these variables were not included in the model.

3.5 Discussion

To our knowledge, this is the first study to attempt to comprehensively assess factors that may impact acceptance of or adherence with newly prescribed PAP therapy in patients with COPD. These pilot results suggest that many patients with COPD can be established on therapy within the first 6 weeks of attempting use at home; however, there remains a subset of patients that do not accept or adhere to PAP therapy and this is not explained by the ventilatory modality initially prescribed. In this pilot data of a prospective cohort of patients with COPD and a SRBD, a high proportion were able to accept and adhere to PAP therapy within six weeks of accessing the treatment at home. Characteristics of the patients with COPD and a SRBD were similar to age and BMI-matched controls with OSA in many of the variables that have been shown to be associated with acceptance or adherence in patients without COPD. With this early data, it

remains unclear whether the acceptance and adherence will be similar between patients with or without COPD.

The World Health Organization has identified non-adherence with therapies to be a key impediment to achieving the benefits of medical interventions, and lists five dimensions of factors that affect adherence: socioeconomic-related factors, health care team/health system-related factors, condition-related factors, therapy-related factors and patient-related factors[14]. In patients with OSA without chronic lung disease, variables known to affect PAP adherence have been summarized as disease/patient characteristics, treatment titration procedure, technological/device related factors and side effects, psychological and social factors[31]. Despite success with treatment, novel barriers to use that this study has identified include challenges such as cost/funding, the concurrent need for home oxygen and PAP therapy, and worsening respiratory symptoms after PAP initiation. With further recruitment, variables that relate to these categories will be further explored, to identify themes that contribute to success with initiating or sustaining PAP therapy.

3.6 Limitations

This study has several limitations that require discussion. First, generalizability of the frequency of barriers to use of PAP therapy from this study to other health care environments or to patients with COPD who do not get referred to PSG would likely be inaccurate. The participants in this study were enriched for a population with complex sleep disorders or significant cardiopulmonary disease, which is expected given that they were referred for PSG rather than using an ambulatory pathway for diagnosis and treatment. Second, patients with COPD without sleep complaints or who do not have access to PSG may have different barriers to use of PAP therapy than the population studied. Third, the assessed characteristics/barriers may be region

specific. For example, funding being a barrier to acceptance of therapy may not be a factor in a region where there are more support for the therapy. Further work will be required to determine if the barriers to success with therapy identified are generalizable to the broader population. Fourth, the low numbers of patients recruited to date may limit the breadth of the barriers identified; however, the sampling frame includes a concentration of patients that may have barriers to success as many of these patients are referred for PSG rather than being entirely managed using ambulatory sleep assessments. Within many sleep centers, access to patients with COPD who are newly prescribed PAP therapy for assessment prior to them attempting treatment is a challenge, with prospective or randomized studies typically enrolling few participants unless they are multicentre studies[32, 33]. In recognition of the low numbers expected, a descriptive analysis of detailed responses to questionnaires administered was provided that represent pilot data to inform hypothesis testing in future targeted studies.

Notwithstanding these limitations, this study has some important strengths. First, comprehensive assessments were performed before and after PAP therapy initiation to characterize patients with COPD and controls. Second, the variables selected for data collection were informed by surveying a panel of experts from several institutions and settings. Third, very few studies to date have systematically assessed barriers to acceptance or adherence in patients with COPD who are prescribed PAP therapy (see Chapter 2) so this study provides novel information that was systematically collected at the time of a new prescription for therapy. Fourth, the use of a control population of patients without chronic lung disease allows for a better understanding of what factors are enriched in this population, and what pulmonary symptoms may change irrespective of the presence of chronic lung disease.

3.6 Conclusion

Success with initiating and sustaining use of PAP therapy in patients with COPD and either obesity with CHRF or OSA can be achieved within a short period after attempting use at home and is not explained by only considering the type of ventilatory modality prescribed. Through this pilot data, patients with COPD are characterized for variables that may be associated with success initiating or sustaining use of PAP therapy. With further recruitment, themes of important variables to assess and address when prescribing PAP therapy to patients with COPD will be better characterized and explored. The results of this work will inform future research, program and policy development that will increase the success initiating and sustaining use of PAP therapy in patients with COPD.

3.7 Acknowledgements

Contributors to this work include Dr. Irvin Mayers, Dr. Brian McNab for patient recruitment and research staff support. Geoffrey Charm and Pradhee Bastola provided assistance with data acquisition.

3.8 Tables

Table 3.1: Patient characteristics

	COPD & SRBD (n=28)	SRBD (n=26)
Age (years)	65 ± 8	63 ± 8
Sex (Male)	11 (39%)	13 (50%)
Body mass index (kg/m^2)	36.4 ± 8.6	38.6 ± 9.7
Current smoking	11 (44%)	4 (15%)
Using home oxygen	10 (36%)	1 (4%)
FEV_1 (% predicted)	52.3 ± 21.0	91.6 ± 16.1
Proportion GOLD stage 3 or 4	12 (42.8%)	0 (0%)
Modified Charlson Co-morbidity Index	3 (IQR 2, 4)	2 (IQR 1,3)
Frailty (EFS-AC questionnaire)	19 (68%)	8 (32%)
Apnea-hypopnea index	22.4 (IQR 9.0, 62,8)	29.2 (IQR 18.5, 45.6)
Oxygen introduced during the diagnostic study for an SpO_2 <83% for 5 minutes	12 (43%)	5 (19%)
Proportion prescribed NIV compared to CPAP	10 (36%)	3 (12%)
Working status		
Night shift	0 (0%)	2 (8%)
Employed	3 (11%)	7 (27%)
Unemployed	5 (18%)	1 (4%)
Retired	18 (64%)	15 (58%)
On disability	0 (0%)	2 (8%)
Highest level of education		
Less than a high school diploma	6 (21%)	2 (8%)
High school diploma	5 (18%)	4 (15%)
Post-secondary training	4 (15%)	7 (27%)
College or university degree	13 (46%)	12 (46%)
Minority ethnic group	3 (11%)	2 (8%)
Companionship status		
Single/never married	4 (14%)	2 (15%)
Married/common-law	20 (71%)	16 (61%)
Divorced/separated	3 (11%)	3 (12%)
Widowed	1 (4%)	5 (19%)
Bed partner	14 (50%)	12 (46%)

Legend: COPD: chronic obstructive pulmonary disease; CPAP: continuous positive airway pressure; EFS-AC: Edmonton Frail Scale – Acute Care; FEV_1 = forced expiratory volume in one second; GOLD = Global Obstructive Lung Disease; NIV: non-invasive ventilation; SpO_2: peripheral oxygen saturation.

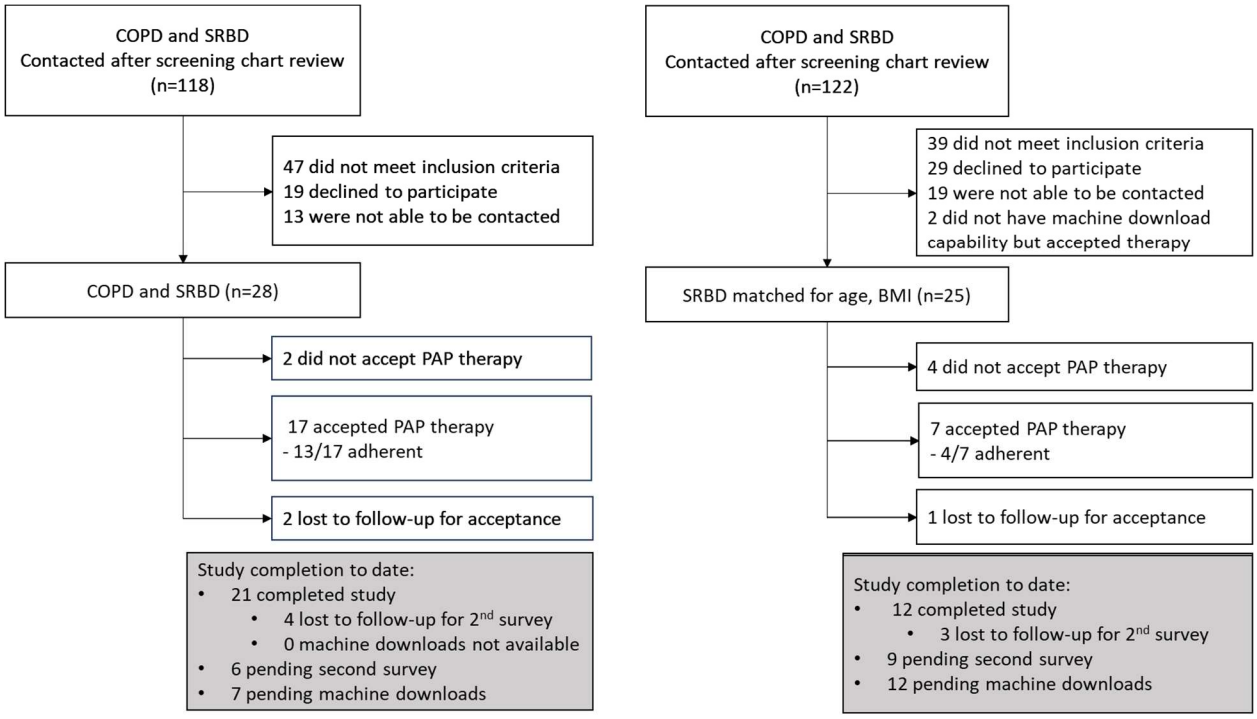
Table 3.2: Research questions designed to assess the bidirectional nature of pulmonary symptoms on use of PAP therapy or use of PAP therapy on pulmonary symptoms.

	COPD & SRBD		**SRBD**	
	No acceptance or non-adherent (n=4)	Adherent (n=13)	No acceptance or non-adherent (n=5)	Adherent (n=4)
"Did cough or shortness of breath affect your comfort wearing the mask" (Yes compared to Unsure or No)	1 (25%)	1 (8%)	2 (40%)	1 (25%)
Does wearing the mask change your (I/W/ND/NC):				
a) cough	1/0/3/0	4/0/9/0	0/1/4/0	0/1/3/0
b) shortness of breath	2/1/1/0	4/1/8/0	1/1/3/0	1/0/3/0
c) sputum production	1/0/2/1	1/1/11/0	1/1/3/0	1/0/3/0
d) chest tightness	1/0/2/1	3/1/9/0	1/2/1/1	1/0/3/0
Summary of the impact on cough, sputum, shortness of breath or chest tightness while wearing the mask:				
a) ≥1 symptom improved	3 (75%)	6 (46%)	3 (60%)	1 (25%)
b) ≥1 symptom worsened	1 (25%)	3 (23%)	2 (40%)	1 (25%)

Legend: I = improves; NC = no comment or prefer not to say; ND = no difference or does not affect; W= worsens. COPD: chronic obstructive pulmonary disease; SRBD: sleep-related breathing disorder.

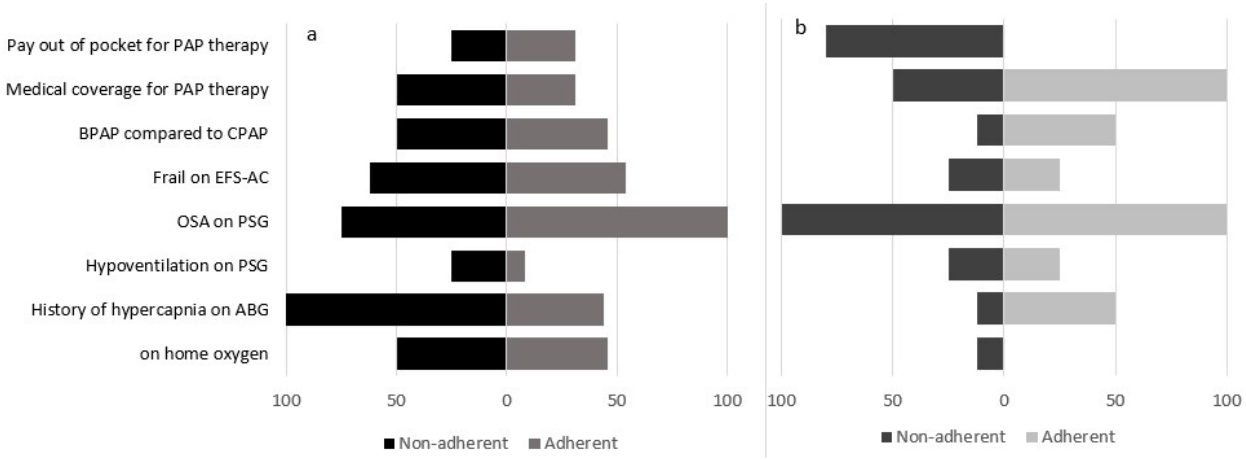
3.7 Figures

Figure 3.1: Flow chart of patient recruitment.



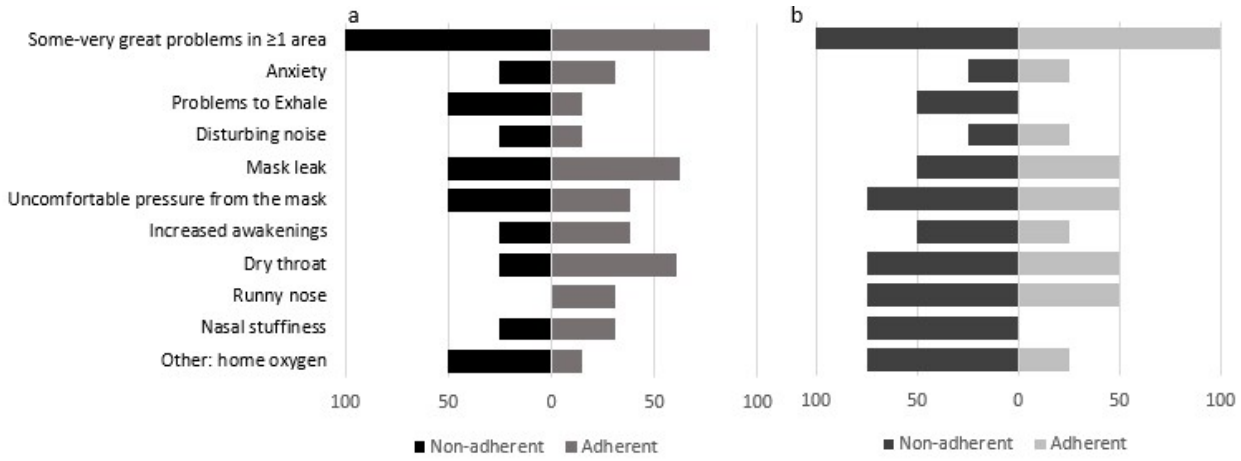
Legend: BMI: body mass index; COPD: chronic obstructive pulmonary disease; PAP: positive airway pressure; SRBD: sleep related breathing disorder.

Figure 3.2: Descriptive characteristics of patients who are successful with therapy compared to those who either do not accept therapy or who use PAP therapy less than four hours/night.



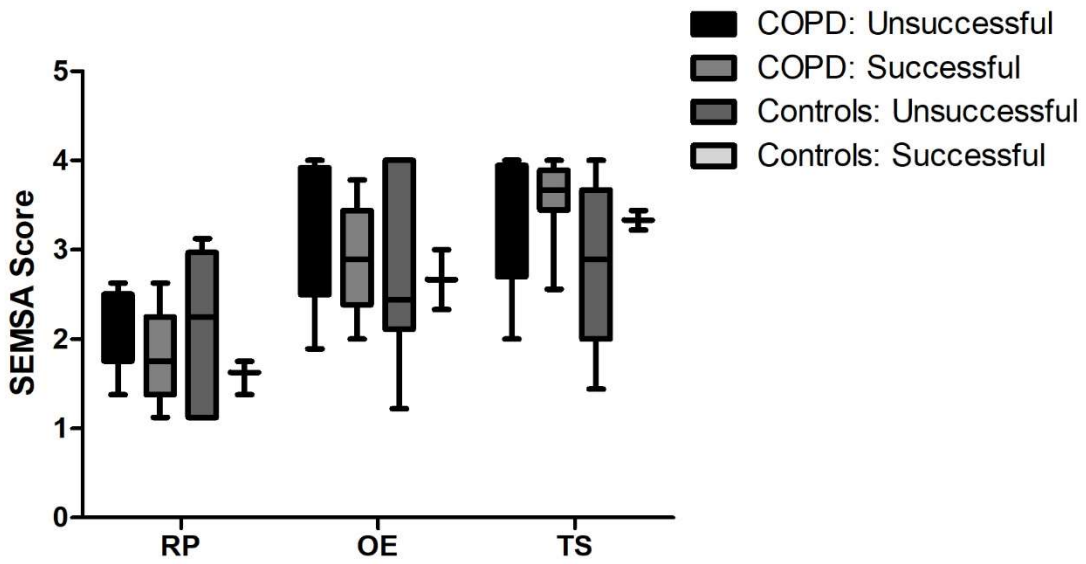
Legend: (a) denotes patients with COPD and a sleep-related breathing disorder prescribed PAP therapy (n=21, 13 of whom were adherent). (b) denotes patients with a sleep-related breathing disorder who are prescribed PAP therapy, matched for age and body mass index (n=12, 4 of whom were adherent).

Figure 3.3: Summary of the commonly reported side effects assessed by the SECI questionnaire.



Legend: (a) denotes patients with COPD and a sleep-related breathing disorder prescribed PAP therapy (n=21, with data from 4/8 non-adherent patients and 13/13 adherent patients). (b) denotes patients with a sleep-related breathing disorder who are prescribed PAP therapy, matched for age and body mass index (n=12, with data from 4/8 non-adherent patients and 4/4 adherent patients).

Figure 3.4: Self Efficacy in Sleep Apnea (SEMSA) questionnaire results by domain.



Legend: Pretreatment expectancies for ability to use PAP therapy in patients with COPD by domain within the SEMSA questionnaire. RP: risk perception. OE: outcome expectancies. TS: treatment self-efficacy.

3.9 References

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Chapter 4: An Overview of a proposed Sleep Research Program at the University of Alberta

4.1 Introduction

As a subspecialty trained sleep physician and respirologist working full-time at a tertiary care centre, I regularly assess and manage patients with chronic lung disease and sleep-related breathing disorders. Presently, there are significant gaps in the evidence guiding management of patients with these overlapping conditions; a state that I often reflect on when completing sleep diagnostic testing or making treatment recommendations. Through this Master's training, my intention has been to build a skillset and collaborations that could lead to an innovative and impactful program of research in sleep disorders for patients with chronic lung disease at the University of Alberta. By doing so, I hope to undertake work that will allow myself, my colleagues and my patients the platform to contribute knowledge that will inform the treatment of these disorders both in Edmonton and across the globe. With the support of the research mentorship and training provided through the School of Public Health, I have now acquired the necessary research skills to conduct high-quality studies. The products of this thesis are summarized here with the intention of demonstrating their contributions to this overarching goal.

First, two projects (the systematic review and the prospective cohort study) have been significantly advanced and are nearing completion. Second, key infrastructure to allow for research within the Sleep Disorders Program has been implemented and a quality improvement program established. In this final thesis chapter, the current state of projects will be summarized along with key learning experiences. Training opportunities that arose from the work undertaken for this thesis will be described. Through this summary, I will demonstrate the research skills

acquired, and highlight the viability of the sleep research program that has been established through this thesis work.

4.2 Current State of Research

4.2.1 Original proposed study in the ED

The proposed study that received granting from the Medicine Strategic Clinical Network, Respiratory subsection, entitled "Prevalence and treatment status of obstructive sleep apnea in patients presenting to the Emergency Department (ED) with an exacerbation of COPD," was not pursued due to restrictions recruiting patients from the ED during the pandemic. The study protocol is in Appendix 6 (Ethics Reference ID: Pro00100459, approved, operational approval not sought after COVID-19 pandemic started and the project was closed July 28, 2022).

While determining the burden of OSA and the treatment status for OSA in patients with COPD who are experiencing moderate-severe exacerbations remains important, this study was paused during the COVID-19 global pandemic of 2020-2023. Most importantly, the institutional pause on non-COVID related research and the loss of staff and resources required for patient recruitment in the Emergency Department (ED) precluded study enrollment. These resources have not been re-established to date and no study funding source has been identified. As such, it was not feasible or ethical to initiate this proposed study. This will be reassessed in the future should infrastructure or financial support be secured.

Despite this set-back, in many ways, this project allowed for significant professional growth. I had the opportunity to develop a research question, receive feedback on a research protocol and study design, draft and receive feedback on a grant submission, and navigate an ethics submission. Most importantly, upon receiving grant funding as the principal investigator, this project afforded me to opportunity to navigate holding research funds, revise research spending

when the pandemic hit, and account for study funds and research productivity at the conclusion of the grant.

4.2.2 Outcome: Systematic Review

This research is nearing completion. The intensive nature of the inclusion/exclusion process for included studies, the need for inclusive search criteria which was evident given the volume of grey literature identified, and the unfunded nature of this study delayed progress and precluded this systematic review from being established as a ***living review***.

Overall, this review demonstrated that PAP therapy was discontinued in a pooled proportion of 14% (95% CI 10–20) of cases within one year of initiation in 56 study arms reporting this measure. This often occurred within 2 weeks of initiation among studies reporting repeated measures. The pooled median adherence was 6.24 hours/day (95% CI 5.80–6.69) in 66 study arms reporting this specific measure. Adherence was higher at 3 and 6 months after initiation than within the first 4 weeks or when reported ≥1 year. Adherence seemed to be achieved within the first 6 months in studies with repeated measures. Overall, a significant proportion of patients with COPD were able to accept and adhere to PAP therapy; however, significant heterogeneity among studies was demonstrated. There was limited evidence for barriers to PAP acceptance and adherence for patients with COPD newly prescribed PAP therapy. With the use of a linear meta-regression, indication for therapy was the only one of five variables that accounted for significant heterogeneity among the study sample estimates for acceptance or adherence. Fewer patients with a SRBD and COPD declined or discontinued PAP therapy within one year of it being prescribed; however, the duration of use was shorter in this population than in patients with CHRF secondary to COPD.

Within studies, barriers to use were not comprehensively reported, other than device intolerance. There was sporadic reporting of barriers to use that spanned all the known categories for challenges with adherence as outlined by the World Health Organization. Whether or not these sporadically identified barriers are important will require more comprehensive assessments and reporting in studies measuring acceptance and adherence to PAP therapy in patients with COPD.

For knowledge translation and mobilization, a protocol was registered with Prospero[45] and published as a protocol paper[51]. Furthermore, an abstract of the preliminary data was accepted to the European Respiratory Society annual conference (European Respiratory Society Congress 2024). After receiving feedback from collaborators and optimizing the data analysis, the paper-based manuscript in Chapter 2 will be updated and this work will be submitted for peer-reviewed publication.

Through conducting the systematic review, I have learned the importance of protocol development, protocol registration and I have begun to appreciate the complexity of review methods. During the next phase of this project, I will continue to grow in my understanding of how to prepare and disseminate the knowledge gained.

5.2.3 Outcome: Prospective Cohort Survey Study

This study is nearing completion. Overall, this study demonstrated that patients with COPD commonly accept and adhere to PAP therapy. Adherence to PAP therapy can be established within 6 weeks of a new prescription intended for long-term use at home. Barriers to acceptance and adherence will be summarized following full study enrollment. Recruited patients are being comprehensively assessed descriptively with the use of questionnaires, physiologic measures, and novel questions about changes in the cardinal symptoms of COPD with the use of PAP therapy.

For knowledge translation and mobilization, the methodology of the survey development was presented at the Canadian Respiratory Conference in 2022 by a student trainee[3]. Pilot data were presented in poster form at the Canadian Thoracic Society annual meeting (Canadian Respiratory Conference) in Toronto, ON, April, 2024[4]. Given the significant barriers to patient recruitment and the results of the pilot study, the study will be closed when >30 participants have completed the study protocol. This will likely occur within the next 3 months. At that time, the data will be updated in the paper-based manuscript in Chapter 3 and submitted for publication as well as used to apply for grant funding.

Based upon the results of the telephone survey study, further work into evaluating barriers to acceptance and adherence to PAP therapy will be undertaken. We will review the data and determine several tools to measure within our clinical program for patients with COPD as a quality improvement project. Pathways that may address barriers to use that could be considered include streamlined access to cognitive behavioural therapy for insomnia or sinonasal assessments and interventions. We will use the pilot data to submit grant applications for qualitative studies to better understand barriers to PAP use within this population, such as exploring barriers to use of oxygen with PAP therapy, the impact of PAP therapy on COPD-related symptoms, and other barriers to use such as ventilator asynchrony and dyspnea at the time of removing the PAP mask. Grant funding will also be pursued to design prospective interventions to address the barriers to use that are identified. Through work on provincial groups, we will use the knowledge obtained to influence policy decisions at a population level that may impact PAP acceptance and adherence.

Through conducting this prospective cohort study, I have learned how to create databases in REDCap and navigate participant recruitment virtually. I have a greater understanding of barriers

to participant recruitment and retention in prospective cohort studies. I have gained experience in mentorship of undergraduate students and learned more about how to work effectively within a team comprised of research assistants.

4.3 Infrastructure and Quality Improvement Projects

4.3.1 Outcome: Research Consents including Chart Review for Eligibility for Study Inclusion

Beginning in June 2021, research consents have been collected at the University of Alberta Hospital Sleep Laboratory and are accessed electronically for research projects that receive ethics approval.

4.3.2 Outcome: Quality Improvement Database

A quality improvement project was implemented at the Sleep Laboratory in July 2021. The technologists collect data on airways disease, pulmonary function testing, weight, body mass index, and whether the patient was titrated on PAP therapy during the overnight study. This data will be used to inform future work reviewing barriers to access for the sleep laboratory to the entire catchment area of the sleep laboratory, to improve the assessment and care of patients with airways disease that attend the sleep laboratory, and to inform the titration protocols within our sleep laboratory.

4.3.3 Outcome: Training Opportunities

The productivity of sleep research that has been generated over the past few years has increased training and mentorship opportunities for undergraduate students and medical students. Our program has now had three students undertake sleep research projects related to this thesis work and have been enjoying the opportunity to develop their research skills in Clinical Epidemiology and to educate them in Sleep Disorder Medicine. Opportunities to have trainees at all levels of

training with an interest in this field will increase their exposure to sleep disorders as they pursue their education and future careers.

Secondly, the academic work that has been a result of this research program to date will allow for our Sleep Program to advance our interests in establishing an accredited fellowship training program in Sleep Disorder Medicine. The planning for this program development is underway with contributions from both adult and pediatric sleep disorder medicine.

4.5 Conclusions

This program of research in Sleep Disorders is based upon robust methodology and the future work will impact the broader academic and clinical specialty community through efforts to disseminate the work in relevant conference proceedings, peer-reviewed publications, and other platforms. The infrastructure and lived experiences from completing this thesis work have provided a strong foundation for future academic work in respiratory and sleep research.

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Appendices

Appendix 1: Prospero registration

Appendix 2: Protocol paper for the systematic review

Appendix 3: Additional Files for Systematic Review (Search Strategy, Adapted Risk of Bias Criteria, Supplemental Methodology, Supplemental Results)

Appendix 4: Directed acyclic graph for telephone survey study

Appendix 5: Study protocol for the prospective cohort study that was stopped prematurely due to the pandemic

Appendix 1: Prospero Registration

Acceptance of and compliance with nocturnal positive airway pressure (PAP) therapy in adults with chronic obstructive pulmonary disease (COPD): a systematic review.

Citation

Cheryl Laratta, Rachel Jen, Sandra Campbell, Brian Rowe, Linn Moore, Scott Kirkland. Acceptance of and compliance with nocturnal positive airway pressure (PAP) therapy in adults with chronic obstructive pulmonary disease (COPD): a systematic review.. PROSPERO 2021 CRD42021259262 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021259262

Review question

The objective of this review is to assess the acceptance of and compliance or adherence with nocturnal positive airway pressure (PAP) therapy for chronic indications such as chronic hypercarbic respiratory failure or sleep-disordered breathing including obstructive sleep apnea disorders (OSA), central sleep apnea syndromes (CSA) or sleep related hypoventilation disorders in adult patients with chronic obstructive pulmonary disease (COPD). Since terms for consistent use of PAP therapy by a patient include both compliance and adherence, we use broad terms in the search for studies; however, we will use the term compliance for the protocol. PAP therapy includes treatment modalities such as continuous positive airway pressure (CPAP), bilevel positive airway pressure (BPAP), or adaptive servoventilation (ASV). We will stratify the primary outcomes by factors such as indication for treatment, type of therapy, and details on the practical implementation of these therapies including location of the titration (e.g., hospital-based, ambulatory or during polysomnography), targets of the titration (e.g., pre-defined duration of use at night or target partial pressure of carbon dioxide on arterial blood gas). Secondary outcomes will include variables associated with acceptance of or compliance with PAP therapy and will be categorized as follows: factors associated with sleep-disordered breathing or COPD, factors associated with PAP therapy delivery, patient-related factors, health system/societal factors, research-specific factors, and a category for factors that fall outside of a pre-defined category. Finally, we will summarize whether PAP uptake or compliance has been associated with clinical outcomes, summarized by outcome type and magnitude and/or direction of effect.

Searches

PROSPERO was first searched and no similar systematic review topics were found. We will search the following electronic databases: Cochrane Library (Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (CENTRAL)), OVID MEDLINE, EBSCO CINAHL, OVID EMBASE, Scopus, Proquest Dissertations & Theses and APA PsycINFO to identify records containing the concepts “obstructive airways disease” (e.g., COPD) and “compliance OR adherence” and “nocturnal ventilation systems”. A combination of Medical Subject Headings (MeSH) and text word searches will be used in the search strategy. No date or language restrictions will be applied. An example of the search strategy to be used is attached in Appendix A. Citation lists from the most relevant articles will be searched. We will contact experts in the field regarding unpublished studies and reviewed the publication lists for the most important authors in the field. We will hand search pulmonary medicine conference abstracts from the American Thoracic Society (ATS), Canadian Thoracic Society (CTS), and European Research Society (ERS) and American College of Chest Physicians (ACCP) as well as sleep disorder medicine conferences from the Associated Professional Sleep (joint venture by the American Academy of Sleep Medicine (AASM) and the Sleep Research Society (SRS)), Canadian Sleep Society (CSS), and the World Sleep Society (WSS) from 2018-2022. We will also select studies from the first 10 pages of a Google Scholar search.

Search strategy

https://www.crd.york.ac.uk/PROSPEROFILES/259262_STRATEGY_20210604.pdf

Types of study to be included

Included: Prospective or retrospective cohort studies, cross-sectional studies, case control studies, case series, case reports or ecological studies. Randomized control trials will also be included if they report the study outcomes of interest.

Excluded: Any study design that excludes patients due to lack of acceptance of or compliance with PAP therapy during a run-in period will be excluded from the review if data from the patients who were excluded during the run-in period are not reported.

We will not exclude studies if they enrol patients who have previously used PAP therapy and are receiving a new prescription; however, we will record this as a study limitation and potential source of bias. We will not include data found on mechanical ventilation at home that is not being used non-invasively (i.e., we will exclude patients with a tracheostomy).

Condition or domain being studied

Chronic obstructive pulmonary disease (COPD) is chronic lung disease characterized by fixed airflow obstruction, small airways disease and emphysema that confers significant morbidity and mortality to affected patients. The use of PAP therapy to optimize COPD management is indicated when the patient has chronic hypercarbic respiratory failure, OSA, CSA or sleep related hypoventilation disorders. Possible modalities of PAP therapy include CPAP, BPAP or ASV, all of which apply a gentle pressure of air to the upper airway during sleep to either maintain airway patency or augment tidal breathing. The benefits for treatment of OSA in patients with COPD has not been examined in prospective randomized control trials; however, include a reduction in hospitalizations or mortality in observational studies. In stable COPD patients with chronic hypercarbic respiratory failure, treatment with PAP therapy may confer reductions in mortality and hospital admissions and improved quality of life. The acceptance of and compliance with nocturnal PAP therapy in patients with COPD is not well understood. Furthermore, barriers to use of PAP therapy in this population has not been summarized. Through this systematic review, we hope to further our understanding of how to support patients with COPD to be successful with nocturnal PAP therapy.

Participants/population

Inclusion criteria:

The study population will be limited to adult subjects (age ≥18 y.o.) with COPD and a new prescription for nocturnal PAP therapy (i.e., CPAP, BPAP, ASV) for either chronic hypercarbic respiratory failure, OSA, CSA or sleep related hypoventilation disorders.

Exclusion criteria:

Pediatrics (age <18 y.o.);

Neuromuscular disease including diaphragmatic paralysis;

Less than 1 week of PAP adherence data for any factors relating to compliance;

Mechanical ventilation through a tracheostomy.

Intervention(s), exposure(s)

Prescription of nocturnal positive airway pressure for chronic use (i.e., CPAP, BPAP, ASV).

Comparator(s)/control

Not applicable.

Context

We will not include long-term use of PAP therapy that is not intended to be followed outside of a hospital setting (i.e. we will accept patients titrated in hospital on PAP therapy for long-term use, but not hospitalized patients treated as an inpatient with no intent to discharge into the community on PAP therapy). We will also not include studies that report on PAP therapy for acute respiratory failure in the context of an exacerbation of COPD or its associated comorbidities. If a patient has been started on long-term nocturnal PAP therapy as an inpatient after receiving PAP therapy for an acute indication, they will be included as there is an intent to discharge these patients into the community on PAP therapy.

Main outcome(s)

PAP acceptance (dichotomous, i.e. established on therapy irrespective of compliance compared to no uptake within a given time period not exceeding 1 year (may be otherwise defined, such as not filling the prescription for PAP, PAP usage 0 hours per night, declined PAP therapy or refused to use PAP therapy within a follow-up time). The definitions of PAP acceptance that are found in the literature will be summarized in detail.

PAP compliance (with a minimum 7 days of data contributing to the outcome measure) will be reported. We will define PAP compliance as both dichotomous (e.g., >4h use per night for >70% of nights or >4 h use per night for 5/7 days) and continuous (e.g., mean hours of use per night) where reporting allows.

Measures of effect

A weighted proportion or weighted average will be the effect measure when there is no comparator. With a comparator, a pooled odds ratio or relative risk or a weighted mean risk difference will be calculated.

Additional outcome(s)

Variables with significant association with PAP uptake or compliance in multivariate analysis categorized as follows with some examples provided:

• Factors associated with OSA, CSA or sleep related hypoventilation disorders or COPD (e.g., Epworth Sleepiness Scale score (ESS), COPD assessment test (CAT), use of home oxygen, apnea-hypopnea index (AHI));

• Factors associated with PAP therapy delivery including settings (e.g., for BPAP, low intensity or high-intensity settings, treatment targeted towards a pre-defined measure or not targeted, use of average volume-assured pressure support (AVAPS); for CPAP, fixed pressure or automated (autoPAP)) or location/mode of titration (e.g., hospital, sleep laboratory or community start and titration of settings; lab-based testing during the titration (level I polysomnogram) or ambulatory based testing during titration (e.g., level II sleep test, level III sleep test, level IV sleep test)) or interface specific factors (mask leak, noise, comfort, claustrophobia, etc.);

• Patient-related factors (e.g., age, sex, socioeconomic status, BMI, marital status, peer/partner support, income, insurance coverage, self-efficacy, health literacy, etc.)

• Health system/societal factors (e.g. follow-up through a community provider or through a specialized sleep centre, etc.);

• Research-specific factors (e.g., PAP therapy provided through study etc);

• Other category.

If multiple comparators or definitions of exposure are used for a factor contributing to PAP acceptance or compliance, we will attempt to narrow the exposures into two groups based upon known data. Where this is not possible, separate groups will be reported.

The relationship between measurements of the primary outcomes of this review and the magnitude and direction of effect of PAP therapy on clinical outcomes examined in the literature in the COPD population will also summarized as a secondary outcome.

Measures of effect

A pooled odds ratio or relative risk or a weighted mean difference will be calculated.

Data extraction (selection and coding)

In the screening phase, two study investigators (CL/RJ) will independently screen titles and abstracts identified by the search strategy for relevance and inclusion. If >>1000 abstracts are identified, one study investigator will exclude obviously irrelevant studies based on title only. Exclusions will not be formally documented in this phase. Articles that are considered for relevance by one author and excluded by the other author will be retained for full text review during the study eligibility phase. The full text of articles deemed relevant in the screening phase will be retrieved for study eligibility in the review. Disagreements between study investigators in the study eligibility phase will be resolved by a third party with reasons for the exclusions documented. Study selection and screening will be completed in Covidence.

Data from primary studies will be extracted by the first author using a pre-designed data extraction form and then independently verified for accuracy and completeness by the second author. Disagreements will be resolved by consensus through discussion or by involving a third reviewer if consensus cannot be reached. If relevant information is suspected to have been collected but not reported, attempts will be made to contact authors for clarification and data.

Data to be extracted are as follows:

Study characteristics: study design, study period, country of origin, funding, patient enrollment process, blinding and follow-up.

Population characteristics: sample size, age, sex/gender, ethnicity, BMI, FEV1, details of sleep diagnostic testing, clinical factors that characterize COPD or sleep-disordered breathing or chronic hypercarbic respiratory failure, inclusion criteria and exclusion criteria, indication for PAP therapy, and history of PAP use

Intervention description: type of PAP therapy and details of delivery and settings, location and targets of PAP titration, and cointerventions. Factors or clinical outcomes that were described or analyzed in multivariate analysis for associations with acceptance or compliance will be recorded.

Risk of bias (quality) assessment

Two reviewers will independently complete the methodological quality assessment using risk of bias tools for each of the primary outcomes (PAP uptake and compliance) as follows. For randomized control trials, the Cochrane Risk of Bias tool version 2.0 will be utilized. For case-control and cohort studies, the NewCastle-Ottawa Scale will be used. For cross-sectional studies, the Newcastle-Ottawa Scale (modified for cross-sectional studies with comparison groups). A summary of the reviewer's quality assessment will reported in risk of bias graphs. Disagreements in risk of bias assessments will be resolved through third party adjudication.

Strategy for data synthesis

A narrative synthesis is planned and will be summarized in evidence tables. Characteristics of the included studies will be summarized including characteristics of the study and study population including categorical and continuous data.

Where possible for the primary or secondary outcomes, the data will undergo quantitative synthesis. For studies without a comparator where the exposure is similarly defined, a weighted proportion or weighted average will be generated. The

standard error of the summary exposure effect will be used to derive a confidence interval, in order to inform the precision of the summary estimate. Where a comparator is available, the data will be synthesized where the exposure and comparator have been similarly defined. A pooled odds ratio (OR) or relative risk (RR) using a random effects model or a weighted mean difference (WMD) using a random effects model will be used to generate summary estimated where there is sufficient outcome data. Statistical heterogeneity will be quantified using the I^2 statistic. A meta-analysis will be performed where sufficient and homogenous data exists. With low-moderate heterogeneity, we will combine them with a Dersimonian and Laird mixed effect model. A funnel plot will be constructed to identify the presence of publication bias if there are more than 10 included studies. Where it is not possible to synthesize the data into a meta-analysis due to high heterogeneity (I^2>70%) in the definition of the exposure, comparator or outcome, differences in the population or inability to compare study designs, we will use effect direction plots or forrest plots to synthesize the study findings within the narrative synthesis. Statistical analyses will be completed using Review Manager Software (RevMan).

Analysis of subgroups or subsets

A subgroup analysis of the primary and secondary outcomes will be performed where possible.

The following groups will inform subgroup analysis

A. indication for PAP therapy (chronic hypercarbic respiratory failure, OSA, CSA or sleep related hypoventilation disorders as defined by study design, outcome of objective testing for sleep-disordered breathing, or assessment of clinical predictors such as BMI and/or clinical prediction tools for OSA)

B. type of PAP therapy prescribed (CPAP, BPAP, ASV)

C. With sufficient data, details on the implementation of this therapy (e.g. location of titration of PAP therapy (ambulatory, hospital-based or within a sleep laboratory), low-intensity versus high-intensity non-invasive ventilation, treatment targeted to achieve a clinical outcome versus treatment that is not titrated to effect, autoPAP versus CPAP).

Contact details for further information

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Type and method of review

Meta-analysis, Narrative synthesis, Systematic review

Anticipated or actual start date

15 June 2021

Anticipated completion date [1 change]

31 August 2023

Funding sources/sponsors

We recognize the Canadian Institutes of Health Research (CIHR) for salary and research funding support (BHR). There was no input from sponsors or institutions in the content or development of this protocol.

Conflicts of interest

Dr. C. Laratta receives renumeration for the interpretation of home sleep apnea tests by Careica Health. The other authors have no relevant conflicts of interest.

None known

Language

English

Country

Canada

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Adult; Humans; Pulmonary Disease, Chronic Obstructive; Sleep Apnea, Obstructive

Date of registration in PROSPERO

13 July 2021

Date of first submission

12 June 2021

Details of any existing review of the same topic by the same authors [1 change]

Stage of review at time of this submission [1 change]

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Revision note

Key revisions have been made to the planned data analysis in order to ensure that the results are clinically applicable and analyzed in a format to be most informative to the information user. In the original planning, the analysis would not have been appropriate for the outcomes of acceptance and adherence so this has been since revised prior to moving into the data extraction phase.

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

13 July 2021

13 July 2021

17 April 2023

Appendix 2: Protocol paper for the systematic review

PLOS ONE

STUDY PROTOCOL

Acceptance of and adherence with long-term positive airway pressure treatment in adults with chronic obstructive pulmonary disease: A systematic review protocol

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Data Availability Statement: No datasets were generated or analyzed during the current study. All relevant data from this study will be made available upon study completion.

Funding: The authors have received no specific funding for this work.

Competing interests: CRL receives renumeration for the interpretation of home sleep apnea tests by Careica Health. SRP reports an unrestricted grant

Abstract

Background

Long-term noninvasive positive airway pressure (PAP) treatment is effective treatment for sleep-related breathing disorders and chronic hypercarbic respiratory failure secondary to chronic obstructive pulmonary disease (COPD). PAP treatment may be delivered as continuous positive airway pressure or noninvasive ventilation. Success in initiating PAP treatment and barriers to its use in adult patients with COPD are largely unknown. This systematic review aims to identify the acceptance of and adherence to PAP treatment prescribed for long-term use in adult patients with COPD and to summarize variables associated with these measures.

Methods

Seven online electronic databases will be searched by an experienced medical librarian to identify records containing the concepts "obstructive airways disease" and "noninvasive positive airway pressure" and "acceptance" or "adherence". Randomized and non-randomized studies of interventions will be included. Citation lists from relevant articles will be reviewed, and experts will be contacted regarding unpublished studies. Abstracts from key conferences between 2018–2023 and Google Scholar search results will be reviewed for inclusion. Titles, abstracts and full texts will be reviewed independently for inclusion by two reviewers. Data extraction will be completed by one author using a pre-established form and primary outcomes confirmed by a second author. Methodological quality will be evaluated. If sufficient data are available for meta-analysis, a pooled summary statistic for the primary outcome will be calculated using a random-effects generic inverse-variance meta-analysis,

from Jazz Pharmaceuticals and consulting fees from Paladin Labs, Jazz Pharmaceuticals and the International Centre for Professional Development in Health and Medicine. The other authors have no relevant conflicts of interest to declare. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

Abbreviations: PAP, positive airway pressure; COPD, chronic obstructive pulmonary disease; PRISMA-P, Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols; CPAP, continuous positive airway pressure; NIV, noninvasive ventilation; OSA, obstructive sleep apnea; PROSPERO, International Prospective Register of Systematic Reviews; BPAP, bilevel positive airway pressure; VAPS, volume assured pressure support; ASV, adaptive servoventilation; CENTRAL, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials; MeSH, Medical Subject Headings; RevMan, Review Manager Software; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; BMI, body mass index; $PaCO_2$, partial pressure of carbon dioxide; AHI, apnea-hypopnea index.

weighted proportion or weighted medians-based approach. Subgroup analysis will explore clinically meaningful sources of heterogeneity. Variables that are associated with acceptance and adherence will be described.

Discussion

Long-term PAP treatment is a complex intervention prescribed to patients with COPD for several indications. Synthesis of the evidence on success with PAP treatment and variables associated with acceptance or adherence will inform program and policy development for supporting patients with COPD who are prescribed this therapy.

Trial registration

Systematic review registration: This protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on July 13, 2021 (registration number CRD42021259262), with revisions submitted on April 17, 2023.

Introduction

Chronic obstructive pulmonary disease (COPD) is a complex, multifaceted disease that may be complicated by respiratory failure and comorbidities such as sleep related breathing disorders that contribute to poor health outcomes [1]. Hypercarbic respiratory failure attributed to COPD is associated with high mortality and a poor quality of life [2]. Obstructive sleep apnea (OSA), the most common sleep-related breathing disorder, is associated with lower health-related quality of life [3] and increased health care utilization [4] in patients with COPD, and may co-exist with chronic hypercarbic respiratory failure [5]. These conditions share a common treatment of positive airway pressure (PAP). While the context within which PAP treatment is prescribed varies among patients with COPD, barriers to success with PAP therapy may be similar across disease indications.

Noninvasive PAP treatment intended for long-term use, generally during sleep, may be delivered as continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV). CPAP is an established therapy for OSA and has been shown to improve quality of life and reduce daytime sleepiness [6], with similar results to NIV [7, 8]. In patients with COPD, observational studies suggest that CPAP treatment for OSA is associated with longer survival [9, 10], longer time to first exacerbation requiring hospitalization [11], fewer Emergency Department (ED) visits [12], and fewer hospitalizations from COPD exacerbations [12, 13]. For sleep related breathing disorders, NIV may be prescribed when CPAP does not achieve physiologic treatment targets [14, 15], to resolve CPAP intolerance [16, 17], or at discharge from hospital for patients with obesity and chronic hypercapnic respiratory failure [18]. NIV is also indicated to treat chronic hypercarbic respiratory failure secondary to COPD as randomized controlled trials support that NIV prevents hospital readmission and intubation as well as improves survival [19], particularly when high intensity NIV is prescribed [20]. Evidence supporting the use of CPAP for chronic hypercapnic respiratory failure is primarily derived in patients with obesity without significant airflow obstruction where CPAP and NIV have similar long-term benefits [21]. Despite the proven benefits, PAP treatment is a complex and challenging intervention to accept and use [22]. It is therefore critically important that as the indications for

PAP treatment in patients with COPD expand, so does our understanding of how to help patients be successful with therapy.

The aim of this review is to characterize the acceptance of and adherence to long-term non-invasive PAP treatment in adult patients with COPD. The World Health Organization identifies broad categories of barriers to intervention adherence [23]. In the context of CPAP, factors that represent challenges to adherence in the general population of patients with OSA are classified as disease characteristics, sociodemographic characteristics, psychosocial factors, treatment titration procedure, technological device factors and side effects [24, 25]. There are, however, contextual factors among patients with COPD that may result in different barriers to PAP adherence compared to other patient populations. These factors include health behaviours, health literacy, baseline symptoms and contact with specialists. Through subgroup analysis of the primary aim, we will explore whether pre-specified variables such as specific disease characteristics or aspects of health service delivery are associated with either acceptance or adherence. The secondary aim is to summarize known variables that are associated with either acceptance or adherence in this population. The results of this review will be used to inform programs and policies designed to support patients with COPD who are prescribed PAP treatment and identify gaps in the literature that need to be addressed through future research.

Materials and methods

Study design

The methods for this systematic review are based upon the methodological frameworks outlined in the Cochrane Handbook for Systematic Reviews [26]. The results will be reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) 2020 statement [27]. For a PRISMA flow diagram, see Fig 1. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42021259262) after confirming that no similar systematic reviews were already registered. This study is exempt from ethics approval as this work is carried out on published documents.

Eligibility criteria

Types of studies. Primary research studies reporting on randomized controlled trials or observational studies will be included; qualitative studies, letters to the editor, opinions and editorials will be excluded. For included studies, only arms of the trial in which PAP treatment was prescribed will be included. Study designs that have acceptance or adherence with PAP treatment as part of the inclusion or exclusion criteria will not be included in this review, unless the excluded participants are also characterized.

Types of participants/population. The review will include data analyses of adult patients (age $\geq$18 years) with COPD who are newly prescribed PAP treatment for long-term use at home for one of the following indications: chronic hypercarbic respiratory failure, OSA, central sleep apnea or sleep related hypoventilation. If a study population includes patients with chronic lung diseases where $<$80% of the patients have COPD, the data for the COPD population will be included only if it is reported separately from the other populations. Studies where all the participants have COPD, however, 20% or more of participants have neuromuscular disease, including diaphragmatic paralysis, or significant lung disease in addition to COPD (e.g., interstitial lung disease), will be excluded in order to decrease the heterogeneity in the study population. Studies will be excluded if they report on PAP treatment for acute respiratory failure in isolation or on patients treated during hospitalization with no intent to discharge on PAP treatment.

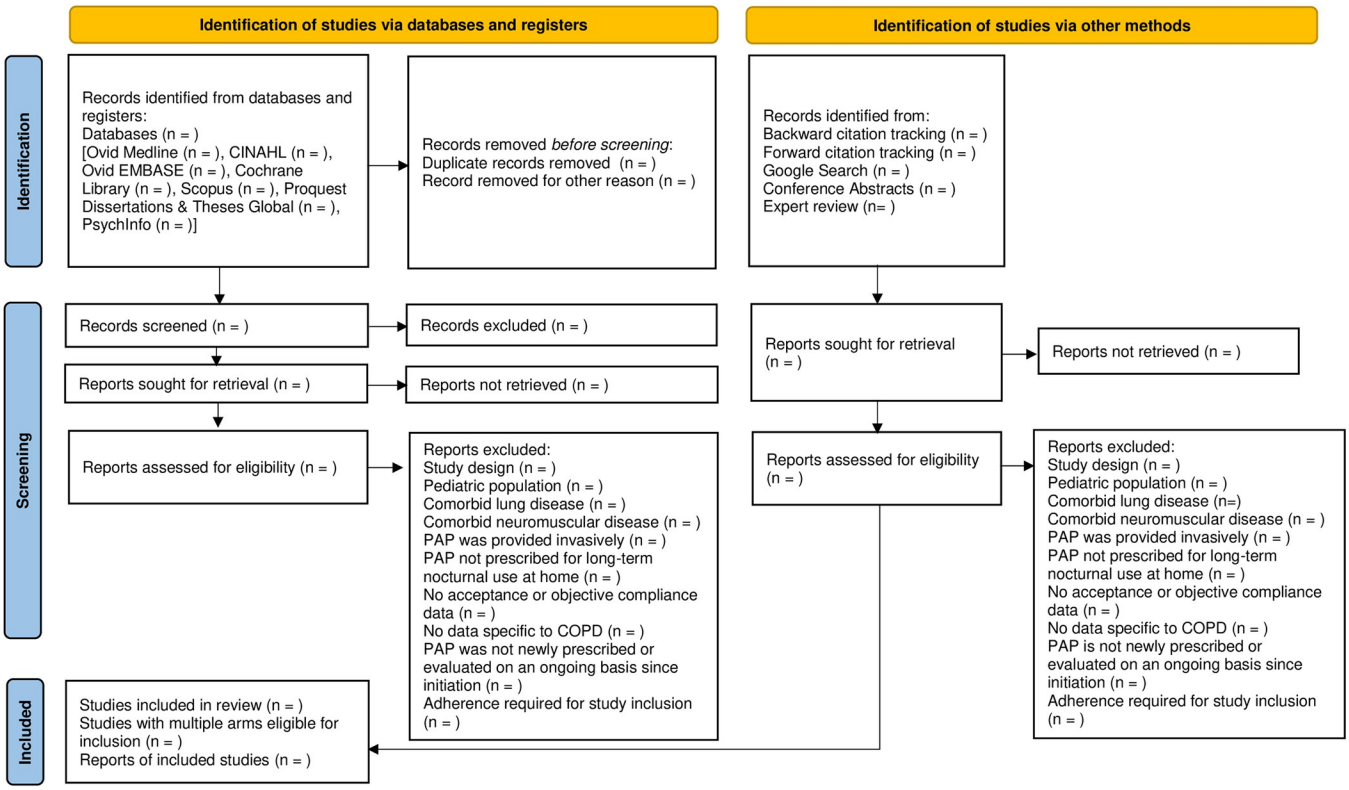

Fig 1. Anticipated flowchart of the included and excluded studies for the systematic review. The flowchart was developed following the following the Preferred Reporting Items for Systematic Reviews and Meta-analysis 2020 statement. CINAHL, Cumulative Index to Nursing and Allied Health Literature; EMBASE, Excerpta Medica Database; COPD, chronic obstructive pulmonary disease; PAP, positive airway pressure.

https://doi.org/10.1371/journal.pone.0287887.g001

Exposures. PAP treatment will be defined by the provision of noninvasive PAP therapy through a nasal or face mask. CPAP is inclusive of fixed pressure or automatic titrating modalities. NIV is inclusive of bilevel positive airway pressure (BPAP), volume assured pressure support (VAPS) or adaptive servoventilation (ASV). Studies assessing mechanical ventilation delivered through an invasive interface such as a tracheostomy will be excluded. For studies that have multiple arms that meet the inclusion criteria, each arm will be summarized as a separate study population for the primary outcomes. Sham PAP will not be incorporated into the primary analysis of acceptance and adherence, as a lower adherence is seen with sham PAP in crossover trials [28]; however, given that sham PAP treatment has also been shown to be associated with lower adherence on CPAP therapy after transition to therapeutic treatment in the general population [28], it will be included in the secondary aim which is to summarize variables that may be associated with acceptance or adherence if there is sufficient data in the study population. During the systematic review, additional exposure variables associated with acceptance or adherence to PAP treatment in multivariate analysis will be collected and summarized. These additional variables will be organized within the World Health Organization framework [23] with two additional categories: research-specific factors (e.g., whether PAP equipment was provided to participants, co-interventions in the study design) and "Other".

Comparator. Not applicable to this systematic review design.

Outcomes. Primary outcomes will be acceptance of and adherence to long-term PAP treatment. Acceptance will be defined as dichotomous (i.e., had use of therapy irrespective of adherence compared to no use of therapy) within a given time period not exceeding 1 year

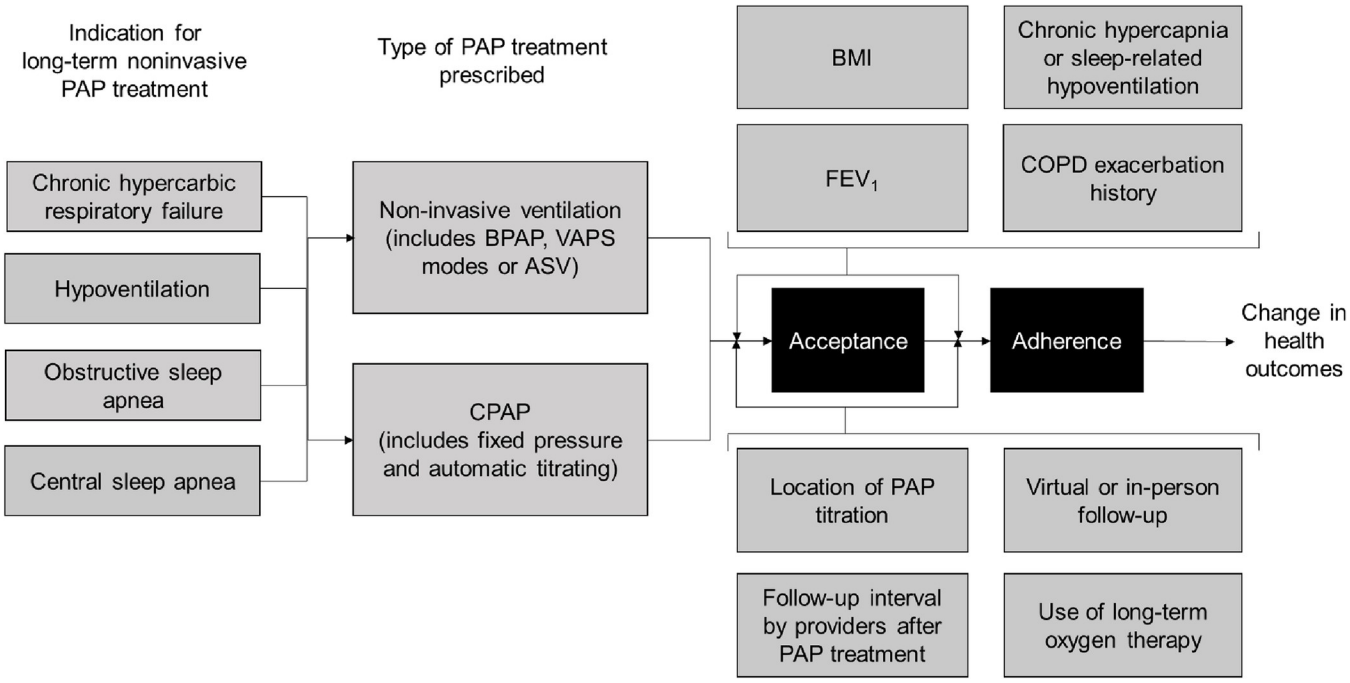

Fig 2. Logic model for summarizing the literature on PAP therapy acceptance and adherence in patients with COPD. Black boxes represent the primary outcomes of this study. Grey boxes represent prespecified clinically important subgroups that may explain some of the heterogeneity in the primary outcomes. White boxes will not be examined through this review. PAP, positive airway pressure; BPAP, bilevel positive airway pressure; VAPS, volume-assured pressure support; ASV, adaptive servoventilation; CPAP, continuous positive airway pressure; COPD, chronic obstructive pulmonary disease; BMI, body mass index; FEV1, forced expiratory volume in one second.

https://doi.org/10.1371/journal.pone.0287887.g002

from the therapy being recommended. Adherence will be determined from machine download data with a minimum of 7 days of follow-up. For studies that only report follow-up after a brief period of use, the adherence measured will be considered a proxy of long-term adherence given available evidence to suggest this in patients with OSA [29–31]. A sensitivity analysis will be conducted for adherence data collected within 1 month of initiating therapy in order to assess whether short term use is a proxy of long-term adherence in the included studies. Adherence will be defined as both dichotomous (e.g., >4 hours use per night for >70% of nights or >4 hours use per night for 5/7 days) and continuous (e.g., mean hours of use per night) where outcome measurement allows. Studies that only report adherence using subjective measures will be excluded. For a logic model, please see Fig 2. The secondary aim is to summarize known variables that are associated with either acceptance or adherence in this population.

Information sources. An experienced librarian and information specialist collaborated to design a comprehensive search strategy with terms for COPD, PAP treatment and adherence or acceptance. The search strategy (see S1 Appendix) was developed for Ovid Medline. This search will be translated into search strategies for CINAHL (EBSCOhost), Ovid EMBASE, the Wiley Cochrane Library (Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (CENTRAL)), Scopus, Proquest Dissertations & Theses Global and APA PsychInfo using the concepts of "obstructive airways disease" (e.g., COPD), "acceptance" or "compliance" or "adherence", and "noninvasive positive pressure ventilation". The search strategy will contain controlled vocabulary (e.g., Medical Subject Headings (MeSH)) and text words searches. There will be no restrictions on date of publication, publication status

or language of publication; translation services will be employed to determine relevance of non-English manuscripts.

Grey literature will be searched including citation lists from the included studies. Corresponding authors of more than one included study will be contacted regarding unpublished studies or relevant literature that may have been missed. The publication lists for the last authors on the included studies will be reviewed. Indexes of conference abstracts will be hand searched from the American Thoracic Society, Canadian Thoracic Society, and European Respiratory Society, American College of Chest Physicians, Associated Professional Sleep Societies (joint venture by the American Academy of Sleep Medicine and the Sleep Research Society), Canadian Sleep Society, and the World Sleep Society from 2018–2023. The first 10 pages of a Google Scholar search will also be reviewed for relevant studies.

Study records

Data management. The results of the searches will be imported into the Covidence software program and duplicates removed (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia). Where possible, statistical analyses will be completed using R statistical software (R Core Team, 2022) or Review Manager Software (RevMan, version 5.4, The Cochrane Collaboration, 2020).

Selection process. Two study investigators (CRL/LEM) will independently screen titles and abstracts identified by the search strategy for inclusion. If a large number of abstracts (>1000) are identified using the proposed search strategy, one study investigator will exclude obviously irrelevant studies based on title alone. Articles that are considered for inclusion by at least one author will be included in the full text review with subsequent documentation of exclusion criteria. In this phase, disagreements will be resolved by consensus or third-party involvement if consensus is not reached to establish the final list of studies to be included.

Data extraction. Data from included studies will be extracted by one of two reviewers (CRL, LEM, SWK) using a pre-designed data extraction form. The data extracted will then be independently verified for accuracy and completeness by the second author. Disagreements will be resolved by consensus through discussion or by adjudication involving a third reviewer. If relevant information is suspected to have been collected but not reported, attempts will be made to contact authors for clarification and data. See Data Extraction Form in Table 1.

Quality assessment. Two reviewers will independently complete the risk or bias/quality assessment for each included study. For randomized control trials, the Cochrane Risk of Bias tool version 2.0 will be utilized. For case-control, cohort and cross-sectional studies, the Newcastle-Ottawa Scale will be used. A summary of the quality assessment will be reported in risk of bias graphs. Disagreements in risk of bias assessments will be resolved through consensus, and if consensus cannot be reached, then using third-party adjudication.

Data synthesis

For the primary outcomes, a narrative synthesis will be performed and both study characteristics and results will be summarized in evidence tables. Following this, the data will undergo quantitative synthesis. For studies on PAP treatment acceptance or adherence, a weighted proportion or weighted average will be generated. The standard error of the weighted average will be used to derive a confidence interval, in order to inform the precision of the summary estimate.

For acceptance, the weighted proportion will subsequently be analyzed by stratifying by the two most common indications for PAP treatment, OSA and chronic hypercarbic respiratory failure, if sufficient data are available. For each subgroup analysis, the summary statistic will be

Table 1. Data extraction form.

Study Characteristics	Extracted Data
General Information	First author, publication year, country/continent/multinational, source of funding, study period, study aims and research question/outcomes measured
Study Population	*General characteristics*: mean/median age, age range, sex, ethnicity, body mass index (BMI) *COPD disease characteristics*: method of defining COPD, forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), FEV1/FVC, diffusing capacity, arterial partial pressure of carbon dioxide ($PaCO_2$), proportion with baseline $PaCO_2$ >45 mmHg, use of home oxygen, exacerbation history, health-related quality of life *Details of PAP treatment*: indication for PAP treatment, Epworth Sleepiness Scale score, details of sleep diagnostic testing and results (type, AHI or surrogate measure, oxygen desaturation index, time spent with an oxygen saturation <90%, nadir oxygen saturation, improvement in $PaCO_2$ or surrogate). *Details of PAP treatment*: including modality, settings, titration procedure or targets, mask interface type, follow-up method, frequency and duration Other Exposures: Variables associated with the primary outcome in multivariate analysis categorized as factors related to PAP indication, PAP treatment delivery or support, social and economic factors, COPD-specific variables, patient-related factors, health system and societal factors, research-specific factors or other
Study Design	Location of recruitment, patient enrollment process, sample size, inclusion and exclusion criteria, history of PAP use prior to study enrollment, how equipment for PAP was accessed (e.g. provided through the study or through insurance etc.), co-interventions, statistical methods used
Primary Outcome Measures	Acceptance, adherence
Authors Conclusions	Conclusions as reported by the authors
Gaps and Limitations Identified by Authors	Key limitations of the study as reported by the authors.

https://doi.org/10.1371/journal.pone.0287887.t001

calculated using a random-effects generic inverse-variance meta-analysis. With this analysis, evidence of statistical heterogeneity will be assessed as a p value from the Chi^2 statistic of <0.10. Statistical heterogeneity will be quantified using the I^2 summary statistic with values of <25%, 25–75% and > 75% representing low, moderate, and high degrees of heterogeneity, respectively. If the odds of acceptance are significantly different based upon whether the indication for treatment was OSA or chronic hypercarbic respiratory failure, the two groups will be analyzed for subsequent causes of heterogeneity separately; otherwise, subgroup analyses for causes of heterogeneity will be conducted on the whole population. The prespecified clinical subgroups selected through consensus by the study team members are as follows:

a. Presence of OSA or chronic hypercarbic respiratory failure as the indication for PAP treatment;

b. Commonly reported physiologic or historical factors of body mass index, forced expiratory volume in one second (FEV_1), awake hypercapnia or sleep related hypoventilation, COPD exacerbation history, long-term oxygen therapy;

c. Type of PAP treatment prescribed with a focus on CPAP or NIV;

d. Location of PAP titration (hospital/polysomnography vs home), follow-up interval, and whether follow-up included in person assessments or virtual assessments after the initial set-up.

For adherence, the outcome measure may be reported as a mean and standard deviation (SD) or a median with other measures of spread such as minimum, maximum or interquartile

range (IQR) or a proportion of adherent patients, where appropriate. If sufficient data are available for analysis of the proportions of adherent patients, a meta-analysis will be performed according to the methodology for acceptance outlined above. For adherence, where the outcome data are reported as a mean and SD or a median with measures of spread, the following analytic techniques will additionally apply. For consistency in reporting into figures, studies with outcomes reported using a median for non-normal distribution will be transformed using the method by Wan *et al.* [32] and Hozo *et al.* [33] to estimate a mean and standard error. The summary effect estimate; however, will be obtained by applying a meta-analysis using a medians-based approach, rather than a transformational method [34]. The use of this analysis does not provide an estimate of between-study heterogeneity; therefore, between-study heterogeneity will be assessed by stratifying the analysis of the difference in medians or means. Initially, the analysis of the weighted averages will be stratified by indication, either OSA or chronic hypercarbic respiratory failure. If it is medians or a mixture of medians and means measured, the data will be synthesized for these subgroups using the quantile estimation method to compare the difference of medians [35]. If means and SD are available for all studies, the summary statistic of a weighted mean difference will be calculated using a random-effects generic inverse-variance meta-analysis as per in the aforementioned methodology. After the weighted mean or median difference between the two groups is calculated, a Z-statistic will be applied. If these summary effect estimates are significantly different, the data will be further analyzed by stratifying the remaining subgroups within each indication. If there is no difference between these two groups, then the data will be analyzed as a whole through stratified analysis along the aforementioned relevant clinical subgroups. Each subgroup analysis will be examined to see if heterogeneity of the primary outcomes is explained by differences in subgroups prespecified below when the Chi^2 distributions are compared using the degrees of freedom for between groups. For each analysis, a funnel plot will be constructed to identify the presence of publication bias if there are more than 10 included studies [26]. A sensitivity analysis will be used to assess the robustness of the results given the inclusion of various study types.

The secondary aim of this study will be to summarize variables found in studies to be associated in multivariate analysis with acceptance or adherence that could explain heterogeneity in the primary outcomes beyond the categories that were prespecified by the study team. For these variables, a narrative synthesis will be initially performed. Attempts will be made to dichotomize variables where there are multiple comparators or definitions (e.g., varying definitions or labels of the exposure rural versus urban). Where this synthesis is not possible, separate groups will be reported. The variables identified will be allocated into prespecified subcategories as previously described:

a. Factors associated with the indication for PAP treatment or variables associated with COPD;

b. Factors associated with PAP treatment delivery or support;

c. Social and economic factors;

d. Patient-related factors;

e. Health system/societal factors;

f. Research-specific factors;

g. Other factors.

Where possible, data for the secondary aim will undergo quantitative synthesis where the exposure and comparator have sufficient data that have been similarly defined (e.g., rural

exposure compared to urban exposure). A similar statistical approach to the analysis of the secondary outcomes will be undertaken as compared to the primary outcomes, depending on whether means, medians or proportions are reported. A pooled odds ratio or relative risk or a mean difference will be used to generate summary estimates where there is sufficient outcome data. No subgroup analyses will be conducted on the secondary outcome. Where it is not possible to synthesize the data into a meta-analysis due to high heterogeneity (I^2>75%), lack of similarity in the way the exposure and comparator have been defined, differences in the population or inability to compare study designs, effect direction plots or forest plots will be used to synthesize the secondary outcomes.

A formal method of documenting confidence in the cumulative estimate (such as GRADE) will not be incorporated as the utility of this systematic review will depend on the health care context.

Timeline

We anticipate finishing the search, screening, data extraction and synthesis by May 2023. Prior to completing the data synthesis, the search will be updated to ensure that all relevant literature has been captured prior to finalizing the study results.

Discussion

This review protocol is novel in that it frames a methodological approach synthesizing the acceptance of and adherence with a complex intervention for which there is not a good comparison group. The strengths of this study are the methodological rigour with a registered and published protocol including detailed reporting of the outcomes and anticipated synthesis of the available data. The study population is well defined, as is the intervention being assessed. The searches for relevant studies will be comprehensive to reduce publication bias. The synthesis of the acceptance and adherence of PAP treatment across indications and interventions will allow for a detailed summary of the evidence. The pre-specified statistical analysis plan will summarize the measures of adherence and acceptance without a comparator, and still explore clinically relevant subgroups within the study population as a cause of heterogeneity in the primary outcomes that would allow for clinically meaningful interpretation of the results. A strength of this study is the additional effort to summarize exposure variables associated with the primary outcomes that were not prespecified by the study team in an effort to highlight any areas for future work going forward to explore heterogeneity in the primary outcomes.

Despite significant effort to ensure a strong methodological approach to this review, several study limitations are anticipated. The literature will be focused on specific indications and subgroups of clinical interest such as chronic hypercarbic respiratory failure in patients with COPD. This may limit generalizability of the synthesis results to the broader COPD population or to certain types of PAP treatment and reduce the value of efforts to quantitatively synthesize these data. Patients with overlapping indications for treatment may be underrepresented in this data synthesis. The statistical analysis may be challenging due to the various measures through which the primary outcomes of the study will be reported. Secondary variables are anticipated to also have variable definitions, which may preclude meaningful synthesis of the data. In anticipation of this, the qualitative and quantitative syntheses were developed to be comprehensive.

Conclusion

To our knowledge, this will be the first systematic review to summarize data on acceptance of and adherence to PAP treatment in patients with COPD. Overall, the use of PAP treatment

comes with a unique set of challenges. Through this protocol work, a clear methodology for a comprehensive and transparent systematic review of the existing literature on PAP acceptance and adherence in patients with COPD has been outlined. The prespecified data synthesis accounts for anticipated challenges with variability in measurement and anticipated analytic challenges of summarizing success with a complex intervention in a heterogeneous study population with heterogeneous measures of the primary outcomes. This review will provide a framework for strong methodological rigour in the synthesis of data on PAP treatment acceptance and adherence in patients with COPD.

Supporting information

S1 Checklist. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: Recommended items to address in a systematic review protocol*.
(PDF)

S1 Appendix. Search strategy for OVID Medline.
(DOCX)

Acknowledgments

We acknowledge the contributions of Mr. Scott W. Kirkland (SWK) who will contribute to data extraction and synthesis in the proposed systematic review.

Author Contributions

Formal analysis: Linn E. Moore.

Methodology: Cheryl R. Laratta, Linn E. Moore, Rachel Jen, Sandra M. Campbell, Joanna E. MacLean, Sachin R. Pendharkar, Brian H. Rowe.

Writing – original draft: Cheryl R. Laratta.

Writing – review & editing: Cheryl R. Laratta, Linn E. Moore, Rachel Jen, Sandra M. Campbell, Joanna E. MacLean, Sachin R. Pendharkar, Brian H. Rowe.

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Appendix 3: Additional Files for Systematic Review (Search Strategy, Adapted Risk of Bias Criteria, Supplemental Methodology, Supplemental Results)

Appendix 3: Table of Contents

1

Supplement 1 (S1): Detailed search strategy

Ovid MEDLINE(R) ALL <1946 to August 18, 2022>

#	Search Statement	Results
1	Lung Diseases, Obstructive/	18267
2	exp Pulmonary Disease, Chronic Obstructive/	64227
3	emphysema*.mp.	38586
4	(chronic* adj3 bronchitis*).mp.	11737
5	(obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)).mp.	132722
6	(COPD or COAD or COBD or AECB).mp.	56347
7	or/1-6	176065
8	Respiratory Therapy/	6960
9	respiration, artificial/ or noninvasive ventilation/ or positive-pressure respiration/ or continuous positive airway pressure/ or intermittent positive-pressure breathing/ or intermittent positive-pressure ventilation/	82080
10	((bipap or nippv or nppv or niv or niav or cpap or ippb or ippv or peep or BPAP or AVAPS or iVAPS or VAPS or PVC or PC or autoPap or APAP or AVS or autosv) not acute).mp.	105840
11	(positive* adj3 pressur* adj5 (ventilat* or respir* or breath* or airway* or continuous or biphasic)).tw.	22854
12	((night* or non-invasive or noninvasive or nocturnal or domestic* or domicil* or home) adj3 ventilat*).mp.	12635
13	or/8-12	191339
14	7 and 13	10222
15	exp "Patient Acceptance of Health Care"/	169714
16	exp "Treatment Adherence and Compliance"/	270649
17	exp Patient Compliance/	84471
18	exp Patient Dropouts/	8387
19	exp Patient Satisfaction/	97925

20	exp Patient Adherence/	84471
21	(((user or patient or treatment* or intervention* or therap*) adj3 (accept* or discontinu* or toleran* or "non adher*" or adher* or nonadher* or complian* or refusal* or refuse or refusing or dropout* or terminat* or abandon* or uptake)) or ("hours of use" or "length of use" or "frequency of use")).mp.	275053
22	or/15-21	402555
23	7 and 13 and 22	440
24	limit 23 to "all child (0 to 18 years)"	45
25	limit 24 to "all adult (19 plus years)"	32
26	24 not 25	13
27	23 not 26	427

3

Embase <1974 to 2022 August 18>

#	Search Statement	Results
1	Lung Diseases, Obstructive/	410
2	exp chronic obstructive lung disease/	159209
3	emphysema*.mp.	52136
4	(chronic* adj3 bronchitis*).mp.	19303
5	(obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)).mp.	240932
6	(COPD or COAD or COBD or AECB).mp.	105556
7	or/1-6	303363
8	respiratory care/	4274
9	respiration, artificial/ and (night* or non-invasive or noninvasive or nocturnal or domestic* or domicil* or home or non-hospital).mp.	15558
10	noninvasive ventilation/ or positive-pressure respiration/ or continuous positive airway pressure/ or intermittent positive-pressure breathing/ or intermittent positive-pressure ventilation/	25047
11	((bipap or nippv or nppv or niv or niav or cpap or ippb or ippv or peep or BPAP or AVAPS or iVAPS or VAPS or PVC or PC or autoPap or APAP or AVS or autosv) not acute).ti,ab,kw.	153354
12	(positive* adj3 pressur* adj5 (ventilat* or respir* or breath* or airway* or continuous or biphasic)).tw.	32862
13	((night* or non-invasive or noninvasive or nocturnal or domestic* or domicil* or home) adj3 ventilat*).mp.	27631
14	or/8-12	202064
15	patient attitude/ or patient compliance/ or patient dropout/ or patient participation/ or patient preference/ or patient satisfaction/ or refusal to participate/ or treatment interruption/ or treatment refusal/	429937
16	(((user or patient or treatment* or intervention* or therap* or consumer*) adj3 (accept* or discontinu* or toleran* or "non adher*" or adher* or nonadher* or complian* or refusal* or refuse or refusing or dropout* or terminat* or abandon* or uptake)) or ("hours of use" or "length of use" or "frequency of use")).ti,ab,kw.	272435

4

17	15 or 16	645528
18	7 and 14 and 17	827
19	remove duplicates from 18	821
20	limit 19 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)	47
21	limit 20 to (adult <18 to 64 years> or aged <65+ years>)	18
22	20 not 21	29
23	19 not 22	792

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APA PsycInfo <1806 to August Week 3 2022>

#	Search Statement	Results
1	("chronic obstructive pulmonary disease" or COPD or COAD or COBD or AECB or emphysema*).mp.	3150
2	((chronic* adj3 bronchitis*) or (obstruct* adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*))).mp.	3677
3	exp Chronic Obstructive Pulmonary Disease/	1664
4	1 or 2 or 3	4189
5	(positive* adj3 pressur* adj5 (ventilat* or respir* or breath* or airway* or continuous or biphasic)).tw.	1200
6	((night* or non-invasive or noninvasive or nocturnal or domestic* or domicil* or home) adj3 ventilat*).mp.	362
7	((bipap or nippv or nppv or niv or niav or cpap or ippb or ippv or peep or BPAP or AVAPS or iVAPS or VAPS or (PVC not catheter*) or (PC not (contract* or "palliative" or pancreat* or "primary care")) or autoPap or APAP or (AVS not (crime* or vehicle*)) or autosv) not acute).mp.	6080
8	5 or 6 or 7	6791
9	"overlap syndrome".mp.	60
10	8 or 9	6848
11	(((user or patient or treatment* or intervention* or therap* or consumer*) adj3 (accept* or discontinu* or toleran* or "non adher*" or adher* or nonadher* or complian* or refusal* or refuse or refusing or dropout* or terminat* or abandon* or uptake)) or ("hours of use" or "length of use" or "frequency of use")).mp.	75176

12	exp Client Satisfaction/	6140
13	exp Client Attitudes/ or exp Treatment Compliance/ or exp Compliance/	45260
14	exp Treatment Dropouts/	2724
15	11 or 12 or 13 or 14	100738
16	10 and 15	465
17	limit 16 to (100 childhood <birth to age 12 yrs> or 120 neonatal <birth to age 1 mo> or 140 infancy <2 to 23 mo> or 160 preschool age <age 2 to 5 yrs> or 180 school age <age 6 to 12 yrs> or 200 adolescence <age 13 to 17 yrs>)	39
18	limit 17 to ("300 adulthood <age 18 yrs and older>" or 320 young adulthood <age 18 to 29 yrs> or 340 thirties <age 30 to 39 yrs> or 360 middle age <age 40 to 64 yrs> or "380 aged <age 65 yrs and older>" or "390 very old <age 85 yrs and older>")	14
19	17 not 18	25
20	16 not 19	440
21	remove duplicates from 20	439

EBSCO CINAHL with Full Text Searched August 22, 2022

#	Query	Results
S1	(MH "Lung Diseases, Obstructive+") OR (MH "Pulmonary Disease, Chronic Obstructive+")	66,800
S2	emphysema	5,617
S3	chronic* N3 bronchitis*	1,406
S4	(obstruct* N3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*))	42,152
S5	(COPD or COAD or COBD or AECB)	19,601
S6	S1 OR S2 OR S3 OR S4 OR S5	86,117
S7	(MH "Respiratory Therapy+")	54,802
S8	(MH "Respiration, Artificial+")	37,371
S9	(MH "Positive-Pressure Respiration, Intrinsic") OR (MH "Continuous Positive Airway Pressure") OR (MH "Intermittent Positive Pressure Breathing") OR (MH "Intermittent Positive Pressure Ventilation")	6,629
S10	((bipap or nippv or nppv or niv or niav or cpap or ippb or ippv or peep or BPAP or AVAPS or iVAPS or VAPS or PVC or PC or autoPap or APAP or AVS or autosv) not acute)	25,004
S11	(positive* N3 pressur* N5 (ventilat* or respir* or breath* or airway* or continuous or biphasic))	12,148
S12	((night* or non-invasive or noninvasive or nocturnal or domestic* or domicil* or home) N3 ventilat*	5,017
S13	S7 OR S8 OR S9 OR S10 OR S11 OR S12	77,944
S14	(MH "Patient Compliance+")	55,950
S15	(MH "Patient Dropouts")	2,292
S16	(MH "Patient Satisfaction+")	62,396
S17	(MH "Treatment Termination") OR (MH "Treatment Refusal+")	7,363
S18	(((user or patient or treatment* or intervention* or therap*) N3 (accept* or discontinu* or toleran* or "non adher*" or adher* or nonadher* or complian* or refusal* or refuse or refusing or dropout* or terminat* or abandon* or uptake)) or ("hours of use" or "length of use" or "frequency of use"))	117,013
S19	S14 OR S15 OR S16 OR S17 OR S18	188,292

S20	S6 AND S13 AND S19	342
S21	S6 AND S13 AND S19 [Limit to children]	36
S22	S6 AND S13 AND S19 [s21 limited to adults]	15
S23	s21 NOT s22	21
S24	s20 NOT s23 [not children not (children and adults0	321

9

SCOPUS (excluding Medline and EMBASE) Searched August 18, 2022 Results =58

(((((TITLE-ABS-KEY (emphysema* OR (chronic* W/3 bronchitis*) OR (obstruct* W/3 (pulmonary OR lung* OR airway* OR airflow* OR bronch* OR respirat*)) OR copd OR coad OR cobd OR aecb)) AND ((TITLE-ABS (((bipap OR nippv OR nppv OR niv OR niav OR cpap OR ippb OR ippv OR peep OR bpap OR avaps OR ivaps OR vaps OR (pvc AND NOT catheter*) OR (pc AND NOT (contract* OR "palliative" OR pancreat* OR "primary care")) OR autopap OR apap OR (avs AND NOT (crime* OR vehicle*)) OR autosv) not AND acute))) OR (TITLE-ABS-KEY (((night* OR non-invasive OR noninvasive OR nocturnal OR domestic* OR domicil* OR home) W/3 ventilat*)) OR TITLE-ABS-KEY ((positive* W/3 pressur* W/5 (ventilat* OR respir* OR breath* OR airway* OR continuous OR biphasic)))))) OR (TITLE-ABS-KEY ("overlap syndrome"))) AND ((TITLE-ABS-KEY (((user OR patient OR treatment* OR intervention* OR therap* OR consumer*) W/3 (accept* OR discontinu* OR toleran* OR "non adher*" OR adher* OR nonadher* OR complian* OR refusal* OR refuse OR refusing OR dropout* OR terminat* OR abandon* OR uptake)))) OR (TITLE-ABS-KEY (("hours of use" OR "length of use" OR "frequency of use")))))) AND NOT (((TITLE-ABS-KEY (pediatric* OR paediatric* OR child* OR newborn* OR congenital* OR infan* OR baby OR babies OR neonat* OR "pre-term" OR preterm OR "premature birth*" OR nicu OR preschool* OR "pre-school*" OR kindergarten* OR "elementary school*" OR "nursery school*" OR schoolchild* OR toddler* OR boy OR boys OR girl* OR "middle school*" OR pubescen* OR juvenile* OR teen* OR youth* OR "high school*" OR adolesc* OR prepubesc* OR "pre-pubesc*") OR SRCTITLE (child* OR pediatric* OR paediatric* OR adolescent))) AND NOT ((TITLE-ABS-KEY (pediatric* OR paediatric* OR child* OR newborn* OR congenital* OR infan* OR baby OR babies OR neonat* OR "pre-term" OR preterm OR "premature birth*" OR nicu OR preschool* OR "pre-school*" OR kindergarten* OR "elementary school*" OR "nursery school*" OR schoolchild* OR toddler* OR boy OR boys OR girl* OR "middle school*" OR pubescen* OR juvenile* OR teen* OR youth* OR "high school*" OR adolesc* OR prepubesc* OR "pre-pubesc*") OR SRCTITLE (child* OR pediatric* OR paediatric* OR adolescent)) AND TITLE-ABS-KEY (adult* OR mature OR elder* OR "senior citizen*" OR parent* OR grandparent* OR mother* OR father* OR grandmother* OR grandfather*)))) AND NOT ((INDEX (medline OR embase)))

10

ProQuest Dissertations and Theses Global Searched August 18, 2022 Results = 18

((ti("overlap syndrome") OR ab("overlap syndrome")) OR ((ti((autosv OR bipap OR nippv OR nppv OR niv OR niav OR cpap OR ippb OR ippv OR peep OR bpap OR avaps OR ivaps OR vaps OR (pvc NOT catheter*) OR (pc NOT (contract* OR "palliative" OR pancreat* OR "primary care")) OR autopap OR apap OR (avs NOT (crime* OR vehicle*)) NOT acute)) OR (ti((positive* NEAR/3 pressur* NEAR/5 (ventilat* OR respir* OR breath* OR airway* OR continuous OR biphasic))) OR ab((positive* NEAR/3 pressur* NEAR/5 (ventilat* OR respir* OR breath* OR airway* OR continuous OR biphasic)))) OR (ti((night* OR noninvasive OR nocturnal OR domestic* OR domicil* OR home) NEAR/3 ventilat*) OR ab((night* OR noninvasive OR nocturnal OR domestic* OR domicil* OR home) NEAR/3 ventilat*))) AND (ti(((emphysema* OR (chronic* NEAR/3 bronchitis*) OR (obstruct* NEAR/3 (pulmonary OR lung* OR airway* OR airflow* OR bronch* OR respirat*)) OR copd OR coad OR cobd OR aecb))) OR ab(((emphysema* OR (chronic* NEAR/3 bronchitis*) OR (obstruct* NEAR/3 (pulmonary OR lung* OR airway* OR airflow* OR bronch* OR respirat*)) OR copd OR coad OR cobd OR aecb)))))) AND ((ti(((user OR patient OR treatment* OR intervention* OR therap* OR consumer*) NEAR/3 (accept* OR discontinu* OR toleran* OR ("non adherence" OR "non adherent" OR "non adherents") OR adher* OR nonadher* OR complian* OR refusal* OR refuse OR refusing OR dropout* OR terminat* OR abandon* OR uptake))) OR ab(((user OR patient OR treatment* OR intervention* OR therap* OR consumer*) NEAR/3 (accept* OR discontinu* OR toleran* OR ("non adherence" OR "non adherent" OR "non adherents") OR adher* OR nonadher* OR complian* OR refusal* OR refuse OR refusing OR dropout* OR terminat* OR abandon* OR uptake)))) OR (ti(("hours of use" OR "length of use" OR "frequency of use")) OR ab(("hours of use" OR "length of use" OR "frequency of use")))) NOT (noft(child*) or noft(infant) or noft(youth*) or noft(teenager*) or noft(adolescen*) or noft(pediatric*))

Cochrane Library Searched August 20, 2022

ID	Search	Hits
#1	MeSH descriptor: [Lung Diseases, Obstructive] explode all trees	20851
#2	MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees	6351
#3	(emphysema* or "chronic bronchitis" or (obstruct* NEAR 3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*))):ti,ab,kw	3591
#4	(COPD or COAD or COBD or AECB):ti,ab,kw	18047
#5	#1 or #2 or #3 or #4	34661
#6	MeSH descriptor: [Respiratory Therapy] explode all trees	8972
#7	MeSH descriptor: [Respiration, Artificial] explode all trees	6974
#8	MeSH descriptor: [Noninvasive Ventilation] explode all trees	340
#9	MeSH descriptor: [Positive-Pressure Respiration, Intrinsic] explode all trees	28
#10	MeSH descriptor: [Continuous Positive Airway Pressure] explode all trees	1290
#11	MeSH descriptor: [Intermittent Positive-Pressure Breathing] explode all trees	63
#12	MeSH descriptor: [Intermittent Positive-Pressure Ventilation] explode all trees	268
#13	(((bipap or nippv or nppv or niv or niav or cpap or ippb or ippv or peep or BPAP or AVAPS or iVAPS or VAPS or PVC or PC or autoPap or APAP or AVS or autosv) not (acute))):ti,ab,kw	25114
#14	((positive* NEAR 3 pressur* NEAR 5 (ventilat* or respir* or breath* or airway* or continuous or biphasic))):ti,ab,kw	42
#15	(((night* or non-invasive or noninvasive or nocturnal or domestic* or domicil* or home) NEAR 3 ventilat*)):ti,ab,kw	303
#16	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15	32462
#17	MeSH descriptor: [Patient Acceptance of Health Care] explode all trees	18557
#18	MeSH descriptor: [Patient Compliance] explode all trees	12696
#19	MeSH descriptor: [Patient Dropouts] explode all trees	2006
#20	MeSH descriptor: [Patient Satisfaction] explode all trees	12816
#21	MeSH descriptor: [Patient Compliance] explode all trees	12696
#22	MeSH descriptor: [Treatment Adherence and Compliance] explode all trees	30335
#23	#17 or #18 or #19 or #20 or #21 or #22	30335
#24	#5 and #16 and #23	57

PROSPERO Searched August 20, 2022

Line	Search for	Hits
#1	MeSH DESCRIPTOR Lung Diseases, Obstructive EXPLODE ALL TREES	1149
#2	pulmonary disease, chronic obstructive	0
#3	MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive EXPLODE ALL TREES	589
#4	emphysema* or "chronic bronchitis" or "obstructive pulmonary" or "obstruct* lung*" or "obstruct* airway*" or "obstruct* airflow*" or	

"obstruct* bronch*" or "obstruct* respir*" or COPD or COAD or COBD or AECB 2722

#5 #1 OR #2 OR #3 OR #4 OR #4 3220

#6 MeSH DESCRIPTOR Respiratory Therapy EXPLODE ALL TREES 746

#7 MeSH DESCRIPTOR Respiration, Artificial EXPLODE ALL TREES 532

#8 MeSH DESCRIPTOR Noninvasive Ventilation EXPLODE ALL TREES 78

#9 MeSH DESCRIPTOR Positive-Pressure Respiration EXPLODE ALL TREES 141

#10 MeSH DESCRIPTOR Continuous Positive Airway Pressure EXPLODE ALL TREES 94

#11 MeSH DESCRIPTOR Intermittent Positive-Pressure Breathing EXPLODE ALL TREES 0

#12 (bipap or nippv or nppv or niv or niav or cpap or ippb or ippv or peep or BPAP or AVAPS or iVAPS or VAPS or PVC or PC or autoPap or APAP or AVS or autosv) not (acute) 1340

#13 "Positive pressure" and (ventilat* or respir* or breath* or airway* or continuous or biphasic) 278

#14 (night* or non-invasive or noninvasive or nocturnal or domestic* or domicil* or home) and (ventilat* 1029

#15 #6 or #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 2760

#16 MeSH DESCRIPTOR Treatment Adherence and Compliance EXPLODE ALL TREES 1283

#17 MeSH DESCRIPTOR Patient Compliance EXPLODE ALL TREES 422

#18 MeSH DESCRIPTOR Patient Dropouts EXPLODE ALL TREES 21

#19 MeSH DESCRIPTOR Patient Satisfaction EXPLODE ALL TREES 284

#20 MeSH DESCRIPTOR Patient Compliance EXPLODE ALL TREES 422

#21 (((user or patient or treatment* or intervention* or therap*) and (accept* or discontinu* or toleran* or "non adher*" or adher* or nonadher* or complian* or refusal* or refuse or refusing or dropout* or terminat* or abandon* or uptake)) or ("hours of use" or "length of use" or "frequency of use")) 34379

#22 #16 or #17 OR #18 OR #19 OR #20 OR #21 34912

#23 #5 AND #15 AND #22 101

#24 pediatric* OR paediatric* OR child* OR newborn* OR congenital* OR infan* OR baby OR babies OR neonat* OR "pre-term" OR preterm OR "premature birth*" OR nicu OR preschool* OR "pre-school*" OR kindergarten* OR "elementary school*" OR "nursery school*" OR schoolchild* OR toddler* OR boy OR boys OR girl* OR "middle school*" OR pubescen* OR juvenile* OR teen* OR youth* OR "high school*" OR adolesc* OR prepubesc* OR "pre-pubesc*" 57186

#25 (adult* OR mature OR elder* OR "senior citizen*" OR parent* OR grandparent* OR mother* OR father* OR grandmother* OR grandfather*) AND (pediatric* OR paediatric* OR child* OR newborn* OR congenital* OR infan* OR baby OR babies OR neonat* OR "pre-term" OR preterm OR "premature birth*" OR nicu OR preschool*

	OR "pre-school*" OR kindergarten* OR "elementary school*" OR "nursery school*" OR schoolchild* OR toddler* OR boy OR boys OR girl* OR "middle school*" OR pubescen* OR juvenile* OR teen* OR youth* OR "high school*" OR adolesc* OR prepubesc* OR "pre-pubesc*")	35275
#26	#24 NOT #25	21911
#27	#23 NOT #26	88

Supplement 2: Adapted risk of bias criteria

1) **Risk of Bias criteria for systematic reviews and randomized interventional trials:** RoB Cochrane v. 2.0

Reference: Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898.

Notes:
For domain 2: use "Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)"

2) **Risk of Bias criteria for observational studies: Newcastle Ottawa Scale– cohort**

Reference: Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Available from: Ottawa Hospital Research Institute (ohri.ca). Accessed January 13, 2024.

Adapted criteria as follows, as there was often not a comparator arm:
Selection

1) Representativeness of the exposed cohort
   a) Truly representative **(1 star)** – e.g. consecutive sampling
   b) Somewhat representative **(1 star)** – all patients within a specific time period
   c) Selected group
   d) No description of the derivation of the cohort

2) Selection of the non-exposed cohort. If the study only includes a single cohort, mark this additional box on the spreadsheet (1 cohort)
   a. Drawn from the same community as the exposed cohort **(1 star).** If there is only one cohort, select this if there were specific inclusion and exclusion criteria for the use of PAP therapy using patient level information (not administrative coding), either using sleep diagnostic testing for sleep-related breathing disorders or specific criteria for chronic hypercarbic respiratory failure
   b. Drawn from a different source
   c. No description of the derivation of the non-exposed cohort

3) Ascertainment of exposure
   a. Secure record (e.g. PAP prescription on medical record, picked up equipment, machine download evidence that machine was used) **(1 star)**
   b. Structured interview **(1 star)**
   c. Written self-report
   d. No description
   e. Other

4) Demonstration that the outcome of interest was not present at the start of the study
   a. Yes **(1 star)** – e.g. excluded patients with prior use of PAP therapy, or only including patients with their first prescription
   b. No

Comparability ***(2 stars)***

1) Comparability of cohorts on the basis of the design or analysis controlled for confounders. If the study only includes a single cohort, answer the following if the study *reports* for any of these factors within the single cohort
    a. The study controls for age, sex **(1 star)**
    b. The study controls for other factors (some measurement or reporting of FEV1 or GOLD stage for COPD in the inclusion/exclusion, patient characteristics, or reporting of acceptance or adherence) **(1 star)**
    c. Cohorts are not comparable on the basis of the design or analysis controlled for confounders

Outcome

1) Assessment of outcome
    a. Independent blind assessment (machine download or did not pick up equipment etc) **(1 star)**
    b. Record linkage **(1 star)**
    c. Self-report
    d. No description
    e. Other

2) Was follow-up long enough for outcomes to occur
    a. Anytime 14 days or greater Yes **(1 star)**
    b. No

3) Was follow-up long enough for outcomes to occur
    a. Anytime 28 days or greater Yes **(1 star)**
    b. No

4) Adequacy of follow-up cohorts
    a. Complete follow-up – all subjects accounted for **(1 star)**
    b. Subjects lost to follow-up unlikely to introduce bias – number lost less than or equal to 20% or description of those lost suggested no different from those followed **(1 star)**
    c. Follow-up rate <80% and no description of those lost OR did not incorporate non-adherent patients who dropped out into compliance reporting
    d. No statement

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor):

Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain.

Section S3: Supplemental Methodology

S3.1 Detailed definitions of the pre-specified covariates

Pre-specified covariates and their respective definitions are as follows:

1. Indication for PAP therapy: Studies were grouped by the indication reflective of >70% of participants within the study or arm of the study as SRBD or CHRF secondary to COPD. All others were categorized as "other". For studies that reported on CHRF in patients with an FEV_1 <50% and did not exclude based upon an elevated body mass index (BMI), they remained in the CHRF category if one SD above the mean or quartile 3 (Q3) of the interquartile range (IQR) did not exceed 36 kg/m^2.
2. Hypercapnia: studies were grouped if all participants had a $PaCO_2 \geq 45$ mmHg vs other.
3. Severity of COPD: studies were grouped by whether one SD above the mean/or above the Q3 median FEV1 was <50% or GOLD III or IV disease was specified vs other
4. Type of PAP therapy: NIV vs CPAP vs mixed modalities/not reported
5. High pressure NIV: studies were grouped by whether the inspired positive airway pressure (IPAP) was >20 cmH2O and expired positive airway pressure (EPAP) <10 cmH2O vs either IPAP ≤20 cmH2O or EPAP ≥10 cmH3O vs IPAP/EPAP not reported and/or CPAP was an intervention.
6. Obesity: Studies were grouped by whether one SD above the mean or Q3 of the median BMI was ≥30 kg/m^2 vs <30 kg/m^2 vs not reported.
7. Timing of initial follow-up: studies were grouped by the initial follow-up visit being within one week vs within 6 weeks vs within 3 months vs ≥6 months or not reported.
8. Follow-up included home visits: Groups included yes vs either no or not reported.
9. Stability of COPD at time of initiating long-term PAP therapy: Studies were grouped as to whether this occurred immediately following an exacerbation vs in chronic stable state vs either a combination or not reported.
10. Age: Used as a continuous measure.
11. Sex: Used as a continuous measure.
12. Time: Used as a continuous measure and as a categorical measure

S4: Supplemental Results

Supplemental Figures:

Figure A1: Acceptance within one year with time as a categorical measure

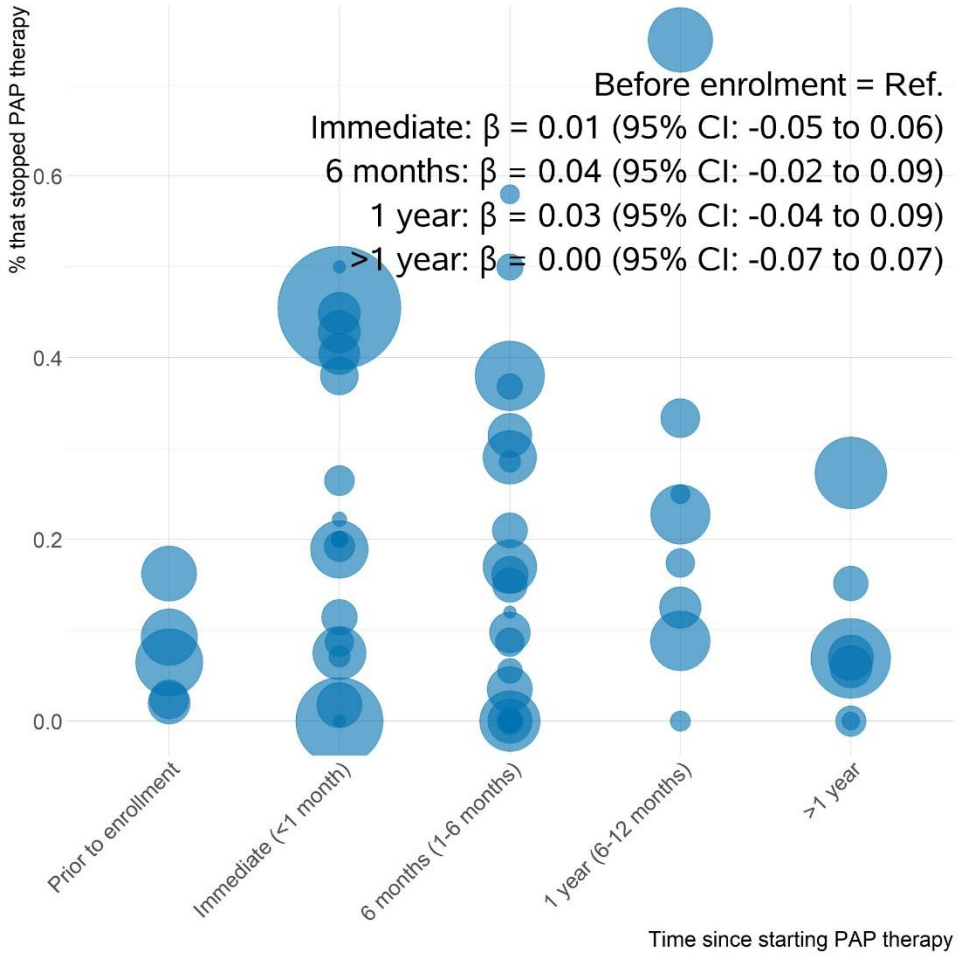

Figure A2: Adherence with time as a continuous measure

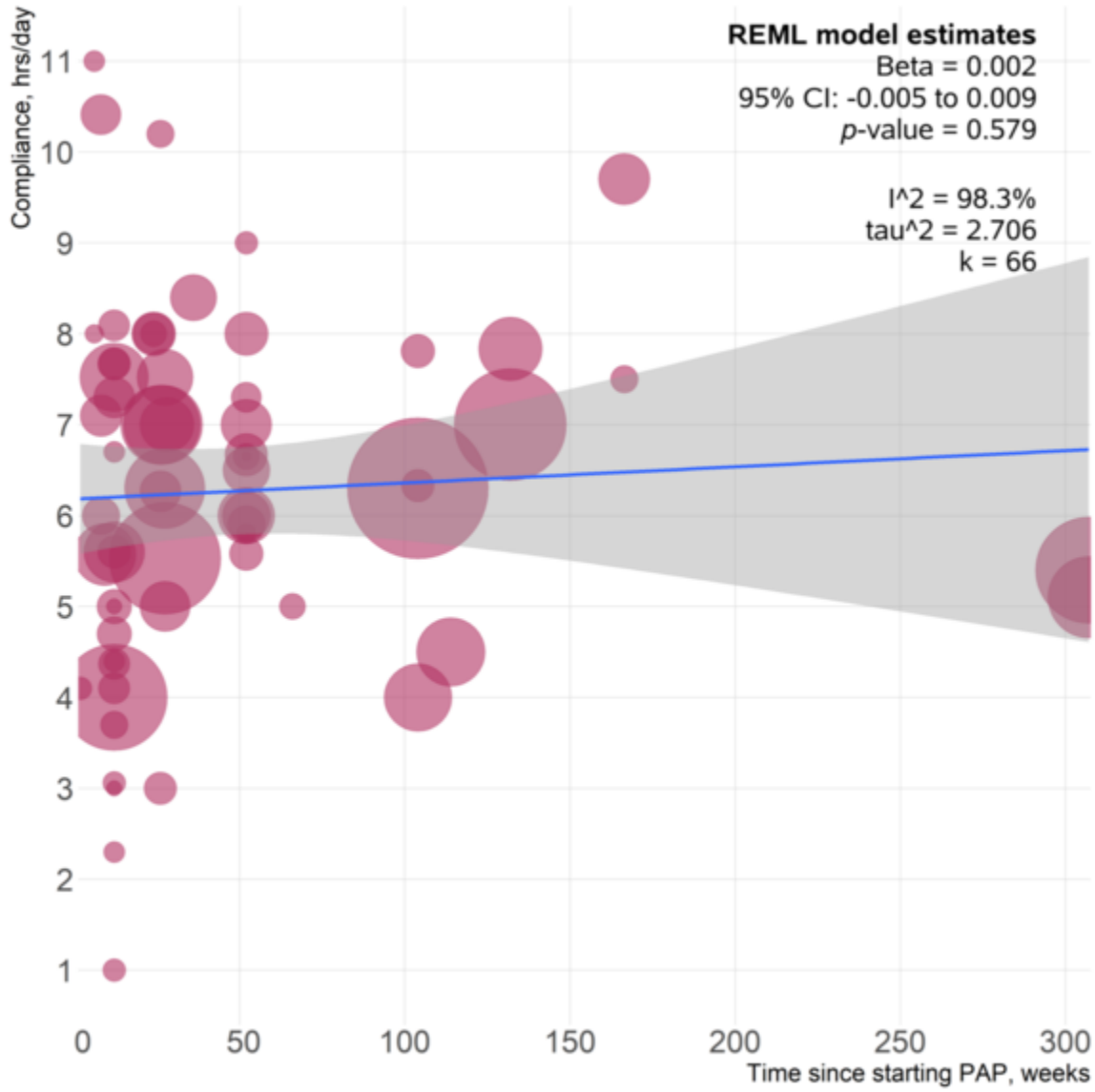

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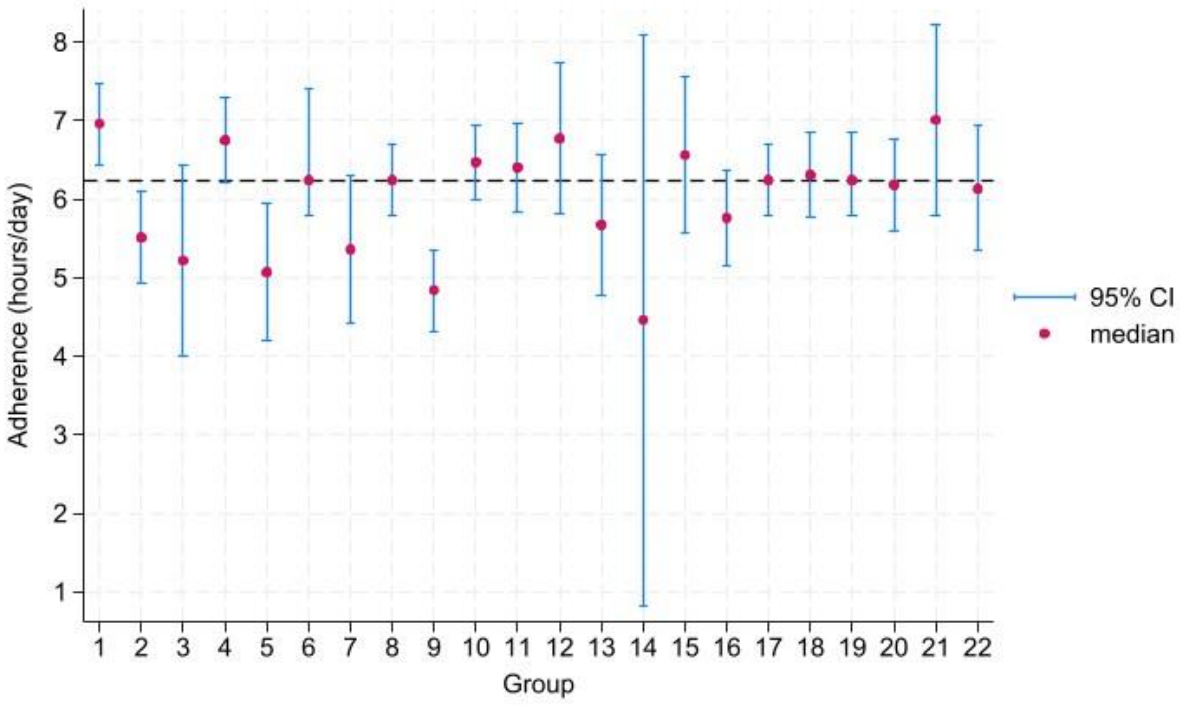
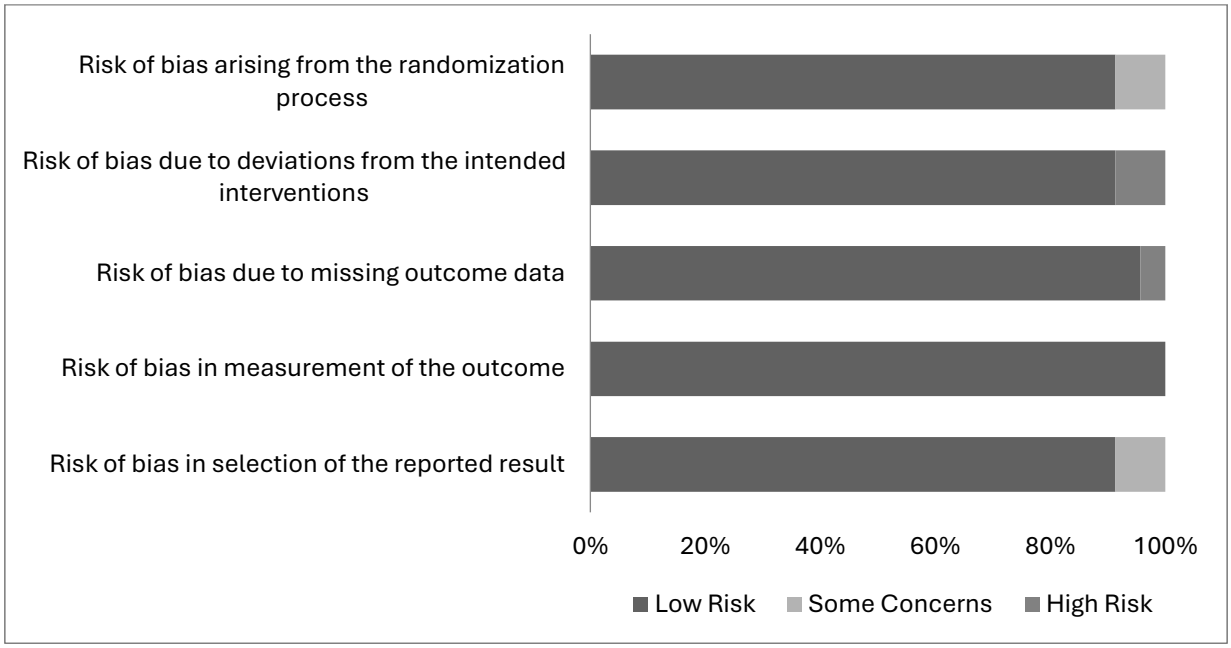
Figure A3: Summary estimates for adherence stratified by pre-specified subgroups



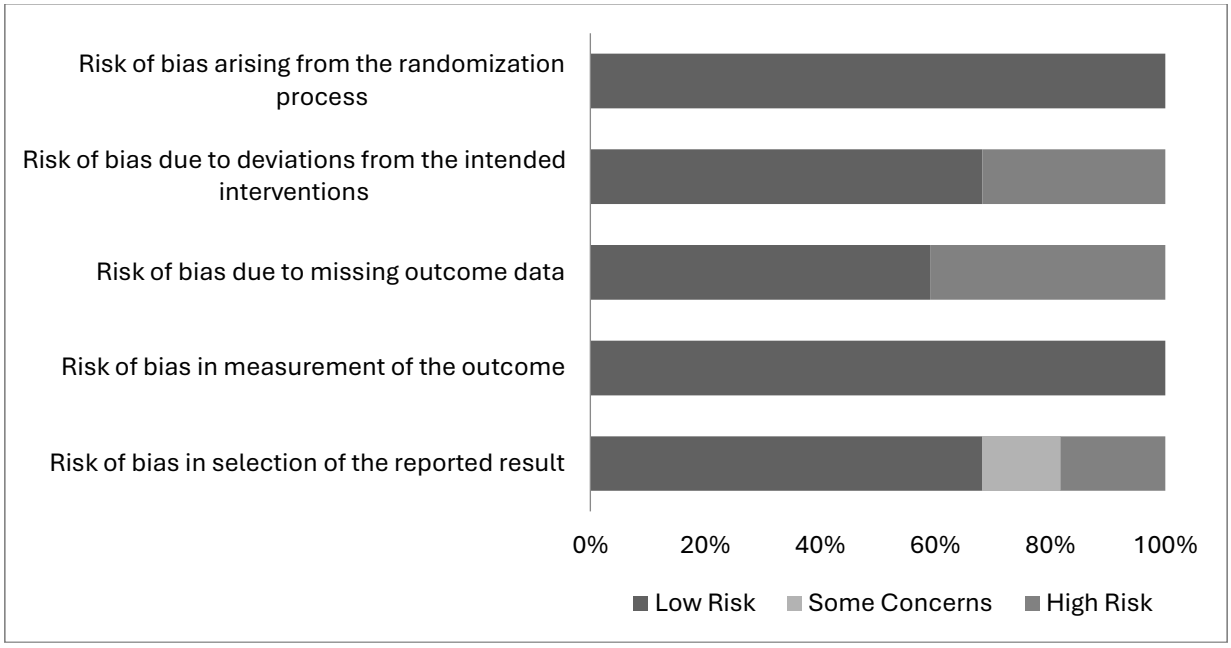
Legend: For group assignments and summary estimates tabulated, see Table A2. Reference line represents the median unstratified adherence across all studies (6.24 hours/day).

Figure A4: Detailed scoring for the risk of bias assessment of included studies

a. Cochrane RoB v2 scores for randomized studies: Acceptance

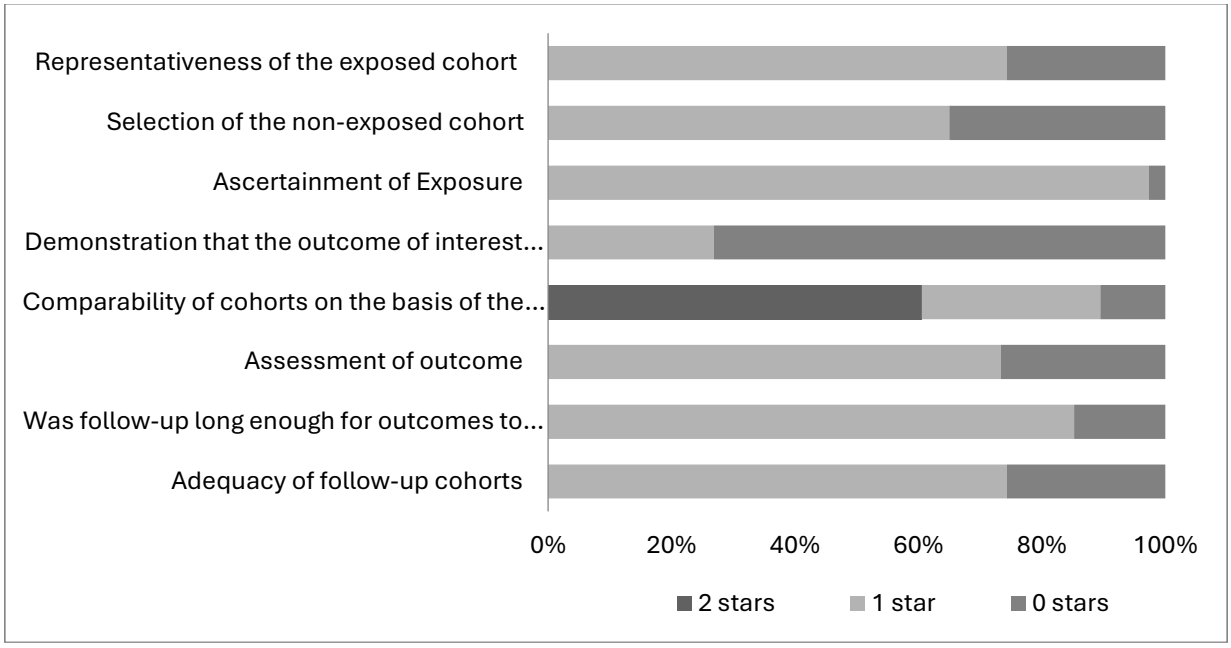


b. Cochrane RoB v2 scores for randomized studies: Adherence



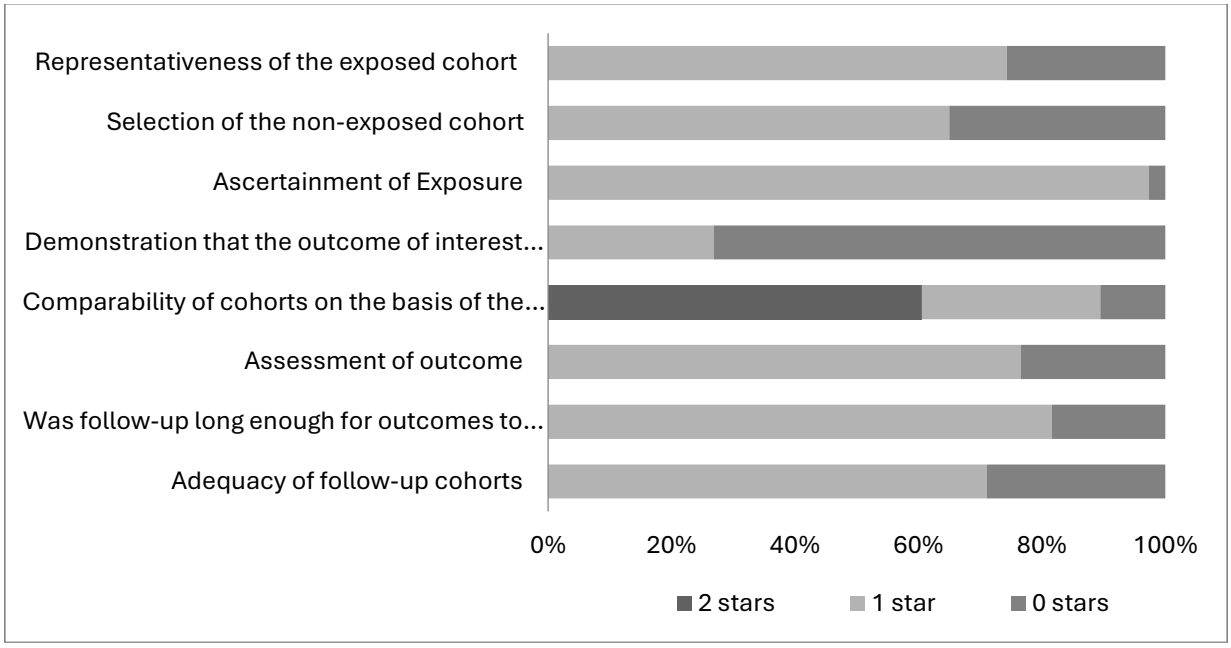
22

c. NOS scores for cohort studies: Acceptance



23

d. NOS scores for cohort studies: Adherence



Tables:
Table A1: Acceptance: Linear meta-regression results for the proportion of patients that decline or discontinue PAP therapy within one year

Covariate	**β (fully adjusted model)**	**β (univariate model)**
Indication 1. OSA vs CHRF secondary to COPD 2. Other vs CHRF secondary to COPD	 -0.54 (95% CI -1.40 to 0.32) -0.32 (95% CI -0.96 to 0.32)	 -0.33 (95% CI -0.64 to -0.01) -0.05 (95% CI -0.41 to 0.32)
Severity of COPD Severe/very severe COPD by FEV1 vs mild/moderate COPD	 -0.27 (95% CI -0.85 to 0.32)	
Hypercapnia Hypercapnia present vs hypercapnia not present in all participants	 -0.03 (95% CI -0.46 to 0.40)	
Type of PAP Therapy NIV vs CPAP Combined or other vs CPAP	 0.31 (95% CI -0.49 to 1.11) 0.25 (95% CI -0.38 to 0.88)	
PAP Settings 1.High pressure compared to low pressure NIV 2.Settings not reported/CPAP vs low pressure NIV	 -0.13 (95% CI 0.49 to 1.11) 0.16 (95% CI -0.23 to 0.56)	

Legend: n=56 arms from 51 studies

Table A2: Groups for the summary estimates for adherence

Subgroup	Group #	high	low	median
Indication: CHRF	1	7.47	6.44	6.96
Indication: OSA	2	6.10	4.93	5.51
Indication: Other	3	6.44	4.01	5.22
BMI <30 kg/m2	4	7.30	6.21	6.75
BMI ≥30 kg/m2	5	5.95	4.19	5.07
BMI not reported	6	7.41	5.80	6.24
Hypercapnia present	7	6.30	4.43	5.36
Hypercapnia not present in all participants	8	6.69	5.80	6.24
Type of PAP therapy: CPAP	9	5.36	4.32	4.84
Type of PAP therapy: NIV	10	6.95	5.99	6.47
Low-intensity NIV	11	6.96	5.84	6.40
High-intensity NIV (IPAP>20 & EPAP <10)	12	7.74	5.81	6.77
Not reported or CPAP	13	6.56	4.78	5.67
Timing of follow-up: ≤1 week	14	8.10	0.82	4.46
Timing of follow-up: ≤6 weeks	15	7.57	5.56	6.56
Timing of follow-up: 3 months	16	6.36	5.16	5.76
Timing of follow-up: ≥6 months or unclear	17	6.69	5.80	6.24
Follow-up location: did not report home visits	18	6.86	5.76	6.31
Follow-up location: included home visits	19	6.85	5.80	6.24
PAP initiated outside of an exacerbation	20	6.77	5.60	6.18
PAP initiated during an exacerbation	21	8.22	5.79	7.01
Unclear whether PAP initiated in stable state	22	6.93	5.34	6.13

Table A3: Adherence: Linear meta-regression results for median hours of use/day of PAP therapy

Covariate	β (fully adjusted model)	β (univariate model)
Indication 1. OSA vs. CHRF secondary to COPD 2. Other vs. CHRF secondary to COPD	 -1.40 (95% CI -3.26 to 0.46) -1.98 (95% CI -3.75 to -0.21)	 -1.46 (95% CI -2.45 to -0.47) -1.66 (95% CI -2.71 to -0.62)
Severity of COPD Severe/very severe COPD vs. included mild-moderate	-0.60 (95% CI -2.21 to 1.02)	
Hypercapnia All hypercapnic vs. contained some not hypercapnic	0.49 (95% CI -0.64 to 1.62)	
Type of PAP Therapy NIV vs. CPAP	1.31 (95% CI -0.46 to 3.08)	
PAP Settings 1.High pressure vs. to low pressure NIV 2.Settings not reported/CPAP vs. low pressure NIV	 -0.17 (95% CI -1.31 to 0.97) 0.42 (95% CI -0.84 to 1.68)	

Legend: n=66 arms from 51 studies

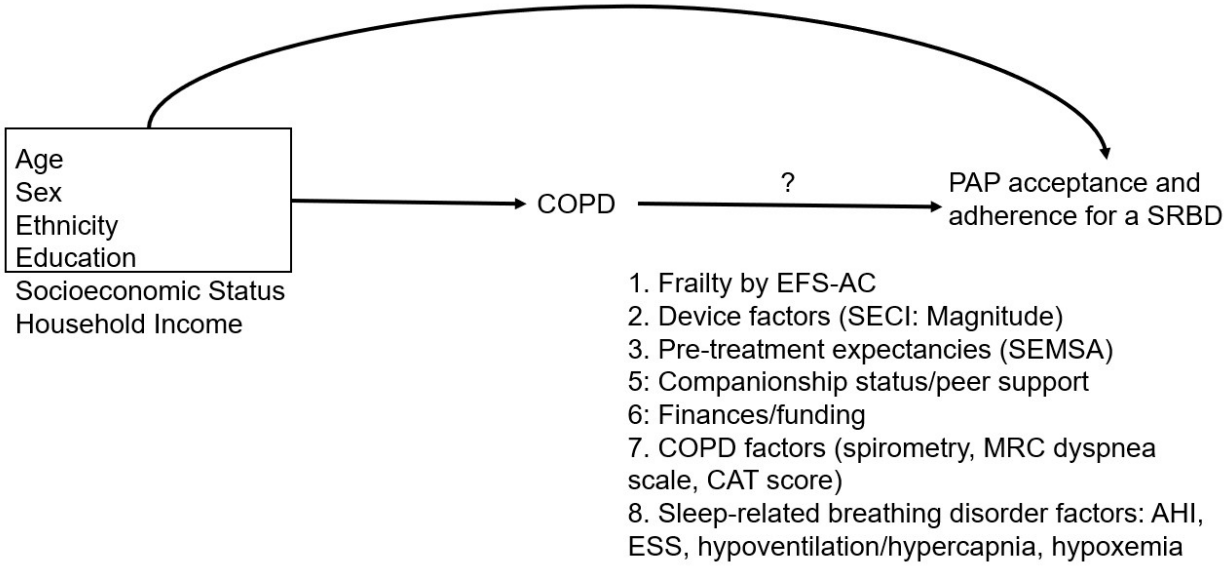
Table A4: Limitations and opportunities/recommendations to improve reporting and data validity for acceptance and adherence with PAP therapy

Limitation	Opportunity/Recommendation
Requirement of patients recruited to studies to attend follow-up and provide a machine download in order to know the primary outcome; variation in timing of adherence measure for each patient	Exploring ways for research team to be added to cloud-based adherence data in order to standardize collection, allow data from patients who pass away to be collected, and obtain an adherence measure for patients that are lost to follow-up
Limited reporting of how many patients are excluded because of the use of NIV as an intervention in a prospective study	Detailed documentation of patients reasons for not being included when it relates to PAP use
Lack of detailed assessment of reasons for stopping therapy earlier	Use of validated tools for barriers to adherence to be incorporated into the study protocol and reported in a supplemental file
Lack of dedicated reporting as to how barriers to adherence were addressed, for example, the multidisciplinary team involvement and timing of assessments, strategies used to address device intolerance	More detailed elaboration of the setting, team members, method and location of follow-up, and interventions for complaints by patients
Variable measure reported for adherence with PAP therapy	Hours of use per day with or without a proportion of adherence should be routinely reported and/or determined through expert consensus. Timing of the measure and the number of patients that contributed data should be routinely reported.
Limited reporting of demographics and patient characteristics of persons offered PAP therapy	Reporting of the initial cohort in an intention to treat analysis would be ideal for RCTs designed going forward. More targeted reporting of the patients that contributed data to a per protocol analysis could then be discussed in more detail.
Pre-selection for adherence was fairly common among studies reporting adherence	Prior to citing literature for adherence, it is key that selection bias is acknowledged.

Appendix 4: Directed acyclic graph for the prospective cohort study

Appendix 4: Directed acyclic graph for prospective cohort study

Figure S1: Directed acyclic graph



Legend: AHI: apnea-hypopnea index; CAT: COPD assessment test; COPD: chronic obstructive pulmonary disease; EFS-AC: Edmonton Frail Scale – Acute Care; ESS: Epworth Sleepiness Scale; MRC: Medical Research Council; PAP: positive airway pressure; SECI: Side Effects to CPAP Treatment Inventory; SEMSA: Self-efficacy Measure for Sleep Apnea; SRBD: sleep-related breathing disorder.

Appendix 5: Study protocol for original proposed prospective cohort study that was stopped prematurely due to the pandemic

May 11, 2020

Prevalence and treatment status of obstructive sleep apnea in patients presenting to the Emergency Department with an exacerbation of COPD.

Authors: Dr. Cheryl Laratta[1,4] (Principal Investigator), MD, MSc (Candidate), FRCPC, DRCPSC

Dr. Brian Rowe[2,4], MD, MSc, CCFP-EM (Collaborator)
Ms. Holly Scott[5], BSc, RPSGT (Collaborator)
Dr. Joanna MacLean[3,4], MD, PhD, FRCPC (Collaborator)
Dr. Sachin Pendharkar[1,5], MD, MSc, FRCPC (Collaborator)
Dr. Brian McNab[1,4], MD, FRCPC (Collaborator)

Program: [1]Department of Medicine
[2]Department of Emergency Medicine
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List of Abbreviations

AECOPD	acute exacerbation of COPD
AHI	apnea-hypopnea index
Bilevel PAP	bilevel positive airway pressure
BMI	body mass index
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
ED	Emergency Department
ESS	Epworth Sleepiness Scale score
FEV1	forced expiratory volume in one second
FVC	forced vital capacity
HSAT	home sleep apnea test
LOTT	long-term oxygen treatment trial
OHS	obesity hypoventilation syndrome
OSA	obstructive sleep apnea
PAP	positive airway pressure, including bilevel PAP and continuous PAP
PSG	polysomnogram
REDCap	Research Electronic Data Capture
STOP-Bang	STOP-Bang questionnaire

Protocol Summary

Full Title: Prevalence and treatment status of obstructive sleep apnea in patients presenting to the Emergency Department with an exacerbation of COPD.

If applicable: Cross-sectional study

Sample Size: N=100

Study Population: Consenting adults age ≥18 y.o. diagnosed with an exacerbation of COPD who attend the Emergency Department at the University of Alberta Hospital

Accrual Period: 12 months

Study Design: Cross-sectional study

Study Duration: July 2020-September 2021

Study Agent/Intervention/Procedure: Survey

Budget: $10,000.00

Funding Source: Respiratory Health Strategic Clinical Network, Alberta Health Services

Study Population: Participants that will be recruited are consenting adults age ≥18 y.o. diagnosed with an exacerbation of chronic obstructive pulmonary disease (COPD) on history, physical examination and chest radiograph by an Emergency Department physician at the University of Alberta Hospital.

Primary Objective: To establish with survey data the prevalence of diagnosed OSA, method of diagnosis, and obstructive sleep apnea (OSA) treatment status in COPD patients accessing the Emergency Department for an exacerbation of COPD.

Secondary Objective: To conduct a pilot feasibility study of the utility of using Alice NightOne devices to confirm OSA in patients with COPD who have risk factors for OSA and are experiencing exacerbations but do not require home oxygen.

Exploratory Objectives: To develop an understanding of the potential for the use of home sleep apnea tests in a diagnostic pathway for the evaluation of sleep disorders in COPD patients experiencing exacerbations.

Endpoints of the study:

- self-reported diagnosis of OSA, method of diagnosis of OSA, and self-reported treatment status
- Home sleep apnea test (HSAT) results in 20 patients who undergo this testing

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1 Introduction/Significance

This document is a clinical research protocol which will serve as the framework by which this project with be conducted. This study will be conducted in compliance with the provided study protocol, Clinical Practice standards and institutional research requirements.

Chronic obstructive pulmonary disease (COPD) is a chronic lung disease characterized by fixed airflow limitation, small airways disease and emphysema, and is associated with significant morbidity and mortality[1]. In Canada, the prevalence of physician-diagnosed COPD is estimated to be 4-5% of the population[2]. Both the high prevalence of COPD and the high morbidity in patients with moderate-severe COPD[3] translates into large costs to the healthcare system driven by exacerbations (AECOPD) which result in emergency department (ED) visits and hospitalizations[4]. In Alberta, an estimated 59% of 64,000 patients living with COPD were hospitalized between 2012 and 2014 with 15% experiencing ≥3 hospitalizations and spending >30 days in hospital[5].

While sleep quality is often poor in patients with COPD[6-8], obstructive sleep apnea may account for some of the symptoms. The estimates of co-occurring obstructive sleep apnea (OSA) and COPD are broad (3-66%) in part due to differences between study populations and how co-morbid OSA was identified[9]. In the general population, OSA is estimated to be underdiagnosed with only 3% of Canadians acknowledging a diagnosis of OSA, but 26% of Canadians having a moderate risk of OSA when asked about the symptoms or risk factors[10]. When OSA co-exists with COPD, patients experience a higher risk of mortality and first hospitalization, as well as an increased frequency of AECOPD compared to COPD patients without OSA[11,12]. The combination also results to higher medical costs than when either condition is present in isolation[9]. Treatment of OSA in patients with COPD has been shown to reduce mortality[13,14] and also exacerbations of COPD requiring hospitalizations[15]. Despite evidence suggesting OSA is an important comorbidity to optimize in patients with COPD, it is unclear how to investigate and diagnose OSA in the large population of COPD patients given limited access to polysomnography[16] and some very limited data on home sleep apnea testing (HSAT)[17]. Recently, a meta-analysis suggested that two validated questionnaires in the general population to identify OSA, STOP-Bang and the Sleep Apnea Clinical Score, may be useful to identify obstructive sleep apnea patients with COPD[18]; however, it was limited by few studies. Significant respiratory disease including COPD is a relative contraindication to use of HSAT in current guidelines. In addition, several home sleep apnea test devices are now being tested in patients with COPD (quality of evidence very low)[19]; however, more studies are being done including the WatchPAT[20] and the Nox-T3 portable monitor[21], as well as overnight oximetry[22], which demonstrate good sensitivity and specificity for OSA in validation studies. There is some data, however, suggesting that there is a high rate of failure of HSAT in patients with COPD which limits the utility of these devices in use in the general population[17]. To date, there has not been attention to developing a diagnostic pathway for obstructive sleep apnea in COPD patients. Due to the lack of clinical care pathways and survey data suggesting that OSA is underrecognized and underdiagnosed in the general population, we suspect OSA is under-recognized and under-treated in COPD patients and the role of HSAT in the diagnostic testing for OSA in COPD remains to be clarified.

2 Study Objectives

Primary Objective

To establish with survey data the prevalence of COPD patients experiencing exacerbations who have undergone screening or been diagnosed with sleep disordered breathing and the method of diagnosis.
To compare their risk profiles for OSA to that of the general Canadian population (SARR survey)

Secondary Objective

To determine whether patients are concerned that they may have unrecognized sleep disordered breathing that could be affecting their health
To determine method of diagnosis and OSA treatment status in COPD patients who are diagnosed with OSA and accessing the ED for an exacerbation of COPD

To conduct a pilot feasibility study of the ability of a home sleep apnea test to confirm OSA in patients with COPD experiencing AECOPD with risk factors for OSA, who do not require oxygen.

Hypothesis

OSA is underrecognized and undertreated in patients with COPD who are experiencing AECOPD requiring ED assessment. HSAT can confirm OSA in COPD patients with risk factors who are not requiring home oxygen and can be used as part of a diagnostic pathway.

3 Patients and Methods

3.1 Study Design

3.1.1 General Design

This is a cross-sectional study will be conducted of consecutive adults ≥18 years old presenting to the University of Alberta Hospital ED with an AECOPD as diagnosed by an ED physician based upon a history, physical examination and chest radiograph. We estimate that approximately 45% of the patients recruited will have a moderate-high pre-test probability of OSA[23]. A convenience sample of 100 patients will be recruited for survey administration. Recruitment will be based upon cluster-based random sampling. To minimize selection bias, participants will need to be identified to the research team within 2 hours of the chest radiograph. At the time of recruitment, consenting patients will complete spirometry and a structured electronic survey collecting missing data on: sleep history, history of diagnosis of OSA, treatment status if diagnosed with OSA and outpatient medical care providers. To characterize the population, we will collect some limited data on socioeconomic status, current COPD control, use of home oxygen therapy. The face validity of the survey will be assessed by a Respirologist, ED physician, patient, and methodologists. In 20 consecutive patients with risk factors for OSA, we will conduct a pilot feasibility study to evaluate the use of HSAT to identify OSA in this population. Exclusion criteria include if a patient has a probable alternative diagnosis to AECOPD, is unstable (e.g. intubated) or has other chronic lung diseases, dementia, or neuromuscular disease. Patients who refuse, feel too unwell to participate, or do not speak English will also be excluded. Administrative data will be used to collect objective data on recent and post ED health care utilization. Records from the Sleep Disorders laboratory will be requested on all patients to determine if they have undergone a polysomnogram (PSG) previously or if they are awaiting one and the study will be reviewed. Patients with a STOP-Bang[24] questionnaire score <3[18], a previous diagnosis of OSA, residence outside of Edmonton city limits, or on long-term oxygen therapy prior to recruitment will be excluded from this pilot study for HSAT use. In the group who will complete a HSAT, a research associate will arrange a time 6-8 weeks after recruitment to bring the equipment to the patient's home and instruct on its use. After completion of the HSAT, a research associate will return to pick up the equipment. The HSAT will be scored/interpreted by a sleep physician.

3.1.2 Primary Outcome Variable

- diagnosis of OSA
- previous work-up for OSA
- treatment status if diagnosed with OSA

3.1.3 Secondary Outcome Variables

- presence of nocturnal hypoxemia or OSA on home sleep apnea test

3.2 Subject Selection and Withdrawal

3.2.1 Inclusion Criteria

Participants that will be recruited are consenting adults age ≥18 y.o. diagnosed with an exacerbation of COPD on history, physical examination and chest radiograph by an ED physician at the University of Alberta Hospital.

3.2.2 Exclusion Criteria

Participants will be excluded if they have a probable alternative diagnosis to AECOPD, is unstable (e.g. intubated) or has other chronic lung diseases, dementia, or neuromuscular disease. Patients who refuse, feel too unwell to participate, or do not speak English will also be excluded

3.3 Study Procedures

All participants will be recruited from the ED of the University of Alberta Hospital. After diagnosing an exacerbation of COPD and obtaining consent for release of information, the ED physician responsible for clinical care for the potential participant will contact the research office. A cluster-based random sampling approach will be used as a research assistant is not available at all times in the ED. During hours of availability of the research assistant, the research assistant will then review the chart of the patients identified as eligible by the ED physician. If the patient meets inclusion criteria, a research assistant will confirm and document consent (see attached Consent Form April 2020).

For a complete list of variables that will be obtained, and the source from which they will be obtained, please refer to Section 4 (Data Handling and Record Keeping). The chart review will occur on the date of recruitment (or within 3 days if insufficient research assistant capacity on the date of recruitment). The accessing of the EDIS system will be completed for the year prior to the date of ED assessment (June 2019-June 2021). Survey data will be collected on the date of recruitment. Spirometry will also be collected on the date of recruitment. For those included in the pilot feasibility study, the home visit will take place 6-8 weeks after recruitment (July 2020-August 2021), at which time the spirometry will be repeated and 2 nights of HSAT data will be arranged. The collection of the HSAT data will occur within 1 week of providing the HSAT equipment, to be arranged with each patient individually at their convenience (July 2020-September 2021). PSG records will be requested for studies that pre-date the date of recruitment to the ED (latest June 2021).

3.4 Statistical Plan

3.4.1 Sample Size Determination

The frequency of comorbid OSA in COPD is estimated to be 10-30% and is associated with increased AECOPD. The rates of OSA may be higher in patients experiencing AECOPD because OSA predisposes to AECOPD. The frequency of obesity in COPD is 50-65% in outpatients, which indicates risk factors for OSA is highly prevalent in the outpatient setting. There is no current data on the rates of unrecognized OSA in patients with AECOPD. Extrapolating the aforementioned data, we suspect 10-50% of the patients presenting with an AECOPD will have OSA, of which an unknown proportion will be unrecognized. We therefore have chosen a sample size of convenience of 100 to inform our primary hypothesis, and hope to complete a HSAT on 20 patients as part of the pilot feasibility study to inform our secondary hypothesis.

3.4.2 Statistical Methods

Access to the SARR data from the general Canadian population will be obtained. Continuous variables will be summarized with mean and standard deviation, with data that does not follow a normal distribution summarized by median and interquartile range. Non-parametric tests will be used to compare those who have a diagnosis of OSA with those who do not, and those who have a moderate-high pre-test probability of OSA based upon validated questionnaires in the general population with those who do not. 95% confidence intervals and p-values will be reported (significance assessed at $p<0.05$). A logistic regression model using backward Wald techniques will be used to determine the factors associated with receiving a sleep assessment and sleep treatment in the community if we frequently encounter patients with a diagnosis of OSA.

4 Data Handling and Record Keeping

All data will be collected by trained research assistants in the ED who have received appropriate ethical and confidentiality training and who are experienced in clinical research. All will be qualified to administer the electronic survey, spirometry and will be trained and educated as to how to apply HSAT equipment. Survey data will be collected electronically into a REDCap database. Data from the chart review, neck circumference, waist circumference, spirometry, and HSAT will be entered into the electronic REDCap database and stored in a password protected, secured encrypted computer in the research area of the ED at the University of Alberta Hospital.

The data at baseline will be collected in the ED on every enrolled patient. The research assistant will assist the patient to complete the survey in order to ensure that all questions are answered. The primary outcome data will be a diagnosis of OSA, method of diagnosis of OSA and treatment status of OSA. Three validated questionnaires are being incorporated into the survey, informed also by demographics (sex, age), physical examination (neck circumference) and list of comorbidities (hypertension): the STOP-Bang questionnaire[25-27], the Sleep Apnea Clinical Score[28], and the Epworth Sleepiness Scale (ESS)[29]. The STOP-Bang score and Sleep Apnea Clinical Score (SACS) will estimate a pre-test probability of OSA as a recent meta-analysis suggested that they may be the most helpful in COPD patients[18]. The remainder of the data collected will characterize the participants by their smoking status, socioeconomic status, COPD (including spirometry), and obesity (height, weight, BMI, waist circumference).

The follow-up visit will be coordinated by the study coordinator. Patients will be contacted by telephone to arrange the time and date of the home visit and home sleep apnea test as well as to arrange a time to collect the equipment. At the home visit, a research assistant will repeat spirometry to evaluate the difference in FEV1 and peak expiratory flow rates between exacerbation and follow-up, as previous work suggest there is a recovery in peak expiratory flow rates to baseline of up to 22 days[30], although more recent work suggests that there is incomplete recovery in the FEV1 36-56 days following the exacerbation[31]. There is also some evidence that suggests that the difference between FEV1 in an exacerbation is -6.65% (90% CI -8.06, -5.23%)[31], but may vary by >10% of the patient's baseline[32]. We will also conduct a HSAT to evaluate for nocturnal hypoxemia or obstructive sleep apnea as a pilot study to assess the utility of HSAT for evaluating for OSA in non-hypoxemic patients with a moderate-high pre-test probability of OSA based upon the validated questionnaires.

Data to be collected:

	Variable (binary=B, ordinal=O, continuous=C)	Reason for collecting
Baseline:		
Chart review:		
Date of recruitment	C	To estimate time between date of assessment and follow-up HSAT
Sex	B	use in STOP-Bang score
Date of birth	C	spirometry to arrange normal values
Healthcare number		to facilitate request of polysomnography data from Edmonton General Hospital, to facilitate

		chart review and EDIS review
Address and telephone number	N/A	to facilitate home visit
Postal code	descriptive	for estimation of income level
CTAS 1-5	O	characterize severity of AECOPD
Outcome of visit: use of bilevel PAP, admission, discharge	B	
Oxygen requirements in the ED	C	
Arterial blood gas (if performed)	C	
Chest radiograph results	descriptive	confirm AECOPD
COVID-19 status	descriptive	characterize research assistant's risk
Electrocardiogram results	descriptive	characterize associated comorbidities, confounders and characterize study sample
Co-morbidities	B	
Medications	B	
EDIS system:		
# exacerbations in last 1 year	O	characterize severity of baseline COPD, health care utilization at baseline
# ED visits in last 1 year	O	
# hospitalizations in last 1 year	O	
Survey incorporating historical elements of 2 validated questionnaires (STOP-Bang, SACS, and ESS)		
See attached survey, version 1	as outlined in survey	Apply STOP-Bang, SACS, and ESS. Will also collect additional historical data to characterize COPD severity as well as history of a sleep assessment/sleep diagnostics and current management of OSA if diagnosed
Examination		
Neck circumference	C	to be used in the STOP-Bang score to estimate risk of OSA
Waist circumference	C	as an estimate of central abdominal obesity
Spirometry		

Height	C	important variables included in the estimation of lung function in patients with COPD
Weight	C	
Date of birth	C	
FEV1	C	
FVC	C	
Home visit at 6-8 weeks:		
Date of discharge from hospital	C	to facilitate timing of home visit
Spirometry		
Height	C	important variables included in the estimation of lung function in patients with COPD
Weight	C	
Date of birth	C	
FEV1	C	
FVC	C	
Home sleep apnea test		
Date of testing (2 nights)	C	To estimate time since ED assessment
Night 1:		
Total recording time	C	important variables measured by HSAT to characterize objective abnormalities in sleep
Total monitoring time	C	
Heart rate (average, highest, lowest)	C	
Number of respiratory events (apneas, hypopneas, central vs obstructive)	O	
Respiratory events index (surrogate for apnea-hypopnea index as sleep time is not recorded)	O	
Oxygen desaturation index	O	
Time spent with SpO2 <90%	C	
Time spent with SpO2 <88%	C	
Supine or non-supine duration of sleep	C	
Occurrence of snoring	B	
Night 2:		
Total recording time	C	important variables measured by HSAT to characterize objective abnormalities in sleep
Total monitoring time	C	
Heart rate (average, highest, lowest)	C	
Number of respiratory events (apneas, hypopneas, central vs obstructive)	O	
Respiratory events index (surrogate for apnea-hypopnea index as sleep time is not recorded)	O	
Oxygen desaturation index	O	
Time spent with SpO2 <90%	C	
Time spent with SpO2 <88%	C	
Supine or non-supine duration of sleep	C	

Occurrence of snoring	B	

4.1 Confidentiality

All research staff will have received training in confidentiality and be experienced in medical research. The research team will have successfully completed all required research ethics training required by the University of Alberta. Throughout the conduct of the study, the Principal Investigator will ensure verbally that all responsibilities of the research personnel concerning participants privacy and confidentiality are understood. All information will be coded with an anonymous study identification number so at no time in the future can data pertaining to the participants be identified by name except by accessing the master list which will be kept separate from the data. Identifying information for the codes is kept on a master list separate from data and will only be accessible to the principal investigator and study coordinator. Electronic records will be password protected and encrypted and maintained in the Emergency Medicine Research Group study coordination area at the University of Alberta Hospital. Paper records will also be stored at the University of Alberta Hospital Emergency Medicine Research Group site in a locked cabinet in a locked office.

4.2 Records Retention

Electronic and paper files will be stored and locked for 25 years following which they will be destroyed in compliance with University of Alberta requirements for destroying confidential material.

4.3 Regulatory Binder

We will create and maintain a regulatory binder to serve as a guidance document for tracking documentation associated with this study, and ensure that we conduct the study in accordance with all University of Alberta regulations.

5 Study Auditing and Inspecting

In the regulatory binder, we will maintain a compilation of the relevant licensing approvals and ethics approval that are required. We will keep a file of receipts and maintain a detailed record of expenses to ensure that the study funds are accounted for. All records will be available for inspection or audit through the research team at any time required.

6 Budget

Respiratory Health Strategic Clinical Network - $10,000

(1) Research staff
- $6000 to cover the salary of a Research Associate at the University of Alberta. We anticipate 150 hours of work at $32 per hour ($4800) with an additional 25% for benefits ($1200).

(2) Materials, Supplies, Services and Travel
   a. $1000 will be allocated for electronic survey development and testing in REDCap.
   b. $420 will be allocated for mileage for a Research Associate at the University of Alberta to travel to 20 participant homes to deliver the HSAT equipment, instruct on its use then return to retrieve the equipment ($0.59/km travel)

(3) Equipment
- $2500 will be allocated to equipment
  Equipment cost breakdown:
  Disposable parts: belt: $18.00/test, cannula: $5.00/test, batteries: $2.00/test
  External hardware: 3 sleep probes: 3*$412/probe

Cleaning supplies and replacement costs for damaged equipment: $764.00

Matching Funds

a. Publication fees and travel to conferences for dissemination of research findings will be covered by the EMeRG as an in-kind contribution.
b. One summer student will be recruited and funded through the Emergency Medicine Research Group (EMeRG; $1,500/month X 4 months)

Donated equipment

a. As an investigator-initiated request, Phillips is considering the donation of 2 Alice NightOne devices to be used for the duration of the research study and then returned

7 Publication Plan

We intend to present this data at the Canadian Respiratory Conference in 2021 and will be submitting manuscripts for peer-reviewed publication. No identifying material will be discussed at conferences or reported in journal publications. All parties contributing funds or equipment to the study will be acknowledged in all conference proceedings and journal publications related to this work.

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9 Attachments

1. STOP-Bang questionnaire
2. Non-exclusive academic license for the STOP-Bang questionnaire that will require review prior to submitting to the UHN
3. Sleep Apnea Clinical Score (no licensing agreement required, permission by score author provided for use)
4. Epworth Sleepiness Scale Score
5. Epworth Sleepiness Scale Score user agreement (awaiting copy for submission by providers, not attached)