Technology Assessment Program

Noninvasive Positive Pressure Ventilation in the Home

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Noninvasive Positive Pressure Ventilation in the Home (with addendum)

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Key Messages

Purpose of review

To evaluate home noninvasive positive pressure ventilation (NIPPV) in adults with chronic respiratory failure in terms of initiation, continuation, effectiveness, adverse events, equipment parameters and required respiratory services. Devices evaluated were home mechanical ventilators (HMV), bi-level positive airway pressure (BPAP) devices, and continuous positive airway pressure (CPAP) devices.

Key messages

- In patients with COPD, home NIPPV as delivered by a BPAP device (compared to no device) was associated with lower mortality, intubations, hospital admissions, but no change in quality of life (low to moderate SOE). NIPPV as delivered by a HMV device (compared individually with BPAP, CPAP, or no device) was associated with fewer hospital admissions (low SOE). In patients with thoracic restrictive diseases, HMV (compared to no device) was associated with lower mortality (low SOE). In patients with neuromuscular diseases, home BPAP (compared to no device) was associated with lower mortality and better quality of life (low SOE). In patients with obesity hypoventilation syndrome, HMV/BPAP mix (compared to no device) was associated with lower mortality (low SOE). BPAP (compared to no device) was associated with improved sleep quality.
- Current evidence is insufficient to assess the comparative effectiveness of many NIPPV device capabilities on patient outcomes; particularly comparing HMV to BPAP. Future studies should address which device capabilities are associated with improved patient outcomes.
- Criteria to initiate home NIPPV and home respiratory services were summarized in this report but varied and were not validated in comparative studies.
- Incidence of non-serious adverse events such as facial rash, dry eyes, mucosal dryness, and mask discomfort across devices was approximately 0.3 events over a median duration of device used of 6 months. The most commonly reported serious adverse event was acute respiratory failure. Based on direct comparisons, we found no statistically significant differences in number of treatment withdrawals or adverse events when comparing different devices or when comparing device use with no device use.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The Centers for Medicare & Medicaid Services requested this report from the EPC Program at AHRQ. AHRQ assigned this report to the following EPC: Mayo Clinic Evidence-based Practice Center (Contract Number: HHSA290201500013I_ HHSA29032004T).

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new health care technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for health care quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality.

If you have comments on this evidence report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov

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A draft of this technology assessment was distributed solely for the purpose of public and peer review. This final report does not represent and should not be construed to represent an AHRQ determination or policy.

This report is based on research conducted by the Mayo Clinic Evidence-based Practice Center (Contract Number: HHSA290201500013I_HHSA29032004T). The findings and conclusions in this document are those of the author(s) who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ and CMS. No statement in this article should be construed as an official position of AHRQ, CMS, or the U.S. Department of Health and Human Services.

None of the investigators has any affiliations or financial involvement related to the material presented in this report.

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

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Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

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Noninvasive Positive Pressure Ventilation in the Home

Structured Abstract

Objectives. To evaluate home noninvasive positive pressure ventilation (NIPPV) in adult patients with chronic respiratory failure in terms of initiation, continuation, effectiveness, adverse events, equipment parameters and required respiratory services. We evaluated respiratory failure primarily due to chronic obstructive pulmonary disease (COPD), thoracic restrictive disorders, neuromuscular disease, and obesity hypoventilation syndrome.

Data sources. National Guideline Clearinghouse, MEDLINE, EMBASE, SCOPUS, Cochrane Central Registrar of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus from January 1, 1995 to June 26, 2018.

Review methods. We included randomized and comparative nonrandomized studies that enrolled adults with chronic respiratory failure who used NIPPV for ≥ 1 month at home (using a home mechanical ventilator [HMV], bi-level positive airway pressure [BPAP] device, or continuous positive airway pressure [CPAP] device).

Results. We included 68 studies evaluating 53,733 patients. In patients with COPD (36 studies), common criteria for NIPPV initiation were hypercapnia (PaCO2 ranging from >45 to >56mmHg), pH>7.35, FEV1 <50% of normal, and/or hypoxia (PaO2 ranging from <55 to <60mmHg or long term oxygen use). BPAP (compared with no device) was associated with reductions in mortality (moderate Strength of Evidence [SOE]), need for intubation (moderate SOE), and hospital admissions (low SOE). HMV (compared individually to BPAP, CPAP, or no device) was associated with fewer hospital admissions (low SOE). In patients with thoracic restrictive diseases (8 studies), common criteria for NIPPV initiation were PaCO2>45mmHg, and FVC<40% normal or MIP<60cmH2O, or nocturnal SaO2<88% for ≥5 consecutive minutes. HMV (compared with no device) was associated with lower mortality (low SOE). In patients with neuromuscular disease (16 studies), common criteria for NIPPV initiation were PaCO2>45mmHg or FVC<50% or MIP <60cmH2O, or nocturnal SaO2 < 88% for ≥5 consecutive minutes. BPAP (compared with no device) was associated with reduced mortality (low SOE), and better quality of life (low SOE). In patients with obesity hypoventilation syndrome (13 studies), common criteria for NIPPV initiation were hypercapnia (PaCO2 ranging from >45 to >53mmHg) and pH>7.35. HMV/BPAP mix (compared with no device) was associated with lower mortality. BPAP (compared with no device) was associated with improved sleep quality. In all conditions, evidence was insufficient to compare initiation criteria or determine the effect of specific home respiratory services on outcomes. Approximately one third of patients who use NIPPV via any device experienced non-serious adverse events such as facial rash, mucosal dryness, mask discomfort, etc. Based on direct comparisons, we found no significant differences in adverse events between devices or between devices and no device.

Conclusions. In patients with COPD, home BPAP (compared to no device) was associated with lower mortality, decreased need for intubations, fewer patients with hospital admissions (though there was no difference in the total number of hospital admissions), but no change in quality of life. In patients with COPD, HMV (compared individually with BPAP, CPAP, or no device) was associated with fewer hospital admissions. In patients with thoracic restrictive diseases,

HMV (compared to no device) was associated with lower mortality. In patients with neuromuscular diseases, home BPAP (compared to no device) was associated with lower mortality and better quality of life. In patients with obesity hypoventilation syndrome, home HMV/BPAP (compared to no device) was associated with lower mortality. Current evidence is not available to assess the comparative effectiveness of many device capabilities on patient outcomes. Criteria to initiate home NIPPV and home respiratory services vary and are not validated in comparative studies.

January 2020 update: An addendum is located at the end of the main report.

Contents

Key Messages iii
Purpose of review iii
Key messages iii
Structured Abstract viii
Evidence Summary 1
Background and Objectives 1
Scope and Key Questions 2
Scope of Review 2
Key Questions 2
Methods 3
Glossary of Terms 3
Results 4
Chronic Obstructive Pulmonary Disease (COPD) 4
Thoracic Restrictive Diseases 6
Neuromuscular Disease (NMD) 6
Obesity Hypoventilation Syndrome 7
Other Respiratory Diseases 8
Mixed Disease Conditions 9
Adverse Events 10
Discussion 10
Findings in Relation to What Is Known 12
Limitations 13
Applicability 13
Suggestions for Future Research 14
Conclusion 14
Abbreviations 15
Introduction 1
Background 1
Scope and Key Questions 2
Scope of the Review 2
Key Questions 2
Organization of the Report 4
Methods 5
Literature Search Strategy 6
Search Strategy 6
Inclusion and Exclusion Criteria 6
Study Selection 6
Data Extraction 6

Assessment of Risk of Bias of Individual Studies 7
Data Synthesis 7
Grading the Strength of Evidence 9
Assessing Applicability 9
Peer Review and Public Commentary 9
Results 11
Literature Searches and Evidence Base 11
Chronic Obstructive Pulmonary Disease (COPD) 12
Key Points-KQ1 13
Key Points-KQ2 15
Key Points-KQ3 22
Key Points-KQ4 23
Thoracic Restrictive Diseases 25
Key Points-KQ1 25
Key Points-KQ2 26
Key Points-KQ3 28
Key Points-KQ4 29
Neuromuscular Disease (NMD) 31
Key Points-KQ1 31
Key Points-KQ2 33
Key Points-KQ3 36
Key Points-KQ4 37
Obesity Hypoventilation Syndrome 41
Key Points-KQ1 41
Key Points-KQ2 43
Key Points-KQ3 46
Key Points-KQ4 47
Other Respiratory Diseases 50
Key Points-KQ1 50
Key Points-KQ2 51
Key Points-KQ3 52
Initiation Criteria and Effectiveness (KQ1 and KQ2): 52
Mixed Disease Conditions 54
Key Points-KQ1 54
Key Points-KQ2 55
Key Points-KQ3 57

Key Points-KQ4 57
Adverse Events 60
Key Points-Adverse Events 60
Discussion 63
Overview 63
Findings in Relation to What Is Known 66
Limitations 67
Applicability 68
Suggestions for Future Research 68
Conclusion 69
References 70
Abbreviations and Acronyms 78

Tables

Table 1. PICOTS (population, interventions, comparisons, outcomes, timing, and setting) 3
Table 2. Rules used to categorize HMV, BPAP, and CPAP 7
Table 3. Categories of adverse events 8
Table 4. Major effectiveness outcomes with SOE (BPAP vs. no device in COPD patients) 14
Table 5. Other effectiveness outcomes (BPAP vs. no device in COPD patients) 15
Table 6. Major effectiveness outcomes with SOE (HMV, BPAP and CPAP in COPD patients) 17
Table 7. Other effectiveness outcomes (HMV, BPAP and CPAP in COPD patients) 18
Table 8. Subgroup analysis of studies in patients with stable COPD vs. patients with a recent exacerbation in studies comparing BPAP to no device 20
Table 9. Major effectiveness outcomes with SOE (HMV vs. no device in patients with thoracic restrictive diseases) 26
Table 10. Other effectiveness outcomes (HMV vs. no device in patients with thoracic restrictive diseases) 26
Table 11. Major effectiveness outcomes with SOE (all devices in patients with neuromuscular disease) 33
Table 12. Other effectiveness outcomes (all devices in patients with neuromuscular disease) 33
Table 13. Major effectiveness outcomes with SOE (all devices in patients with obesity hypoventilation syndrome) 43
Table 14. Other effectiveness outcomes (all devices in patients with obesity hypoventilation syndrome) 44
Table 15. Effectiveness of HMV vs. no device in patients with other respiratory diseases 50
Table 16. Major effectiveness outcomes with SOE (all devices in studies with mixed disease conditions) 55
Table 17. Other effectiveness outcomes (all devices in studies with mixed disease conditions) 55
Table 18. Incidence rate of adverse events by device. 59
Table 19. Types of reported serious adverse events 60
Table 20. Comparisons of total number of adverse events and by devices and diseases 60
Table 21. Summary of device effectiveness in patients with COPD 63
Table 22. Summary of device effectiveness in patients with thoracic restrictive diseases 64
Table 23. Summary of device effectiveness in patients with neuromuscular disease 64
Table 24. Summary of device effectiveness in patients with obesity hypoventilation syndrome 64

Table 25. Summary of device effectiveness in patients with other respiratory diseases 64
Table 26. Summary of device effectiveness in patients with mixed respiratory diseases 64

Figures

Figure 1. Analytic framework.....5
Figure 2. Studies by disease, device, and study design 11
Figure 3. Evidence map for effectiveness of device use.....63

Appendixes

Appendix A. Flow Chart
Appendix B. Search Strategy
Appendix C. Excluded Studies
Appendix D. Characteristics of Included Studies
Appendix E. Risk of Bias
Appendix F. Results from the Included Studies
Appendix G. Guidelines
Appendix H. Figures
Appendix I. Post-hoc subgroup analysis
Appendix J. References for Appendixes

Evidence Summary

Background and Objectives

Chronic respiratory failure is a common medical condition characterized by the inability to maintain normal oxygen ($PaO_2 \geq 60mmHg$) and/or carbon dioxide ($PaCO_2 \leq 45mmHg$) levels. Many diseases may lead to chronic respiratory failure, including chronic obstructive pulmonary disease (COPD), thoracic restrictive diseases (TRD) such as kyphoscoliosis, neuromuscular diseases (NMD), and obesity hypoventilation.[1] Associated with increased morbidity and mortality, chronic respiratory failure may range from mild to severe and may be stable or progressive.

Chronic respiratory failure with hypercapnia may be treated with chronic mechanical ventilation. Mechanical ventilator devices are broadly classified into two categories: home mechanical ventilators (HMV) and bi-level positive airway pressure (BPAP) devices.[1] While both HMV and BPAP devices provide positive pressure ventilation, their technical features may vary and overlap considerably. Variability includes: interface (tracheostomy or mask), mode of ventilation (such as pressure targeted versus volume targeted), respiratory circuit (such as single-limb versus double-limb), monitoring capability, safety and alarm systems, and internal battery life. Devices also differ by level of oversight and servicing. In addition, certain device features (such as the ability to perform lung volume recruitment) may only be available with certain devices and settings.

If deemed to be feasible and safe, using these devices in the home setting is preferred to other settings such as intensive care units (ICUs), ventilator weaning units, or long-term care hospitals. Advantages of home use include lower costs, greater independence, increased quality of life, decreased risk of healthcare-associated infections, and reduced use of acute care facilities.[2-4] The number of patients using long-term HMVs and BPAP devices in the home setting is growing—and this patient population is increasingly differentiated from patients with acute respiratory failure who use such devices in the hospital setting.[5] In addition, the cost of caring for patients with medical conditions associated with chronic respiratory failure is also growing, with estimates as high as $50 billion annually in the United States for COPD alone.[6]

For patients who use home mechanical ventilation through a noninvasive interface, or noninvasive positive pressure ventilation (NIPPV), selecting the optimal device type (HMV versus BPAP versus continuous positive airway pressure [CPAP]) and device settings is imperative. Depending on the severity of illness, patients with chronic hypercapnic respiratory failure may require no, intermittent, or continuous ventilatory support. Failing to adequately treat chronic respiratory failure with the appropriate device could potentially result in sudden or gradual hypoxemia and/or hypercapnia. This can lead to poor quality of life, sleepiness, hospital admission, intubation, and even respiratory arrest and death.[1, 7] Some patients have progressive respiratory failure and may require advanced ventilatory capabilities as their disease progresses.

Currently, substantial variability exists regarding the usage, prescribing patterns, policies, and guidelines for noninvasive HMVs, BPAPs, and CPAPs.[8, 9] While a number of guidelines address home use of BPAPs and HMVs, there is marked variability in the conclusions, recommendations, and evidence basis for these guidelines.[10-13] With current practice and guideline variability, there is a clear need to synthesize the best available evidence to guide prescribing.[14]

This systematic review evaluates home NIPPV in adult patients with chronic respiratory failure primarily due to chronic obstructive pulmonary disease (COPD), thoracic restrictive

disorders, and neuromuscular disease. Other causes of respiratory failure were included due to additional interest.

Scope and Key Questions

Scope of Review

This systematic review addresses initiation and continuation of home NIPPV including the effectiveness, equipment settings, and related respiratory services for patients with chronic respiratory failure. The systematic review also highlights areas of controversy and identifies needs for future research. NIPPV in other settings were excluded (e.g. long term acute care hospital, skilled nursing facility, etc.)

Key Questions

KQ1. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements considered for the initiation and continuation of noninvasive positive pressure ventilation supplied by a Home Mechanical Ventilator (HMV), Bi-level Positive Airway Pressure device (BPAP), and Continuous Positive Airway Pressure device (CPAP) in the home through a noninvasive interface for the population of patients with chronic respiratory failure due to neuromuscular diseases, thoracic restrictive diseases, chronic obstructive pulmonary diseases (COPD), or other lung diseases (cystic fibrosis, bronchiectasis)?

a. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements (e.g., reduction in hypercapnia) considered for the initiation and continuation of noninvasive positive pressure mechanical ventilation supplied by a HMV through a noninvasive interface in the home?
b. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements (e.g., reduction in hypercapnia) considered for the initiation and continuation of noninvasive positive pressure ventilation supplied as a BPAP through a noninvasive interface in the home?
c. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements (e.g., reduction in hypercapnia) considered for the initiation and continuation of noninvasive positive pressure ventilation supplied as a CPAP through a noninvasive interface in the home?

KQ2. In each of the above groups, what is the effect of HMV, BPAP, or CPAP use on patient outcomes, including mortality, hospitalization, admission/readmission to intensive care unit (ICU), need for intubation, outpatient visits, emergency room visits, disease exacerbations, quality of life (QoL), activities of daily living (ADL), dyspnea, sleep quality, exercise tolerance, and adverse events?

KQ3. What are the equipment parameters that are used in each of the above groups?

a. What are the parameters of ventilator usage (e.g., mode as determined by trigger, control and cycling variables)?

b. What are the equipment parameters that are necessary to achieve desired outcomes (e.g., flow capabilities, settings, etc.)?
c. What are the parameters of prescribed patient usage (e.g., frequency of use, duration of use throughout the day, other)?
d. In each of the above populations, what are the parameters of patient compliance with the prescribed usage of the equipment?

KQ4. What respiratory services, other than the technical support of the use of the prescribed equipment, are being provided to the above patients in the home (e.g., patient education, ongoing smoking cessation, respiratory therapist led home care)?

KQ5. What are the professional guidelines and statements that address KQ1 to KQ4?

Methods

We followed the established methodologies of systematic reviews as outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Comparative Effectiveness Reviews.[15] The study protocol is registered in the international prospective register of systematic reviews (PROSPERO #: CRD42018085676) and published on the AHRQ Website (https://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/topicrefinement/hmv-protocol.pdf). The full report details our literature search strategy, inclusion and exclusion criteria, and data synthesis. We also discuss our assessments of risk of bias and strength of evidence.

Glossary of Terms

Term	Description
Invasive mechanical ventilation	Delivery of mechanical ventilation through a permanent interface such as tracheostomy (not covered in this report).
Noninvasive positive pressure ventilation (NIPPV)	Delivery of mechanical ventilation using a BPAP or HMV device through a temporary interface such as a tight fitting mask.
Continuous positive airway pressure (CPAP)	A machine that delivers a single level of positive airway pressure throughout the entire respiratory cycle (inspiration and expiration).
Bi-level positive airway pressure (BPAP)	A machine that delivers two levels of positive airway pressure. On inspiration, the machine delivers an inspiratory positive airway pressure (IPAP). On expiration, the machine delivers an expiratory positive airway pressure (EPAP). BPAP devices may also be referred to as respiratory assist devices (RADs).
Home mechanical ventilator (HMV)	A machine capable of delivering pressure targeted, volume targeted, and/or volume preset ventilation outside of the hospital setting. HMVs are usually the machine of choice for patients with tracheostomy, but may also be used in patients via a noninvasive interface. Compared to BPAP machines, HMVs typically have additional monitoring, ventilator control, safety, and backup power features. HMVs are classified by the United States Food and Drug Administration (FDA) as “life support devices.”[5]

Term	Description
HMV/BPAP mix	Cohorts where part of the cohort used NIPPV via a HMV device, part of the cohort used NIPPV via a BPAP device, and outcomes were only reported for the combined cohort.
BPAP S (spontaneous)	All breaths are initiated by patient effort (spontaneous breaths).
BPAP ST (spontaneous/timed)	In addition to breaths initiated by patient effort, a backup respiratory rate is set to ensure a minimum number of breaths per minute.
BPAP volume assured pressure support	The machine monitors and automatically adjusts the levels of pressure support to achieve an average target tidal volume.
Pressure support ventilation	The machine delivers air at a preset inspiratory pressure. The duration of each breath and the respiratory rate are determined by patient effort.
Pressure control ventilation	The machine delivers a preset inspiratory pressure. The duration of each breath and the respiratory rate are preset. Tidal volume may vary.
Volume control ventilation	The machine delivers a preset tidal volume and respiratory rate. Tidal volume is fixed regardless of patient effort.
Assist control	Patients can initiate spontaneous breaths above the preset respiratory rate. Breath delivery may be volume or pressure controlled.

Abbreviations and Acronyms are listed at the end of this Evidence Summary and on page 70 of the Main Report.

Results

The literature search identified 6,097 citations, with 86 additional citations identified through reference mining, grey literature search, Key Informants, and public comments. We included 68 original studies with a total of 53,733 patients in the systematic review. Studies were conducted in the United States (5), Canada (1), Europe (53), Asia (4), Australia (3), Africa (1), and South America (1). We also identified 13 relevant clinical practice guidelines (summarized in the main report).

Chronic Obstructive Pulmonary Disease (COPD)

Thirty-six studies[7, 16-51] evaluating 51,175 patients were included. Studies evaluated HMV (5),[32, 35, 44, 46, 48] BPAP (30),[7, 16, 17, 20-30, 33, 34, 36, 37, 41-43, 50, 51] CPAP (2),[19, 23] and HMV/BPAP mix (2)[47, 49] use. Studies were conducted in the United States (4), Canada (1), Europe (26), Asia (3), Africa (1), and Australia (1). We identified eight clinical practice guidelines.[13, 52-58]

Overall risk of bias in RCTs was rated as moderate to high for issues related to blinding and possible risk of conflicts of interest from study sponsorship. In observational studies, the risk of bias was also high due to the lack of clarity about patient selection methods, prognostic balance, and unknown conflicts of interest.

Initiation Criteria for COPD (KQ1):

The criteria used to start NIPPV were variable but most commonly included: hypercapnia (PaCO2 ranging from >45 to >56mmHg), pH>7.35, FEV1 <50% of normal, and/or hypoxia (PaO2 ranging from <55 to <60mmHg or long term oxygen use). While some studies used singular criterion to initiate NIPPV (e.g. hypercapnia), other studies used combined criteria (e.g.

hypercapnia and hypoxia). For studies that used combined criteria, no two studies used the exact same laboratory parameters or cut-off points.

NIPPV was initiated in patients with stable COPD or in patients after hospitalization for acute exacerbation of COPD (AECOPD).

No studies compared the initiation criteria among different devices (HMV vs. BPAP vs. CPAP).

Processes used to titrate NIPPV were variable and used the following targets: reduction in hypercapnia, reduction in hypoxia, achievement of target tidal volumes, and reduction in patient symptoms.

Device Effectiveness for COPD (KQ2):

BPAP (compared with no device) was associated with significantly lower mortality (SOE: moderate), need for intubation (SOE: moderate), hospital admissions (SOE: low).

HMV (compared individually with BPAP, CPAP, or no device) was associated with significantly fewer hospital admissions (SOE: low).

Stratified analysis based on disease stability showed that in patients with stable COPD, BPAP (compared with no device) was associated with significantly lower mortality, higher activities of daily living, and reduced dyspnea. In patients with a recent exacerbation, BPAP (compared with no device) was associated with significantly reduced need for intubation.

Device Characteristics for COPD (KQ3):

For BPAP devices, the modes utilized were BPAP spontaneous [S], BPAP spontaneous/timed [ST], BPAP volume assured pressure support ventilation, and pressure controlled ventilation.

For HMV devices, the modes utilized were pressure support ventilation and pressure controlled ventilation.

For CPAP devices, the mode utilized was CPAP.

Prescribed device usage per day varied from ≥5-8 hours (in seven BPAP studies) and >12 hours (in one HMV study). Actual mean device usage per day ranged from 4.5-9.0 hours.

Respiratory Services for COPD (KQ4):

Evidence is lacking to determine the effect of specific respiratory home services on outcomes.

Respiratory services provided in the home included: telephone hotline staffed by nurses, scheduled phone calls by respiratory therapists, home visits by respiratory therapists, smoking cessation, and a comprehensive home care program with evaluation and treatment of physical, occupational, and dietary needs.

For all conditions, information related to clinical guidelines (KQ5) can be found in Results section as well as Appendix Table G.2 of the full report.

Thoracic Restrictive Diseases

Eight studies[43, 44, 51, 59-63] evaluating 204 patients were included. Studies evaluated HMV (3), [35, 44, 61-63] BPAP (4), [43, 51, 59, 60] and HMV/BPAP mix (1) use. Studies were conducted in Europe (7) and Asia (1). We identified six clinical practice guidelines. [13, 52, 53, 55, 56, 64]

Overall risk of bias of the included studies was rated as moderate due to unclear conflicts of interest and inadequate follow-up in the observational studies.

Initiation Criteria for Thoracic Restrictive Diseases (KQ1):

The criteria used to start NIPPV were variable and most commonly included: PaCO2 >45mmHg, FVC<40% or MIP <60cmH2O, or nocturnal SaO2 < 88% for ≥ 5 consecutive minutes.

All studies enrolled patients with stable disease (not in acute respiratory failure).

No studies compared the initiation criteria between different devices or evaluated criteria for device continuation.

Processes used to titrate NIPPV were variable and used the following targets: reduction in hypercapnia, reduction in hypoxia, achievement of target tidal volumes, and reduction in patient symptoms.

Device Effectiveness for Thoracic Restrictive Diseases (KQ2):

HMV (compared with no device) was associated with significantly lower mortality (SOE: low).

No studies compared outcomes between HMV and BPAP devices.

Device Characteristics for Thoracic Restrictive Diseases (KQ3):

For BPAP devices, the modes utilized were BPAP ST and BPAP NOS (unclear which mode).

For HMV devices, the modes utilized were pressure-controlled ventilation, volume assist controlled ventilation, and volume/pressure cycled NOS.

Prescribed usage included ≥7 hours/day. Actual mean device usage per day ranged from 6.0-7.3 hours.

Respiratory Services for Thoracic Restrictive Diseases (KQ4):

Evidence is lacking to determine the effect of specific respiratory home services on outcomes.

Respiratory services provided in the home included: telephone hotline.

Neuromuscular Disease (NMD)

Sixteen studies[51, 59, 60, 65-77] evaluating 1,111 patients were included. Studies evaluated HMV (3), [66, 68, 73] and BPAP (11), [51, 59, 60, 65, 67-72, 75] and HMV/BPAP mix (3) [25, 74, 76, 77] use. Studies were conducted in the US (1), Europe (14), and South America (1). We identified 10 clinical practice guidelines. [13, 52, 53, 55, 56, 64, 78-81]

Overall risk of bias was rated as moderate to high for issues related to blinding, risk of allocation concealment, outcome reporting in the RCT, and unknown conflicts of interest and high risk of outcome assessment in observational studies.

Initiation Criteria for Neuromuscular Disease (KQ1):

The criteria used to start NIPPV were variable and most commonly included: PaCO2 >45mmHg or FVC<50% or MIP <60cmH2O, or nocturnal SaO2 < 88% for ≥ 5 consecutive minutes.

No studies compared the initiation criteria between different devices or evaluated criteria for device continuation.

Processes used to titrate NIPPV were variable and used the following targets: reduction in hypercapnia, reduction in hypoxia, and reduction in patient symptoms.

Device Effectiveness for Neuromuscular Disease (KQ2):

BPAP (compared with no device) was associated with significantly lower mortality (SOE: low) and better quality of life (SOE: low).

Device Characteristics for Neuromuscular Disease (KQ3):

For BPAP devices, the modes utilized were BPAP ST and BPAP NOS (unclear if S or ST)

For HMV devices, the modes utilized were pressure support and volume assist controlled ventilation.

Prescribed device usage per day varied from ≥4-7 hours. Actual mean device usage per day ranged from 3.8-9.3 hours.

Respiratory Services for Neuromuscular Disease (KQ4):

Respiratory services provided in the home included: telephone hotline, scheduled phone calls, and cough assistance including mechanical cough assist devices provided by a respiratory therapist.

Weekly telemonitoring was associated with significantly lower rates of office visits, ER visits, and hospital admission, with no change in mortality.

Obesity Hypoventilation Syndrome

Thirteen studies[43, 48, 51, 61, 82-90] evaluating 890 patients were included. Studies evaluated HMV (2), [48, 61] BPAP (9),[25, 43, 51, 82, 83, 85-89], and CPAP (3), [82, 84, 87]and HMV/BPAP mix (3),[84, 90, 91] use. Studies were conducted in the United States (0), Europe (10), Australia (2), and Asia (1). We identified five clinical practice guidelines. [13, 52, 53, 55, 56]

Overall risk of bias was rated as moderate for issues related to blinding and risk of conflicts of interest in the RCT and selective patient population in observational studies.

Initiation Criteria for Obesity Hypoventilation Syndrome (KQ1):

The criteria used to start NIPPV were variable but most commonly included: hypercapnia (PaCO2 ranging from >45 to >53mmHg) and pH>7.35.

No studies compared the initiation criteria among different devices or evaluated criteria for device continuation.

Processes used to titrate NIPPV were variable and used the following targets: reduction in hypercapnia, reduction in hypoxia (including nocturnal hypoxia), achievement of target tidal volumes, and reduction in patient symptoms.

Device Effectiveness for Obesity Hypoventilation Syndrome (KQ2):

HMV/BPAP mix (compared with no device) was associated with significantly lower mortality (SOE: low).

BPAP (compared with no device) was associated with significantly improved sleep quality.

Device Characteristics for Obesity Hypoventilation Syndrome (KQ3):

For BPAP devices, the modes utilized were BPAP ST, BPAP S, and BPAP NOS (unclear if S or ST).

For HMV devices, the modes utilized were volume/pressure cycled NOS, pressure support and pressured controlled ventilation as well as a mixture of bi-level BPAP/HMV, each with assured volume modes.

Respiratory Services for Obesity Hypoventilation Syndrome (KQ4):

Evidence is lacking to determine the effect of home-based lifestyle counseling by nurses.

Other Respiratory Diseases

Other respiratory diseases included cystic fibrosis, bronchiectasis, and interstitial lung disease. Two studies[43, 92] evaluating 42 patients were included. Studies evaluated HMV (1) [92] and BPAP (1) [43] use. One study was conducted in Europe and one in Asia. We identified three clinical practice guidelines. [13, 56, 64]

Overall risk of bias was rated as moderate due to selective patient population and unclear risk of conflict of interest in the observational studies.

Initiation Criteria for Other Respiratory Diseases (KQ1):

The criteria used to start NIPPV were variable but most commonly included: diagnosis of diffuse parenchymal lung disease and/or bronchiectasis, hypoxia (long-term oxygen use), and/or hypercapnia (PaCO2 not specified).

No studies compared the initiation criteria between different devices or evaluated criteria for device continuation.

Processes used to titrate NIPPV were variable with the following targets used: reduction in hypercapnia, reduction in hypoxia (including nocturnal hypoxia), and achievement of target tidal volumes.

Device Effectiveness for Other Respiratory Diseases (KQ2):

Mortality, hospital admission, quality of life, or need for intubation were not evaluated.

HMV (compared with no device) was associated with significantly shorter length of hospital stay in patients with bronchiectasis.

Device Characteristics for Other Respiratory Diseases (KQ3):

The BPAP mode utilized was BPAP ST. The HMV mode utilized was volume assist control ventilation mode.

Respiratory Services for Other Respiratory Diseases (KQ4):

No studies described respiratory services provided in the home.

Mixed Disease Conditions

Mixed disease conditions included studies that reported outcomes for cohorts of patients with multiple different causes of chronic respiratory failure, rather than reporting outcomes by individual causes of chronic respiratory failure. For example, a study may have enrolled patients with COPD and OHS and only reported the outcomes for the entire combined cohort, rather than individually by cause of chronic respiratory failure. Five studies[35, 93-96] evaluating 331 patients were included. Studies evaluated HMV (4) [35, 93, 94, 96] and BPAP (1) [95] use. Studies were conducted in Europe (4) and one in Asia. We identified six clinical practice guidelines.

Overall risk of bias was rated as moderate. The RCTs were unable to blind patients, providers, or outcome assessors, and had unclear risk of allocation concealment. The observational studies were found to have selective patient populations and high risk of outcome assessment.

Initiation Criteria for Mixed Disease Conditions (KQ1):

The criteria used to start NIPPV were variable but most commonly included PaCO2>45mmHg, hypoxia (nocturnal SaO2 < 88% for ≥ 5 consecutive minutes), and/or pH ≥7.35.

HMV started in the home setting compared to HMV started in the hospital was not associated with differences in mortality or quality of life (in patients with NMD or TRD).

No major differences were found in the criteria used to initiate a BPAP or a HMV device.

Processes used to titrate NIPPV were variable with the following targets used: reduction in hypercapnia, reduction in hypoxia, and achievement of target tidal volumes.

Device Effectiveness for Mixed Disease Conditions (KQ2):

BPAP (compared with no device) was associated with significantly reduced hospital admissions in patients with COPD, asthma, or bronchiectasis (SOE: low).

Device Characteristics for Mixed Disease Conditions (KQ3):

BPAP devices used mode BPAP NOS (unclear if S or ST)

For HMV devices, the modes utilized were pressure controlled ventilation, volume assist control ventilation, volume control ventilation, and pressure/volume controlled ventilation NOS.

Respiratory Services for Mixed Disease Conditions (KQ4):

Evidence is lacking to determine the effect of telephone hotline and scheduled phone calls on outcomes.

Adverse Events

Only 19 out of the 68 included studies (27.94%) evaluated adverse events. A majority of these studies did not use a consistent approach for evaluation and reporting.

Serious events (such as mortality, hospitalization, and need for intubation) were commonly classified as study outcomes and were infrequently and non-uniformly classified as serious adverse events.

The pooled incidence of reported non-serious adverse events was 0.35 for HMV, 0.31 for BPAP, 0.27 for HMV/BMPAP mix, 0.39 for CPAP, and <0.001 for no device groups.

The pooled incidence of reported serious adverse events was <0.001 for HMV, 0.01 for BPAP, 0.09 for CPAP, and <0.001 for no device groups.

Based on direct comparison, we found no statistically significant differences in total number of treatment withdrawals or adverse events (serious plus other) when comparing different devices or when comparing device use with no device use.

Discussion

We conducted a systematic review to assess the effectiveness of home NIPPV (using HMV, BPAP, and/or CPAP devices) in adults with chronic respiratory failure. We assessed the criteria considered for initiation and continuation, respiratory services provided in the home, adverse events, and summarized relevant clinical practice guidelines. Regarding outcomes associated with device use, overall, we found only two studies that directly compared a HMV device with a BPAP device (one study in patients with COPD and one study in patients with NMD).

When evaluating patients with chronic respiratory failure who may benefit from NIPPV in the home setting, key clinical considerations include 1) when to start NIPPV and 2) which device type (HMV vs. BPAP) and device mode are needed to deliver acceptable and safe ventilation. These considerations may vary based on the underlying etiology of chronic respiratory failure (COPD vs. thoracic restrictive disease vs. neuromuscular diseases vs. obesity hypoventilation vs. other). In general, included studies evaluated the efficacy of starting chronic home NIPPV in patients with moderate to severe stable disease and/or patients with unstable disease in current acute respiratory exacerbation.

The following tables summarize the findings by condition, device, and comparator.

Table 1. Summary of device effectiveness in patients with COPD

Device	Comparator(s)	Findings (Strength of evidence)
HMV	Individually with BPAP, CPAP, or no device	Fewer hospital admissions (low SOE)
BPAP	no device	Lower mortality (moderate SOE) Reduced need for intubation (moderate SOE) Fewer hospital admissions (low SOE)

BPAP: bi-level positive airway pressure, CPAP: continuous positive airway pressure, HMV: home mechanical ventilator, ICU: intensive care unit, SOE: strength of evidence, ST: spontaneous/timed mode

Table 2. Summary of device effectiveness in patients with thoracic restrictive diseases

Device	Comparator(s)	Findings
HMV	no device	Lower mortality (low SOE)

HMV: home mechanical ventilator, SOE: strength of evidence

Table 3. Summary of device effectiveness in patients with neuromuscular disease

Device	Comparator(s)	Findings
BPAP	no device	Lower mortality (low SOE) Better quality of life (low SOE)

BPAP: bi-level positive airway pressure, HMV: home mechanical ventilator, SOE: strength of evidence

Table 4. Summary of device effectiveness in patients with obesity hypoventilation syndrome

Device	Comparator(s)	Findings
HMV/BPAP mix	no device	Lower Mortality (low SOE)
BPAP	no device	Better sleep quality

BPAP: bi-level positive airway pressure, CPAP: continuous positive airway pressure, HMV: home mechanical ventilator, SOE: strength of evidence

Table 5. Summary of device effectiveness in patients with other respiratory diseases

Device	Comparator(s)	Findings
HMV	no device	Mortality, hospital admission, quality of life, or need for intubation was not evaluated. Shorter length of hospital stay

HMV: home mechanical ventilator, SOE: strength of evidence. Other respiratory diseases included cystic fibrosis, bronchiectasis, and interstitial lung disease.

Table 6. Summary of device effectiveness in patients with mixed disease conditions

Device	Comparator(s)	Findings
BPAP	no device	Fewer hospital admissions (low SOE)

BPAP: bi-level positive airway pressure, SOE: strength of evidence. Mixed disease conditions included cohorts of patients with one or more of COPD, thoracic restrictive diseases, neuromuscular disease, obesity hypoventilation syndrome, or other respiratory diseases.

We found no major differences in the criteria considered for initiation of a HMV versus BPAP device—and included studies did not directly address this clinical question. The most common criteria for initiation of home NIPPV using a HMV and/or BPAP device were 1) COPD (hypercapnia [PaCO2 ranging from >45 to >56mmHg], pH>7.35, FEV1 <50% of normal, and/or hypoxia [PaO2 ranging from <55 to <60mmHg or long term oxygen use]), 2) thoracic restrictive diseases (PaCO2>45mmHg, stable disease, and FVC<40% normal or MIP<60cmH2O, or nocturnal SaO2<88% for ≥ 5 consecutive minutes), 3) neuromuscular disease (PaCO2>45mmHg or FVC<50% or MIP <60cmH2O, or nocturnal SaO2 < 88% for ≥ 5 consecutive minutes), 4) obesity hypoventilation syndrome (hypercapnia [PaCO2 ranging from >45 to >53mmHg] and pH>7.35), 5) other respiratory diseases (hypercapnia and hypoxia).

Respiratory services provided in the home were variable and included: telephone hotline, scheduled phone calls, home visits, smoking cessation, cough assistance instruction and devices, and dietary and lifestyle counseling. Only one RCT evaluated the efficacy of home respiratory services and found that BPAP ST with weekly telemonitoring (compared with BPAP ST alone) in NMD patients was associated with fewer office visits, fewer ER visits, fewer hospital admissions, and no difference in mortality.

Serious and non-serious adverse events were reported in patients in the HMV, BPAP, CPAP, and no device groups. Incidence rate of non-serious adverse events (such as facial rash, mucosal dryness, mask discomfort, etc.) was around 0.3. Reported serious adverse events were rare. The most commonly reported serious adverse event was acute respiratory failure, which occurred in patients using BPAP or CPAP as well as in patients using no devices. The recognition that patients using NIPPV devices may experience serious adverse events such as acute respiratory failure should be interpreted with the following considerations: First, reporting of serious adverse events was not uniform across studies, with a majority of studies not reporting serious adverse events and a majority of the remaining studies reporting no serious adverse events. Second, many studies that reported serious adverse events such as acute respiratory failure in patients who used NIPPV devices also reported that acute respiratory failure occurred, sometimes at even higher rates, in patients who used no devices. Third, outcomes such as death, hospitalization, and need for intubation were considered as primary efficacy outcomes and were not re-reported as serious adverse events in this review. Therefore, recognition of serious adverse events should be balanced with efficacy data showing benefit in mortality, hospitalization, and need for intubation in many disease categories. Fourth, comparative studies found no statistically significant differences in adverse events or treatment withdrawals among device type.

Findings in Relation to What Is Known

This systematic review provides evidence that in patients with nearly every disease condition, NIPPV was associated with both a statistically and clinically significant reduction in mortality. In addition, in patients with COPD, NIPPV was associated with fewer hospitalizations, fewer intubations, reduced dyspnea and no change in quality of life. In patients with COPD, NIPPV via HMV (compared individually to BPAP, CPAP, or no device) was associated with fewer hospital admissions (SOE: low). For patients with TRD, NMD, OHS, and other lung diseases, NIPPV was also associated with improved exercise tolerance, improved quality of life, reduced dyspnea, improved sleep quality, and shorter length of hospital stay in individual populations. Published guidelines varied with regards to criteria used to start NIPPV, criteria used to titrate NIPPV, recommended equipment parameters to use in specific disease conditions, and recommended respiratory services, all with various levels of evidence. While many guidelines recommended initiation of home NIPPV for daytime hypercapnia ($PaCO2 \geq 45mmHg$), some guidelines recommended initiation of home NIPPV prior to the development of daytime hypercapnia. In COPD, some guidelines recommend initiation of home NIPPV in patients with chronic daytime hypercapnia and/or recurrent episodes of acute hypercapnic respiratory failure, some guidelines cite insufficient evidence to recommend such practices.

While some guidelines recommended certain clinical circumstances when provision of an HMV was preferred to a BPAP machine, there is currently not convincing comparative evidence to support or refute these recommendations. For example, two English language guidelines (one from Germany and one from Australia) recommended an HMV device with an alternative backup power source, alarms to signal “mask off” or “low pressure” or “power failure,” and a second backup ventilator for patients with any disease condition whose device use approached >16 or >18 hours/day. [52, 97] Guidelines also recommend the volume controlled or volume cycled features of HMV machines when pressure controlled ventilation failed to prevent hypercapnia in patients with NMD, TRD, and OHS and when patients with any condition had difficulty triggering inspiration. [52, 97] Our review also found significant heterogeneity in the specific patient characteristics used to initiate home NIPPV. While most studies used hypercapnia (commonly,

but not always defined as PaCO2 ≥ 45mmHg) as one criteria to initiate home NIPPV, there were several other disease specific and variable criteria used to initiate home NIPPV. We found no existing comparative evidence to support or refute guideline recommendations of using HMV when device use approached >16 hours/day.

The guidelines included in this study were published between 1999 and 2016. In total, this systematic review included 11 studies published since 2016, the year of publication of the most recent guidelines.

Limitations

Despite conducting a comprehensive literature search, we were unable to find sufficient evidence to identify ideal criteria to initiate and continue home NIPPV via different devices (KQ1), optimized equipment settings (KQ3), or impact of home respiratory services (KQ4). Qualitative syntheses of these KQs were also limited by heterogeneity of the included studies (population, inclusion/exclusion criteria, targets and process of device titration, devices used, follow up duration, length of use of device, and study design). Our findings were also limited by lack of standard reporting of the following characteristics: 1) device type (i.e., difficulty in differentiating HMV from BPAP), 2) device used (e.g., manufacturer and model), 3) key device characteristics (e.g., mode used), and 4) device titration protocol and targets. For effectiveness and adverse events of home NIPPV (KQ2), the majority of the studies evaluated BPAP and no device in stable COPD patients. The evidence for comparative effectiveness of different devices and different modes is scarce, as well as the evidence for conditions other than stable COPD (i.e., COPD after recent exacerbation, OHS, NMD, or TRD, etc.). The evaluation of adverse events was also limited by the fact that most of the included studies did not evaluate adverse events and the majority of the rest did not use a consistent approach for reporting and evaluation. We could not statistically evaluate publication bias because the number of studies included in a direct comparison was small (n<10). We judged included studies to have medium to high risk of bias because of possible conflicts of interests (i.e., funded by device manufacturers), lack of blinding in RCTs and lack of representativeness of patient populations in observational studies. In addition, we only included studies published in English, which limited our ability to evaluate non-English studies. Furthermore, most included studies were conducted in European countries, many of which offer home respiratory therapy services to users of home NIPPV. Authors from these studies may have not explicitly mentioned each of the home respiratory services available to participants in included studies. In addition, we excluded studies that enrolled pediatric patients, which led to the exclusion of several studies in patients with severe, progressive NMD. Finally, we should note that we were unable to identify any studies that met our inclusion criteria that evaluated patients who required continuous, 24-hour noninvasive mechanical ventilation as administered via a mask or mouthpiece interface. Such patients, often with severe NMD, cannot survive without continuous mechanical ventilation, which precludes enrolling such patients in trials evaluating the comparative effectiveness of HMV versus no device use.

Applicability

Several issues limit the applicability of the stated findings. First, included studies were conducted in various locations across the globe. The provision of home NIPPV in different countries may differ based on devices available, devices commonly used, titration protocols, guidelines for home device use, associated respiratory services included, and coverage/payment

for home NIPPV. In addition, the classification of devices as either a HMV and/or BPAP machine may differ in the United States compared with other locations. Second, several devices used in the included studies were not FDA approved. Third, several devices used in the included studies were older models that may no longer be available. Fourth, there is no data on several newer devices developed in the past 5-10 years. Fifth, patients in randomized controlled trials may significantly differ from those encountered in practice.

Suggestions for Future Research

Future comparative research should define which patient populations would benefit from NIPPV delivered by a HMV compared to a BPAP device. Populations that may benefit from a HMV include patients who require daytime NIPPV for a certain number of hours, patients with continued hypercapnia despite maximal BPAP use, patients who have rapidly progressively disease, or patients who have experienced adverse events despite BPAP use. Such populations may benefit from the tighter ventilator parameters, modes, monitoring, alarm features, and a second back up ventilator as offered by use of a HMV device. Such evidence would improve clinician ability to determine which features and device types are optimal for specific patient populations. In addition, future comparative research should evaluate when to initiate NIPPV, especially evaluating the utility of starting NIPPV in patients with stable disease versus following an episode of acute decompensation. Furthermore, comparative research should define which patient populations would benefit from advanced BPAP modes such as volume assured pressure support versus other BPAP modes. There is a need to determine the optimal targets and process of device titration.

RCTs often provide the highest level of evidence. Nevertheless, it may be unethical to enroll some patient populations with chronic respiratory failure in RCTs. In such patient populations, other study designs should be considered such as single arm interventional studies (e.g. before and after studies). In addition, comparative effectiveness of invasive mechanical ventilation and 24-hour noninvasive mechanical ventilation could be considered. Studies of pediatric patients who used continuous 24-hour noninvasive mechanical ventilation may be used as a guide and provide additional information to inform studies and use of continuous noninvasive mechanical ventilation on adult patients. Therefore, future evidence synthesis should evaluate pediatric studies as well as single-arm studies (such as before and after studies), as enrolling such patients in trials evaluating the comparative effectiveness of HMV versus no device use would be unethical.

At last, the potential benefit of home respiratory therapy services for several patient populations remains uncharacterized and would benefit from further studies designed to evaluate this specific aspect. Future studies should include impact on patient-centered outcomes including quality of life.

Conclusion

In patients with COPD, home BPAP (compared to no device) was associated with lower mortality, intubations, hospital admissions, and dyspnea. There was no change in quality of life (pooled analysis of 9 studies). In patients with COPD, HMV (compared individually with BPAP, CPAP, or no device) was associated with fewer hospital admissions. In patients with TRD, home HMV (compared to no device) was associated with lower mortality and better exercise tolerance. In patients with NMD, home BPAP (compared to no device) was associated

with lower mortality, better quality of life, and reduced dyspnea. In patients with obesity hypoventilation syndrome, home HMV/BPAP mix (compared to no device) was associated with lower mortality; home BPAP (compared to no device) was associated with improved sleep quality. Current comparative evidence is not available to assess the impact of many device capabilities on patient outcomes. Criteria to initiate home NIPPV and home respiratory services vary and are not validated in comparative studies.

Abbreviations

ADL	Activities of daily living
AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
AHRQ	Agency for Healthcare Research and Quality
BMI	Body mass index
BPAP	Bi-level positive airway pressure
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
EPAP	Expiratory positive airway pressure
EPC	Evidence-based Practice Center
ER	Emergency room
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
HMV	Home mechanical ventilators
ICU	Intensive care unit
IPAP	Inspiratory positive airway pressure
Kg	Kilogram
KQ	Key Question
m	meters
MIP	Maximal inspiratory pressure
mmHg	Millimeters of mercury
NIPPV	Non-invasive positive pressure ventilation
NMD	Neuromuscular diseases
NOS	Not otherwise specified
OHS	Obesity hypoventilation syndrome
PaCO2	Partial pressure of arterial carbon dioxide
pH	Potential of hydrogen
QoL	Quality of life
RADS	Respiratory assist devices
RCT	Randomized controlled trial

S	Spontaneous mode
SaO2	Arterial blood oxygen saturation
SOE	Strength of evidence
ST	Spontaneous/timed breath mode
TRD	Thoracic restrictive diseases

References

1. King AC. Long-term home mechanical ventilation in the United States. Respir Care. 2012 Jun;57(6):921-30; discussion 30-2. doi: 10.4187/respcare.01741. PMID: 22663967.
2. Bach JR, Intintola P, Alba AS, et al. The ventilator-assisted individual. Cost analysis of institutionalization vs rehabilitation and in-home management. Chest. 1992 Jan;101(1):26-30. PMID: 1729079.
3. Marchese S, Lo Coco D, Lo Coco A. Outcome and attitudes toward home tracheostomy ventilation of consecutive patients: a 10-year experience. Respir Med. 2008 Mar;102(3):430-6. doi: 10.1016/j.rmed.2007.10.006. PMID: 18023334.
4. MacIntyre NR, Epstein SK, Carson S, et al. Management of patients requiring prolonged mechanical ventilation: report of a NAMDRC consensus conference. Chest. 2005 Dec;128(6):3937-54. doi: 10.1378/chest.128.6.3937. PMID: 16354866.
5. Simonds AK. Home Mechanical Ventilation: An Overview. Ann Am Thorac Soc. 2016 Nov;13(11):2035-44. doi: 10.1513/AnnalsATS.201606-454FR. PMID: 27560387.
6. Guarascio AJ, Ray SM, Finch CK, et al. The clinical and economic burden of chronic obstructive pulmonary disease in the USA. Clinicoecon Outcomes Res. 2013;5:235-45. doi: 10.2147/ceor.s34321. PMID: 23818799.
7. Murphy PB, Rehal S, Arbane G, et al. Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation: A Randomized Clinical Trial. JAMA. 2017 Jun 06;317(21):2177-86. doi: 10.1001/jama.2017.4451. PMID: 28528348.
8. MacIntyre E, Asadi L, McKim DA, et al. Clinical outcomes associated with home mechanical ventilation: A systematic review. Can Respir J. 2015 Sep 30. PMID: 26422402.
9. Lloyd-Owen SJ, Donaldson GC, Ambrosino N, et al. Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. Eur Respir J. 2005 Jun;25(6):1025-31. doi: 10.1183/09031936.05.00066704. PMID: 15929957.
10. Miller RG, Jackson CE, Kasarskis EJ, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2009 Oct 13;73(15):1218-26. doi: 10.1212/WNL.0b013e3181bc0141. PMID: 19822872.
11. McKim DA, Road J, Avendano M, et al. Home mechanical ventilation: a Canadian Thoracic Society clinical practice guideline. Can Respir J. 2011 Jul-Aug;18(4):197-215. PMID: 22059178.
12. Windisch W, Walterspacher S, Siemon K, et al. Guidelines for non-invasive and invasive mechanical ventilation for treatment of chronic respiratory failure. Published by the German Society for Pneumology (DGP). Pneumologie. 2010 Oct;64(10):640-52. doi: 10.1055/s-0030-1255558. PMID: 20799159.
13. Respiratory Network Domiciliary Non-Invasive Ventilation Working Group. Domiciliary non-invasive ventilation in adult patients-a consensus statement. NSW Agency for Clinical Innovation; 2012. https://www.aci.health.nsw.gov.au/__data/assets/pdf_file/0008/159794/ACI-NIV-guidelines.pdf. Accessed on August 28 2017.
14. Lewarski JS, Gay PC. Current issues in home mechanical ventilation. Chest. 2007 Aug;132(2):671-6. doi: 10.1378/chest.07-0558. PMID: 17699139.

15. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; January 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.

16. Oscroft NS, Chadwick R, Davies MG, et al. Volume assured versus pressure preset non-invasive ventilation for compensated ventilatory failure in COPD. Respiratory Medicine. 2014 Oct;108(10):1508-15. doi: https://dx.doi.org/10.1016/j.rmed.2014.07.010. PMID: 25123526.

17. Paone G, Conti V, Biondi-Zoccai G, et al. Long-term home noninvasive mechanical ventilation increases systemic inflammatory response in chronic obstructive pulmonary disease: a prospective observational study. Mediators of Inflammation. 2014;2014:503145. doi: https://dx.doi.org/10.1155/2014/503145. PMID: 24976687.

18. Galli JA, Krahnke JS, James Mamary A, et al. Home non-invasive ventilation use following acute hypercapnic respiratory failure in COPD. Respiratory Medicine. 2014 May;108(5):722-8. doi: https://dx.doi.org/10.1016/j.rmed.2014.03.006. PMID: 24702885.

19. Bhatt SP, Peterson MW, Wilson JS, et al. Noninvasive positive pressure ventilation in subjects with stable COPD: a randomized trial. International Journal of Copd. 2013;8:581-9. doi: https://dx.doi.org/10.2147/COPD.S53619. PMID: 24293994.

20. Duiverman ML, Wempe JB, Bladder G, et al. Two-year home-based nocturnal noninvasive ventilation added to rehabilitation in chronic obstructive pulmonary disease patients: a randomized controlled trial. Respiratory Research. 2011 Aug 23;12:112. doi: https://dx.doi.org/10.1186/1465-9921-12-112. PMID: 21861914.

21. Duiverman ML, Wempe JB, Bladder G, et al. Nocturnal non-invasive ventilation in addition to rehabilitation in hypercapnic patients with COPD. Thorax. 2008 Dec;63(12):1052-7. PMID: 18710905.

22. Oscroft NS, Quinnell TG, Shneerson JM, et al. Long-term non-invasive ventilation to manage persistent ventilatory failure after COPD exacerbation. Respirology. 2010 Jul;15(5):818-22. doi: https://dx.doi.org/10.1111/j.1440-1843.2010.01787.x. PMID: 20546195.

23. Cheung APS, Chan VL, Liong JT, et al. A pilot trial of non-invasive home ventilation after acidotic respiratory failure in chronic obstructive pulmonary disease. International Journal of Tuberculosis & Lung Disease. 2010 May;14(5):642-9. PMID: 20392360.

24. Casanova C, Celli BR, Tost L, et al. Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. Chest. 2000 Dec;118(6):1582-90. PMID: 11115443.

25. Garrod R, Mikelsons C, Paul EA, et al. Randomized controlled trial of domiciliary noninvasive positive pressure ventilation and physical training in severe chronic obstructive pulmonary disease. American Journal of Respiratory & Critical Care Medicine. 2000 Oct;162(4 Pt 1):1335-41. doi: https://dx.doi.org/10.1164/ajrccm.162.4.9912029. PMID: 11029341.

26. Clini E, Sturani C, Porta R, et al. Outcome of COPD patients performing nocturnal non-invasive mechanical ventilation. Respiratory Medicine. 1998 Oct;92(10):1215-22. PMID: 9926152.

27. Clini E, Vitacca M, Foglio K, et al. Long-term home care programmes may reduce hospital admissions in COPD with chronic hypercapnia. European Respiratory Journal. 1996 Aug;9(8):1605-10. PMID: 8866580.

28. Zhou L, Li X, Guan L, et al. Home noninvasive positive pressure ventilation with built-in software in stable hypercapnic COPD: A short-term prospective, multicenter, randomized, controlled trial. International Journal of COPD. 2017 27 Apr;12:1279-86. doi: http://dx.doi.org/10.2147/COPD.S127540. PMID: 615975404.

29. Marquez-Martin E, Ruiz FO, Ramos PC, et al. Randomized trial of non-invasive ventilation combined with exercise training in patients with chronic hypercapnic failure due to chronic obstructive pulmonary disease. Respiratory Medicine. 2014 Dec;108(12):1741-51. PMID: 25456710.

30. Kohnlein T, Windisch W, Kohler D, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. The Lancet Respiratory Medicine. 2014 Sep;2(9):698-705. PMID: 25066329.

31. De Backer L, Vos W, Dieriks B, et al. The effects of long-term noninvasive ventilation in hypercapnic COPD patients: a randomized controlled pilot study. International Journal of Copd. 2011;6:615-24. PMID: 22135493.

32. Dreher M, Storre JH, Schmoor C, et al. High-intensity versus low-intensity non-invasive ventilation in patients with stable hypercapnic COPD: a randomised crossover trial. Thorax. 2010 Apr;65(4):303-8. PMID: 20388753.

33. McEvoy RD, Pierce RJ, Hillman D, et al. Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. Thorax. 2009 Jul;64(7):561-6. PMID: 19213769.

34. Tsolaki V, Pastaka C, Karetsi E, et al. One-year non-invasive ventilation in chronic hypercapnic COPD: effect on quality of life. Respiratory Medicine. 2008 Jun;102(6):904-11. PMID: 18280131.

35. Windisch W, Dreher M, Storre JH, et al. Nocturnal non-invasive positive pressure ventilation: physiological effects on spontaneous breathing. Respiratory Physiology & Neurobiology. 2006 Feb 28;150(2-3):251-60. PMID: 15990366.

36. Gay PC, Hubmayr RD, Stroetz RW. Efficacy of nocturnal nasal ventilation in stable, severe chronic obstructive pulmonary disease during a 3-month controlled trial. Mayo Clinic Proceedings. 1996 Jun;71(6):533-42. PMID: 8642881.

37. Gad DM, El-Shafey AM. Non-invasive positive pressure ventilation and exercise training in patients with stable hypercapnic chronic obstructive pulmonary disease. Egyptian Journal of Chest Diseases and Tuberculosis. 2015 01 Jan;64(1):51-6. PMID: 601158661.

38. Sin DD, Wong E, Mayers I, et al. Effects of nocturnal noninvasive mechanical ventilation on heart rate variability of patients with advanced COPD. Chest. 2007 January;131(1):156-63. PMID: 46122988.

39. Heinemann F, Budweiser S, Jörres RA, et al. The role of non-invasive home mechanical ventilation in patients with chronic obstructive pulmonary disease requiring prolonged weaning. Respirology. 2011;16(8):1273-80.

40. Budweiser S, Hitzl A, Jörres R, et al. Impact of noninvasive home ventilation on long-term survival in chronic hypercapnic COPD: a prospective observational study. International journal of clinical practice. 2007;61(9):1516-22.

41. Clini E, Sturani C, Rossi A, et al. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. European Respiratory Journal. 2002;20(3):529-38.

42. Struik F, Sprooten R, Kerstjens H, et al. Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. Thorax. 2014:thoraxjnl-2014-205126.

43. Salturk C, Karakurt Z, Takir HB, et al. Comparison of exercise capacity in COPD and other etiologies of chronic respiratory failure requiring non-invasive mechanical ventilation at home: retrospective analysis of 1-year follow-up. International Journal of Copd. 2015;10:2559-69. doi: https://dx.doi.org/10.2147/COPD.S91950. PMID: 26648713.

44. Hitzl AP, Jorres RA, Heinemann F, et al. Nutritional status in patients with chronic respiratory failure receiving home mechanical ventilation: impact on survival. Clinical Nutrition. 2010 Feb;29(1):65-71. doi: https://dx.doi.org/10.1016/j.clnu.2009.08.002. PMID: 19695747.

45. Funk G-C, Breyer M-K, Burghuber OC, et al. Long-term non-invasive ventilation in COPD after acute-on-chronic respiratory failure. Respiratory Medicine. 2011 Mar;105(3):427-34. PMID: 21111590.

46. Vasquez MM, McClure LA, Sherrill DL, et al. Positive Airway Pressure Therapies and Hospitalization in Chronic Obstructive Pulmonary Disease. American Journal of Medicine. 2017 Jul;130(7):809-18. doi: https://dx.doi.org/10.1016/j.amjmed.2016.11.045. PMID: 28089799.

47. Duiverman ML, Maagh P, Magnet FS, et al. Impact of High-Intensity-NIV on the heart in stable COPD: a randomised cross-over pilot study. Respiratory Research. 2017 05 02;18(1):76. PMID: 28464911.

48. Blankenburg T, Benthin C, Pohl S, et al. Survival of hypercapnic patients with COPD and obesity hypoventilation syndrome treated with high intensity non invasive ventilation in the daily routine care. Open Respiratory Medicine Journal. 2017;11:31-40.

49. Durao V, Grafino M, Pamplona P. Chronic respiratory failure in patients with chronic obstructive pulmonary disease under home noninvasive ventilation: Real-life study. Pulmonology. 2018 Apr 05;05:05. PMID: 29628437.

50. Oscroft NS, Quinnell TG, Shneerson JM, et al. The effects of withdrawing long-term nocturnal non-invasive ventilation in COPD patients. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2010;7(2):111-6.

51. Tsolaki V, Pastaka C, Kostikas K, et al. Noninvasive ventilation in chronic respiratory failure: effects on quality of life. Respiration. 2011;81(5):402-10.

52. Windisch W, Walterspacher S, Siemon K, et al. Guidelines for non-invasive and invasive mechanical ventilation for treatment of chronic respiratory failure. Pneumologie. 2010;64(10):640-52.

53. McKim DA, Road J, Avendano M, et al. Home mechanical ventilation: a Canadian Thoracic Society clinical practice guideline. Canadian Respiratory Journal. 2011 Jul-Aug;18(4):197-215. PMID: 22059178.

54. Ambrosino N, Casaburi R, Chetta A, et al. 8th International conference on management and rehabilitation of chronic respiratory failure: The long summaries - Part 3. Multidisciplinary Respiratory Medicine. 2015 06 Oct;10 (1) (no pagination)(29). PMID: 606265044.

55. Porte P. Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation - A consensus conference report. Chest. 1999;116(2):521-34. PMID: 29382139.

56. National Guideline C. BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. 2016.

57. National Guideline C. VA/DoD clinical practice guideline for the management of chronic obstructive pulmonary disease. 2014.

58. National Institute for H, Clinical E. National Clinical Guideline Centre for Acute and Chronic Conditions. Chronic obstructive pulmonary disease. Management of chronic obstructive pulmonary disease in adults in primary and secondary care. National Institute for Health and Clinical Excellence. 2010.

59. Domenech-Clar R, Nauffal-Manzur D, Perpina-Tordera M, et al. Home mechanical ventilation for restrictive thoracic diseases: effects on patient quality-of-life and hospitalizations. Respiratory Medicine. 2003 Dec;97(12):1320-7. PMID: 14682414.

60. Nauffal D, Domenech R, Martinez Garcia MA, et al. Noninvasive positive pressure home ventilation in restrictive disorders: outcome and impact on health-related quality of life. Respiratory Medicine. 2002 Oct;96(10):777-83. PMID: 12412976.

61. Masa JF, Celli BR, Riesco JA, et al. The obesity hypoventilation syndrome can be treated with noninvasive mechanical ventilation. Chest. 2001;119(4):1102-7. doi: http://dx.doi.org/10.1378/chest.119.4.1102. PMID: 32679437.

62. Schonhofer B, Wallstein S, Wiese C, et al. Noninvasive mechanical ventilation improves endurance performance in patients with chronic respiratory failure due to thoracic restriction. Chest. 2001 May;119(5):1371-8. PMID: 11348941.

63. Buyse B, Meersseman W, Demedts M. Treatment of chronic respiratory failure in kyphoscoliosis: oxygen or ventilation? European Respiratory Journal. 2003 Sep;22(3):525-8. PMID: 14516146.

64. Hardinge M, Annandale J, Bourne S, et al. British Thoracic Society guidelines for Home Oxygen use in adults. Thorax. 2015 June;70:i1-i43. PMID: 608676290.

65. Gonzalez-Bermejo J, Morelot-Panzini C, Arnol N, et al. Prognostic value of efficiently correcting nocturnal desaturations after one month of non-invasive ventilation in amyotrophic lateral sclerosis: A retrospective monocentre observational cohort study. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2013 September;14(5-6):373-9. doi: http://dx.doi.org/10.3109/21678421.2013.776086. PMID: 369532783.

66. Sanjuan-Lopez P, Valino-Lopez P, Ricoy-Gabaldon J, et al. Amyotrophic lateral sclerosis: impact of pulmonary follow-up and mechanical ventilation on survival. A study of 114 cases. Archivos de Bronconeumologia. 2014 Dec;50(12):509-13. doi: https://dx.doi.org/10.1016/j.arbres.2014.04.010. PMID: 24931271.

67. Pinto AC, Evangelista T, Carvalho M, et al. Respiratory assistance with a non-invasive ventilator (Bipap) in MND/ALS patients: survival rates in a controlled trial. Journal of the Neurological Sciences. 1995 May;129 Suppl:19-26. PMID: 7595610.

68. Sancho J, Servera E, Morelot-Panzini C, et al. Non-invasive ventilation effectiveness and the effect of ventilatory mode on survival in ALS patients. Amyotrophic Lateral sclerosis & Frontotemporal Degeneration. 2014 Mar;15(1-2):55-61. PMID: 24266679.

69. Sivori M, Rodriguez GE, Pascansky D, et al. Outcome of sporadic amyotrophic lateral sclerosis treated with non-invasive ventilation and riluzole. Medicina. 2007;67(4):326-30. PMID: 17891927.

70. Lo Coco D, Marchese S, Pesco MC, et al. Noninvasive positive-pressure ventilation in ALS: predictors of tolerance and survival. Neurology. 2006 Sep 12;67(5):761-5. PMID: 16899545.

71. Bourke SC, Tomlinson M, Williams TL, et al. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. Lancet Neurology. 2006 Feb;5(2):140-7. PMID: 16426990.

72. Pinto A, Almeida JP, Pinto S, et al. Home telemonitoring of non-invasive ventilation decreases healthcare utilisation in a prospective controlled trial of patients with amyotrophic lateral sclerosis. Journal of Neurology, Neurosurgery & Psychiatry. 2010 Nov;81(11):1238-42. doi: https://dx.doi.org/10.1136/jnnp.2010.206680. PMID: 20826878.

73. Sancho J, Martinez D, Bures E, et al. Bulbar impairment score and survival of stable amyotrophic lateral sclerosis patients after noninvasive ventilation initiation. Erj Open Research. 2018 Apr;4(2). PMID: 29670892.

74. Vitacca M, Montini A, Lunetta C, et al. Impact of an early respiratory care programme with non-invasive ventilation adaptation in patients with amyotrophic lateral sclerosis. European Journal of Neurology. 2018 Mar;25(3):556-e33. PMID: 29266547.

75. Bertella E, Banfi P, Paneroni M, et al. Early initiation of night-time NIV in an outpatient setting: A randomized non-inferiority study in ALS patients. European Journal of Physical and Rehabilitation Medicine. 2017;53(6):892-9.

76. Aboussouan LS, Khan SU, Meeker DP, et al. Effect of noninvasive positive-pressure ventilation on survival in amyotrophic lateral sclerosis. Annals of internal medicine. 1997;127(6):450-3.

77. Farrero E, Prats E, Povedano M, et al. Survival in amyotrophic lateral sclerosis with home mechanical ventilation: the impact of systematic respiratory assessment and bulbar involvement. Chest. 2005;127(6):2132-8.

78. National Guideline C. Motor neurone disease: assessment and management. 2016.

79. National Guideline C. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. 2009.

80. Finder JD, Birnkrant D, Carl J, et al. Respiratory care of the patient with Duchenne muscular dystrophy: ATS consensus statement. American journal of respiratory and critical care medicine. 2004;170(4):456.

81. National Guideline C. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS) — revised report of an EFNS task force. 2012.

82. Howard ME, Piper AJ, Stevens B, et al. A randomised controlled trial of CPAP versus non-invasive ventilation for initial treatment of obesity hypoventilation syndrome. Thorax. 2017 May;72(5):437-44. doi: https://dx.doi.org/10.1136/thoraxjnl-2016-208559. PMID: 27852952.

83. Ojeda Castillejo E, de Lucas Ramos P, López Martin S, et al. Noninvasive Mechanical Ventilation in Patients With Obesity Hypoventilation Syndrome. Long-term Outcome and Prognostic Factors. Archivos de Bronconeumologia. 2013. doi: 10.1016/j.arbr.2014.06.016.

84. Masa JF, Corral J, Alonso ML, et al. Efficacy of Different Treatment Alternatives for Obesity Hypoventilation Syndrome. Pickwick Study. American Journal of Respiratory & Critical Care Medicine. 2015 Jul 01;192(1):86-95. PMID: 25915102.

85. Borel J-C, Tamisier R, Gonzalez-Bermejo J, et al. Noninvasive ventilation in mild obesity hypoventilation syndrome: a randomized controlled trial. Chest. 2012 Mar;141(3):692-702. PMID: 21885724.

86. Murphy PB, Davidson C, Hind MD, et al. Volume targeted versus pressure support non-invasive ventilation in patients with super obesity and chronic respiratory failure: a randomised controlled trial. Thorax. 2012 Aug;67(8):727-34. PMID: 22382596.

87. Piper AJ, Wang D, Yee BJ, et al. Randomised trial of CPAP vs bilevel support in the treatment of obesity hypoventilation syndrome without severe nocturnal desaturation. Thorax. 2008 May;63(5):395-401. PMID: 18203817.

88. Priou P, Gagnadoux F, Tesse A, et al. Endothelial dysfunction and circulating microparticles from patients with obstructive sleep apnea. The American journal of pathology. 2010;177(2):974-83.

89. Masa JF, Corral J, Caballero C, et al. Non-invasive ventilation in obesity hypoventilation syndrome without severe obstructive sleep apnoea. Thorax. 2016:thoraxjnl-2016-208501.

90. de Llano LAP, Golpe R, Piquer MO, et al. Short-term and long-term effects of nasal intermittent positive pressure ventilation in patients with obesity-hypoventilation syndrome. Chest. 2005;128(2):587-94.

91. Corral J, Mogollon MV, Sanchez-Quiroga MA, et al. Echocardiographic changes with non-invasive ventilation and CPAP in obesity hypoventilation syndrome. Thorax. 2018 Apr;73(4):361-8. PMID: 29146865.

92. Benhamou D, Muir JF, Raspaud C, et al. Long-term efficiency of home nasal mask ventilation in patients with diffuse bronchiectasis and severe chronic respiratory failure: a case-control study. Chest. 1997 Nov 05;112(5):1259-66. PMID: 9367466.

93. Hazenberg A, Kerstjens HAM, Prins SCL, et al. Initiation of home mechanical ventilation at home: a randomised controlled trial of efficacy, feasibility and costs. Respiratory Medicine. 2014 Sep;108(9):1387-95. doi: https://dx.doi.org/10.1016/j.rmed.2014.07.008. PMID: 25081652.

94. Munoz X, Crespo A, Marti S, et al. Comparative study of two different modes of noninvasive home mechanical ventilation in chronic respiratory failure. Respiratory Medicine. 2006 Apr;100(4):673-81. doi: https://dx.doi.org/10.1016/j.rmed.2005.08.008. PMID: 16194600.

95. Chiang L-L, Liu C-Y, Ho S-C, et al. Efficacy of nocturnal nasal positive pressure ventilation in hypercapnic patients with severe obstructive lung diseases. Chang Gung Medical Journal. 2004 Feb;27(2):98-106. PMID: 15095954.

96. Crespo A, Munoz X, Torres F, et al. Noninvasive home mechanical ventilation in elderly patients. Gerontology. 2010;56(2):150-6. doi: https://dx.doi.org/10.1159/000237874. PMID: 19752508.

97. Network AR. Domiciliary Non-Invasive Ventilation in Adult Patients: A Consensus Statement. 2012.

Introduction

Background

Chronic respiratory failure is a common medical condition characterized by the inability to maintain normal oxygen ($PaO_2 \geq 60mmHg$) and/or carbon dioxide ($PaCO_2 \leq 45mmHg$) levels. Many diseases may lead to chronic respiratory failure including chronic obstructive pulmonary disease (COPD), thoracic restrictive diseases (TRD) such as kyphoscoliosis, neuromuscular diseases (NMD), and obesity hypoventilation. [1] Associated with increased morbidity and mortality, chronic respiratory failure may range from mild to severe and may be stable or progressive.

Chronic respiratory failure may be treated with chronic mechanical ventilation. Mechanical ventilator devices are broadly classified into two categories: home mechanical ventilators (HMV) and bi-level positive airway pressure (BPAP) devices. [1] While both HMV and BPAP devices provide positive pressure ventilation, their technical features may vary and overlap considerably. Variability includes: interface (tracheostomy or mask), mode of ventilation (such as pressure targeted versus volume targeted versus volume preset), respiratory circuit (such as single-limb versus double-limb), monitoring capability, safety and alarm systems, and internal battery life. Devices also differ by level of oversight and servicing. In addition, certain device features (such as the ability to perform lung volume recruitment) may only be available with certain devices and settings.

If deemed to be feasible and safe, using these devices in the home setting is preferred to other settings such as intensive care units (ICUs), ventilator weaning units, or long-term care hospitals. Advantages of home use include lower costs, greater independence, increased quality of life, decreased risk of healthcare associated infections, and reduced use of acute care facilities.[2-4] The number of patients using long-term HMVs and BPAP devices is growing—and this patient population is increasingly differentiated from patients with acute respiratory failure who use such devices in the hospital setting.[5] In addition, the cost of caring for patients with medical conditions associated with chronic respiratory failure is also growing, with estimates as high as $50 billion annually in the United States for COPD alone.[6]

For patients who use home mechanical ventilation through a noninvasive interface, or noninvasive positive pressure ventilation (NIPPV), selecting the optimal device type (HMV versus BPAP versus continuous positive airway pressure [CPAP]) and device settings is imperative. Depending on the severity of illness, patients with chronic hypercapnic respiratory failure may require no, intermittent, or continuous ventilatory support. Failing to adequately treat chronic respiratory failure with the appropriate device could potentially result in sudden or gradual hypoxemia and/or hypercapnia. This can lead to poor quality of life, sleepiness, hospital admission, intubation, and even respiratory arrest and death. [1, 7] Some patients have progressive respiratory failure and may require advanced ventilatory capabilities as their disease progresses.

Currently, substantial variability exists regarding the usage, prescribing patterns, policies, and guidelines among noninvasive HMVs, BPAPs, and CPAPs.[8, 9] While a number of guidelines address home use of BPAPs and HMVs, there is marked variability in the conclusions, recommendations, and evidence basis for these guidelines. [10-13] With current practice and guideline variability, there is a clear need to synthesize the best available evidence to guide prescribing. [14]

This systematic review evaluates home NIPPV in adult patients with chronic respiratory failure primarily due to chronic obstructive pulmonary disease (COPD), thoracic restrictive

disorders, and neuromuscular disease. Other causes of respiratory failure were included due to additional interest.

Scope and Key Questions

Scope of the Review

This systematic review addresses initiation and continuation of home NIPPV including the effectiveness, equipment settings, and related respiratory services for patients with chronic respiratory failure. The systematic review also highlights areas of controversy and identifies needs for future research. NIPPV in other settings were excluded (e.g. long-term acute care hospital, skilled nursing facility, etc.)

Key Questions

The following Key Questions (KQs) were determined based on input from multiple key informants, Centers for Medicare and Medicaid Services (CMS) and the public (drafted KQs were posted for public comment from November 3, 2017 to November 17, 2017). The related PICOTS (population, interventions, comparisons, outcomes, timing, and setting) are listed in Table 1.

KQ1. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements considered for the initiation and continuation of noninvasive positive pressure ventilation supplied by a Home Mechanical Ventilator (HMV), Bi-level Positive Airway Pressure device (BPAP), and Continuous Positive Airway Pressure device (CPAP) in the home through a noninvasive interface for the population of patients with chronic respiratory failure due to neuromuscular diseases (NMD), thoracic restrictive diseases (TRD), chronic obstructive pulmonary diseases (COPD), or other lung diseases (cystic fibrosis, bronchiectasis)?

a. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements (e.g., reduction in hypercapnia) considered for the initiation and continuation of noninvasive positive pressure mechanical ventilation supplied by a HMV through a noninvasive interface in the home?
b. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements (e.g., reduction in hypercapnia) considered for the initiation and continuation of noninvasive positive pressure ventilation supplied as a BPAP through a noninvasive interface in the home?
c. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements (e.g., reduction in hypercapnia) considered for the initiation and continuation of noninvasive positive pressure ventilation supplied as a CPAP through a noninvasive interface in the home?

KQ2. In each of the above groups, what is the effect of HMV, BPAP, or CPAP use on patient outcomes, including mortality, hospitalization, admission/readmission to intensive care unit (ICU), need for intubation, outpatient visits, emergency room visits, disease exacerbations, quality of life (QoL), activities of daily living (ADL), dyspnea, sleep quality, exercise tolerance, and adverse events?

KQ3. What are the equipment parameters that are used in each of the above groups?

a. What are the parameters of ventilator usage (e.g., mode as determined by trigger, control and cycling variables)?
b. What are the equipment parameters that are necessary to achieve desired outcomes (e.g., flow capabilities, settings, etc.)?
c. What are the parameters of prescribed patient usage (e.g., frequency of use, duration of use throughout the day, other)?
d. In each of the above populations, what are the parameters of patient compliance with the prescribed usage of the equipment?

KQ4. What respiratory services, other than the technical support of the use of the prescribed equipment, are being provided to the above patients in the home (e.g., patient education, ongoing smoking cessation, respiratory therapist led home care)?

KQ5. What are the professional guidelines and statements that address KQ1 to KQ4?

Table 1. PICOTS (population, interventions, comparisons, outcomes, timing, and setting)

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Populations	Humans Adults 18 years and older Patients with: COPD Obesity hypoventilation syndrome Neuromuscular disease Thoracic cage abnormality Interstitial lung disease Cystic fibrosis Bronchiectasis	Animals Children (age < 18 years) Patients in whom the indication for the device was the lone diagnosis of: Any sleep apnea (obstructive, central, complex) Congestive heart failure
Interventions	Noninvasive mask or mouthpiece: HMV BPAP CPAP	Mechanical insufflation and exsufflation device / cough assist device High flow nasal cannula oxygen Negative pressure ventilators Patients with tracheostomy
Comparators	Usual care (i.e. no HMV/BPAP/CPAP) Different type of noninvasive mechanical ventilation Different modes of same equipment Other noninvasive ventilation (Studies that reported outcomes of interest (e.g. mortality) in two or more groups of patients based on different patient characteristics, laboratory criteria, ventilator parameters, or respiratory services will also be included)	Invasive ventilation (e.g. tracheostomy)
Outcomes	Mortality Hospitalization Admission/readmission to intensive care unit (ICU) Need for intubation Outpatient visits Emergency room visits Disease exacerbations Quality of life (QoL) Activities of daily living (ADL) Dyspnea Sleep quality Exercise tolerance Adverse events	None

PICOTS Elements	Inclusion Criteria	Exclusion Criteria
Timing	At least 1 month of treatment in home settings	None
Settings	Therapy (BPAP, CPAP, HMV) administered and studied at home or assisted living. Therapy could have been started at hospital / ICU but must be evaluated in the study as an outpatient treatment.	Therapy (BPAP, CPAP, HMV) administered only in: • Nursing home/skilled nursing facility (SNF) • Long term acute care facility (LTACH) • Hospital step down unit • Hospital chronic ventilator unit / ventilator weaning unit
Study design	Original data Any sample size RCTs, nonrandomized comparative studies (prospective and retrospective) Relevant systematic reviews, or meta-analyses (used for identifying additional studies) Clinical guideline	*In vitro* studies Non-original data (e.g. narrative reviews, editorials, letters, or erratum) Non-comparative observational studies, case series Qualitative studies Cost-benefit analysis Cross-sectional (i.e., non-longitudinal) studies Before-after studies Survey
Publications	Studies published in 1995 and after	Studies published before 1995

BPAP: bi-level positive airway pressure, COPD: chronic obstructive pulmonary disease, CPAP: continuous positive airway pressure, HMV: home mechanical ventilation, KQ: key question, PICOTS: populations, interventions, comparators, outcomes, timing, and settings, RCT: randomized controlled trial

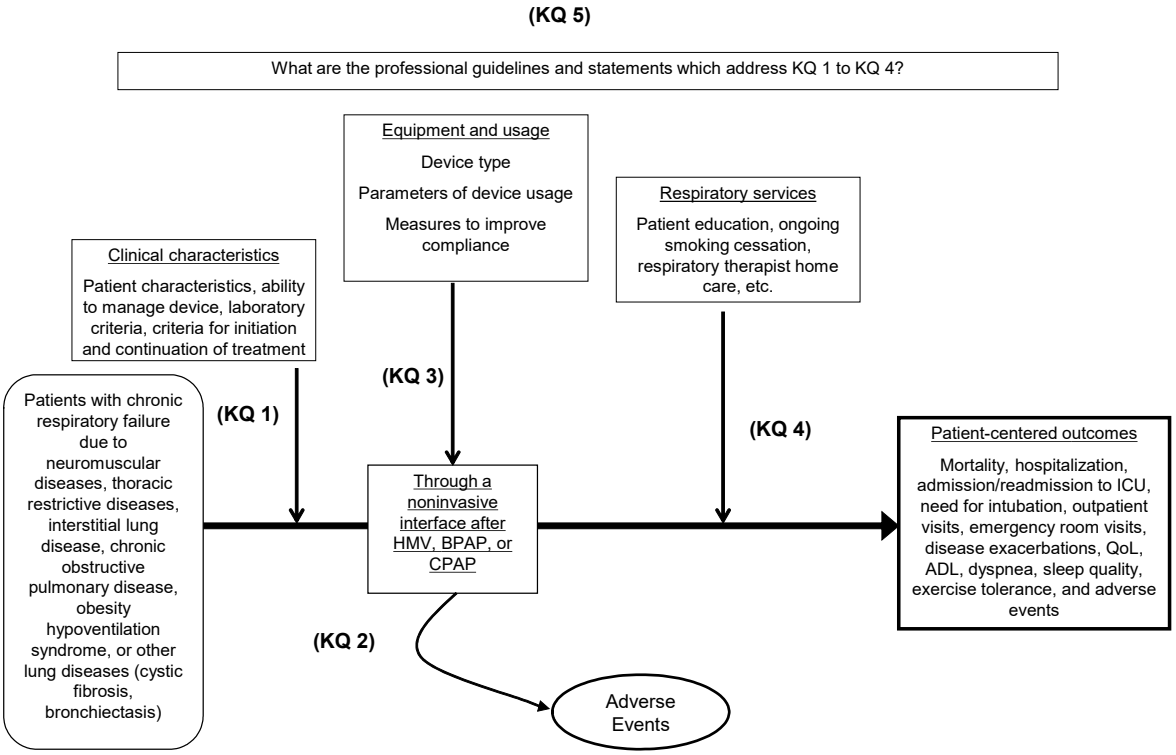
Organization of the Report

In this report, we first presented the methods used to collect, screen, and synthesize the literature. The results section was organized first by disease conditions (chronic obstructive pulmonary disease, thoracic restrictive diseases, neuromuscular disease, obesity hypoventilation syndrome, other lung diseases, and mixed disease conditions) and then by KQs. Adverse events were summarized at the end of the results, regardless of disease conditions. After the results section, we summarized our findings, findings in relation to what is known, limitations, applicability of the findings, future research needs, and conclusion.

Methods

We developed an analytic framework to guide the process of the systematic review (Figure 1). We followed the established methodologies of systematic reviews as outlined in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Comparative Effectiveness Reviews.[15] The reporting complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.[98] The study protocol is registered in the international prospective register of systematic reviews (PROSPERO #: CRD42018085676) and published on the AHRQ Web site (https://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/topicrefinement/hmv-protocol.pdf).

Figure 1. Analytic framework



Literature Search Strategy

Search Strategy

We conducted a comprehensive literature search of eight databases, including National Guideline Clearinghouse, Embase, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily, MEDLINE, Cochrane Central Registrar of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus from January 1, 1995 to June 26, 2018. We also searched Food and Drug Administration (FDA) Establishment Registration & Device Listing, ClinicalTrials.gov, Health Canada, Medicines and Healthcare Products Regulatory Agency (MHRA), AHRQ's Horizon Scanning System, conference proceedings, patient advocate group websites, and medical society websites. Relevant clinical guidelines, systematic reviews, and meta-analysis, as well as reference mining of relevant publications, were used to identify additional literature. An experienced librarian, with the help of the study investigators, developed the search strategy (Appendix B) and conducted the search. An independent information specialist peer reviewed the search strategy.

Inclusion and Exclusion Criteria

The eligible studies had to meet all the following criteria: 1) Adults 18 years and older with chronic respiratory failure due to neuromuscular diseases, thoracic restrictive diseases, chronic obstructive pulmonary diseases (COPD), obesity hypoventilation syndrome , or other lung diseases (cystic fibrosis, bronchiectasis); 2) received noninvasive positive pressure ventilation supplied by a Home Mechanical Ventilator (HMV), Bi-level Positive Airway Pressure device (BPAP), or Continuous Positive Airway Pressure device (CPAP) through noninvasive interface; 3) received at least 1 month of treatment at home or assisted living; 4) compared with usual care; different type of noninvasive mechanical ventilation, different modes of same equipment, or other noninvasive ventilation; 5) reported patient-centered outcomes, and 6) published after 1995 and in English only. We included randomized controlled trials (RCTs), nonrandomized comparative studies (prospective and retrospective), and clinical guidelines. We did not restrict study location, or sample size. The detailed inclusion and exclusion criteria can be found in Table 1.

Study Selection

Independent reviewers, working in pairs, screened the titles and abstracts of all citations using pre-specified inclusion and exclusion criteria. Studies included by either reviewer were retrieved for full-text screening. Independent reviewers, again working in pairs, screened the full-text version of eligible references. Discrepancies between the reviewers were resolved through discussions and consensus. If consensus could not be reached, a third reviewer resolved the difference.

Data Extraction

We developed a standardized data extraction form to extract study characteristics (author, study design, inclusion and exclusion criteria, patient characteristics, laboratory criteria, intervention, comparisons, outcomes, equipment parameters, respiratory services, and related items for assessing study quality and applicability). The standardized form was pilot-tested by all

study team members using 10 randomly selected studies. We iteratively continued testing the form until no additional items or unresolved questions existed. After we finalized the form, reviewers worked independently to extract study details. A second reviewer reviewed data extraction and resolved conflicts.

Assessment of Risk of Bias of Individual Studies

We evaluated the risk of bias of the included study using predefined criteria. For RCTs, we used the Cochrane Collaboration's Risk of Bias tool to assess sequence generation; allocation concealment; participant, personnel, and outcome assessor blinding; attrition bias; incomplete outcome data; selective outcome reporting; and other sources of bias (e.g. conflict of interest, imbalance of baseline characteristics).[99] Each domain was rated as high, low, or unclear risk. For observational studies, we selected appropriate items from the Newcastle-Ottawa Scale, including representativeness of the patients, ascertainment of exposure and outcomes, adequacy of follow-up, and possible conflicts of interest.[100] Each item was rated as high, low, or unclear risk. Finally, we gave an overall risk of bias for each study with focus on sequence generation, allocation concealment, and other sources of bias for RCTs and representativeness and ascertainment of exposure and outcomes for observational studies.

Data Synthesis

We qualitatively summarized key features/characteristics (e.g. study populations, design, intervention, outcomes, device model, equipment parameters, and conclusions) of the included studies and presented them in evidence tables by each disease and device.

Table 2 lists rules we used to categorize HMV device, BPAP device, or CPAP device.

Table 2. Rules used to categorize HMV, BPAP, and CPAP

Device	Rules
HMV	1) The study reported the device model/manufacturer, and the device was classified as a life support ventilator by either the FDA or the manufacturer listed information, or 2) The study reported the device to be a life support device, or 3) The study reported the device was also able to be used interchangeably with invasive mechanical ventilation through a tracheostomy or endotracheal tube, or 4) The study reported the mode to be (or the device was capable of) continuous mandatory ventilation (CMV) in either a pressure controlled PC-CMV (AC-PC) or volume controlled VC- CMV (AC-VC) configuration.
BPAP	1) The study reported the device model/manufacturer, and the device was classified as a BPAP machine or respiratory assist device (RAD) by either the FDA or the manufacturer listed information, or 2) The study reported the device to be an exclusive BPAP machine. 3) Devices were categorized as BIPAP ST if the mode utilized intermittent mandatory ventilation IMV (back up rate) with pressure support (IPAP) PC-IMV. BIPAP S if breath delivery was continuous spontaneous ventilation CSV with pressure support (IPAP) PC-CSV.
CPAP	1) The study reported the device model/manufacturer, and the device was classified as a CPAP machine either by the FDA or the manufacturer listed information, or 2) The study reported the device to be a CPAP machine.

BPAP/BIPAP: bi-level positive airway pressure, CMV: continuous mandatory ventilation, CPAP: continuous positive airway pressure, CSV: continuous spontaneous ventilation, FDA: Food and Drug Administration, HMV: home mechanical ventilation, IMV: intermittent mandatory ventilation, IPAP: inspiratory positive airway pressure, PC-CMV: pressure controlled continuous mandatory ventilation, PC-CSV: pressure controlled continuous spontaneous ventilation, PC-IMV: pressure controlled intermittent mandatory ventilation, RAD: respiratory assist device, S: spontaneous mode, ST: spontaneous/timed mode, VC-CMV: volume controlled continuous mandatory ventilation

Adverse events were grouped into adverse events likely due to device use, including 1) mask, tubing (interface) related problems, 2) problems related to nasal route; and 3) pressure, airflow related problems. All adverse events that were likely not linked to device use were grouped as other adverse events (Table 3).

Table 3. Categories of adverse events

Type of adverse events	Example
Serious adverse events	Death, hospitalization, and need for intubation were reported as primary efficacy outcomes. Acute respiratory failure Any life-threatening event/illness Any disability or permanent damage Any required intervention to prevent impairment (such as pacemaker) Any congenital anomaly/birth defect
Non serious adverse events	Skin symptoms (e.g. facial rash, nasal ulceration) Eye symptoms (e.g. dry eyes, conjunctivitis) Nose/mouth symptoms (e.g. nasal stuffiness, rhinorrhea, nosebleed, mucosal dryness, oral air leak) Gastrointestinal symptoms (e.g. gastric distension, aerophagia) Device/mask intolerance (e.g. claustrophobia, discomfort, noncompliance) Other

We conducted meta-analyses to quantitatively combine study findings. All analyses were conducted based on the intention-to-treat principle for RCTs and the number of patients initially assigned to the intervention for observational studies. We calculated odds ratio (OR) and corresponding 95-percent confidence intervals for binary outcomes. For continuous outcomes, we extracted or calculated the difference between post intervention and baseline for each group for all observational studies and for RCTs (whenever possible). When the difference between post intervention and baseline was not presented in RCTs, we extracted post intervention data instead as baseline between groups was typically balanced. When studies used different measures for the same outcome (e.g. Epworth Sleepiness Scale and Pittsburgh Sleep Quality Index for sleep quality), we calculated standardized mean difference (SMD). When studies used the same outcome measure, we used the original scale. For count data (i.e. a patient may have more than one event, e.g. number of hospital admissions), we calculated rate ratio (ratio of the incidence rate of events within a given time between the intervention and the control). For adverse events, we calculated incidence rate by adverse events and type of device. The DerSimonian and Laird random effect method was used except when the number of studies included in the comparison was less than three. The fixed effect model based on the Mantel and Haenszel method was used in that case because of concern about instability of between study variance [101] We evaluated heterogeneity between studies using I^2 indicator. Subgroup analysis was only possible when BPAP was compared with no device. We conducted ad-hoc analyses (stable COPD vs. COPD with recent exacerbation). Per peer reviewers' suggestions, we added post-hoc subgroup analyses on different levels of hypercapnia (PaCO2) used as an initiation criterion for initiation of NIPPV. The cutoffs (PaCO2>=45 to 49 mmHg, PaCO2 >=50 to 51 mmHg, PaCO2 >=52 mmHg or greater) were selected to reflect those commonly reported by the clinical guidelines and to investigate a dose response of PaCO2 and clinical outcomes. The details of the post-hoc analyses are listed in Appendix I. We compared the effect sizes from the post-hoc subgroup analyses to the pooled effect sizes of all data to evaluate reporting bias. We

were unable to use statistical methods (e.g. funnel plots, Egger's regression test, etc.) to assess publication bias because the number of studies included in the analysis was small (n<20).[102] All statistical analyses were conducted using Stata/SE version 15.1 (StataCorp LLC, College Station, TX).

Grading the Strength of Evidence

We graded the strength of the body of evidence (SOE) as per the EPC methods guide on assessing the strength of evidence.[15] We designated four outcomes to be most critical to patients and conducted SOE rating for these major outcomes (mortality, need for intubation, quality of life and all-cause hospital admissions). We produced summary of evidence tables for the major outcomes that include data source, effect size, SOE rating; and rationale for judgments made on each domain of evidence rating. Other outcomes were either encompassed in these constructs (e.g., symptoms or functional test as a part of quality of life) or were not well ascertained (e.g., cause specific hospitalization). These other outcomes are summarized in tables showing the data source, study type and the effect size.

RCTs start as high SOE and observational studies start as low SOE. We considered the following SOE domains: the methodological limitations of the studies (i.e., risk of bias); precision (based on the size of the body of evidence, number of events, and confidence intervals); directness of the evidence to the KQs (focusing on whether the outcomes were important to patients vs surrogates); consistency of results (based on qualitative and statistical approaches to evaluate for heterogeneity); and the likelihood of reporting and publication bias. When confidence intervals were very wide showing substantial benefit and harm and the number of patients was small; we rated SOE as insufficient due to severe imprecision.

Based on this assessment and the initial study design, we assigned a SOE rating as high, moderate, low, or 'insufficient evidence to estimate an effect.'

Assessing Applicability

We followed the procedures outlined in the EPC Methods Guide for Comparative Effectiveness Reviews to assess the applicability of the findings within and across studies.[15] We focused on whether the populations and interventions in existing studies are representative of current practice. For studies to have good applicability, the devices used in research need to have similar parameters and characteristics to those available in the US at the present time. The characteristics of individuals enrolled in the studies should be similar to typical patients with the targeted conditions described in the PICOTS in terms of disease severity and comorbidities and threshold for being prescribed HMV, BIPAP and CPAP. Patients in the studies should not have excessive home support than what is feasible in real life; otherwise, applicability was judged as limited.

This congruence between research and practice as it relates to applicability was evaluated qualitatively and reported narratively. Research gaps in the topic area were reported in the Discussion.

Peer Review and Public Commentary

A draft report was posted for peer review and public comments between September 10 and October 1, 2018. We revised and finalized the draft report in response to comments. However,

the findings and conclusions are those of the authors, who are responsible for the contents of the report.

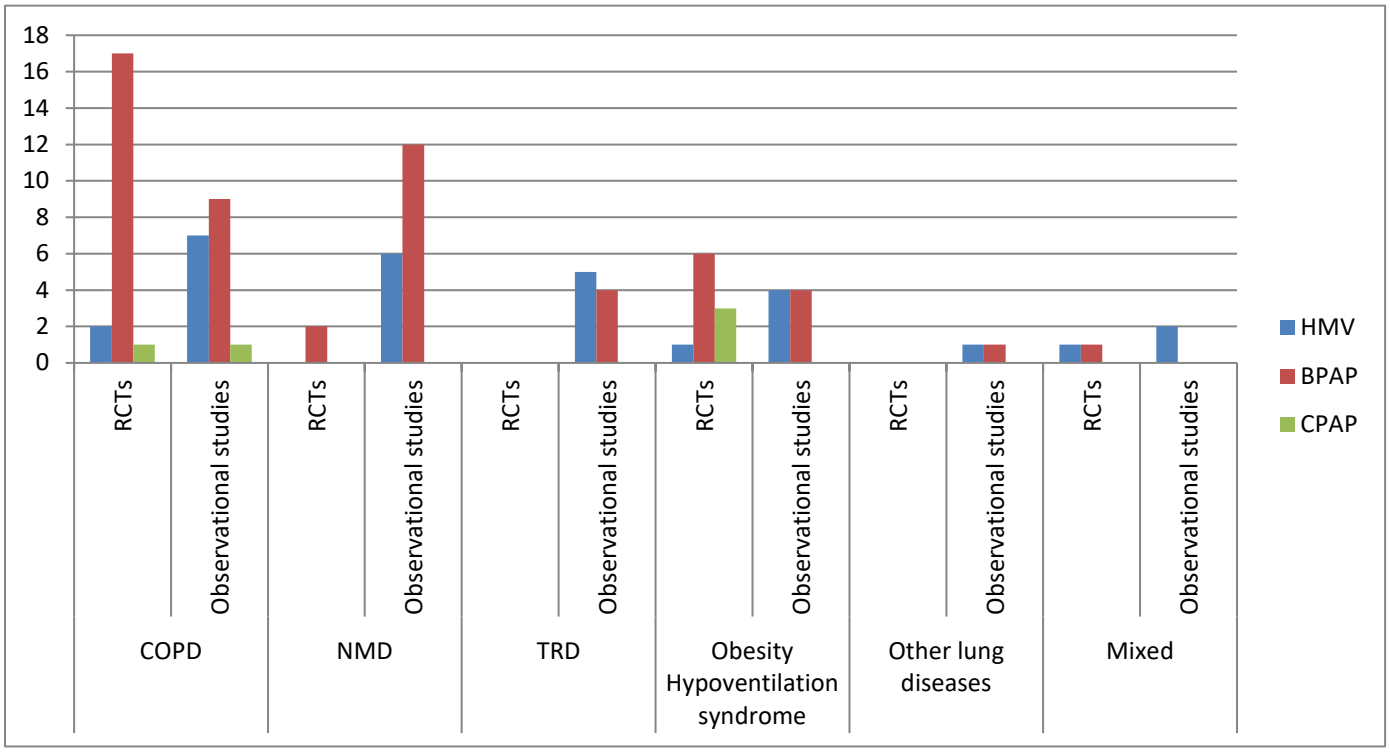
Results

Literature Searches and Evidence Base

The literature search identified 6,097 citations. An additional 86 citations were identified through reference missing, grey literature search; and from Key Informants and public comments. There were 68 original studies with a total of 53,733 patients that met inclusion criteria and were included in the systematic review (Appendix Figure A.1.). These studies addressed chronic respiratory failure due to chronic obstructive pulmonary Disease (COPD) (n=36),[7, 16-51] neuromuscular diseases (NMD) (n=16) [51, 59, 60, 65-77], thoracic restrictive diseases (TRD) (n=8),[43, 44, 51, 59-63] obesity hypoventilation syndrome (OHS) (n=13), [43, 48, 51, 61, 82-90] or other lung diseases (bronchiectasis, cystic fibrosis, interstitial lung disease, etc.) (n=2).[43, 92] In total, five studies[35, 93-96] included patients with mixed conditions and were reported as a separate section. Of these included 68 studies, 14 evaluated Home Mechanical Ventilator (HMV),[32, 35, 39, 44, 46-49, 61-63, 66, 68, 73, 74, 76, 77, 84, 90-94, 96] 48 evaluated Bi-level Positive Airway Pressure device (BPAP),[7, 16-31, 33, 34, 36-43, 45, 46, 50, 51, 59, 60, 65, 67-72, 75, 82, 83, 85-89, 95] and 5 evaluated Continuous Positive Airway Pressure device (CPAP),[23, 46, 82, 84, 87] and 8 studies evaluated HMV/BPAP mix.[47, 49, 62, 74, 76, 77, 84, 90, 91] Studies were conducted in the United States (n=5), Canada (n=1), Europe (n=53), Asia (4), Australia (3), Africa (1), and South America (1). We also identified 13 relevant clinical practice guidelines. Of these guidelines, eight gave recommendations for COPD, [52-55, 58, 97, 103, 104] ten gave recommendations for neuromuscular diseases,[52, 53, 55, 64, 80, 97, 103, 105-107] six for thoracic restrictive diseases, [52, 53, 55, 64, 97, 103] five for obesity hypoventilation syndrome, [52, 53, 55, 97, 103] three for other lung diseases, [52, 64, 97, 103] and six for all diseases in general.[52, 53, 55, 64, 97, 103]

Figure 2 summarizes the number of studies included per disease condition by device and study design. A list of the studies excluded at the full-text review stage is in Appendix C. A search of ClinicalTrials.gov identified eight ongoing clinical trials.

Figure 2. Number of studies by disease, device, and study design



BPAP: bi-level positive airway pressure, COPD: chronic obstructive pulmonary disease, CPAP: continuous positive airway pressure, HMV: home mechanical ventilation, NMD: neuromuscular diseases, RCT: randomized controlled trial, TRD: thoracic restrictive diseases

Chronic Obstructive Pulmonary Disease (COPD)

Thirty-six studies[7, 16-51] described criteria for initiation of HMV, BPAP, and/or CPAP devices in patients with COPD. A total of 51,175 patients were included. The characteristics of the studies are listed in Appendix Table D.1. Five evaluated HMV,[32, 35, 44, 46, 48] thirty BPAP,[7, 16-31, 33-38, 41-45, 50, 51] two CPAP[19, 23]and two used HMV/BPAP mix [47, 49]. These studies were conducted in the United States (n=4), Canada (n=1), Europe (n=26), Asia (3), Africa (1), and Australia (1). There were 20 randomized controlled trials (RCTs) and 16 observational studies .We also identified eight clinical practice guidelines relevant to Key Question (KQ) 1-4(Appendix Table G-2).[52-55, 58, 97, 103, 104]

Overall risk of bias in the RCTs was rated as moderate to high due to the inability to blind patients and providers, for not blinding outcome assessors, and for the possible risk of conflicts of interest due to study sponsors (Appendix Table E.1.). In observational studies, the risk of bias was also high due to the same reasons as well as the lack of clarity of patient selection methods and likelihood of prognostic imbalance (Appendix Table E.2).

KQ1. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements considered for the initiation and continuation of noninvasive positive pressure ventilation supplied by a Home Mechanical Ventilator (HMV), Bi-level Positive Airway Pressure device (BPAP), and Continuous Positive Airway Pressure device (CPAP) in the home through a noninvasive interface?

Key Points-KQ1

- The criteria used to start noninvasive positive pressure ventilation (NIPPV) were variable but most commonly included: hypercapnia (PaCO2 ranging from >45 to >56mmHg), pH>7.35, FEV1 <50% of normal, and/or hypoxia (PaO2 ranging from <55 to <60mmHg or long term oxygen use). While some studies used singular criterion to initiate NIPPV (e.g. hypercapnia), other studies used combined criteria (e.g. hypercapnia and hypoxia). For studies that used combined criteria, no two studies used the exact same laboratory parameters or cut-off points.
- NIPPV was initiated in patients with stable COPD or in patients after hospitalization for acute exacerbations.
- No studies compared the initiation criteria among different devices (HMV vs. BPAP vs. CPAP).
- Processes used to titrate NIPPV were variable and used the following targets: reduction in hypercapnia, reduction in hypoxia, achievement of target tidal volumes, and reduction in patient symptoms.

Thirty-six studies[7, 16-51] described criteria for initiation of HMV, BPAP, and/or CPAP devices in patients with COPD. Thirty-one studies[7, 16-42, 47-49, 51] evaluated patients who had not yet started home NIPPV, four studies[43-46, 50] evaluated patients with established home NIPPV use, and one study did not comment.[46]

No studies directly compared the outcomes of patients based on different criteria of device initiation or compared initiation criteria between different devices (HMV vs. BPAP vs. CPAP).

The following patient and laboratory criteria were used to start home NIPPV using a HMV, BPAP, and or CPAP device:

FEV1

Sixteen studies[7, 16, 17, 20-22, 25, 26, 28, 29, 31, 33, 34, 37, 40, 42, 50] enrolled patients with FEV1<50% of normal (GOLD stage III and IV). Other FEV1 cutoff points considered for device use were FEV1 <45%,[24] FEV1<40%,[36] FEV1 <30%,[30] FEV1 30-49%,[27] and FEV1 <30% or FEV1 <50% plus chronic respiratory failure.[32] FEV1 cutoff points were not specified in 14 studies.[18, 19, 23, 35, 38, 39, 41, 43-46 47-49, 51]

PaCO2

Twenty-five studies used PaCO2 measurements for device initiation with varying cutoff levels: PaCO2 >56mmHg,[22] >55mmHg,[40] >53mmHg,[7, 16, 30, 39, 48] >50mmHg,[17, 27, 34, 37, 41 47]>46mmHg,[33] >45mmHg,[18, 20, 21, 23, 26, 29, 31, 32, 36, 42, 45] and <52mmHg.[19]

pH

Ten studies used pH >7.35 for device initiation.[16, 20-22, 26, 30, 35, 41, 48, 50, 51] One study used pH >7.30,[7] and three studies enrolled patients with pH<7.35.[23, 39, 40]

PaO2

Seven studies used hypoxemia as an initiation criteria. Three studies enrolled patients with PaO2 < 60mmHg.[26, 29, 34] One study enrolled patients with PaO2 < 55mmHg (or less than 60mmHg + polycythemia, pulmonary hypertension, or cor pulmonale).[7] Three additional studies enrolled patients on LTOT.[26, 27, 33]

Stable disease versus recent exacerbation

Twenty-three studies enrolled patients with stable disease (no recent exacerbation).[19-21, 24-26, 28-30, 32-38, 40, 41, 44, 47-51]Eleven studies enrolled patients with recent exacerbation.[7, 17, 18, 23, 27, 31, 39, 42, 43, 45] Two studies enrolled both patients with recent exacerbation and stable disease.[16, 22] One study did not comment on stable disease versus recent exacerbation.[46]

Other

Other criteria for initiation of devices include ST90 (sleep time with oxygen saturation below 90%) <30%,[7] PtcCO2 (transcutaneous carbon dioxide) >68mmHg.[16]

Targets of device titration

Studies reported using maximum tolerated respiratory pressures (such as IPAP and/or EPAP) or other device changes needed to achieve the following goals:

1. Tidal volumes or minute ventilation: tidal volume 6mL/kg measured body weight,[17] tidal volume 7-10mL/kg,[23] tidal volume >8mL/kg,[26, 27] reproduction of daytime minute ventilation at night.[16]
2. Reduction in hypercapnia: maximum reduction in PaCO2,[32, 35, 40, 47-49] maximum reduction in PtcCO2,[16] PaCO2<45mmHg,[20, 21, 42] PaCO2<49mmHg, 20% reduction in baseline PaCO2, 5% reduction in PaCO2.[31, 34, 41]
3. Reduction in hypoxia: PaO2>60mmHg.[20, 21, 29, 31]
4. Improvement in patient symptoms (reduced respiratory rate, accessory muscle use, dyspnea).[24, 34]
5. Maximum tolerated IPAP or IPAP/EPAP difference without other identifiable targets.[21, 25, 28, 37, 38]
6. Set pressures with no titration.[36]

Device continuation

One randomized study of 26 COPD patients reported criteria for device continuation (PaCO2>45mmHg) after one night without NIPPV. After 12 months, ten patients (77%) in the

treatment withdrawal group, but only two patients (15%) in treatment continuation group, experienced clinical worsening (p = 0.0048). [45]

KQ2. What is the effect of HMV, BPAP, or CPAP use on patient outcomes, including mortality, hospitalization, admission/readmission to intensive care unit (ICU), need for intubation, outpatient visits, emergency room visits, disease exacerbations, quality of life (QoL), activities of daily living (ADL), dyspnea, sleep quality, exercise tolerance, and adverse events?

Key Points-KQ2

- BPAP (compared with no device) was associated with significantly lower mortality (strength of the body of evidence [SOE]: moderate), need for intubation (SOE: moderate), hospital admissions (SOE: low).
- HMV (compared individually with BPAP, CPAP, or no device) was associated with significantly fewer hospital admissions (SOE: low).
- Stratified analysis based on disease stability showed that in patients with stable COPD, BPAP (compared with no device) was associated with significantly lower mortality, higher activities of daily living, and reduced dyspnea. In patients with a recent exacerbation, BPAP (compared with no device) was associated with significantly reduced need for intubation.

When comparing BPAP to no device (15 RCTs[7, 19-21, 24, 25, 28-31, 33, 36, 38, 41, 42, 50] and 6 observational studies[18, 26, 27, 34, 37, 40]), BPAP was associated with significantly better outcomes in terms of mortality (moderate SOE), need for intubation (moderate SOE), number of patients with hospital admissions (low SOE), number of ER admissions, number of patients with ICU admissions, dyspnea, and shuttle walk test. We found no significant difference in other patient outcomes. Comparative effectiveness evidence with SOE rating for major outcomes is summarized in Table 4. Other outcomes are summarized in Table 5. Forest plots are available in in Appendix Table H.1.

Table 4. Major effectiveness outcomes with SOE (BPAP vs. no device in COPD patients)

Outcome	Conclusion	Study Design	Rationale for Strength of Evidence (SOE)	Overall Evidence Strength (Direction of Effect)
Mortality	OR*: 0.66; 95% CI: 0.51 to 0.87; I^2=5.9% 55 fewer per 1000 patients (103 fewer to 8 fewer)	8 RCTs[7, 20, 21 24, 28, 30, 33, 41, 42] and 5 Observational studies[18, 26, 27, 34, 40]; 1,423 pts	Risk of bias	Moderate (reduction with BPAP)
Need for intubation	OR*: 0.34; 95% CI: 0.14 to 0.83; I^2=0.0%	1 RCT[24] and 2 Observational studies[18, 34]; 267 pts	Risk of bias	Moderate (reduction with BPAP)

Outcome	Conclusion	Study Design	Rationale for Strength of Evidence (SOE)	Overall Evidence Strength (Direction of Effect)
	80 fewer per 1000 patients (148 fewer to 13 fewer)			
Quality of life (higher score represents better outcome)	SMD*: 0.15, 95% CI: -0.03 to 0.32; I^2=65.0%	9 RCTs[7, 20, 21, 42 25, 28-30, 33, 50] and 1 Observational study [34]; 977pts	Risk of bias and severe imprecision	Insufficient
Number of hospital admissions	Rate Ratio*: 0.95; 95% CI: 0.90 to 1.01; I^2=0.0%; Follow up: 18.5 months	3 RCTs[24, 33, 41] and 2 Observational studies[27, 34]; 326 pts	Risk of bias and imprecision	Low (reduction with BPAP)
	OR: 0.22; 95% CI: 0.11 to 0.43; I2=N/A 353 fewer per 1000 patients (494 fewer to 211 fewer)	1 Observational study[18]; 166 pts	SOE is determined based on study design; no other factors modify SOE	Low (reduction with BPAP)

BPAP: bi-level positive airway pressure, CI: confidence interval, ER: emergency room, ICU: intensive care unit, N/A: not applicable, OR: odds ratio, Pts: patients; RCT: randomized controlled trial, SMD: standardized mean difference, WMD: weighted mean difference.

***:** Pooled effect size from meta-analysis

Table 5. Other effectiveness outcomes (BPAP vs. no device in COPD patients)

Outcome	Conclusion	Study Design
Number of patients with hospital admissions for respiratory causes	OR: 0.98; 95% CI: 0.56 to 1.71; I^2=N/A	1 RCT[42]; 201 pts
Length of hospital stay (days)	No significant difference reported on two RCTs[41, 42]; 1 observational study [34]reported significant reduction (6.6 days vs. 16.0 days, p=0.02)	2 RCTs[41, 42] and 1 Observational Study[34]; 333 pts
Number of ER admissions	Rate Ratio: 0.72; 95% CI: 0.60 to 0.85; I^2=N/A; Follow up: 12 months	1 RCT[30]; 195 pts
Number of ICU admissions	Rate Ratio*: 0.43; 95% CI: 0.18 to 1.05; I^2=0.0%; Follow up; 21 months	1 RCT[41] and 1 Observational study[27]; 81 pts
Number of patients with ICU admissions	OR: 0.18; 95% CI: 0.07 to 0.46; I^2=N/A	1 Observational study[18] ; 166 pts
Number of exacerbations	Rate Ratio*: 0.97; 95% CI: 0.84 to 1.13; I^2=0.0%; Follow up; 11.4	3 RCTs[19-21, 42] and 1 Observational Study[34]; 352 pts
Number of patients with exacerbations	OR: 0.84; 95% CI: 0.26 to 2.68; I^2=N/A	1 RCT[24]; 44 pts
Activities of daily living (ADL) (higher score represents better outcome)	SMD*: 0.08, 95% CI: -0.12 to 0.28; I^2=46.7%	3 RCTs[20, 25, 42]; 318 pts
Dyspnea (higher score represents better outcome)	SMD*: 0.22, 95% CI: 0.03 to 0.42; I^2=44.3%	6 RCT[19, 20, 25, 29, 41, 42]; 468 pts

Outcome	Conclusion	Study Design
Sleep quality (higher score represents better outcome)	SMD*:0.12; 95% CI: -0.06 to 0.30, I^2=0.0%	2 RCTs[19, 41]; 120 pts
6-minute walk distance test	WMD*: 23.80 meters; 95% CI: -12.24 to 59.84; I^2=55.2%	7 RCTs[19-21, 29, 31, 36, 38, 41] ; 271 pts
Shuttle walk test	WMD: 72 meters; 95% CI: 12.9 to 131; I2=N/A	1 RCT[25]; 45 pts

BPAP: bi-level positive airway pressure, CI: confidence interval, ER: emergency room, ICU: intensive care unit, N/A: not applicable, OR: odds ratio, Pts: Patients; RCT: randomized controlled trial, SMD: standardized mean difference, WMD: weighted mean difference.

*: Pooled effect size from meta-analysis

Two observational studies compared HMV to no device in COPD patients.[17, 39] There was no significant difference in mortality (OR= 0.56, 95% CI: 0.29 to 1.08). However, patients in the HMV group had significantly less hospital admissions (Rate Ratio= 0.50; 95% CI: 0.35 to 0.71; p<0.01).

A large retrospective study of administrative claims data compared hospital admissions between HMV (315 patients), BPAP (9,156 patients), and CPAP (39,385 patients).[46] The HMV group were found to have significantly larger reduction of any hospitalization (post-treatment period vs. pre-treatment period) (OR=0.21, 95% CI: 0.15 to 0.30) than those with CPAP (OR=0.67, 95% CI: 0.65 to 0.70) or BPAP (OR=0.40, 95% CI: 0.37 to 0.43) (p<0.001). For COPD-related hospitalization, the HMV group also had significantly larger reduction (OR=0.29, 95% CI: 0.18 to 0.47) than the CPAP group (OR=0.52, 95% CI: 0.47 to 0.59) (p=0.01).

One RCT compared CPAP with BPAP in 49 COPD patients who survived an episode of acute hypercapnic respiratory failure (AHRF).[23] After a follow-up of 12 months, 7 out of 23 patients in the BPAP group developed severe COPD exacerbation with AHRF while 14 out of 26 patients in the CPAP group had severe exacerbation with AHRF (OR: 0.38, 95% CI: 0.12 to 1.22; p=0.10). Eight patients in the BPAP group withdrew from the study, compared with four patients in the CPAP group (OR: 2.93; 95% CI: 0.75 to 11.52; p=0.12).

One RCT compared BPAP volume assured pressure support ventilation to BPAP ST.[16] The BPAP volume assured pressure support ventilation group had significantly shorter hospital stay than the BPAP ST group (3.3 days vs. 5.2 days, p=0.02). There was no significant difference on mortality (OR=0.47, 95% CI: 0.04 to 5.69; p=0.56), exercise tolerance, dyspnea, quality of life, or sleep quality after 3-month follow-up.

One RCT compared HMV (pressure-controlled ventilation) to HMV (pressure support ventilation).[32] There were no significant difference on quality of life (Severe Respiratory Insufficiency Questionnaire Summary Score), and 6-minute walk distance test.

One RCT compared high intensity HMV (pressure-controlled ventilation) to low intensity HMV (pressure-controlled ventilation).[47] After 6 weeks, there was no statistical difference between two groups on quality of life (the COPD assessment test, WMD: 2.30, 95% CI: -2.35 to 6.95).

One retrospective observational study compared BPAP ST started in acute exacerbation of COPD (AECOPD) to BPAP ST started in stable disease and found significantly shorter survival time in the AECOPD group (median: 28.6 months vs. 52.6 months, p=0.03).[22]

One retrospective observational study compared HMV/BPAP mix started in AECOPD to HMV/BPAP mix started in stable COPD.[49] There were no difference on number of hospital admission for respiratory causes (changes before and after NIPPV per year: -0.6 vs. -0.3, p=0.46) and length of hospital stay for respiratory causes (changes before and after NIPPV per year: -9.8 days vs. -1.7 days, p=0.09).

One RCT compared patients treated by BPAP for 6 months to patients treated by BPAP for more than 6 months.[45] Patients who received BPAP more than 6 months had significantly increases (43%) in the 6-minute walk distance test, while the group with 6-month treatment decreased by 11% (p =0.04). No significant difference was found on quality of life (the Saint George's Respiratory Questionnaire) between the two groups.

Comparative effectiveness evidence with SOE rating for major outcomes is summarized in Table 6. Other outcomes are summarized in Table 7. Forest plots are available in in Appendix Table H.1.

Table 6. Major effectiveness outcomes with SOE (HMV, BPAP and CPAP in COPD patients)

Comparison	Outcome	Conclusion	Study Design (sample size)	Rationale for Strength of Evidence (SOE)	Overall Evidence Strength (Direction of Effect)
HMV vs. no device	Mortality	OR*:0.56; 95% CI: 0.29 to 1.08, I^2=84.3%	2 Observational studies[17, 39]	Risk of bias, heterogeneity and severe imprecision	Insufficient
	Number of hospital admissions	Rate Ratio: 0.50; 95% CI: 0.35 to 0.71; I^2=N/A	1 Observational study (93 patients) [17],	SOE is determined based on study design; no other factors modify SOE	Low (reduction with HMV)
HMV vs. CPAP	Number of patients with hospitalization	Significantly less in HMV than CPAP (p<0.001)	1 Observational study[46]	SOE is determined based on study design; no other factors modify SOE	Low (reduction with HMV)
HMV vs. BPAP	Number of patients with hospitalization	Significantly less in HMV than BPAP (p<0.001)	1 Observational study[46]	SOE is determined based on study design; no other factors modify SOE	Low (reduction with HMV)

Comparison	Outcome	Conclusion	Study Design (sample size)	Rationale for Strength of Evidence (SOE)	Overall Evidence Strength (Direction of Effect)
BPAP volume assured pressure support ventilation vs. BPAP ST	Mortality	OR:0.47; 95% CI: 0.04 to 5.69; p=0.56	1 RCT[16]	Severe imprecision	Insufficient
	Quality of life (Saint George's Respiratory Questionnaire, higher score represents worse outcome)	WMD: -4.700; 95% CI: -15.97 to 6.57; I^2=N/A	1 RCT[16]	Severe imprecision	Insufficient
HMV (pressure controlled ventilation) vs. HMV (pressure support ventilation)	Quality of life (Severe Respiratory Insufficiency Questionnaire Summary Score, higher score represents better outcome)	WMD: -0.14, 95% CI: -4.90 to 4.60; I^2=N/A	1 RCT[32]	Severe imprecision	Insufficient

AECOPD: acute exacerbation of chronic obstructive pulmonary disease, BPAP: bi-level positive airway pressure, CI: confidence interval, COPD: chronic obstructive pulmonary disease, CPAP: continuous positive airway pressure, HMV: home mechanical ventilation, N/A: not applicable, NOS: not otherwise specified, OR: odds ratio, RCT: randomized controlled trial, ST: spontaneous/timed mode, WMD: weighted mean difference

*: Pooled effect size from meta-analysis

Table 7. Other effectiveness outcomes (HMV, BPAP and CPAP in COPD patients)

Comparison	Outcome	Conclusion	Study Design (sample size)
HMV vs. CPAP	Number of patients with COPD related hospitalization	Significantly less in HMV than CPAP (p=0.01)	1 Observational study[46]
BPAP vs. CPAP	Number of patients with exacerbations	OR: 0.38, 95% CI: 0.12 to 1.22; p=0.10	1 RCT[23]
BPAP volume assured pressure support ventilation vs. BPAP ST	Length of hospital stay (days)	-1.9 days, p=0.02	1 RCT[16]
	Shuttle Walk Test	WMD: -4.00 meters; 95% CI:-54.24 to 46.24; I^2=N/A	1 RCT[16]
	Sleep quality (Epworth Sleepiness Scale, higher score represents worse outcome)	WMD: -2.700; 95% CI: -6.07 to 0.67; I^2=N/A	1 RCT[16]
	Dyspnea (Medical research council scale, higher score represents worse outcome)	WMD: -0.700; 95% CI: -1.60 to 0.20; I^2=N/A	1 RCT[16]
HMV (pressure	6-minute walk distance test (meters)	WMD: 14; 95% CI: -42 to 70; I^2=N/A	1 RCT[32]

Comparison	Outcome	Conclusion	Study Design (sample size)
controlled ventilation) vs. HMV (pressure support ventilation)			
BPAP ST started in AECOPD vs. BPAP ST started in stable COPD	Survival time	28.6 months vs. 52.6 months, p=0.03	1 Observational study[22]
BPAP NOS for 6 months vs. BPAP NOS for more than 6 months	6-minute walk distance test	43% increase vs. 11 decrease, p=0.04	1 RCT[45]
	Quality of life (Saint George's Respiratory Questionnaire)	57 vs. 53, p=0.80	1 RCT[45]
HMV/BPAP mix started in AECOPD vs. HMV/BPAP mix started in stable disease	Number of hospital admission for respiratory causes (changes before and after the intervention)	-0.6 vs. -0.3, p=0.46	1 Observational study[49]
	Length of hospital stay for respiratory causes (days per year, changes before and after the intervention)	-9.8 vs. -1.7, p=0.09	1 Observational study[49]
HMV/BPAP mix (pressure controlled ventilation) (high intensity) vs. HMV/BPAP mix (pressure support ventilation) (low intensity)	Quality of life (the COPD assessment test, higher score represents worse outcome)	WMD: 2.30, 95% CI: -2.35 to 6.95, I2=N/A	1 RCT[47]

AECOPD: acute exacerbation of chronic obstructive pulmonary disease, BPAP: bi-level positive airway pressure, CI: confidence interval, COPD: chronic obstructive pulmonary disease, CPAP: continuous positive airway pressure, HMV: home mechanical ventilation, N/A: not applicable, NOS: not otherwise specified, OR: odds ratio, RCT: randomized controlled trial, ST: spontaneous/timed mode, WMD: weighted mean difference

*: Pooled effect size from meta-analysis

We conducted subgroup analyses between stable and recent exacerbation in studies comparing BPAP to no device (Table 8). In patients with stable COPD, BPAP was associated with significantly lower mortality, higher activities of daily living, and reduced dyspnea. In patients with recent exacerbation, BPAP was associated with significantly reduced need for intubation. More improvement in dyspnea were found in patients with stable COPD (p=0.005). There was no other significant difference between stable COPD and recent exacerbation.

Table 8. Subgroup analysis of studies in patients with stable COPD vs. patients with a recent exacerbation in studies comparing BPAP to no device

Outcome	COPD	Conclusion	Interaction p value
Mortality	Stable	OR:0.62; 95% CI:0.42 to 0.92	0.65
	Recent exacerbation	OR:0.71; 95% CI: 0.47 to 1.08	
Need for intubation	Stable	OR:0.43; 95% CI:0.08 to 2.46	0.75
	Recent exacerbation	OR: 0.31; 95%CI: 0.11 to 0.89	
Number of exacerbations	Stable	Rate ratio:0.96; 95% CI: 0.81 to 1.14	0.81
	Unstable	Rate Ratio:1.00; 95% CI: 0.76 to 1.32	
Number of hospital admissions	Stable	Rate Ratio:0.86; 95% CI: 0.68 to 1.09	0.95
	Unstable	Rate Ratio: 0.88; 95% CI: 0.44 to 1.77	
Number of ICU admissions	Stable	Rate Ratio:0.52; 95% CI: 0.18 1.53	0.54
	Unstable	Rate Ratio:0.29; 95% CI:0.06 to 1.39	
Activities of daily living (ADL) (higher score represents better outcome)	Stable	SMD:0.22; 95% CI: 0.00 to 0.44	0.07
	Unstable	SMD: -0.02; 95% CI: -0.16 to 0.12	
Quality of life (higher score represents better outcome)	Stable	SMD: 0.24; 95%CI:-0.04 to 0.52	0.17
	Unstable	SMD: 0.03; 95% CI:-0.08 to 0.14	
Dyspnea (higher score represents better outcome)	Stable	SMD: 0.33; 95% CI:0.15 to 0.50	0.005
	Unstable	SMD: 0.01; 95% CI: -0.13 to 0.15	
6-minute walk distance test	Stable	WMD: 21.45; 95% CI: -17.32 to 60.21	0.65
	Unstable	WMD: 57.00; 95% CI: -93.03 to 207.03	

CI: confidence interval, COPD: chronic obstructive pulmonary disease, ICU: intensive care unit, OR: odds ratio, SMD: standardized mean difference, WMD: weighted mean difference

Appendix I. listed the post-hoc subgroup analyses of the levels of hypercapnia (PaCO2) used as a criterion for the initiation of NIPPV. These findings suggested that higher PaCO2 levels may be associated with improved quality of life compared to lower levels (PaCO2 ≥52 mmHg: SMD 0.22; 95% CI: -0.05 to 0.50 vs. PaCO2 ≥50 to 51: 0.97; 95% CI: 0.36, 1.58 vs. PaCO2 ≥45 to 49: -0.05; 95% CI: -0.16 to 0.06). The effect size for quality of life for cutoff PaCO2 ≥50 to 51 mmHg was also higher than the overall effect size (SMD: 0.97; 95% CI: 0.36 to 1.58 vs. SMD: 0.15, 95% CI: -0.03 to 0.32); however, this was driven by a single nonrandomized study. Differences in mortality and hospital readmissions favored higher initiation criteria but were not statistically different (Appendix Figures H.11-13.). There were no other significant difference between the subgroups and overall pooled effect sizes.

KQ3. What are the equipment parameters that are used? a) What are the parameters of ventilator usage (e.g. mode as determined by trigger, control and cycling variables)? b) What are the equipment parameters that are necessary to achieve desired outcomes (e.g. flow capabilities, settings, etc.)? c) What are the parameters of prescribed patient usage (e.g. frequency of use, duration of use throughout the day, other)? d) In each of the above populations, what are the parameters of patient compliance with the prescribed usage of the equipment?

Key Points-KQ3

- For BPAP devices, the modes utilized were BPAP S, BPAP ST, BPAP volume assured pressure support ventilation, and pressure controlled ventilation.
- For HMV devices, the modes utilized were pressure support ventilation and pressure controlled ventilation.
- For CPAP devices, the mode utilized was CPAP.
- Prescribed device usage per day varied from ≥5-8 hours (in seven BPAP studies) and >12 hours (in one HMV study). Actual mean device usage per day ranged from 4.5-9.0 hours.

Thirty studies evaluated patients who used BPAP devices.[16, 18, 19, 31, 35, 38, 44-46 7, 16, 17, 20-30, 33, 34, 36, 37, 41-43, 50, 51] Seventeen studies evaluated patients who used BPAP ST.[7, 16, 17, 20-23, 26-30, 34, 36, 37, 41, 43, 51] BPAP ST equipment parameters included IPAP, EPAP, and a spontaneous/timed (ST) breathing mode with a backup respiratory rate. Three studies evaluated patients who used BPAP S.[24, 25, 33] BPAP S equipment parameters included IPAP, EPAP and a spontaneous (S) mode without a backup respiratory rate. One study evaluated patients who used BPAP volume assured pressure support ventilation.[16] Volume assured pressure support ventilation equipment parameters included IPAP, EPAP, and a target minute ventilation. Three studies evaluated patients who used BPAP pressure controlled ventilation.[35, 44, 50] BPAP pressure controlled ventilation equipment parameters included IPAP, EPAP, backup respiratory rate, and inspiratory time. Six studies evaluated patients who used BPAP NOS (unclear which mode).[18, 19, 31, 38, 45, 46] Four studies evaluated patients who used HMV devices in the pressure support ventilation and pressure controlled ventilation modes.[32, 35, 44, 48] Pressure support equipment parameters included inspiratory pressure, PEEP, inspiratory flow trigger and expiratory flow trigger. Pressure controlled ventilation parameters included inspiratory pressure, PEEP, inspiratory time, and respiratory rate. One study did not specify the mode of HMV.[46] Two studies evaluated patients who used a mixture of bi-level BPAP and HMV devices.[47, 49] Two studies evaluated patients who used CPAP devices.[19, 23] CPAP equipment parameters included CPAP.

Twenty-seven studies reported the model and manufacturer of the device used.[7, 16, 17, 19-22, 24-29, 31-36, 38, 40-42, 47-51]One study reported the manufacturer of the device used only.[30]

For BPAP, seven studies reported the prescribed daily device use which included ≥5 hours,[31, 34] ≥6 hours,[7, 19, 30] and >8 hours.[23, 25] For HMV, only one study reported the prescribed daily device use, which was >12 hours.[48] Actual daily device usage ranged from mean of 4.5-9.0 hours/day. Actual mean recorded IPAP ranged from 12.0-31.6 cmH2O. Actual mean recorded EPAP ranged from 3.9-6.0 cmH2O. Actual respiratory rates ranged from 8.0-20.7 breaths/minute.

KQ4. What respiratory services, other than the technical support of the use of the prescribed equipment, are being provided to the above patients in the home (e.g. patient education, ongoing smoking cessation, respiratory therapist led home care)?

Key Points-KQ4

- Evidence is lacking to determine the effect of specific respiratory home services on outcomes.
- Respiratory services provided in the home included: telephone hotline staffed by nurses, scheduled phone calls by respiratory therapists, home visits by respiratory therapists, smoking cessation, and a comprehensive home care program with evaluation and treatment of physical, occupational, and dietary needs.

Fifteen studies[7, 16, 19, 22, 23, 25, 27, 30, 33, 36, 49, 51, 96] described respiratory services provided in the home. These services included a telephone hotline staffed by healthcare professionals including nurses, respiratory therapists, and/or others,[16, 22, 23, 30, 33, 96] scheduled phone calls by nurses, respiratory therapists and/or others,[19, 25, 27, 36] home visits by nurses, respiratory therapists, and/or others,[19] and smoking cessation services NOS.[7, 49] One study described provision of a home care program that included initial evaluation of physical, occupational, and dietary needs; monthly physician visits; monthly education about treatments and correct medication use and coping strategies; periodic phone calls.[27]

KQ5. What are the professional guidelines and statements which address KQ 1 to KQ 4?

Information related to clinical guidelines can be found in Appendix Table G.2.

Initiation Criteria and Effectiveness (KQ1 and KQ2):

Six guidelines gave recommendations regarding initiation criteria in patients with COPD, with recommendations ranging from insufficient evidence to recommend NIPPV in COPD to presenting specific initiation criteria. No guidelines specifically addressed criteria to initiate NIPPV via HMV versus BPAP.

2015 International (meeting in Pescara, Italy)[54]

Long-term non-invasive ventilation should be reserved to individual patients. Once stable hypercapnia is proven, NIPPV may improve survival and health status. Therefore, despite recent studies adding some new data, the authors cannot recommend the widespread use of this therapeutic intervention after an episode of acute-on-chronic respiratory failure in COPD.

2012 Australia[13]

Nocturnal non-invasive ventilation is indicated in COPD with PaCO2 > 50 mmHg, where there is evidence of signs and symptoms of sleep disordered breathing, and full polysomnogram (PSG) demonstrates nocturnal hypoventilation (based on a measure of PaCO2) that is not corrected or made worse by long term oxygen therapy alone.

2011 Canada[53]

The use of long-term NIPPV cannot be widely recommended in patients with stable COPD. Long-term NIPPV in COPD should only be considered on an individual basis. One subgroup of patients with COPD in which long-term NIPPV could be considered are those with severe hypercapnia (PaCO2 >55 mmHg) experiencing repeated episodes of acute hypercapnic

respiratory failure that require in-hospital ventilatory support. However, definitive proof of efficacy of long-term NIPPV in these patients will need to await future studies.

2010 Germany[52]

Long-term NIPPV is indicated when there are symptoms that indicate chronic respiratory failure and reduced quality of life and one of the following criteria:

- chronic daytime hypercapnia with PaCO2 ≥ 50mmHg
- nocturnal hypercapnia with PaCO2 ≥ 55mmHg
- stable daytime hypercapnia with 46–50mmHg and a rise in PTcCO2 to ≥ 10mmHg during sleep
- stable daytime hypercapnia with PaCO2 46–50mmHg and at least 2 acute exacerbations accompanied by respiratory acidosis that required hospitalization within the last 12 months
- following an acute exacerbation needing ventilatory support, according to clinical estimation)

2010 United Kingdom[58]

Long-term NIPPV should be considered in patients with chronic hypercapnic ventilatory failure who have required assisted ventilation (whether invasive or non-invasive) during an exacerbation or who are hypercapnic or acidotic on long-term oxygen therapy.

1999 United States[57]

Long-term NIPPV is indicated when there are symptoms (e.g. fatigue, dyspnea, morning headache, etc.) and one of the following:

- PaCO2 > 55 mm Hg
- PaCO2 of 50 to 54 mm Hg and nocturnal desaturation
- PaCO2 of 50 to 54 mm Hg and hospitalization related to recurrent (two in a 12-month period) episodes of hypercapnic respiratory failure.

Device Characteristics (KQ3):

One guideline gave recommendations on device characteristics and titration. No guidelines specifically addressed criteria to initiate NIPPV via HMV versus BPAP.

2010 Germany[52]

The aim of the ventilation is to normalize PaCO2; sufficiently high ventilation pressures are required to achieve this. Controlled ventilation mode with ventilation pressures from 20 to 40 megabar (mbar). Pressure escalation until normocapnia or maximum tolerance is reached. Rapid increase in inspiratory pressure (0.1 to 0.2 seconds). PEEP can be useful for assisted- or assisted-controlled ventilation. Minimal duration of therapy: 4.5 hours/day. The introduction of non-invasive ventilation in the hospital can take up to two weeks.

Respiratory Services (KQ4):

We did not identify guidelines that provided recommendations regarding home respiratory services for patients with COPD.

Thoracic Restrictive Diseases

Eight [43, 44, 51, 59-63] studies with a total of 204 patients were included. The characteristics of the studies are listed in appendix Table D.1. Three evaluated HMV, [44, 61, 63] four BPAP, [43, 51, 59, 60] zero CPAP and one used HMV/BPAP mix. [62] These studies were conducted in the United States (n=0), Canada (n=0), Europe (n=7), and Asia (n=1). All studies were observational. We also identified six clinical practice guidelines relevant to KQ1-4(Appendix).[52, 53, 55, 64, 97, 103]

Overall risk of bias of the included studies was rated as moderate due to unclear conflict of interest (62.5%) and inadequate follow-up (37.5%) in the observational studies (Appendix Tables E.1 and E.2.).

KQ1. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements considered for the initiation and continuation of noninvasive positive pressure ventilation supplied by a Home Mechanical Ventilator (HMV), Bi-level Positive Airway Pressure device (BPAP), or Continuous Positive Airway Pressure device (CPAP) in the home through a noninvasive interface?

Key Points-KQ1

- The criteria used to start NIPPV were variable and most commonly included: PaCO2 >45mmHg, FVC<40% or MIP <60cmH2O or nocturnal SaO2 < 88% for ≥ 5 consecutive minutes.
- All studies enrolled patients with stable disease (not in acute respiratory failure).
- No studies compared the initiation criteria between different devices or evaluated criteria for device continuation.
- Processes used to titrate NIPPV were variable and used the following targets: reduction in hypercapnia, reduction in hypoxia, achievement of target tidal volumes, and reduction in patient symptoms.

Eight studies[43, 44, 51, 59-63] described criteria for initiation of HMV, BPAP, and/or CPAP devices in patients with TRD. Six studies[43, 51, 59-62] evaluated patients who had not yet started home device use and two studies[44, 63] evaluated patients with established home device use.

No studies directly evaluated differences between the criteria to start different devices (HMV vs. BPAP vs. CPAP). Indirectly, the criteria used to start each device were not different.

The following patient and laboratory criteria were used to start home NIPPV using a HMV, BPAP, and or CPAP device:

Included Diseases

Studies enrolled patients with the following diagnoses: kyphoscoliosis, fibrothorax, thoracoplasty, or post-tuberculosis sequelae. Only one study defined the definition of kyphoscoliosis by Cobb scoliosis angle >90 degrees.[61]

PaCO2

Five studies included patients with hypercapnia: PaCO2 >45mmHg,[51, 59, 60, 62]and >47mmHg.[61]

Stable disease versus recent exacerbation

Five studies enrolled patients with stable disease (no infection in past 3 months, stable PaCO2 for past 3 months, no hospital admission in past 1 month, absence of severe acidosis)[59-62] [51](563,593,1723,30000), and 3 studies did not comment on stability of disease.[43, 44, 63]

Others

Two studies also included patients with FVC<40% or MIP <60cmH2O, or nocturnal SaO2 < 88% for ≥ 5 consecutive minutes.[59, 60]

Targets of device titration

Most studies reported using maximum tolerated respiratory pressures (such as IPAP and/or EPAP) needed to achieve the following stated goals: "desired tidal volume" NOS,[43] normal PaCO2 or a reduction in baseline PaCO2 by ≥10mmHg,[59] maximum change in blood gasses NOS,[60] and maximum reduction in PaCO2 as well as optimal patient tolerance, lowest air leakage, and nocturnal SaO2>90%.[61]

Device continuation

No studies described criteria for device continuation.

KQ2. What is the effect of HMV, BPAP, or CPAP use on patient outcomes, including mortality, hospitalization, admission/readmission to intensive care unit (ICU), need for intubation, outpatient visits, emergency room visits, disease exacerbations, quality of life (QoL), activities of daily living (ADL), dyspnea, sleep quality, exercise tolerance, and adverse events?

Key Points-KQ2

- HMV (compared with no device) was associated with significantly lower mortality (SOE: low).
- No studies compared outcomes between HMV and BPAP devices.

One observational study of 33 patients with kyphoscoliosis and chronic respiratory insufficiency compared HMV plus long-term oxygen therapy to long-term oxygen therapy.[63] With a follow-up from 1 year to 11 years, patients treated with HMV plus long-term oxygen were found to have significantly lower mortality than those treated with long-term oxygen alone (OR=0.13, 95% CI: 0.03 to 0.67).

In another observational study, ten stable patients with mild-to-moderate chronic respiratory failure (PaCO2 between 45 mm Hg and 55 mm Hg) were treated with HMV at night for 3 months.[62] These patients were compared with ten matching patients who received standard care without HMV. Patients with HMV were found to have significantly better improvements in inspiratory threshold loading test (WMD: 450.00; 95% CI: 273.17 to 626.83), cycle ergometer test (WMD: 240.0; p<0.001), and shuttle walking test (WMD: 100.00; p<0.001) than patients with standard care. Comparative effectiveness evidence with SOE rating for major outcomes is summarized in Table 9. Other outcomes are summarized in Table 10.

Table 9. Major effectiveness outcomes with SOE (HMV vs. no device in patients with thoracic restrictive diseases)

Outcome	Conclusion	Study Design (sample Size)	Rationale for Strength of Evidence (SOE)	Overall Evidence Strength (Direction of Effect)
Mortality	OR:0.13; 95% CI: 0.03 to 0.67, I2=N/A 433 fewer per 1000 patients (735 fewer to 131 fewer)	1 Observational study (33 patients) [63]	SOE is determined based on study design; no other factors modify SOE.	Low (reduction with HMV)

CI: confidence interval, HMV: home mechanical ventilation, N/A: not applicable, OR: odds ratio, WMD: weighted mean difference

Table 10. Other effectiveness outcomes (HMV vs. no device in patients with thoracic restrictive diseases)

Outcome	Conclusion	Study Design (sample Size)
Physical activity (Inspiratory Threshold Loading test, endurance time)	WMD: 450.00; 95% CI: 273.17 to 626.83; I^2=N/A	1 Observational study (20 patients) [62]
Physical activity (Cycle Ergometry Test, endurance time)	WMD: 240.00; p<0.001; I2=N/A	1 Observational study(20 patients) [62]
Physical activity (Inspiratory Threshold Loading test, endurance time)	WMD: 100.00; p<0.001; I^2=N/A	1 Observational study(20 patients)[62]

CI: confidence interval, HMV: home mechanical ventilation, N/A: not applicable, OR: odds ratio, WMD: weighted mean difference

KQ3. What are the equipment parameters that are used? a) What are the parameters of ventilator usage (e.g. mode as determined by trigger, control and cycling variables)? b) What are the equipment parameters that are necessary to achieve desired outcomes (e.g. flow capabilities, settings, etc.)? c) What are the parameters of prescribed patient usage (e.g. frequency of use, duration of use throughout the day, other)? d) In each of the above populations, what are the parameters of patient compliance with the prescribed usage of the equipment?

Key Points-KQ3

- For BPAP devices, the modes utilized were BPAP ST and BPAP NOS (unclear which mode)
- For HMV devices, the modes utilized were pressure-controlled ventilation, volume assist controlled ventilation, and volume/pressure cycled NOS.
- Prescribed usage included ≥7 hours/day. Actual mean device usage per day ranged from 6.0-7.3 hours.

Four studies evaluated patients who used BPAP devices.[43, 51, 59, 60] Two studies evaluated patients who used BPAP ST.[43, 51] BPAP ST equipment parameters included IPAP, EPAP, and a spontaneous/timed (ST) breathing mode with a backup respiratory rate. No studies evaluated patients who used BPAP S. Two studies evaluated patients who used BPAP NOS (unclear if ST or S mode).[59, 60] No studies evaluated patients who used volume assured pressure support (VAPS) ventilation. Five studies evaluated patients who used HMV devices. [35, 44, 61-63] HMV equipment parameters used were pressure controlled ventilation,[35, 44] volume assist control ventilation,[62] and volume/pressure cycled NOS.[61, 63] No studies evaluated patients who used CPAP devices.

Six studies reported the model and manufacturer of the device used.[51, 59-63] Two studies did not report the model or manufacturer of the device used.[43, 44]

The prescribed daily device use of included studies was ≥7 hours daily.[59] Actual device usage ranged from mean of 6.0-7.3 hours/day. Actual mean recorded IPAP ranged from 20.9-22.0 cmH2O. Actual mean recorded EPAP ranged from 4.2-5.3 cmH2O. One study reported actual respiratory rates of mean 19.1 breaths/minute.

KQ4. What respiratory services, other than the technical support of the use of the prescribed equipment, are being provided to the above patients in the home (e.g. patient education, ongoing smoking cessation, respiratory therapist led home care)?

Key Points-KQ4

- Evidence is lacking to determine the effect of specific respiratory home services on outcomes.
- Respiratory services provided in the home included: telephone hotline

One study described respiratory services provided in the home, which included a telephone hotline staffed by healthcare professionals including nurses, respiratory therapists, and/or others.[59]

KQ5. What are the professional guidelines and statements which address KQ 1 to KQ 4?

Information related to clinical guidelines can be found in Appendix Table G.4.

Initiation Criteria and Effectiveness (KQ1 and KQ2):

Six guidelines gave recommendations regarding initiation criteria in patients with thoracic restrictive diseases. No guidelines specifically addressed criteria to initiate NIPPV via HMV versus BPAP.

2016 United Kingdom[56]

Planned elective domiciliary non-invasive ventilation is preferable to crisis management in NMD and chest wall disorders. This reduces the risk of acute presentation and provides a proven alternative to invasive mechanical ventilation, which risks prolonged or permanent tracheostomy ventilation. Noninvasive ventilation (NIV) should almost always be trialed in the acutely unwell patients with NMD or chest wall disorders with hypercapnia. Do not wait for acidosis to develop. In patients with NMD or chest wall disorders, non-invasive ventilation should be considered in acute illness when vital capacity is known to be <1 L and respiratory rate >20, even if normocapnic. In patients with NMD or chest wall disorders, nocturnal non-invasive ventilation should usually be continued following an episode of acute hypercapnic respiratory failure, pending discussion with a home ventilation service. Domiciliary non-invasive ventilation is effective in treating chronic hypercapnia, improves long-term survival and preserves a good or acceptable quality of life.

2015 United Kingdom[64]

Non-invasive ventilation should be the treatment of choice for patients with NMD or chest wall disease causing type 2 respiratory failure.

2012 Australia[13]

Non-invasive ventilation in patients with respiratory insufficiency from chest wall disease provides greater physiological and symptomatic relief over oxygen alone. Non-invasive ventilation should be trialed in all patients with chest wall disorders with evidence of nocturnal hypoventilation.

2011 Canada[53]

Long-term nocturnal non-invasive ventilation should be offered to all patients with kyphoscoliosis who have developed chronic hypercapnic respiratory failure.

2010 Germany[52]

The following indication criteria are valid when symptoms of chronic respiratory failure and a reduced quality of life are present (at least one criterion must be fulfilled):

- Chronic daytime hypercapnia with PaCO2 ≥ 45mmHg
- Nocturnal hypercapnia with PaCO2 ≥ 50mmHg
- Daytime normocapnia with a rise in PTcCO2 of ≥ 10mmHg during the night
- Patients without manifest hypercapnia but with severe, restrictive ventilatory dysfunction (vital capacity < 50% predicted), must undergo a short-term (within 3 months) clinical control examination including polygraphy.

Non-invasive ventilation is the primary treatment option for home mechanical ventilation of restrictive thoracic disease patients with chronic respiratory failure. The most important criteria for the advent of long-term non-invasive ventilation are hypercapnia in combination with the typical symptoms of ventilatory insufficiency, and the reduction in quality of life.

1999 United States[57]

Indications for usage: Symptoms (such as fatigue, dyspnea, morning headache, etc.) and one of the following physiologic criteria:

- PaCO2 ≥ 45 mm Hg
- Nocturnal oximetry demonstrating oxygen saturation ≤ 88% for 5 consecutive minutes
- For progressive neuromuscular disease, maximal inspiratory pressures < 60 cmH2O or FVC <50% predicted.

Device Characteristics (KQ3):

Three guidelines gave recommendations on device characteristics and titration. No guidelines specifically addressed criteria to initiate NIPPV via HMV versus BPAP.

2016 United Kingdom[56]

In patients with NMD or chest wall disorders, consider controlled ventilation as triggering may be ineffective.

2012 Australia[13]

Both pressure and volume preset ventilation is likely to be equally effective in chest wall disease, but there is a subset of patients which may demonstrate the need for volume ventilation if adequately titrated pressure preset fails to significantly improve diurnal hypercapnia.

2010 Germany[52]

Non-invasive ventilation in pressure- and volume-limited modes is feasible. With set pressure, maximal ventilation pressure often reaches 20–25 mbar. Changeover from set pressure to set volume should be taken into account in order to improve ventilation. EPAP is generally not necessary if bronchial obstructions are absent.

Respiratory Services (KQ4):

One guideline gave recommendations regarding home respiratory services for patients with thoracic restrictive diseases.

2011 Canada[53]

Methods to assist secretion clearance should be initiated when peak cough flow is <270 L/min

Neuromuscular Disease (NMD)

Sixteen studies[51, 59, 60, 65-77] with a total of 1,111 patients were included. The characteristics of the studies are listed in Appendix Table D.1. Three evaluated HMV,[66, 68, 73] eleven BPAP,[51, 59, 60, 65, 67-72, 75] zero CPAP and three used HMV/BPAP mix.[74, 76, 77] These studies were conducted in the United States (n=1), Canada (n=0), Europe (n=14), and South America (n=1). There were 2 RCTs and 14 observational studies. We also identified ten clinical practice guidelines relevant to KQ1-4(Appendix Table G.3.).[52, 53, 55, 64, 80, 97, 103, 105-107]

Overall risk of bias was rated as moderate to high due to inability to blind patients, providers, or outcome assessors, unclear risk of allocation concealment and outcome reporting in the RCT and unknown conflict of interest and high risk of outcome assessment in observational studies (Appendix Tables E.1. and E.2.).

KQ1. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements considered for the initiation and continuation of noninvasive positive pressure ventilation supplied by a Home Mechanical Ventilator (HMV), Bi-level Positive Airway Pressure device (BPAP), and Continuous Positive Airway Pressure device (CPAP) in the home through a noninvasive interface?

Key Points-KQ1

- The criteria used to start NIPPV were variable and most commonly included: PaCO2 >45mmHg) or FVC<50% or MIP <60cmH2O, or nocturnal SaO2 < 88% for ≥ 5 consecutive minutes.
- No studies compared the initiation criteria between different devices or evaluated criteria for device continuation.
- Processes used to titrate NIPPV were variable and used the following targets: reduction in hypercapnia, reduction in hypoxia, and reduction in patient symptoms.

Sixteen studies[51, 59, 60, 65-71, 73-77] described criteria for initiation and/or continuation of HMV or BPAP devices in patients with NMD. Fourteen studies[51, 59, 60, 66-71, 73-77] evaluated patients who had not yet started home device use and two studies[60, 65] evaluated patients with established home device use.

No studies directly evaluated differences between the criteria to start different devices (HMV vs. BPAP vs. CPAP). Indirectly, the criteria used to start each device were not different.

The following patient and laboratory criteria were used to start home NIPPV using a HMV, BPAP, and or CPAP device:

Patient characteristics

Five studies enrolled patients with the following characteristics PaCO2>45mmHg or FVC<50% or MIP <60cmH2O, or nocturnal SaO2 < 88% for ≥ 5 consecutive minutes.[59, 60, 68-70] One study enrolled patients with PaCO2>45mmHg and FVC<50% and nocturnal SaO2 < 90% for ≥ 5% of time.[73] One study enrolled patients with PaCO2>45mmHg or FVC<70% or MIP <70% or subjective respiratory discomfort or 20% decline in MIP or FVC over 3 months.[75] One study enrolled patients with orthopnea with Pimax<60% or "symptomatic daytime hypercapnia."[71] One study enrolled patients with PaCO2>45mmHg and symptoms of nocturnal hypoventilation. [51] One study enrolled patients with PaCO2>45mmHg or dyspnea on exertion or orthopnea or FVC<60%. [76] One study enrolled patients with FVC≤50% predicted or a decrease in FVC of ≥500mL on two consecutive office visits or PaCO2>45mmHg or desaturations in nocturnal pulse oximetry (<90% during 5 consecutive minutes).[77]

Included Diseases

Studies enrolled patients with the following diagnoses: ALS (based on El Escorial criteria or not otherwise specified)[65-77] and NMD not otherwise specified.[59, 60 51]

Targets of device titration

Most studies reported using maximum tolerated respiratory pressures (such as IPAP and/or EPAP) needed to achieve the following stated goals: normalization of blood gasses, symptom relief, elimination of hypoxia (daytime and nocturnal).

Device continuation

No studies described criteria for device continuation.

KQ2. What is the effect of HMV, BPAP, or CPAP use on patient outcomes, including mortality, hospitalization, admission/readmission to intensive care unit (ICU), need for intubation, outpatient visits, emergency room visits, disease exacerbations, quality of life (QoL), activities of daily living (ADL), dyspnea, sleep quality, exercise tolerance, and adverse events?

Key Points-KQ2

- BPAP (compared with no device) was associated with significantly lower mortality (SOE: low), better quality of life (SOE: low).

Three studies (1 RCT[71] and 2 Observational studies[67, 69]) compared BPAP to no device. BPAP was associated with significantly lower mortality than no device (OR=0.04, 95% CI: 0.00 to 0.34, low SOE). Patients with BPAP were also found to have better median survival length (219 days vs. 171 days, p=0.01) and quality of life measured by SF-36 mental components (168 vs. 99, p<0.01) and physical component (150 vs. 81, p<0.01).

One observational study of 140 ALS patients compared HMV (volume assist control ventilation) to no device.[73] The HMV group was found to have significantly longer survival time than the group not treated with any device (mean: 18.50 months vs. 3.00 months, p=0.001). The significant difference was also found in patients with no or moderate bulbar dysfunction (mean: 20.00 months vs. 3.00 months, p=0.0001) and in patients with severe bulbar dysfunction (mean: 13.00 months vs. 3.00 months, p=0.001).

One observational study of 144 ALS patients compared HMV (volume cycled) to BPAP (pressure cycled) and found no significant difference on length of survival (median 15.00 months vs. median 15.00 months, p=0.53).[68]

One RCT compared BPAP outpatient initiation to BPAP inpatient initiation in 50 ALS patients.[75] After 3-month follow up, the group with outpatient initiation was not significantly different from the group with inpatient initiation on dyspnea and sleep quality.

One observational study evaluated BPAP patients who were "correctly ventilated" to those "insufficiently ventilated" patients.[65] The "correctly ventilated" patients had significantly lower mortality than those "insufficiently ventilated" patients (OR= 0.25; 95% CI: 0.10 to 0.64).

One prospective observational study evaluated the daily use of BPAP in ALS patients.[70] The group with >=4 hours/days use had significantly longer survival time from BPAP start to death (median: 18 months (interquartile range: 7 to 28) vs. 6 months (interquartile range: 3 to 12), p<0.001).

One observational study compared HMV started after outpatient pulmonary evaluation to HMV started in an emergency situation in hospital.[66] Patients started HMV after outpatient pulmonary evaluation had significantly longer length of survival than those started in an emergency setting (mean survival: 12.3 months vs. 2.8 months, p<0.004).

One observational study compared HMV/BPAP mix started early with FVC>=80% to HMV/BPAP mix started late with FVC<80%.[74] The patients started early were found to have significantly longer survival time (31.33 months vs. 27.51 months, p=0.01) and lower mortality (HR: 0.46, 95% CI: 0.29 to 0.74; p=0.001) than the patients started late.

One observational study compared HMV/BPAP mix in tolerant patients (n=18) to intolerant patients (n=21).[76] The intolerant patients had significantly higher mortality than the tolerant patients (OR: 20.00, 95% CI: 2.19 to 182.44, p<0.01).

One observational study compared HMV/BPAP mix before protocol initiation to HMV/BPAP mix after protocol initiation in 64 ALS patients.[77] No significant difference on survival time was observed between the two groups (p=0.84).

Comparative effectiveness evidence with SOE rating for major outcomes is summarized in Table 11. Other outcomes are summarized in Table 12. Forest plots are available in in Appendix Table H.2.

Table 11. Major effectiveness outcomes with SOE (all devices in patients with neuromuscular disease)

Comparison	Outcome	Conclusion	Study Design (sample size)	Rationale for Strength of Evidence (SOE)	Overall Evidence Strength (Direction of Effect)
BPAP vs. No Device	Mortality	OR*: 0.04; 95% CI: 0.00 to 0.34; I^2=0.0% 334 fewer per 1000 patients (537 fewer to 131 fewer)	2 Observational studies (73 patients) [67, 69]	SOE is determined based on study design; no other factors modify SOE	Low (reduction with BPAP)
	Quality of life (SF-36 physical component, (higher score represents better outcome))	WMD:69; p=0.01; I^2=N/A	1 RCT(41 patients) [71]	Severe imprecision (single study with a small number of patient)	Low (increased QoL scores with BPAP)

BPAP: bi-level positive airway pressure, CI: confidence interval, HMV: home mechanical ventilation, N/A: not applicable, OR: odds ratio, RCT: randomized controlled trial, SF-36: Medical Outcomes Study Questionnaire Short Form, ST: spontaneous/timed mode, WMD: weighted mean difference

*: Pooled effect size from meta-analysis

Table 12. Other effectiveness outcomes (all devices in patients with neuromuscular disease)

Comparison	Outcome	Conclusion	Study Design (sample size)
BPAP vs. No Device	Length of survival Dyspnea, (Chronic Respiratory Disease Questionnaire, dyspnea, higher score represents better outcome)	Median 219 days vs. 171 days; p=0.01 WMD:147; p<0.001; I^2=N/A	1 RCT(41 patients) [71]
HMV vs. BPAP	Length of survival	Median:15.00 months vs. 15.00 months; p=0.53	1 Observational study (144 patients)[68]
HMV vs. No Devices	Length of survival	Mean: 18.50 months, vs. 3.00 months, p=0.001	1 Observational study (140 patients)[73]
BPAP "correctly ventilated" vs. BPAP "insufficiently ventilated"	Mortality	OR:0.25; 95% CI: 0.10 to 0.64; I^2=N/A	1 Observational study (82 patients)[65]
BPAP >=4 hours daily vs. <4 hours daily	Length of survival	Median: 18 months (interquartile range: 7 to 28) vs. 6 months (interquartile range: 3 to 12); p<0.001	1 Observational study (71 patients)[70]
BPAP volume assured pressure support ventilation outpatient initiation vs. BPAP volume assured pressure support ventilation inpatient initiation	Dyspnea (measured by VAS score, (higher score represents worse outcome))	Daily dyspnea: WMD: -0.37, p=0.19 Night dyspnea: WMD: 0.03, p=0.97	1 RCT (50 patients)[75]
	Sleep quality (measured by VAS score, (higher score represents better outcome))	WMD: -1.57, p=0.12	1 RCT (50 patients)[75]
HMV/BPAP mix started in FVC≥ 80% (early) vs. HMV/BPAP mix started in FVC <80% (late)	Mortality	HR: 0.46, 95% CI: 0.29 to 0.74; p=0.001	1 Observational study (194 patients)[74]
	Length of survival	Mean survival: 31.33 months vs. 27.51 months, p=0.01	1 Observational study (194 patients)[74]
HMV (pressure support ventilation mode or BPAP ST mode) started after outpatient pulmonary evaluation vs. HMV (pressure support ventilation mode or BPAP ST mode) started in an emergency situation without prior outpatient pulmonary evaluation	Length of survival	Mean survival: 12.3 months vs. 2.8 months; p<0.004	1 Observational study[66]

BPAP: bi-level positive airway pressure, CI: confidence interval, HMV: home mechanical ventilation, N/A: not applicable, OR: odds ratio, RCT: randomized controlled trial, SF-36: Medical Outcomes Study Questionnaire Short Form, ST: spontaneous/timed mode, WMD: weighted mean difference

*: Pooled effect size from meta-analysis

KQ3. What are the equipment parameters that are used? a) What are the parameters of ventilator usage (e.g. mode as determined by trigger, control and cycling variables)? b) What are the equipment parameters that are necessary to achieve desired outcomes (e.g. flow capabilities, settings, etc.)? c) What are the parameters of prescribed patient usage (e.g. frequency of use, duration of use throughout the day, other)? d) In each of the above populations, what are the parameters of patient compliance with the prescribed usage of the equipment?

Key Points-KQ3

- For BPAP devices, the modes utilized were BPAP ST, BPAP NOS (unclear if S or ST), and BPAP volume assured pressure support.
- For HMV devices, the modes utilized were pressure support, pressure control, and volume assist controlled ventilation.
- Prescribed device usage per day varied from ≥4-7 hours. Actual mean device usage per day ranged from 3.8-9.3 hours.

Thirteen studies evaluated patients who used BPAP devices.[51, 59, 60, 65, 67-72, 75-77] Six studies evaluated patients who used BPAP ST.[51, 65, 68, 70-72] BPAP ST equipment parameters included IPAP, EPAP, and a spontaneous/timed (ST) breathing mode with a backup respiratory rate. No studies evaluated patients who used BPAP S. One study evaluated patients who used BPAP volume assured pressure support.[75]Four studies evaluated patients who used BPAP NOS (unclear if ST or S mode).[59, 60, 67, 69] Five studies evaluated patients who used HMV devices.[66, 68, 73, 76, 77] HMV modes were volume assist control ventilation and pressure support ventilation. One study evaluated patients who used either BPAP or HMV devices.[74] No studies evaluated patients who used CPAP devices.

Thirteen studies reported the model and manufacturer of the device used.[51, 59, 60, 65, 66, 68, 70-73, 75-77] Three studies did not report the model or manufacturer of the device used.[67, 69, 74]

The prescribed daily device use of included studies ranged from ≥4-7 hours/day. Actual device usage ranged from mean of 3.8-9.3 hours/day. Actual mean recorded IPAP ranged from 12.0-15.0 cmH2O. Actual mean recorded EPAP ranged from 4.0-5.0 cmH2O. Actual mean respiratory rates ranged from 11-14 breaths/minute.

KQ4. What respiratory services, other than the technical support of the use of the prescribed equipment, are being provided to the above patients in the home (e.g. patient education, ongoing smoking cessation, respiratory therapist led home care)?

Key Points-KQ4

- Respiratory services provided in the home included: telephone hotline, scheduled phone calls, and cough assistance including mechanical cough assist devices provided by a respiratory therapist.
- Weekly telemonitoring was associated with significantly lower rates of office visits, ER visits, and hospital admission, with no change in mortality.

Eleven studies[51, 59, 60, 65, 66, 68, 70-73, 77] described respiratory services provided in the home. These services included a telephone hotline staffed by healthcare professionals including nurses, respiratory therapists, and/or others,[51, 59, 60, 72, 77], phone calls by nurses, respiratory therapists and/or others,[66] instruction and provision of cough assistance including mechanical cough assist devices by a respiratory therapist.[65, 66, 68, 70, 71]

One RCT evaluated the effectiveness of home telemonitoring in 40 ALS patients treated by BPAP ST.[72] The BPAP ST + Weekly telemonitoring group had significantly lower number of office visits (IRR: 0.34, 95% CI: 0.29 to 0.38); ER visits (IRR: 0.19; 95% CI: 0.10 to 0.37); hospital admission (IRR: 0.17; 95% CI: 0.07 to 0.41). There was no significant difference on mortality (OR: 1.00; 95% CI: 0.24 to 4.18) or median survival time (from BPAP adoption to death) (865 days vs. 334 days, p=0.13).

KQ5. What are the professional guidelines and statements which address KQ 1 to KQ 4?

Information related to clinical guidelines can be found in Appendix Table G.3.

Initiation Criteria and Effectiveness (KQ1 and KQ2):

Nine guidelines gave recommendations regarding initiation criteria in patients with neuromuscular diseases.

2016 United Kingdom[56]

Planned elective domiciliary non-invasive ventilation is preferable to crisis management in NMD and chest wall disorders. This reduces the risk of acute presentation and provides a proven alternative to invasive mechanical ventilation which risks prolonged or permanent tracheostomy ventilation. Non-invasive ventilation should almost always be trialed in the acutely unwell

patients with NMD or chest wall disorders with hypercapnia. Do not wait for acidosis to develop. In patients with NMD or chest wall disorders, non-invasive ventilation should be considered in acute illness when vital capacity is known to be <1 L and respiratory rate >20, even if normocapnic. In patients with NMD or chest wall disorders, nocturnal non-invasive ventilation should usually be continued following an episode of AHRF, pending discussion with a home ventilation service. Domiciliary non-invasive ventilation is effective in treating chronic hypercapnia, improves long-term survival and preserves a good or acceptable quality of life.

2016 United Kingdom[78]

The following patients should receive evaluation by a respiratory ventilation service: Patients with PaCO2 > 6 kPa or patients with PaCO2 ≤ 6 kPa but they have any symptoms or signs of respiratory impairment, particularly orthopnea. Consider urgent introduction of non-invasive ventilation for people with NMD who develop worsening respiratory impairment and are not already using non-invasive ventilation.

2012 Australia[13]

The institution of non-invasive ventilation is recommended in patients with rapidly progressive respiratory muscle weakness associated with orthopnea, hypercapnia or symptomatic sleep hypoventilation (sleep fragmentation/ daytime hypersomnolence/ morning headaches and cognitive dysfunction). The elective commencement of NIV is preferred over non-elective tracheostomy intermittent positive pressure ventilation despite the improved survival advantage. In spinal cord injury: non-invasive ventilation is indicated when there is intractable or refractory sputum retention, atelectasis, respiratory tract infection or type-I respiratory failure (PaO2 < 80 mmHg, SpO2 <95%). Non-invasive ventilation is indicated when there is intolerance of CPAP for treatment of OSA, especially in cases of spinal cord injury at C6 or above.

2012 Europe[81]

NIPPV should be considered in preference to invasive mechanical ventilation in patients with symptoms or signs of respiratory insufficiency. NIPPV can prolong survival for many months and may improve the patient's quality of life.

2011 Canada[53]

Non-invasive ventilation should be offered to patients with any one of the following: Orthopnea; Daytime hypercapnia; Symptomatic sleep disordered breathing; FVC <50% predicted; sniff nasal pressure (SNP) <40 cmH2O or PImax<40 cmH2O. Non-invasive ventilation should be considered the preferred option for ventilation even when ventilation is required 24 h per day.

2010 Germany[52]

One of the following criteria:

- chronic daytime hypercapnia with PaCO2 ≥ 45mmHg
- nocturnal hypercapnia with PaCO2 ≥ 50mmHg
- daytime normocapnia with a rise in PTcCO2 of ≥ 10mmHg during the night
- a rapid, significant reduction in vital capacity.

At the first signs of nocturnal hypercapnia, the patient should be offered non-invasive ventilation therapy rather than waiting until the hypercapnia extends into the daytime period. There are no

indications for prophylactic mechanical ventilation in the absence of symptoms or hypoventilation.

2009 United States[79]

Non-invasive ventilation may be considered at the earliest sign of nocturnal hypoventilation or respiratory insufficiency in order to improve compliance with non-invasive ventilation in patients with ALS.

2004 United States[80]

Consider daytime ventilation when measured waking Pco2 exceeds 50 mm Hg or when hemoglobin saturation remains < 92% while awake.

1999 United States[57]

Indications for usage: Symptoms (such as fatigue, dyspnea, morning headache, etc.) and one of the following physiologic criteria:

- PaCO2 ≥ 45 mm Hg
- nocturnal oximetry demonstrating oxygen saturation ≤ 88% for 5 consecutive minutes
- for progressive neuromuscular disease, maximal inspiratory pressures < 60 cm H2O or FVC <50% predicted.

Device Characteristics (KQ3):

Two guidelines gave recommendations regarding device characteristics and titration.

2016 United Kingdom[56]

In patients with NMD or chest wall disorders, consider controlled ventilation as triggering may be ineffective.

2011 Canada[53]

Ventilator settings should be adjusted for optimal patient comfort and improvement of symptoms. ABGs and/or nocturnal oximetry and/or polysomnography are not required, but may be helpful in some circumstances. When bi-level pressure ventilators are used for non-invasive ventilation, a backup rate is recommended. Individualize the decision about the transition from nocturnal non-invasive ventilation to daytime ventilation by carefully evaluating patient factors (symptoms, bulbar involvement, patient preference, etc.) and available resources. In patients requiring daytime ventilation, strongly consider mouthpiece ventilation as an alternative to invasive tracheostomy.

Respiratory Services (KQ4):

Eight guidelines gave recommendations regarding home respiratory services for patients with neuromuscular diseases.

2016 United Kingdom[56]

In patients with neuromuscular disease (NMD), mechanical insufflation and exsufflation should be used, in addition to standard physiotherapy techniques, when cough is ineffective and there is sputum retention.

2016 United Kingdom[78]

Offer cough augmentation techniques such as manual assisted cough to people with NMD who cannot cough effectively. Consider unassisted breath stacking and/or manual assisted cough as the first-line treatment for people with NMD who have an ineffective cough. For patients with bulbar dysfunction, or whose cough is ineffective with unassisted breath stacking, consider assisted breath stacking (for example, using a lung volume recruitment bag). Consider a mechanical cough assist device if assisted breath stacking is not effective, and/or during a respiratory tract infection.

2012 Australia[13]

Patients with a baseline peak cough flow (PCF) < 270 L/min should have access to equipment, which can provide insufflation and a mechanical cough in-exsufflation. Training of insufflation should commence when vital capacity (VC) < 2L or 50% predicted. As manual assisted coughing techniques (e.g. abdominal thrust) further enhance PCF, they should be incorporated with insufflation or mechanical in-exsufflation techniques, where possible. For patients with VC < 1 to 1.5L, insufflations should precede manual assisted coughing techniques (e.g. abdominal thrusts).

2012 Europe[81]

The patient and caregiver should be taught the technique of assisting expiratory movements using a manual-assisted cough (can also be performed by a physical therapist). The use of a mechanical insufflator–exsufflator may be helpful, particularly in the setting of an acute respiratory infection. A portable home suction device and a room humidifier may be of use.

2011 Canada[53]

Lung volume recruitment maneuvers should be introduced with declining vital capacity. In ALS, Methods to assist secretion clearance should be initiated when PCF is <4.25 L/s or the Norris bulbar core is <29. In Duchenne Muscular Dystrophy, methods to assist secretion clearance should be initiated when PCF <270 L/min. In Spinal Cord Injury, Regular airway clearance techniques (lung volume recruitment, manually assisted coughing, and mechanical in-exsufflation), clinical assessment and ongoing monitoring of pulmonary function is recommended to ensure adequate airway clearance.

2010 Germany[52]

A reduced cough impulse (peak cough flow; PCF < 270 l/min) can lead to acute decompensations and increased incidence of aspiration pneumonia. Measures to eliminate secretions should therefore be taken when SaO2< 95%, or a 2–3% drop in the patient's individual best value occurs. Step-based secretion management consists of measures to increase intrapulmonary volume via air stacking, frog breathing or manual hyperinflation, as well as assisted coughing techniques or mechanical cough assistants (CoughAssist ®, Pegaso Cough®)

The measurement of coughing capacity in NMD patients is obligatory. Coughing weakness (PCF < 270 l/min) indicates the need for the initiation of secretion management.

2009 United States[79]

Mechanical insufflation/exsufflation) may be considered to clear secretions in patients with ALS who have reduced peak cough flow, particularly during an acute chest infection. There are

insufficient data to support or refute high frequency chest wall oscillation for clearing airway secretions in patients with ALS.

2004 United States[80]

Patients with Duchenne muscular dystrophy should be taught strategies to improve airway clearance and how to employ those techniques early and aggressively. Use assisted cough technologies in patients whose clinical history suggests difficulty in airway clearance, or whose peak cough flow is less than 270 L/minute and/or whose maximal expiratory pressures are less than 60 cm H2O. The committee strongly supports use of mechanical insufflation-exsufflation in patients with Duchenne muscular dystrophy and also recommends further studies of this modality. Home pulse oximetry is useful to monitor the effectiveness of airway clearance during respiratory illnesses and to identify patients with Duchenne muscular dystrophy needing hospitalization.

Obesity Hypoventilation Syndrome

Thirteen studies[43, 48, 51, 61, 82-91] with a total of 890 patients were included. The characteristics of the studies are listed in Appendix Table D.1. Two evaluated HMV,[48, 61] nine BPAP, [43, 51, 82, 83, 85-88] three CPAP[82, 84, 87], and two used HMV/BPAP mix.[25, 84, 90, 91] These studies were conducted in the United States (n=0), Canada (n=0), Europe (n=10), Australia (n=2), and Asia (n=1). There were six RCTs and seven observational studies. We also identified five clinical practice guidelines relevant to KQ1-4(Appendix).[52, 53, 55, 97, 103]

Overall risk of bias was rated as moderate due to inability to blind patients or provider assessors, high risk of conflicts of interest in the RCT and selective patient population in observational studies (Appendix Table E.1. and E.2.).

KQ1. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements considered for the initiation and continuation of noninvasive positive pressure ventilation supplied by a Home Mechanical Ventilator (HMV), Bi-level Positive Airway Pressure device (BPAP), and Continuous Positive Airway Pressure device (CPAP) in the home through a noninvasive interface?

Key Points-KQ1

- The criteria used to start NIPPV were variable but most commonly included: hypercapnia (PaCO2 ranging from >45 to >53mmHg) and pH>7.35.
- No studies compared the initiation criteria among different devices or evaluated criteria for device continuation.
- Processes used to titrate NIPPV were variable and used the following targets: reduction in hypercapnia, reduction in hypoxia (including nocturnal hypoxia), achievement of target tidal volumes, and reduction in patient symptoms.

Thirteen studies described criteria for initiation and/or continuation of HMV, BPAP, and/or CPAP devices in patients with OHS,[43, 48, 51, 61, 82-90] all of which evaluated patients who had not yet started home device use. There were no major differences in criteria used to start BPAP versus HMV.

Elevated BMI

All studies enrolled patients with elevated BMI: >30 kg/m2,[43, 48, 51, 82-85, 87, 89, 90] ≥30 kg/m2,[88] >33 kg/m2,[61] and >40kg/m2.[86]

Hypercapnia

All studies enrolled patients with hypercapnia: PaCO2>45mmHg,[43, 51, 82-89] >47mmHg,[61], >50 mmHg[90] and >53mmHg.[48] All studies reported that PaCO2 measurements should be performed in patients while awake and in a stable state. Some studies included normal pH as a way of ensuring a stable respiratory state: pH 7.35-7.45,[82] pH>7.35.[48, 51, 84, 86, 89]

Other causes of hypercapnia ruled out

All studies reported including patients in whom other causes of hypercapnia/hypoventilation had been excluded such as COPD, NMD, TRD, respiratory depressant medications, narcolepsy, or severe heart failure.

Other characteristics

One study excluded patients with SaO2 <80% for 10 minutes in absence of apnea, TcCO2 during REM ≥10mmHg, increase in afternoon to morning PaCO2 ≥10mmHg in patients with awake PaCO2 >55 mmHg.[87]

Targets of device titration

Studies reported using maximum tolerated respiratory pressures (such as IPAP and/or EPAP) or other device changes needed to achieve the following goals:

1) Reduction in hypercapnia: maximum reduction in PaCO2,[48, 61, 84, 88] PaCO2<45mmHg,[83] reduction in baseline PaCO2 ≥5mmHg,[83] PaCO2≤65mmHg,[90] 5% reduction in baseline PaCO2,[51], and improvement in PaCO2.[89]

2) Tidal volumes or minute ventilation: desired tidal volume.[82, 89] [INSERT MASA]

3) Overcome "obstructive events and nocturnal hypoventilation."[82, 86]

4) Patient tolerance, air leakage.[48, 51, 61, 88, 89]

5) Absence of hypoxia: SaO2>90%.[83, 84, 89, 90]

Device continuation

No studies described criteria for device continuation.

KQ2. What is the effect of HMV, BPAP, or CPAP use on patient outcomes, including mortality, hospitalization, admission/readmission to intensive care unit (ICU), need for intubation, outpatient visits, emergency room visits, disease exacerbations, quality of life (QoL), activities of daily living (ADL), dyspnea, sleep quality, exercise tolerance, and adverse events?

Key Points-KQ2

- HMV/BPAP mix (compared with no device) was associated with significantly lower mortality (SOE: low).
- BPAP (compared with no device) was associated with significantly improved sleep quality.

Two RCTs of 96 OHS patients compared BPAP to CPAP.[82, 87] No significant difference was found on hospital admission, sleep quality, quality of life, exercise tolerance, or withdrawals.

One RCT randomized 221 patients to CPAP (n=80), HMV/BPAP (n=71), or lifestyle modification (n=70) and follow these patients for 2 months.[84] The HMV/BPAP group and the CPAP group reported significantly better sleep quality measured by Epworth Sleepiness Scale than the lifestyle modification group (HMV/BPAP: -3.80; 95% CI: -5.36 to -2.25; CPAP: -3.30; 95% CI: -4.76 to -1.84). No significant difference between the HMV/BPAP and CPAP group. Patients treated by HMV/BPAP were found to have significant better outcomes on 6-minute walk distance tests than CPAP (26.00 meters; 95% CI: 6.70 to 45.30). There was no difference between groups on quality of life (SF-36).

One observational study[90] of 69 patients compared HMV/BPAP mix to no device. Patients treated without any device had significantly higher mortality rate (OR= 14.88, 95% CI: 3.18 to 69.68, p= 0.001).

Two RCTs of 123 patients compared BPAP to lifestyle counseling.[85, 89] The BPAP group were found to have significantly more improvements on sleep quality (Epworth Sleepiness Score, -1.64; 95% CI:-3.08 to -0.20, p=0.03) and quality of life (SF-36 Mental Component) (p=0.04) than those in the lifestyle counseling group. There was no significant difference on 6-minute walk distance test and SF-36 Physical Component.

One RCT randomized 50 patients with obesity hypoventilation syndrome to either BPAP volume assured pressure support ventilation or BPAP ST.[86] There was no statistically significant difference on quality of life (Severe Respiratory Insufficiency Questionnaire summary score, mean difference: 5, p=0.21), or sleep quality (Epworth Sleepiness Score; 1, p=0.43)

One observational study[88] retrospectively compared BPAP in acute exacerbation to BPAP in stable hypercapnia in 130 OHS patients. There was no significant difference on mortality (OR= 1.27, 95% CI: 0.49 to 3.27, p=0.63).

Comparative effectiveness evidence with SOE rating for major outcomes is summarized in Table 13. Other outcomes are summarized in Table 14. Forest plots are available in in Appendix Table H.3.

Table 13. Major effectiveness outcomes with SOE (all devices in patients with obesity hypoventilation syndrome)

Comparison	Outcome	Conclusion	Study Design (sample size)	Rationale for Strength of Evidence (SOE)	Overall Evidence Strength (Direction of Effect)
BPAP vs. CPAP	Number of patients with hospital admissions	OR;1.08; 95% CI: 0.35 to 5.41; I2=N/A 7 more per 1000 patients (145 fewer to 159 more)	1 RCT (60 patients) [82]	Severe imprecision	Insufficient
	Quality of life (SF-36 Physical Component, higher score represents better outcome)	WMD*: -0.89; 95% CI: -5.57 to 3.80; I^2=0.0%	2 RCTs (96 patients) [82, 87]	Risk of bias and severe imprecision	Insufficient
HMV/BPAP mix (all with bi-level pressure with assured volume) vs.no device	Quality of life (SF-36 Physical Component, higher score represents better outcome)	WMD: 1.60; 95% CI: -0.98 to 4.18; I^2=N/A	1 RCT (141 patients) [84]	Severe imprecision	Insufficient
HMV/BPAP mix (all with bi-level pressure with assured volume) vs. CPAP	Quality of life (SF-36 Physical Component, higher score represents better outcome)	WMD: 0.60; 95% CI: -2.21 to 3.41; I^2=N/A	1 RCT(151 patients) [84]	Severe imprecision	Insufficient
CPAP vs. no device	Quality of life (SF-36 Physical Component, higher score represents better outcome)	WMD: 1.00; 95% CI: -1.52 to 3.52; I^2=N/A	1 RCT(150 patients) [84]	Severe imprecision	Insufficient
BPAP vs. no device	Quality of life (SF-36 Physical Component, higher score represents better outcome)	WMD: 2.20; 95% CI:-1.96 to 6.36; I^2=N/A	1 RCT (86 patients)[89]	Severe imprecision	Insufficient
BPAP vs. no device	Quality of life (SF-36 Mental Component, higher score represents better outcome)	WMD: 5.00; 95% CI: 0.02 to 9.98; I^2=N/A	1 RCT (86 patients)[89]	Severe imprecision	Insufficient

Comparison	Outcome	Conclusion	Study Design (sample size)	Rationale for Strength of Evidence (SOE)	Overall Evidence Strength (Direction of Effect)
HMV/BPAP mix vs. no device	Mortality	OR: 0.07; 95% CI: 0.01 to 0.31; I^2=N/A	1 Observational study (69 patients)[90]	SOE is determined based on study design; no other factors modify SOE	Low (reduction with HMV/BPAP)
BPAP volume assured pressure support ventilation vs. BPAP ST	Quality of life (Severe Respiratory Insufficiency Questionnaire summary score, higher score represents better outcome)	Mean: 5, p=0.21	1 RCT(50 patients)[86]	Severe imprecision	Insufficient

BPAP: bi-level positive airway pressure, CI: confidence interval, CPAP: continuous positive airway pressure, HMV: home mechanical ventilation, N/A: not applicable, OR: odds ratio, RCT: randomized controlled trial, SF-36: Medical Outcomes Study Questionnaire Short Form, ST: spontaneous/timed mode, WMD: weighted mean difference

*: Pooled effect size from meta-analysis

Table 14. Other effectiveness outcomes (all devices in patients with obesity hypoventilation syndrome)

Comparison	Outcome	Conclusion	Study Design (sample size)
BPAP vs. CPAP	Sleep Quality (Epworth Sleepiness Scale, higher score represents worse outcome)	WMD*: 0.35; 95% CI: -2.23 to 2.29; I^2=0.0%	2 RCTs (96 patients) [82, 87]
HMV/BPAP mix (all with bi-level pressure with assured volume) vs.no device	6-minute walk distance test (meters)	WMD: 16.00; 95% CI: -4.70 to 36.70; I^2=N/A	1 RCT (141 patients) [84]
	Sleep Quality (Epworth Sleepiness Scale, higher score represents worse outcome)	WMD: -3.80; 95% CI: -5.36 to -2.25; I^2=N/A	1 RCT(141 patients) [84]
HMV/BPAP mix (all with bi-level pressure with assured volume) vs. CPAP	Physical activity (6-minute walk distance test, meters)	WMD: 26.00; 95% CI: 6.70 to 45.30; I^2=N/A	1 RCT(151 patients) [84]
	Sleep Quality (Epworth Sleepiness Scale, higher score represents worse outcome)	WMD: -0.50; 95% CI: -2.05 to 1.05; I^2=N/A	1 RCT (151 patients) [84]

Comparison	Outcome	Conclusion	Study Design (sample size)
CPAP vs. no device	Quality of life (SF-36 Physical Component, higher score represents better outcome)	WMD: 1.00; 95% CI: -1.52 to 3.52; I^2=N/A	1 RCT(150 patients) [84]
BPAP vs no device	Sleep quality (Epworth Sleepiness Scale, higher score represents worse outcome)	WMD: -1.64; 95% CI:-3.08 to -0.20; I^2=0.0%	2 RCT (123 patients) [85, 89]
BPAP vs no device	Physical activity (6-minute walk distance test, meters)	WMD: 36.20; 95% CI: -12.27 to 84.67; I^2=N/A	1 RCT (86 patients)[89]
BPAP volume assured pressure support ventilation vs. BPAP ST	Sleep quality (Epworth Sleepiness Score, higher score represents worse outcome)	Mean: 1, p=0.43	1 RCT (50 patients)[86]

BPAP: bi-level positive airway pressure, CI: confidence interval, CPAP: continuous positive airway pressure, HMV: home mechanical ventilation, N/A: not applicable, OR: odds ratio, RCT: randomized controlled trial, SF-36: Medical Outcomes Study Questionnaire Short Form, ST: spontaneous/timed mode, WMD: weighted mean difference

*: Pooled effect size from meta-analysis

KQ3. What are the equipment parameters that are used? a) What are the parameters of ventilator usage (e.g. mode as determined by trigger, control and cycling variables)? b) What are the equipment parameters that are necessary to achieve desired outcomes (e.g. flow capabilities, settings, etc.)? c) What are the parameters of prescribed patient usage (e.g. frequency of use, duration of use throughout the day, other)? d) In each of the above populations, what are the parameters of patient compliance with the prescribed usage of the equipment?

Key Points-KQ3

- For BPAP devices, the modes utilized were BPAP ST, BPAP S, and BPAP NOS (unclear if S or ST)
- For HMV devices, the modes utilized were volume/pressure cycled NOS, pressure support and pressured controlled ventilation as well as a mixture of bi-level BPAP/HMV each with assured volume modes.

Ten studies[43, 51, 82, 83, 85-90] evaluated patients who used BPAP devices. Six studies[43, 51, 82, 83, 85, 86] evaluated patients who used BPAP ST. BPAP ST equipment parameters included IPAP, EPAP, and a spontaneous/timed (ST) breathing mode with a backup respiratory rate. One study evaluated patients who used BPAP S.[87] BPAP S equipment parameters included IPAP, EPAP and a spontaneous (S) mode without a backup respiratory rate. Two studies evaluated patients who used volume assured pressure support (VAPS) ventilation.[86, 89] Volume assured pressure

support ventilation equipment parameters included IPAP, EPAP, and a target minute ventilation. One study evaluated patients who used a mixture of bi-level BPAP and HMV devices each with assured volume modes.[84] One study evaluated patients who used HMV devices with a combination of volume or pressure cycled modes.[61] One study evaluated patients with a combination of BPAP and/or HMV devices.[90] One study evaluated patients who used HMV devices with either pressure controlled or pressure support ventilation.[48] One study evaluated patients who used BPAP, mode not otherwise specified.[88] Three studies evaluated patients who used CPAP devices.[82, 84, 87] CPAP equipment parameters included CPAP with spontaneous breathing.

Eight studies reported the model and manufacturer of the device used.[48, 51, 61, 83-86, 90] Five studies did not report the model or manufacturer of the device used.[43, 82, 87-89] We did not report mask type used, use of a humidifier, or use of supplemental oxygen.

KQ4. What respiratory services, other than the technical support of the use of the prescribed equipment, are being provided to the above patients in the home (e.g. patient education, ongoing smoking cessation, respiratory therapist led home care)?

Key Points-KQ4

- Evidence is lacking to determine the effect of specific respiratory home services on outcomes.
- Respiratory services provided in the home included: lifestyle counseling by nurses.

Two studies described respiratory services provided in the home. These services included life style counseling by nurses.[84, 85]

KQ5. What are the professional guidelines and statements which address KQ 1 to KQ 4?

Information related to clinical guidelines can be found in Appendix Table G.5.

Initiation Criteria and Effectiveness (KQ1 and KQ2):

Five guidelines gave recommendations regarding initiation criteria in patients with obesity hypoventilation syndrome.

2016 United Kingdom[56]

In patients with OHS, non-invasive ventilation should be started in acute hypercapnic respiratory failure using the same criteria as in acute exacerbation of COPD (pH<7.35 and pCO2 >6.5 kPa persist or develop despite optimal medical therapy). Following an episode of acute hypercapnic respiratory failure referral to a home ventilation service is recommended. Patients with OSA, OHS or overlap syndrome should not have nocturnal oxygen therapy alone ordered. It can be considered in patients with evidence of established ventilatory failure, where it should be given with non-invasive ventilation support.

2012 Australia[13]

Indications for non-invasive ventilation in OHS include an awake PaCO2 >45mmHg and failure of CPAP therapy as evidence by either sustained oxygen desaturation during sleep or an increase in nocturnal daytime or nocturnal CO2 >8mmHg. Positive airway pressure is first line therapy in patients with OHS, although adjunctive oxygen therapy is likely to be required, at least initially, for a significant number of patients. Auto-titrating and home studies are not appropriate for this patient group. A full PSG should be performed during manual titration in order to identify the nature of the sleep disordered breathing and response to CPAP pressure. Many individuals will respond to initial intervention with CPAP. Titration should commence in CPAP mode to document the patient's response to abolition of upper airway obstruction alone. Bi-level support should be used as initial therapy in patients presenting with acute decompensated respiratory failure. After 3 months, a CPAP titration should be undertaken to determine long-term therapy. The need for and type of nocturnal PAP therapy should be reassessed if significant weight loss occurs.

2011 Canada[53]

Non-invasive ventilation is the treatment of choice for OHS. In patients with OHS who have a minor degree of nocturnal desaturation and no nocturnal rise in PaCO2, CPAP is a reasonable initial therapy provided that follow-up is arranged within one to three months to evaluate response to therapy. Polysomnography is useful for titrating and confirming efficacy of bi-level pressures. Under circumstances when access to more than one device (bi-level PAP or CPAP) is limited, bi-level therapy is recommended. In patients with OHS who experience significant nocturnal desaturation or a nocturnal increase in PaCO2, bi-level PAP remains the therapy of choice.

2010 Germany[52]

Due to the high prevalence of an accompanying obstructive sleep apnea syndrome (90% of cases), primary sleep diagnostics by means of polysomnography are necessary. The indication of non-invasive ventilation for patients with symptomatic chronic respiratory failure under adequate CPAP therapy yields to the following situations: A ≥ 5 minute-long increase in nocturnal PTcCO2 > 55mmHg and in PaCO2 ≥ 10 mmHg, respectively, in comparison to the awake state or Desaturations < 80% SaO2 over ≥ 10 minutes. In the case of severe hypercapnia or symptomatic, severe co-morbidity, primary non-invasive ventilation can be implemented according to the physician's assessment. If the first control visit (including poly(somno)graphy under CPAP therapy) reveals no improvement in the characteristic symptoms of chronic hypoventilation or the absence of daytime normocapnia ("non-responder"), transfer of the patient to non-invasive ventilation is indicated. CPAP or non-invasive ventilation are the primary treatment options for HMV of patients with OHS. An accompanying loss of weight should also be aimed for.

An initial attempt at CPAP treatment under polysomnographical conditions should take place in patients without significant co-morbidities. In the presence of significant co-morbidities, however, primary non-invasive ventilation therapy can be indicated. Persistent hypoventilation under CPAP (≥ 5 minute-long increase in PTcCO2 > 55mmHg and PaCO2 ≥ 10 mmHg, respectively, in comparison to normocapnia during the awake state, or desaturation < 80% over ≥ 10 minutes) is an indication for non-invasive ventilation. Significant weight loss can enable a

change from non-invasive ventilation to CPAP therapy, or even an attempt at resting the treatment.

1999 United States[57]

Before considering NIPPV for a patient with nocturnal hypoventilation from causes other than COPD or neuromuscular disease, a physician with demonstrated skills and experience in NIPPV must establish and document an appropriate diagnosis from this category on the basis of history and physical examination. A PSG is required for diagnosis of sleep apnea. A CPAP trial is recommended if OSA is documented unless a previous CPAP trial was unsuccessful or there is significant hypoventilation that is believed to be unlikely to respond to CPAP alone. Indications for usage of NIPPV: PSG criteria for OSA not responsive to CPAP; PSG criteria for mixed sleep apnea not responsive to CPAP; Central sleep apnea; other forms of nocturnal hypoventilation.

Device Characteristics (KQ3):

Two guidelines gave recommendations on device characteristics and titration.

2016 United Kingdom[56]

High inspiratory positive airway pressure (IPAP) and expiratory positive airway pressure (EPAP) settings are commonly required in patients with OHS (e.g., IPAP>30, EPAP>8). Volume control (or volume assured) modes of providing non-invasive ventilation may be more effective when high inflation pressures are required.

2010 Germany[52]

Titration of CPAP pressure until hypoventilation is eliminated. For non-invasive ventilation therapy, increase EPAP until obstructions are eliminated accompanied by titration of inspiratory pressure. In the case of considerable weight loss, a repeated attempt at CPAP, a change from non-invasive ventilation to CPAP, or a rest in treatment are all possible under poly(somno)graphical control. Weight loss should be part of the long-term treatment plan.

Respiratory Services (KQ4):

We did not identify guidelines that provided recommendations regarding home respiratory services for patients.

Other Respiratory Diseases

Other respiratory diseases included cystic fibrosis, bronchiectasis, and interstitial lung disease. Two studies[43, 92] with a total of 42 patients were included. The characteristics of the studies are listed in Appendix Table D.1. One evaluated HMV[92], one BPAP, [43] zero CPAP, and zero with HMV/BPAP mix. These studies were conducted in the United States (n=0), Canada (n=0), Europe (n=1), and Asia (n=1). Both studies were observational. We also identified three clinical practice guidelines relevant to KQ1-4(Appendix Table G.6.).[52, 64, 97, 103]

Overall risk of bias was rated as moderate due to selective patient population and unclear risk of conflict of interest in the observational studies (Appendix Table E.1 and E.2.).

KQ1. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements considered for the initiation and continuation of noninvasive positive pressure ventilation supplied by a Home Mechanical Ventilator (HMV), Bi-level Positive Airway Pressure device (BPAP), and Continuous Positive Airway Pressure device (CPAP) in the home through a noninvasive interface?

Key Points-KQ1

- The criteria used to start NIPPV were variable but most commonly included: diagnosis of diffuse parenchymal lung disease and/or bronchiectasis, hypoxia (long-term oxygen use), and/or hypercapnia (PaCO2 not specified).
- No studies compared the initiation criteria between different devices or evaluated criteria for device continuation.
- Processes used to titrate NIPPV were variable with the following targets used: reduction in hypercapnia, reduction in hypoxia (including nocturnal hypoxia), and achievement of target tidal volumes.

Two described criteria for initiation of HMV, BPAP, and/or CPAP devices in patients with other lung diseases.[43, 92]

Disease diagnosis

Studies enrolled patients with diffuse parenchymal lung diseases[43] and diffuse bronchiectasis.[92]

Other characteristics

One study enrolled patients with hypoxemia and hypercapnia NOS[43] and a second study enrolled patients already on home HMV and LTOT.[92]

Targets of device titration

Targets of device titration included “desired tidal volume”[43] and normal PaO2 mmHg without deterioration in PaCO2.[92]

Device continuation

No studies described criteria for device continuation.

KQ2. What is the effect of HMV, BPAP, or CPAP use on patient outcomes, including mortality, hospitalization, admission/readmission to intensive care unit (ICU), need for intubation, outpatient visits, emergency room visits, disease exacerbations, quality of life (QoL), activities of daily living (ADL), dyspnea, sleep quality, exercise tolerance, and adverse events?

Key Points-KQ2

- Mortality, hospital admission, quality of life, or need for intubation were not evaluated.
- HMV (compared with no device) was associated with significantly shorter length of hospital stay in patients with bronchiectasis.

One case control study compared HMV (volume cycled) plus long-term oxygen therapy to long-term oxygen therapy only in 28 patients with diffuse bronchiectasis and severe chronic respiratory failure.[92] The reduction of length of hospital stay in the HMV and long-term oxygen therapy group was significantly higher than those in the long-term oxygen therapy group (WMD=-42.00 days per year, 95% CI; -76.37 to -7.63). No significant difference was found on length of survival. Results are summarized in Table 15.

Table 15. Effectiveness of HMV vs. no device in patients with other respiratory diseases

Comparison	Outcome	Conclusion	Study Design (sample size)
HMV vs. No Device	Length of survival	Median 45 months vs. 48 months, p>0.05	1 Observational study (28 patients) [92]
	Length of hospital stay (changes before and after intervention) days per year	WMD: -42.00; 95% CI: -76.37 to -7.63; p=0.02, I2=N/A	1 Observational study (28 patients) [92]

CI: confidence interval, HMV: home mechanical ventilation, N/A: not applicable, WMD: weighted mean difference

KQ3. What are the equipment parameters that are used? a) What are the parameters of ventilator usage (e.g. mode as determined by trigger, control and cycling variables)? b) What are the equipment parameters that are necessary to achieve desired outcomes (e.g. flow capabilities, settings, etc.)? c) What are the parameters of prescribed patient usage (e.g. frequency of use, duration of use throughout the day, other)? d) In each of the above populations, what are the parameters of patient compliance with the prescribed usage of the equipment?

Key Points-KQ3

- The BPAP mode utilized was BPAP ST
- The HMV mode utilized was volume assist control ventilation mode.

One study evaluated patients who used BPAP ST.[43] BPAP ST equipment parameters included IPAP, EPAP, and a spontaneous/timed (ST) breathing mode with a backup respiratory rate. One study evaluated patients who used HMV, volume assist control ventilation.[92] No studies reported the model or manufacturer of the device used. We did not report mask type used, use of a humidifier, or use of supplemental oxygen.

KQ4. What respiratory services, other than the technical support of the use of the prescribed equipment, are being provided to the above patients in the home (e.g. patient education, ongoing smoking cessation, respiratory therapist led home care)?

No studies described respiratory services provided in the home.

KQ5. What are the professional guidelines and statements which address KQ 1 to KQ 4?

Information related to clinical guidelines can be found in Appendix Table G.6.

Initiation Criteria and Effectiveness (KQ1 and KQ2):

Two guidelines gave recommendations regarding initiation criteria.

2016 United Kingdom[56]

In asthma: Acute (or acute on chronic) episodes of hypercapnia may complicate chronic asthma. This condition closely resembles COPD and should be managed as such.

In bronchiectasis: In patients with non- cystic fibrosis bronchiectasis, NIV should be started in acute hypercapnic respiratory failure using the same criteria as in AECOPD (pH<7.35 and pCO2 >6.5 kPa persist or develop despite optimal medical therapy).

In cystic fibrosis: In patients with cystic fibrosis, NIV is the treatment of choice when ventilatory support is needed.

2012 Australia[13]

In cystic fibrosis: Individuals with awake SpO2<94% or spirometry (FEV1<65% predicted) are at risk of nocturnal oxygen desaturation. Overnight oximetry should be undertaken in individuals meeting these criteria. Non-invasive ventilation is indicated if daytime CO2>45mmHg and nocturnal gas exchange shows SpO2<90% for >5% of TST and/or a rise in TcCO2 / ETCO2 from nonrapid eye movement to rapid eye movement>5mmHg during room air

breathing occurs. Nocturnal NIV is more effective than oxygen therapy in controlling nocturnal hypoventilation in patients with hypercapnic CF lung disease. Bi-level ventilation should be trialed initially. Volume ventilation may offer additional benefits in some individuals especially if work of breathing is high. NIV does not appear to increase the incidence of pneumothorax, but this is a relatively common occurrence in this population. Therefore, patients need to be educated regarding the symptoms of pneumothorax and should seek immediate medical attention should these symptoms arise. Changes in awake blood gases are not the best measure of the effectiveness of NIV in CF. Changes in symptoms, exertional dyspnea and exercise tolerance, and control of nocturnal hypoventilation are better indicators of the patient's response to therapy.

In hypercapnic central sleep apnea: Awake PaCO2 > 45 mmHg in the absence of lung and chest wall abnormalities, skeletal malformations and neuromuscular disorders, in combination with symptoms consistent with sleep disordered breathing warrant a full PSG. In patients with isolated sleep hypoventilation, titrate NIV settings in a spontaneous-timed mode, during a full polysomnogram. Where hypercapnic central apnea is caused from pharmacological intake (e.g. opioid-based derivatives), referrals to chronic pain team or relevant prescribing body should be made with the aim of reducing medication intake in order to improve central events and stabilize oxygen saturations. Overall patient management should be performed by specialized teams. Any signs of chest infection should be reviewed and managed promptly, especially in the case of congenital central hypoventilation syndrome where a lack of dyspnea in response to pneumonia may mask severe respiratory compromise.

Device Characteristics (KQ3):

We did not identify guidelines that provided recommendations on device characteristics and titration.

Respiratory Services (KQ4):

One guideline gave recommendations regarding home respiratory services for patients.

2016 United Kingdom[56]

In patients with cystic fibrosis, specialized physiotherapy is needed to aid sputum clearance.

Mixed Disease Conditions

Mixed disease conditions included studies that reported outcomes for patients with multiple different causes of chronic respiratory failure. For example, a study may have enrolled patients with COPD and OHS and only reported the outcomes for the entire combined cohort, rather than individually by cause of chronic respiratory failure. Five studies[35, 93-96] with a total of 311 patients were included. The characteristics of the studies are listed in Appendix Table D.1. Four evaluated HMV, [35, 93, 94, 96] one BPAP,[95] zero CPAP, and zero HMV/BPAP mix. These studies were conducted in the United States (n=0), Canada (n=0), Europe (n=4), and Asia (n=1). There were two RCTs and three observational studies. We also identified six clinical practice guidelines relevant to KQ1-4 for patients with any cause of chronic respiratory failure (Appendix Table G.1.)[52, 53, 55, 64, 97, 103]

Overall risk of bias was rated as moderate. The RCTs were unable to blind patients, providers, or outcome assessors and they had unclear risk of allocation concealment (Appendix TableE.1.). The observational studies were found to have selective patient populations and a high risk of outcome assessment in observational studies (Appendix Table E.2.).

KQ1. What are the patient characteristics and/or laboratory criteria and/or target level measurable improvements considered for the initiation and continuation of noninvasive positive pressure ventilation supplied by a Home Mechanical Ventilator (HMV), Bi-level Positive Airway Pressure device (BPAP), and Continuous Positive Airway Pressure device (CPAP) in the home through a noninvasive interface?

Key Points-KQ1

- The criteria used to start NIPPV were variable but most commonly included PaCO2>45mmHg, hypoxia (nocturnal SaO2 < 88% for ≥ 5 consecutive minutes), and/or pH ≥7.35.
- HMV started in the home setting compared to HMV started in the hospital was not associated with differences in mortality or quality of life (in patients with NMD or TRD).
- No major differences were found in the criteria used to initiate a BPAP or a HMV device.
- Processes used to titrate NIPPV were variable with the following targets used: reduction in hypercapnia, reduction in hypoxia, and achievement of target tidal volumes.

Five studies[35, 93-96] described criteria for initiation and/or continuation of HMV, BPAP, and/or CPAP devices in patients with mixed respiratory diseases. Four studies [35, 93-95] evaluated patients who had not yet started home device use and one study evaluated patients with previous device use.[96] There were no major differences in criteria used to start BPAP versus HMV.

Disease diagnosis

Studies enrolled patients with TRD, OHS, NMD, COPD, and Other (which included asthma, bronchiectasis, and any “stable respiratory disease”).

Other characteristics

Studies used the following laboratory criteria for enrollment: pH ≥7.35 (7100), PaCO2>45mmHg,[93, 94]

PaCO2>50mmHg,[95] nocturnal SaO2 < 88% for ≥ 5 consecutive minutes.[95]

Stable disease versus acute exacerbation

One study enrolled patients who started home NIPPV during or shortly after acute exacerbation[95] and 3 studies enrolled patients with stable disease (no current or recent exacerbation).[35, 93, 94] One study did not report this information.

Targets of device titration

Most studies reported using maximum tolerated respiratory pressures (such as IPAP and/or EPAP) needed to achieve the following stated goals: maximum decrease in PaCO2, tidal volume of 8-10mL/kg, normalization of PaO2.

Device continuation

No studies described criteria for device continuation.

KQ2. What is the effect of HMV, BPAP, or CPAP use on patient outcomes, including mortality, hospitalization, admission/readmission to intensive care unit (ICU), need for intubation, outpatient visits, emergency room visits, disease exacerbations, quality of life (QoL), activities of daily living (ADL), dyspnea, sleep quality, exercise tolerance, and adverse events?

Key Points-KQ2

- BPAP (compared with no device) was associated with significantly reduced hospital admissions (SOE: low) in a mixed population of patients with COPD, asthma, or bronchiectasis.

In one RCT, 37 severe hypercapnic obstructive lung diseases (chronic obstructive pulmonary disease (COPD), asthma, and bronchiectasis) were randomized to receive BPAP or standard treatment.[95] Patients in the BPAP group was found to have significantly better outcomes on 6-minute walk distance (WMD: 99.80; 95% CI: 34.14 to 165.46; p<0.01), number of hospitalization per patient (WMD: -2.30: 95% CI: -3.36 to -1.24; p<0.001), and length of hospital stay (WMD: -37.70; 95% CI: -57.68 to -17.72; p<0.001). There was no statistical difference between the two groups on resting Borg score and Borg score at the end of a 6-minute walk test. Four patients from the BPAP group withdrew from the study due to intolerance of BPAP device.

One retrospective observational study compared HMV volume assist control ventilation to HMV volume control in patients with NMD or TRD.[94] There was no statistically significant difference

on mortality (OR= 0.91, 95% CI: 0.28 to 2.96, p=0.88) or the number of hospital admissions (0.17 per patient in HMV volume assist/control mode vs. 0.04 per patient in HMV volume control mode, p=0.11).

In one RCT, 77 patients with NMD or TRD were randomized to start HMV at home or start HMV in the hospital.[93] There was no significantly difference on mortality (OR=2.80, 95% CI: 0.51 to 15.43) or quality of life (Severe Respiratory Insufficiency, SF-36) between the two groups.

Comparative effectiveness evidence with SOE rating for major outcomes is summarized in Table 16. Other outcomes are summarized in Table 17.

Table 16. Major effectiveness outcomes with SOE (all devices in studies with mixed disease conditions)

Comparison	Outcome	Conclusion	Study Design (sample size)	Rationale for Strength of Evidence (SOE)	Overall Evidence Strength (Direction of Effect)
BPAP vs. no device	Number of hospitalization per patients	-2.30; 95% CI -3.36 to -1.24; I2=N/A	1 RCT (37 patients)[95]	Imprecision	Low (reduction with BPAP)
HMV volume assist control ventilation vs. HMV volume control	Mortality	OR: 0.91, 95% CI: 0.28 to 2.96, p=0.88 9 fewer per 1000 patients (116 fewer to 99 more)	1 RCT (126 patients)[94]	Severe imprecision	insufficient
	Number of hospital admissions	Rate ratio: 4.25, p=0.11; Follow up: 12 months	1 RCT(126 patients)[94]	Severe imprecision	insufficient
HMV started at home vs. HMV started in the hospital	Mortality	OR: 2.80, 95% CI: 0.51 to 15.43 80 more per 1000 patients (48 fewer to 208 more)	1 RCT (77 patients)[93]	Severe imprecision	insufficient
	Quality of life (Severe Respiratory Insufficiency, SF-36)	No statistical difference on all domains	1 RCT(77 patients)[93]	Severe imprecision	insufficient

BPAP: bi-level positive airway pressure, CI: confidence interval, HMV: home mechanical ventilation,, N/A: not applicable, OR: odds ratio, RCT: randomized controlled trial, SF-36: Medical Outcomes Study Questionnaire Short Form, WMD: weighted mean difference

Table 17. Other effectiveness outcomes (all devices in studies with mixed disease conditions)

Comparison	Outcome	Conclusion	Study Design (sample size)
BPAP vs. no device	6-minute walk distance test (meters)	WMD: 99.80; 95% CI: 34.14 to 165.46; I2=N/A	1 RCT (37 patients) [95]
	Length of hospital stay (days)	-37.70; 95% CI: -57.68 to -17.72; I2=N/A	1 RCT (37 patients)[95]

BPAP: bi-level positive airway pressure, CI: confidence interval, HMV: home mechanical ventilation, N/A: not applicable, OR: odds ratio, RCT: randomized controlled trial, SF-36: Medical Outcomes Study Questionnaire Short Form, WMD: weighted mean difference

KQ3. What are the equipment parameters that are used? a) What are the parameters of ventilator usage (e.g. mode as determined by trigger, control and cycling variables)? b) What are the equipment parameters that are necessary to achieve desired outcomes (e.g. flow capabilities, settings, etc.)? c) What are the parameters of prescribed patient usage (e.g. frequency of use, duration of use throughout the day, other)? d) In each of the above populations, what are the parameters of patient compliance with the prescribed usage of the equipment?

Key Points-KQ3

- BPAP devices used mode BPAP NOS (unclear if S or ST)
- For HMV devices, the modes utilized were pressure controlled ventilation, volume assist control ventilation, volume control ventilation, and pressure/volume controlled ventilation NOS.

One study evaluated patients who used BPAP NOS (unclear if ST or S mode).[95] Four studies evaluated patients who used HMV devices.[35, 93, 94, 96] HMV modes utilized were pressure controlled ventilation, volume assist control ventilation, volume control ventilation, and pressure or volume controlled ventilation NOS. No studies evaluated CPAP use.

Two studies reported the model and manufacturer of the device used.[35, 93] Three studies did not report the model or manufacturer of the device used.[94-96] We did not report mask type used, use of a humidifier, or use of supplemental oxygen.

KQ4. What respiratory services, other than the technical support of the use of the prescribed equipment, are being provided to the above patients in the home (e.g. patient education, ongoing smoking cessation, respiratory therapist led home care)?

Key Points-KQ4

- Evidence is lacking to determine the effect of specific respiratory home services on outcomes.

- Respiratory services provided in the home included: telephone hotline and scheduled phone calls

Two studies described respiratory services provided in the home, which included a telephone hotline staffed by healthcare professionals including nurses, respiratory therapists, and/or others[94], and scheduled phone calls by respiratory therapists every 2 weeks to ensure compliance.[95]

KQ5. What are the professional guidelines and statements which address KQ 1 to KQ 4?

Information related to clinical guidelines can be found in Appendix Table G.1.

Initiation Criteria and Effectiveness (KQ1 and KQ2):

Two guidelines gave recommendations regarding initiation criteria in patients with any cause of chronic respiratory failure.

2015 United Kingdom[64]

Treatment with modalities of ventilatory support should be considered for patients who are hypercapnic.

2012 Australia[13]

Generally NIV should be commenced when there is evidence of: Daytime hypercapnia, PaCO2 ≥45mmHg and/or Evidence of nocturnal hypoventilation (in order of recommendation), such as: A rise in PaCO2 of ≥ 8mmHg between evening and morning ABGs or other accurate CO2 surrogate; An acute peak rise of ≥ 8mmHg in TcCO2 or ETCO2; A rise in TcCO2 or ETCO2 > 50mmHg for more than 50% of total sleep time. Whilst not ideal - when a measure of CO2 is not available - nocturnal oximetry demonstrates sustained oxygen desaturation ≤ 88% for 5 consecutive minutes or SpO2 <90% for >10% of total sleep time and symptoms of significant sleep disordered breathing associated with nocturnal obstructive or hypopneic events and/or Otherwise unexplained potential co-morbidity of sleep disorders, such as refractory hypertension, pulmonary hypertension, right heart failure, polycythemia, cardiovascular disease or stroke.

Device Characteristics (KQ3):

Three guidelines gave recommendations on device characteristics and titration.

2016 United Kingdom[56]

Pressure-targeted ventilators are the devices of choice for acute NIV. A full face mask (FFM) should usually be the first type of interface used. A range of masks and sizes is required and staff involved in delivering NIV need training in and experience of using them. NIV circuits must allow adequate clearance of exhaled air through an exhalation valve or an integral exhalation port on the mask. As patients recover from acute hypercapnic respiratory failure, ventilator requirements change and ventilator settings should be reviewed regularly.

2012 Australia[13]

Simple bi-level devices are suitable for individuals requiring nocturnal and limited daytime ventilatory support only. However, more sophisticated volume or hybrid devices are indicated for patients requiring more than 18 hours/day or where bi-level devices have proven to be inadequate. Ventilator dependent individuals should be titrated on and use ventilators which have been approved for life support and have an alternative battery source to mains power. They also should be supplied with an appropriate back-up ventilator. Machines with "mask off" or "low pressure" and "power failure" alarms are recommended for ventilator dependent patients and in disorders where there is a potential inability to arouse from an interruption to ventilation or when there is an absence of ventilatory responses when awake. Titration for long-term NIV settings should occur when the patient is chronically stable (pH>7.35) and free from exacerbation. Adequate IPAP-EPAP difference is required to ameliorate hypoventilation. A Bi-level ventilation should be commenced in the spontaneous mode, unless there is specific evidence that the patient is unable to trigger the machine once baseline leak and settings have been optimized Complete correction of sleep disordered breathing during the initial titration night is not necessary for improvement of daytime blood gases and symptoms to occur.

Spontaneous-timed mode flow generator, or a ventilator, to be provided if Spontaneous mode device does not allow correction of sustained hypercapnia in the presence of central apnea or persisting hypoventilation. Ventilators using flow triggering or volume-cycled mandatory ventilation may be required for patients experiencing difficulty in triggering inspiration

2010 Germany[52]

In life-supporting ventilation, or for patients unable to remove their own face masks, a ventilation machine with an internal battery is required (ISO 10651-2: 2004). If the patient's ability to breathe spontaneously is greatly reduced (daytime ventilation time > 16 hours), an external battery pack with a capacity of at least 8–10 hours is required. If the duration of mechanical ventilation exceeds 16 hours/day, an additional identical ventilator must be provided. The replacement of the existing ventilator with a different type of machine or the adjustment of the ventilation mode must each take place under hospital conditions in a center specialized for mechanical ventilation.

The basic requirements for ventilators were determined according to ISO-Standards, distinguishing between "Home care ventilators for ventilator-dependent patients" (ISO 10651-2: 2004) and "Home-care ventilatory support devices" (ISO 10651-6: 2004).

A second ventilator and an external battery pack are necessary if ventilation periods exceed 16 hours/day. Every non-invasively-ventilated patient requires at least one reserve mask. A humidifier is a mandatory requirement for invasive ventilation and is also useful for non-invasive ventilation if typical symptoms are present. In NMD patients with cough insufficiency and in children, selective use of a pulse oximeter is necessary.

Respiratory Services (KQ4):

One guideline gave recommendations regarding home respiratory services for patients.

2011 Canada[53]

Education and preventive strategies in airway clearance must precede the need for mechanical ventilation whenever possible. In the absence of contraindications, lung volume

recruitment (i.e. air stacking) techniques should be introduced with the measurement of peak cough flows and maximum insufflation capacity in those with peak cough flows <270 L/min. Manually assisted coughing is recommended alone or in addition to lung volume recruitment to increase peak cough flows to >270 L/min. In the absence of contraindications, mechanical in-exsufflation should be recommended for patients unable to achieve peak cough flows >270 L/min with lung volume recruitment and/or manually assisted coughing, particularly during respiratory infection. A government-funded ventilatory service is necessary to provide appropriate access to equipment and respiratory care.

Adverse Events

Key Points-Adverse Events

- Only 19 out of the 68 included studies (27.94%) evaluated adverse events. A majority of these studies did not use a consistent approach for evaluation and reporting.
- Serious events (such as mortality, hospitalization, and need for intubation) were commonly classified as study outcomes and were infrequently and non-uniformly classified as serious adverse events.
- The pooled incidence of reported non-serious adverse events was 0.35 for HMV, 0.31 for BPAP, 0.27 for HMV/BPAP mix, 0.39 for CPAP, and <0.001 for no device groups.
- The pooled incidence of reported serious adverse events was <0.001 for HMV, 0.01 for BPAP, 0.09 for CPAP, and <0.001 for no device groups.
- Based on direct comparisons, we found no statistically significant differences in total number of treatment withdrawals or adverse events (serious plus other) when comparing different devices or when comparing device use with no device use.

42 out of the 68 included studies (61.76 %) did not evaluate adverse events and a majority of the rest of the studies did not use a consistent approach for evaluation and reporting. Serious events (such as mortality, hospitalization, and need for intubation) were commonly classified as study outcomes and were infrequently and non-uniformly classified as serious adverse events.

19 studies (12 RCTs[16, 19-21, 24, 25, 28, 30, 45, 82, 84, 85, 91, 95] and 7[26, 27, 34, 59, 60, 94, 96] observational studies) reported a total of 264 adverse events in 1297 patients. Table 3 presents the description of the adverse events categories. Table 18 shows the pooled incidence rate of adverse events by device.

Table 18. Incidence rate of adverse events by device

Device	Serious adverse events Incidence rate and 95% CI	Non-serious adverse events Incidence rate and 95% CI	Total adverse events Incidence rate and 95% CI
HMV	IR: 0.00; 95% CI: 0.00 to 0.00	IR: 0.35; 95% CI: 0.27 to 0.46	IR: 0.35; 95% CI: 0.27 to 0.46
BPAP	IR: 0.01; 95% CI: 0.00 to 0.05	IR: 0.31; 95% CI: 0.16 to 0.58	IR: 0.23; 95% CI: 0.15 to 0.36
HMV/BPAP mix	Not reported/not evaluated	IR: 0.27; 95% CI: 0.15 to 0.50	IR: 0.27; 95% CI: 0.16 to 0.42
CPAP	IR: 0.09; 95% CI: 0.03 to 0.26	IR: 0.39; 95% CI: 0.27 to 0.56	IR: 0.35; 95% CI: 0.25 to 0.49
No device	IR: 0.00; 95% CI: 0.00 to 0.01	IR: 0.00; 95% CI: 0.00 to 0.00	IR: 0.00; 95% CI: 0.00 to 0.00

BPAP: bi-level positive airway pressure, CI: confidence interval, CPAP: continuous positive airway pressure, HMV: home mechanical ventilation, IR: incidence rate

The pooled incidence rate of non-serious adverse events was <0.001 in patients with no device use and ranged from 0.27-0.39 in patients using HMV, BPAP, and CPAP devices. The most common non-serious adverse events included skin symptoms (e.g. facial rash, nasal ulceration), eye symptoms (e.g. dry eyes, conjunctivitis), nose/mouth symptoms (e.g. nasal stuffiness, rhinorrhea, nosebleed, mucosal dryness, oral air leak), gastrointestinal symptoms (e.g. gastric distension, aerophagia), and device/mask intolerance (e.g. claustrophobia, discomfort, noncompliance).

The pooled incidence rate of serious adverse events was <0.001 in HMV, 0.01 in BPAP, 0.09 in CPAP, and <0.001 in patients using no device. The types of serious adverse events are listed in Table 19. Death, hospitalization, and intubation were reported as primary efficacy outcomes and were not re-reported as serious adverse events in this review. The most commonly reported serious adverse event was acute respiratory failure.

Table 19. Types of reported serious adverse events

Device type	Serious adverse events	Number of cases, patients at risk, and studies
BPAP	Acute respiratory failure	29 cases out of 178 patients (5 studies) [27, 45, 59, 60, 85]
	Treatment failure (combined endpoint of use<2h/night, hospital admission for respiratory failure, or PaCO2>60)	4 cases out of 29 patients (1 study)[82]
	Aortic dissection	1 case out of 37 patients (1 study) [20, 21]
	Transient ischemic attack	1 case out of 23 patients (1 study)[25]
CPAP	Treatment failure (combined endpoint of use<2h/night, hospital admission for respiratory failure, or PaCO2>60){Howard, 2017 #23}	4 cases out of 31 patients (1 study)[82]
HMV	Not reported/not evaluated	
HMV/BPAP mix	Not reported/not evaluated	
No device	Acute respiratory failure	13 cases out of 30 patients (2 studies)[27, 45]
	Ischemic stroke	1 case out of 35 patients (1 study)[20, 21]
	Arrhythmia requiring pacemaker	1 case out of 18 patients (1 study)[85]

Table 20 summarizes the direct comparisons of total number of adverse events and withdrawals by device and disease reported by individual studies. We found no statistically significant difference in withdrawals and total number of adverse events when comparing devices or when comparing device use with no device use.

Table 20. Comparisons of total number of adverse events by devices and diseases*

Disease	Comparison	Adverse events	Findings
COPD	BPAP vs. no device	Total number of withdrawals	OR:1.17; 95% CI: 0.59 to 2.33; I^2=53.5%
		Total number of adverse events	Rate Ratio: 1.16, 95% CI: 0.23 to 5.73, I^2=71.0%
	BPAP IVAPS vs. BPAP ST	Total number of withdrawals	OR: 1.00; 95% CI: 0.18 to 5.67; I^2=N/A
		Total number of adverse events	2 cases in BPAP IVAPS and 0 case in BPAP ST
NMD	HMV vs. BPAP	Total number of withdrawals	0 in both groups
OHS	HMV/BPAP mix (all with bi-level pressure with assured volume) vs.no device	Total number of withdrawals	OR: 2.44; 95% CI: 0.61 to 9.86, I^2=N/A
		Total number of adverse events	19 non serious adverse in HMV/BPAP mix and 0 non serious adverse in no device
	HMV/BPAP mix (all with bi-level pressure with assured volume) vs. CPAP	Total number of withdrawals	OR: 0.69; 95% CI: 0.25 to1.88, I^2=N/A
		Total number of adverse events	Rate Ratio: 0.69; 95% CI: 0.39 to 1.22; I^2=N/A

Disease	Comparison	Adverse events	Findings
	CPAP vs. no device	Total number of withdrawals	OR: 3.56; 95% CI: 0.95 to 13.33; I^2=N/A
		Total number of adverse events	32 non serious adverse in CPAP and 0 non serious adverse in no device
	BPAP vs no device	Total number of withdrawals	OR: 0.94; 95% CI: 0.06 to 16.33; I^2=N/A
		Total number of adverse events	Rate Ratio: 0.95; 95% CI: 0.06 to 15.15; I^2=N/A
	BPAP vs. CPAP	Total number of withdrawals	OR: 2.22; 95% CI: 0.19 to 25.91; I^2=N/A
		Total number of adverse events	Rate Ratio: 1.07; 95% CI: 0.27 to 4.27; I^2=N/A
NMD, TRD	1) HMV volume assist/control mode 2) HMV volume control mode	Total number of adverse events	Rate Ratio: 1.19; 95% CI: 0.63 to 2.26; I^2=N/A
COPD, and other	BPAP vs. no device	Total number of withdrawals	OR: 1.62; 95% CI:0.37 to 7.05; I^2=N/A
		Total number of adverse events	19 cases in BPAP vs. 0 case in no device

BPAP: bi-level positive airway pressure, CI: confidence interval, CPAP: continuous positive airway pressure, HMV: home mechanical ventilation, NMD: neuromuscular diseases, OHS: obesity hypoventilation syndrome

*: Only studies reported direct comparisons between devices or between device use with no device use were evaluated in this table.

Discussion

Overview

We conducted a systematic review to assess the effectiveness of home noninvasive positive pressure ventilation (NIPPV) (using home mechanical ventilators (HMV), bi-level positive airway pressure (BPAP), and/or continuous positive airway pressure (CPAP) devices) in adults with chronic respiratory failure. We assessed the criteria considered for initiation and continuation of home NIPPV, respiratory services provided in the home, adverse events, and summarized relevant clinical practice guidelines.

When evaluating patients with chronic respiratory failure who may benefit from NIPPV in the home setting, key clinical considerations include 1) when to start NIPPV and 2) which device type (HMV vs. BPAP) and device mode are needed to deliver acceptable and safe ventilation. These considerations may vary based on the underlying etiology of chronic respiratory failure (chronic obstructive pulmonary diseases [COPD] vs. thoracic restrictive disease vs. neuromuscular diseases vs. obesity hypoventilation vs. other). In general, included studies evaluated the efficacy of starting chronic home NIPPV in patients with moderate to severe stable disease and/or patients with unstable disease in current acute respiratory exacerbation.

Figure 3 summarizes the distribution of evidence for device effectiveness by disease conditions. Most of the evidence concentrated on the comparison between BPAP and no device in patients with COPD, while comparisons between devices and other conditions were scarce.

Figure 3. Evidence map for effectiveness of device use.

Chronic Obstructive Pulmonary Disease (COPD)

	HMV	BPAP	CPAP	No Device
HMV	2 RCTs	1 Obs	1 Obs	2 Obs
BPAP		1 RCT, 1 Obs	2 RCTs	15 RCTs, 6 Obs
CPAP				
No Device				

Thoracic Restrictive Diseases

	HMV	BPAP	CPAP	No Device
HMV				2 Obs
BPAP				
CPAP				
No Device				

Neuromuscular Disease (NMD)

	HMV	BPAP	CPAP	No Device
HMV	1 Obs	1 Obs		1 Obs
BPAP		1 RCT, 2 Obs		1 RCT, 2 Obs
CPAP				
No Device				

Obesity Hypoventilation Syndrome

	HMV	BPAP	CPAP	No Device
HMV				
BPAP		1 RCT, 1 Obs	2 RCTs	2 RCTs
CPAP				1 RCT
No Device				

Other Respiratory Diseases

	HMV	BPAP	CPAP	No Device
HMV				1 Obs
BPAP				
CPAP				
No Device				

Figure legend: HMV: home mechanical ventilation; BPAP: bi-level positive airway pressure, CPAP: continuous positive airway pressure; RCT: randomized controlled trial; Obs: observational study. The colored cell shows the number of RCTs and observational studies for the comparisons between devices. Red shows no existing studies; yellow shows 1 RCT or only observational studies; and green shows more than one RCT.

The following tables summarize device effectiveness by condition, device, and comparator.

Table 21. Summary of device effectiveness in patients with COPD

Device	Comparator(s)	Findings (Strength of evidence)
HMV	individually with BPAP, CPAP, or No device	Fewer hospital admissions (low SOE)
BPAP	No device	Lower mortality (moderate SOE) Reduced need for intubation (moderate SOE) Fewer hospital admissions (low SOE)

BPAP: bi-level positive airway pressure, CPAP: continuous positive airway pressure, HMV: home mechanical ventilator, ICU: intensive care unit, SOE: strength of evidence, ST: spontaneous/timed mode

Table 22. Summary of device effectiveness in patients with thoracic restrictive diseases

Device	Comparator(s)	Findings
HMV	No device	Lower mortality (low SOE)

HMV: home mechanical ventilator, SOE: strength of evidence

Table 23. Summary of device effectiveness in patients with neuromuscular disease

Device	Comparator(s)	Findings
BPAP	No device	Lower mortality (low SOE) Better quality of life (low SOE)

BPAP: bi-level positive airway pressure, HMV: home mechanical ventilator, SOE: strength of evidence

Table 24. Summary of device effectiveness in patients with obesity hypoventilation syndrome

Device	Comparator(s)	Findings
HMV/BPAP mix	No device	Low mortality (low SOE)
BPAP	No device	Better sleep quality

Table 25. Summary of device effectiveness in patients with other respiratory diseases

Device	Comparator(s)	Findings
HMV	No device	Mortality, hospital admission, quality of life, or need for intubation was not reported.

HMV: home mechanical ventilator, SOE: strength of evidence. Other respiratory diseases included cystic fibrosis, bronchiectasis, and interstitial lung disease.

Table 26. Summary of device effectiveness in patients with mixed disease conditions

Device	Comparator(s)	Findings
BPAP	No device	Fewer hospital admissions (low SOE)

BPAP: bi-level positive airway pressure, SOE: strength of evidence. Mixed disease conditions included cohorts of patients with one or more of COPD, thoracic restrictive diseases, neuromuscular disease, obesity hypoventilation syndrome, or other respiratory diseases.

We found no major differences in the criteria considered for initiation of a HMV versus BPAP device—and included studies did not directly address this clinical question. The most common criteria for initiation of home noninvasive positive pressure ventilation (NIPPV) using a HMV and/or BPAP device were 1) COPD (hypercapnia [(PaCO2 ranging from >45 to >56mmHg], pH>7.35, FEV1<50% normal, and/or hypoxia [PaO2 ranging from <55 to <60mmHg or long term oxygen use]), 2) thoracic restrictive diseases (PaCO2>45mmHg, FVC<40% normal or MIP<60cmH2O, or nocturnal SaO2<88% for ≥ 5 consecutive minutes), 3) neuromuscular disease (PaCO2>45mmHg or FVC<50% or MIP <60cmH2O, or nocturnal SaO2 < 88% for ≥ 5 consecutive minutes), 4) obesity hypoventilation syndrome (hypercapnia [PaCO2 ranging from >45 to >53mmHg] and pH>7.35), 5) other respiratory diseases (diagnosis of diffuse parenchymal lung disease and/or bronchiectasis, hypoxia [long term oxygen use], and/or hypercapnia [PaCO2 not specified]).

Respiratory services provided in the home were variable and included: telephone hotline, scheduled phone calls, home visits, smoking cessation, cough assistance instruction and devices, and dietary and lifestyle counseling. Only one RCT evaluated the efficacy of home respiratory services and found that BPAP ST with weekly telemonitoring (compared with BPAP ST alone) in NMD patients was associated with fewer office visits, fewer emergency room visits, fewer hospital admissions, and no difference in mortality.

Serious and non-serious adverse events were reported in patients in the HMV, BPAP, CPAP, and no device groups. Incidence of non-serious adverse events (such as facial rash, mucosal dryness, mask discomfort, etc.) were approximately 0.30 across devices. Reported serious adverse events were rare. The most commonly reported serious adverse event was acute respiratory failure, which occurred in patients in using BPAP, CPAP, as well as patients using no devices. The recognition that patients using NIPPV devices may experience serious adverse events such as acute respiratory failure should be interpreted with the following considerations: First, reporting of serious adverse events was not uniform across studies, with a majority of studies not reporting serious adverse events and a majority of the remaining studies reporting no serious adverse events. Second, many studies that reported serious adverse events such as acute respiratory failure in patients who used NIPPV devices also reported that acute respiratory failure occurred, sometimes at even higher rates, in patients who used no devices. Third, outcomes such as death, hospitalization, and need for intubation were considered as primary efficacy outcomes and were not re-reported as serious adverse events in this review. Therefore, recognition of serious adverse events should be balanced with efficacy data showing benefit in mortality, hospitalization, and need for intubation in many disease categories. Fourth, comparative studies found no statistically significant differences in adverse events or treatment withdrawals among device type (Table 19).

Findings in Relation to What Is Known

This systematic review provides evidence that in patients with nearly every disease condition, NIPPV was associated with both a statistically and clinically significant reduction in mortality. In addition, in patients with COPD, NIPPV was associated with fewer hospitalizations, fewer intubations, reduced dyspnea and no change in quality of life. In patients with COPD, NIPPV via HMV (compared individually to BPAP, CPAP, or no device) was associated with fewer hospital admissions (SOE: low). For patients with TRD, NMD, OHS, and other lung diseases, NIPPV was also associated with improved exercise tolerance, improved quality of life, reduced dyspnea, improved sleep quality, and shorter length of hospital stay in individual populations. Published guidelines varied with regards to criteria used to start NIPPV, criteria used to titrate NIPPV, recommended equipment parameters to use in specific disease conditions, and recommended respiratory services, all with various levels of evidence. While many guidelines recommended initiation of home NIPPV for daytime hypercapnia ($PaCO2 \geq 45mmHg$), some guidelines recommended initiation of home NIPPV prior to the development of daytime hypercapnia. In patients with COPD, some guidelines recommend initiation of home NIPPV in patients with chronic daytime hypercapnia and/or recurrent episodes of acute hypercapnic respiratory failure, some guidelines cite insufficient evidence to recommend such practices.

While some guidelines recommended certain clinical circumstances when provision of an HMV was preferred to a BPAP machine, there is currently not convincing comparative evidence to support or refute these recommendations. For example, two English language guidelines (one from Germany and one from Australia) recommended an HMV device with an alternative backup power source, alarms to signal “mask off” or “low pressure” or “power failure,” and a second backup ventilator for patients with any disease condition whose device use approached >16 or >18 hours/day. [52, 97] Guidelines also recommend the volume controlled or volume cycled

features of HMV machines when pressure controlled ventilation failed to prevent hypercapnia in patients with NMD, TRD, and OHS and when patients with any condition had difficulty triggering inspiration. [52, 97] Our review also found significant heterogeneity in the specific patient characteristics used to initiate home NIPPV. While most studies used hypercapnia (commonly, but not always defined as PaCO2 ≥ 45mmHg) as one criteria to initiate home NIPPV, there were several other disease specific and variable criteria used to initiate home NIPPV. We found no existing comparative evidence to support or refute guideline recommendations of using HMV when device use approached >16 hours/day.

The guidelines included in this study were published between 1999 and 2016. In total, this systematic review included 11 studies published since 2016, the year of publication of the most recent guidelines.

Limitations

Despite conducting a comprehensive literature search, we were unable to find sufficient evidence to identify ideal criteria to initiate and continue home NIPPV via different devices (Key Question [KQ1]), optimized equipment settings (KQ3), or impact of home respiratory services (KQ4). Qualitative syntheses of these KQs were also limited by heterogeneity of the included studies (population, inclusion/exclusion criteria, targets and process of device titration, devices used, follow up length, length of use of device, and study design). Our findings were also limited by lack of standard reporting of the following characteristics: 1) device type (i.e., difficulty in differentiating HMV from BPAP), 2) device used (e.g., manufacturer and model), 2) key device characteristics (e.g., mode used), and 3) device titration protocol and targets. For effectiveness and adverse events of home NIPPV (KQ2), the majority of the studies evaluated BPAP and no device in stable COPD patients. The evidence for comparative effectiveness of different devices and different modes is scarce, as well as the evidence for conditions other than stable COPD (i.e., COPD after recent exacerbation, OHS, NMD, or TRD, etc.). The evaluation of adverse events was also limited by the fact that most of the included studies did not evaluate adverse events and majority of the rest did not use a consistent approach for report and evaluation. We could not statistically evaluate publication bias because the number of studies included in a direct comparison was small (n<10). We judged included studies to have medium to high risk of bias because of possible conflicts of interests (i.e., funded by device manufacturers), lack of blinding in RCTs and lack of representativeness of patient population in observational studies. In addition, we only included studies published in English, which limited our ability to evaluate non-English studies. Furthermore, most included studies were conducted in European countries, many of which offer home respiratory therapy services to users of home NIPPV. Authors from these studies may have not explicitly mentioned each of the home respiratory services available to participants in included studies. In addition, we excluded studies that enrolled pediatric patients, which led to the exclusion of several studies in patients with severe, progressive NMD. Finally, we should note that we were unable to identify any studies that met our inclusion criteria that evaluated patients who required continuous, 24-hour noninvasive mechanical ventilation as administered via a mask or mouthpiece interface. Such patients, often with severe NMD, cannot survive without continuous mechanical ventilation, which precludes enrolling such patients in trials evaluating the comparative effectiveness of HMV versus no device use.

Applicability

Several issues limit the applicability of the stated findings. First, included studies were conducted in various locations across the globe. The provision of home NIPPV in different countries may differ based on devices available, devices commonly used, titration protocols, guidelines for home device use, associated respiratory services included, and coverage/payment of home NIPPV. In addition, the classification of devices as either an HMV and/or BPAP machine may differ in the United States compared with other locations. Second, several devices used in the included studies were not FDA approved. Third, several devices used in the included studies were older models that may no longer be available. Fourth, there are no data on several newer devices developed in the past 5-10 years. Fifth, patients in randomized controlled trials may significantly differ from those encountered in practice.

Suggestions for Future Research

Future comparative research should define which patient populations would benefit from NIPPV delivered by a HMV compared to a BPAP device. Populations that may benefit from a HMV include patients who require daytime NIPPV for a certain number of hours, patients with continued hypercapnia despite maximal BPAP use, patients who have rapidly progressively disease, or patients who have experienced adverse events despite BPAP use. Such populations may benefit from the tighter ventilator parameters, modes, monitoring, alarm features, and a second back up ventilator as offered by use of an HMV device. Such evidence would improve clinician ability to determine which features and device types are optimal for specific patient populations. In addition, future comparative research should evaluate when to initiate NIPPV, especially evaluating the utility of starting NIPPV in patients with stable disease versus following an episode of acute decompensation. Furthermore, comparative research should define which patient populations would benefit from advanced BPAP modes such as volume assured pressure support compared with other BPAP modes. There is a need to determine the optimal targets and process of device titration.

RCTs often provide the highest level of evidence. Nevertheless, it may be unethical to enroll some patient populations with chronic respiratory failure in RCTs. In such patient populations, other study designs should be considered such as single arm interventional studies (e.g. before and after studies). In addition, comparative effectiveness of invasive mechanical ventilation and 24-hour noninvasive mechanical ventilation could be considered. Studies of pediatric patients who used continuous 24-hour noninvasive mechanical ventilation may be used as a guide and provide additional information to inform studies and use of continuous noninvasive mechanical ventilation on adult patients. Therefore, future evidence synthesis should evaluate pediatric studies as well as single-arm studies (such as before and after studies), as enrolling such patients in trials evaluating the comparative effectiveness of HMV versus no device use would be unethical.

At last, the potential benefit of home respiratory therapy services for several patient populations remains uncharacterized and would benefit from further studies designed to evaluate this specific aspect. Future studies should include impact on patient-centered outcomes including quality of life.

Conclusion

In patients with COPD, home BPAP (compared to no device) was associated with lower mortality, intubations, hospital admissions, and dyspnea. There was no change in quality of life (pooled analysis of 9 studies). In patients with COPD, HMV (compared individually with BPAP, CPAP, or no device) was associated with fewer hospital admissions. In patients with thoracic restrictive diseases, home HMV (compared to no device) was associated with lower mortality and better exercise tolerance. In patients with neuromuscular diseases, home BPAP (compared to no device) was associated with lower mortality, better quality of life, and reduced dyspnea. In patients with obesity hypoventilation syndrome, home HMV/BPAP mix (compared to no device) was associated with lower mortality; home BPAP (compared to no device) was associated with improved sleep quality. Current comparative evidence is not available to assess the impact of many device capabilities on patient outcomes. Criteria to initiate home NIPPV and home respiratory services vary and are not validated in comparative studies.

References

1. King AC. Long-term home mechanical ventilation in the United States. Respir Care. 2012 Jun;57(6):921-30; discussion 30-2. doi: 10.4187/respcare.01741. PMID: 22663967.
2. Bach JR, Intintola P, Alba AS, et al. The ventilator-assisted individual. Cost analysis of institutionalization vs rehabilitation and in-home management. Chest. 1992 Jan;101(1):26-30. PMID: 1729079.
3. Marchese S, Lo Coco D, Lo Coco A. Outcome and attitudes toward home tracheostomy ventilation of consecutive patients: a 10-year experience. Respir Med. 2008 Mar;102(3):430-6. doi: 10.1016/j.rmed.2007.10.006. PMID: 18023334.
4. MacIntyre NR, Epstein SK, Carson S, et al. Management of patients requiring prolonged mechanical ventilation: report of a NAMDRC consensus conference. Chest. 2005 Dec;128(6):3937-54. doi: 10.1378/chest.128.6.3937. PMID: 16354866.
5. Simonds AK. Home Mechanical Ventilation: An Overview. Ann Am Thorac Soc. 2016 Nov;13(11):2035-44. doi: 10.1513/AnnalsATS.201606-454FR. PMID: 27560387.
6. Guarascio AJ, Ray SM, Finch CK, et al. The clinical and economic burden of chronic obstructive pulmonary disease in the USA. Clinicoecon Outcomes Res. 2013;5:235-45. doi: 10.2147/ceor.s34321. PMID: 23818799.
7. Murphy PB, Rehal S, Arbane G, et al. Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation: A Randomized Clinical Trial. JAMA. 2017 Jun 06;317(21):2177-86. doi: 10.1001/jama.2017.4451. PMID: 28528348.
8. MacIntyre E, Asadi L, McKim DA, et al. Clinical outcomes associated with home mechanical ventilation: A systematic review. Can Respir J. 2015 Sep 30. PMID: 26422402.
9. Lloyd-Owen SJ, Donaldson GC, Ambrosino N, et al. Patterns of home mechanical ventilation use in Europe: results from the Eurovent survey. Eur Respir J. 2005 Jun;25(6):1025-31. doi: 10.1183/09031936.05.00066704. PMID: 15929957.
10. Miller RG, Jackson CE, Kasarskis EJ, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2009 Oct 13;73(15):1218-26. doi: 10.1212/WNL.0b013e3181bc0141. PMID: 19822872.
11. McKim DA, Road J, Avendano M, et al. Home mechanical ventilation: a Canadian Thoracic Society clinical practice guideline. Can Respir J. 2011 Jul-Aug;18(4):197-215. PMID: 22059178.
12. Windisch W, Walterspacher S, Siemon K, et al. Guidelines for non-invasive and invasive mechanical ventilation for treatment of chronic respiratory failure. Published by the German Society for Pneumology (DGP). Pneumologie. 2010 Oct;64(10):640-52. doi: 10.1055/s-0030-1255558. PMID: 20799159.
13. Respiratory Network Domiciliary Non-Invasive Ventilation Working Group. Domiciliary non-invasive ventilation in adult patients-a consensus statement. NSW Agency for Clinical Innovation; 2012. https://www.aci.health.nsw.gov.au/__data/assets/pdf_file/0008/159794/ACI-NIV-guidelines.pdf. Accessed on August 28 2017.

14. Lewarski JS, Gay PC. Current issues in home mechanical ventilation. Chest. 2007

Aug;132(2):671-6. doi: 10.1378/chest.07-0558. PMID: 17699139.
15. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(14)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality; January 2014. Chapters available at: www.effectivehealthcare.ahrq.gov.
16. Oscroft NS, Chadwick R, Davies MG, et al. Volume assured versus pressure preset non-invasive ventilation for compensated ventilatory failure in COPD. Respiratory Medicine. 2014 Oct;108(10):1508-15. doi: https://dx.doi.org/10.1016/j.rmed.2014.07.010. PMID: 25123526.
17. Paone G, Conti V, Biondi-Zoccai G, et al. Long-term home noninvasive mechanical ventilation increases systemic inflammatory response in chronic obstructive pulmonary disease: a prospective observational study. Mediators of Inflammation. 2014;2014:503145. doi: https://dx.doi.org/10.1155/2014/503145. PMID: 24976687.
18. Galli JA, Krahnke JS, James Mamary A, et al. Home non-invasive ventilation use following acute hypercapnic respiratory failure in COPD. Respiratory Medicine. 2014 May;108(5):722-8. doi: https://dx.doi.org/10.1016/j.rmed.2014.03.006. PMID: 24702885.
19. Bhatt SP, Peterson MW, Wilson JS, et al. Noninvasive positive pressure ventilation in subjects with stable COPD: a randomized trial. International Journal of Copd. 2013;8:581-9. doi: https://dx.doi.org/10.2147/COPD.S53619. PMID: 24293994.
20. Duiverman ML, Wempe JB, Bladder G, et al. Two-year home-based nocturnal noninvasive ventilation added to rehabilitation in chronic obstructive pulmonary disease patients: a randomized controlled trial. Respiratory Research. 2011 Aug 23;12:112. doi: https://dx.doi.org/10.1186/1465-9921-12-112. PMID: 21861914.
21. Duiverman ML, Wempe JB, Bladder G, et al. Nocturnal non-invasive ventilation in addition to rehabilitation in hypercapnic patients with COPD. Thorax. 2008 Dec;63(12):1052-7. PMID: 18710905.
22. Oscroft NS, Quinnell TG, Shneerson JM, et al. Long-term non-invasive ventilation to manage persistent ventilatory failure after COPD exacerbation. Respirology. 2010 Jul;15(5):818-22. doi: https://dx.doi.org/10.1111/j.1440-1843.2010.01787.x. PMID: 20546195.
23. Cheung APS, Chan VL, Liong JT, et al. A pilot trial of non-invasive home ventilation after acidotic respiratory failure in chronic obstructive pulmonary disease. International Journal of Tuberculosis & Lung Disease. 2010 May;14(5):642-9. PMID: 20392360.
24. Casanova C, Celli BR, Tost L, et al. Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. Chest. 2000 Dec;118(6):1582-90. PMID: 11115443.
25. Garrod R, Mikelsons C, Paul EA, et al. Randomized controlled trial of domiciliary noninvasive positive pressure ventilation and physical training in severe chronic obstructive pulmonary disease. American Journal of Respiratory & Critical Care Medicine. 2000 Oct;162(4 Pt 1):1335-41. doi: https://dx.doi.org/10.1164/ajrccm.162.4.9912029. PMID: 11029341.
26. Clini E, Sturani C, Porta R, et al. Outcome of COPD patients performing nocturnal non-invasive mechanical ventilation. Respiratory Medicine. 1998 Oct;92(10):1215-22. PMID: 9926152.
27. Clini E, Vitacca M, Foglio K, et al. Long-term home care programmes may reduce hospital admissions in COPD with chronic hypercapnia. European Respiratory

Journal. 1996 Aug;9(8):1605-10. PMID: 8866580.
28. Zhou L, Li X, Guan L, et al. Home noninvasive positive pressure ventilation with built-in software in stable hypercapnic COPD: A short-term prospective, multicenter, randomized, controlled trial. International Journal of COPD. 2017 27 Apr;12:1279-86. doi: http://dx.doi.org/10.2147/COPD.S127540. PMID: 615975404.
29. Marquez-Martin E, Ruiz FO, Ramos PC, et al. Randomized trial of non-invasive ventilation combined with exercise training in patients with chronic hypercapnic failure due to chronic obstructive pulmonary disease. Respiratory Medicine. 2014 Dec;108(12):1741-51. PMID: 25456710.
30. Kohnlein T, Windisch W, Kohler D, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. The Lancet Respiratory Medicine. 2014 Sep;2(9):698-705. PMID: 25066329.
31. De Backer L, Vos W, Dieriks B, et al. The effects of long-term noninvasive ventilation in hypercapnic COPD patients: a randomized controlled pilot study. International Journal of Copd. 2011;6:615-24. PMID: 22135493.
32. Dreher M, Storre JH, Schmoor C, et al. High-intensity versus low-intensity non-invasive ventilation in patients with stable hypercapnic COPD: a randomised crossover trial. Thorax. 2010 Apr;65(4):303-8. PMID: 20388753.
33. McEvoy RD, Pierce RJ, Hillman D, et al. Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. Thorax. 2009 Jul;64(7):561-6. PMID: 19213769.
34. Tsolaki V, Pastaka C, Karetsi E, et al. One-year non-invasive ventilation in chronic hypercapnic COPD: effect on quality of life. Respiratory Medicine. 2008 Jun;102(6):904-11. PMID: 18280131.
35. Windisch W, Dreher M, Storre JH, et al. Nocturnal non-invasive positive pressure ventilation: physiological effects on spontaneous breathing. Respiratory Physiology & Neurobiology. 2006 Feb 28;150(2-3):251-60. PMID: 15990366.
36. Gay PC, Hubmayr RD, Stroetz RW. Efficacy of nocturnal nasal ventilation in stable, severe chronic obstructive pulmonary disease during a 3-month controlled trial. Mayo Clinic Proceedings. 1996 Jun;71(6):533-42. PMID: 8642881.
37. Gad DM, El-Shafey AM. Non-invasive positive pressure ventilation and exercise training in patients with stable hypercapnic chronic obstructive pulmonary disease. Egyptian Journal of Chest Diseases and Tuberculosis. 2015 01 Jan;64(1):51-6. PMID: 601158661.
38. Sin DD, Wong E, Mayers I, et al. Effects of nocturnal noninvasive mechanical ventilation on heart rate variability of patients with advanced COPD. Chest. 2007 January;131(1):156-63. PMID: 46122988.
39. Heinemann F, Budweiser S, Jörres RA, et al. The role of non-invasive home mechanical ventilation in patients with chronic obstructive pulmonary disease requiring prolonged weaning. Respirology. 2011;16(8):1273-80.
40. Budweiser S, Hitzl A, Jörres R, et al. Impact of noninvasive home ventilation on long-term survival in chronic hypercapnic COPD: a prospective observational study. International journal of clinical practice. 2007;61(9):1516-22.
41. Clini E, Sturani C, Rossi A, et al. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. European Respiratory Journal. 2002;20(3):529-38.
42. Struik F, Sprooten R, Kerstjens H, et al. Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after

ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. Thorax. 2014:thoraxjnl-2014-205126.
43. Salturk C, Karakurt Z, Takir HB, et al. Comparison of exercise capacity in COPD and other etiologies of chronic respiratory failure requiring non-invasive mechanical ventilation at home: retrospective analysis of 1-year follow-up. International Journal of Copd. 2015;10:2559-69. doi: https://dx.doi.org/10.2147/COPD.S91950. PMID: 26648713.
44. Hitzl AP, Jorres RA, Heinemann F, et al. Nutritional status in patients with chronic respiratory failure receiving home mechanical ventilation: impact on survival. Clinical Nutrition. 2010 Feb;29(1):65-71. doi: https://dx.doi.org/10.1016/j.clnu.2009.08.002. PMID: 19695747.
45. Funk G-C, Breyer M-K, Burghuber OC, et al. Long-term non-invasive ventilation in COPD after acute-on-chronic respiratory failure. Respiratory Medicine. 2011 Mar;105(3):427-34. PMID: 21111590.
46. Vasquez MM, McClure LA, Sherrill DL, et al. Positive Airway Pressure Therapies and Hospitalization in Chronic Obstructive Pulmonary Disease. American Journal of Medicine. 2017 Jul;130(7):809-18. doi: https://dx.doi.org/10.1016/j.amjmed.2016.11.045. PMID: 28089799.
47. Duiverman ML, Maagh P, Magnet FS, et al. Impact of High-Intensity-NIV on the heart in stable COPD: a randomised cross-over pilot study. Respiratory Research. 2017 05 02;18(1):76. PMID: 28464911.
48. Blankenburg T, Benthin C, Pohl S, et al. Survival of hypercapnic patients with COPD and obesity hypoventilation syndrome treated with high intensity non invasive ventilation in the daily routine care. Open Respiratory Medicine Journal. 2017;11:31-40.
49. Durao V, Grafino M, Pamplona P. Chronic respiratory failure in patients with chronic obstructive pulmonary disease under home noninvasive ventilation: Real-life study. Pulmonology. 2018 Apr 05;05:05. PMID: 29628437.
50. Oscroft NS, Quinnell TG, Shneerson JM, et al. The effects of withdrawing long-term nocturnal non-invasive ventilation in COPD patients. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2010;7(2):111-6.
51. Tsolaki V, Pastaka C, Kostikas K, et al. Noninvasive ventilation in chronic respiratory failure: effects on quality of life. Respiration. 2011;81(5):402-10.
52. Windisch W, Walterspacher S, Siemon K, et al. Guidelines for non-invasive and invasive mechanical ventilation for treatment of chronic respiratory failure. Pneumologie. 2010;64(10):640-52.
53. McKim DA, Road J, Avendano M, et al. Home mechanical ventilation: a Canadian Thoracic Society clinical practice guideline. Canadian Respiratory Journal. 2011 Jul-Aug;18(4):197-215. PMID: 22059178.
54. Ambrosino N, Casaburi R, Chetta A, et al. 8th International conference on management and rehabilitation of chronic respiratory failure: The long summaries - Part 3. Multidisciplinary Respiratory Medicine. 2015 06 Oct;10 (1) (no pagination)(29). PMID: 606265044.
55. Porte P. Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation - A consensus conference report. Chest. 1999;116(2):521-34. PMID: 29382139.
56. National Guideline C. BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. 2016.
57. National Guideline C. VA/DoD clinical practice guideline for the management of

chronic obstructive pulmonary disease. 2014.
58. National Institute for H, Clinical E. National Clinical Guideline Centre for Acute and Chronic Conditions. Chronic obstructive pulmonary disease. Management of chronic obstructive pulmonary disease in adults in primary and secondary care. National Institute for Health and Clinical Excellence. 2010.
59. Domenech-Clar R, Nauffal-Manzur D, Perpina-Tordera M, et al. Home mechanical ventilation for restrictive thoracic diseases: effects on patient quality-of-life and hospitalizations. Respiratory Medicine. 2003 Dec;97(12):1320-7. PMID: 14682414.
60. Nauffal D, Domenech R, Martinez Garcia MA, et al. Noninvasive positive pressure home ventilation in restrictive disorders: outcome and impact on health-related quality of life. Respiratory Medicine. 2002 Oct;96(10):777-83. PMID: 12412976.
61. Masa JF, Celli BR, Riesco JA, et al. The obesity hypoventilation syndrome can be treated with noninvasive mechanical ventilation. Chest. 2001;119(4):1102-7. doi: http://dx.doi.org/10.1378/chest.119.4.1102. PMID: 32679437.
62. Schonhofer B, Wallstein S, Wiese C, et al. Noninvasive mechanical ventilation improves endurance performance in patients with chronic respiratory failure due to thoracic restriction. Chest. 2001 May;119(5):1371-8. PMID: 11348941.
63. Buyse B, Meersseman W, Demedts M. Treatment of chronic respiratory failure in kyphoscoliosis: oxygen or ventilation? European Respiratory Journal. 2003 Sep;22(3):525-8. PMID: 14516146.
64. Hardinge M, Annandale J, Bourne S, et al. British Thoracic Society guidelines for Home Oxygen use in adults. Thorax. 2015 June;70:i1-i43. PMID: 608676290.
65. Gonzalez-Bermejo J, Morelot-Panzini C, Arnol N, et al. Prognostic value of efficiently correcting nocturnal desaturations after one month of non-invasive ventilation in amyotrophic lateral sclerosis: A retrospective monocentre observational cohort study. Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration. 2013 September;14(5-6):373-9. doi: http://dx.doi.org/10.3109/21678421.2013.776086. PMID: 369532783.
66. Sanjuan-Lopez P, Valino-Lopez P, Ricoy-Gabaldon J, et al. Amyotrophic lateral sclerosis: impact of pulmonary follow-up and mechanical ventilation on survival. A study of 114 cases. Archivos de Bronconeumologia. 2014 Dec;50(12):509-13. doi: https://dx.doi.org/10.1016/j.arbres.2014.04.010. PMID: 24931271.
67. Pinto AC, Evangelista T, Carvalho M, et al. Respiratory assistance with a non-invasive ventilator (Bipap) in MND/ALS patients: survival rates in a controlled trial. Journal of the Neurological Sciences. 1995 May;129 Suppl:19-26. PMID: 7595610.
68. Sancho J, Servera E, Morelot-Panzini C, et al. Non-invasive ventilation effectiveness and the effect of ventilatory mode on survival in ALS patients. Amyotrophic Lateral sclerosis & Frontotemporal Degeneration. 2014 Mar;15(1-2):55-61. PMID: 24266679.
69. Sivori M, Rodriguez GE, Pascansky D, et al. Outcome of sporadic amyotrophic lateral sclerosis treated with non-invasive ventilation and riluzole. Medicina. 2007;67(4):326-30. PMID: 17891927.
70. Lo Coco D, Marchese S, Pesco MC, et al. Noninvasive positive-pressure ventilation in ALS: predictors of tolerance and survival. Neurology. 2006 Sep 12;67(5):761-5. PMID: 16899545.
71. Bourke SC, Tomlinson M, Williams TL, et al. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. Lancet Neurology. 2006 Feb;5(2):140-7. PMID: 16426990.

72. Pinto A, Almeida JP, Pinto S, et al. Home telemonitoring of non-invasive ventilation decreases healthcare utilisation in a prospective controlled trial of patients with amyotrophic lateral sclerosis. Journal of Neurology, Neurosurgery & Psychiatry. 2010 Nov;81(11):1238-42. doi: https://dx.doi.org/10.1136/jnnp.2010.206680 . PMID: 20826878.
73. Sancho J, Martinez D, Bures E, et al. Bulbar impairment score and survival of stable amyotrophic lateral sclerosis patients after noninvasive ventilation initiation. Erj Open Research. 2018 Apr;4(2). PMID: 29670892.
74. Vitacca M, Montini A, Lunetta C, et al. Impact of an early respiratory care programme with non-invasive ventilation adaptation in patients with amyotrophic lateral sclerosis. European Journal of Neurology. 2018 Mar;25(3):556-e33. PMID: 29266547.
75. Bertella E, Banfi P, Paneroni M, et al. Early initiation of night-time NIV in an outpatient setting: A randomized non-inferiority study in ALS patients. European Journal of Physical and Rehabilitation Medicine. 2017;53(6):892-9.
76. Aboussouan LS, Khan SU, Meeker DP, et al. Effect of noninvasive positive-pressure ventilation on survival in amyotrophic lateral sclerosis. Annals of internal medicine. 1997;127(6):450-3.
77. Farrero E, Prats E, Povedano M, et al. Survival in amyotrophic lateral sclerosis with home mechanical ventilation: the impact of systematic respiratory assessment and bulbar involvement. Chest. 2005;127(6):2132-8.
78. National Guideline C. Motor neurone disease: assessment and management. 2016.
79. National Guideline C. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. 2009.
80. Finder JD, Birnkrant D, Carl J, et al. Respiratory care of the patient with Duchenne muscular dystrophy: ATS consensus statement. American journal of respiratory and critical care medicine. 2004;170(4):456.
81. National Guideline C. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS) — revised report of an EFNS task force. 2012.
82. Howard ME, Piper AJ, Stevens B, et al. A randomised controlled trial of CPAP versus non-invasive ventilation for initial treatment of obesity hypoventilation syndrome. Thorax. 2017 May;72(5):437-44. doi: https://dx.doi.org/10.1136/thoraxjnl-2016-208559. PMID: 27852952.
83. Ojeda Castillejo E, de Lucas Ramos P, López Martin S, et al. Noninvasive Mechanical Ventilation in Patients With Obesity Hypoventilation Syndrome. Long-term Outcome and Prognostic Factors. Archivos de Bronconeumologia. 2013. doi: 10.1016/j.arbr.2014.06.016.
84. Masa JF, Corral J, Alonso ML, et al. Efficacy of Different Treatment Alternatives for Obesity Hypoventilation Syndrome. Pickwick Study. American Journal of Respiratory & Critical Care Medicine. 2015 Jul 01;192(1):86-95. PMID: 25915102.
85. Borel J-C, Tamisier R, Gonzalez-Bermejo J, et al. Noninvasive ventilation in mild obesity hypoventilation syndrome: a randomized controlled trial. Chest. 2012 Mar;141(3):692-702. PMID: 21885724.
86. Murphy PB, Davidson C, Hind MD, et al. Volume targeted versus pressure support non-invasive ventilation in patients with super obesity and chronic respiratory failure: a randomised controlled trial. Thorax. 2012 Aug;67(8):727-34. PMID: 22382596.
87. Piper AJ, Wang D, Yee BJ, et al. Randomised trial of CPAP vs bilevel support in the treatment of obesity

hypoventilation syndrome without severe nocturnal desaturation. Thorax. 2008 May;63(5):395-401. PMID: 18203817.
88. Priou P, Gagnadoux F, Tesse A, et al. Endothelial dysfunction and circulating microparticles from patients with obstructive sleep apnea. The American journal of pathology. 2010;177(2):974-83.
89. Masa JF, Corral J, Caballero C, et al. Non-invasive ventilation in obesity hypoventilation syndrome without severe obstructive sleep apnoea. Thorax. 2016:thoraxjnl-2016-208501.
90. de Llano LAP, Golpe R, Piquer MO, et al. Short-term and long-term effects of nasal intermittent positive pressure ventilation in patients with obesity-hypoventilation syndrome. Chest. 2005;128(2):587-94.
91. Corral J, Mogollon MV, Sanchez-Quiroga MA, et al. Echocardiographic changes with non-invasive ventilation and CPAP in obesity hypoventilation syndrome. Thorax. 2018 Apr;73(4):361-8. PMID: 29146865.
92. Benhamou D, Muir JF, Raspaud C, et al. Long-term efficiency of home nasal mask ventilation in patients with diffuse bronchiectasis and severe chronic respiratory failure: a case-control study. Chest. 1997 Nov 05;112(5):1259-66. PMID: 9367466.
93. Hazenberg A, Kerstjens HAM, Prins SCL, et al. Initiation of home mechanical ventilation at home: a randomised controlled trial of efficacy, feasibility and costs. Respiratory Medicine. 2014 Sep;108(9):1387-95. doi: https://dx.doi.org/10.1016/j.rmed.2014.07.008. PMID: 25081652.
94. Munoz X, Crespo A, Marti S, et al. Comparative study of two different modes of noninvasive home mechanical ventilation in chronic respiratory failure. Respiratory Medicine. 2006 Apr;100(4):673-81. doi: https://dx.doi.org/10.1016/j.rmed.2005.08.008. PMID: 16194600.
95. Chiang L-L, Liu C-Y, Ho S-C, et al. Efficacy of nocturnal nasal positive pressure ventilation in hypercapnic patients with severe obstructive lung diseases. Chang Gung Medical Journal. 2004 Feb;27(2):98-106. PMID: 15095954.
96. Crespo A, Munoz X, Torres F, et al. Noninvasive home mechanical ventilation in elderly patients. Gerontology. 2010;56(2):150-6. doi: https://dx.doi.org/10.1159/000237874. PMID: 19752508.
97. Network AR. Domiciliary Non-Invasive Ventilation in Adult Patients: A Consensus Statement. 2012.
98. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS medicine. 2009;6(7):e1000097.
99. Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions Version 5.1.0 [updated March 2011]: The Cochrane Collaboration; 2011.
100. Wells G, Shea B, O'connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.
101. Guyatt G, Rennie D, Meade M, et al. Users' guides to the medical literature: McGraw-Hill Medical:; 2015.
102. Ioannidis JP, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey. CMAJ. 2007 Apr 10;176(8):1091-6. doi: 10.1503/cmaj.060410. PMID: 17420491.
103. Davidson AC, Banham S, Elliott M, et al. BTS/ICS guideline for the ventilatory management of acute hypercapnic respiratory failure in adults. Thorax. 2016 Apr;71 Suppl 2:ii1-35. doi: 10.1136/thoraxjnl-2015-208209. PMID: 26976648.
104. STATEMENTS Q. VA/DoD CLINICAL PRACTICE GUIDELINE FOR

THE MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE.
105. National Clinical Guideline C. National Institute for Health and Care Excellence: Clinical Guidelines. Motor Neurone Disease: Assessment and Management. London: National Institute for Health and Care Excellence (UK)
Copyright (c) National Clinical Guideline Centre, 2016.; 2016.
106. Miller RG, Jackson CE, Kasarskis EJ, et al. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2009 Oct 13;73(15):1218-26. doi: 10.1212/WNL.0b013e3181bc0141. PMID: 19822872.
107. Andersen PM, Abrahams S, Borasio GD, et al. EFNS guidelines on the clinical management of amyotrophic lateral sclerosis (MALS)--revised report of an EFNS task force. Eur J Neurol. 2012 Mar;19(3):360-75. doi: 10.1111/j.1468-1331.2011.03501.x. PMID: 21914052.

Abbreviations and Acronyms

ADL	Activities of daily living
AECOPD	Acute exacerbation of chronic obstructive pulmonary disease
AHRF	Acute hypercapnic respiratory failure
AHRQ	Agency for Healthcare Research and Quality
ALS	Amyotrophic lateral sclerosis
BMI	Body mass index
BPAP	Bi-level positive airway pressure
CI	Confidence interval
cmH2O	Centimeters of water (pressure)
CMS	Centers for Medicare and Medicaid Services
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
EPAP	Expiratory positive airway pressure
EPC	Evidence-based Practice Center
ER	Emergency room
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in one second
FFM	Full face mask
FVC	Forced vital capacity
H2O	Water
HMV	Home mechanical ventilators
ICU	Intensive care unit
IPAP	Inspiratory positive airway pressure
IR	Incidence rate
IRR	Incidence rate ratio
Kg	Kilogram
KQ	Key Question
LTACH	Long-term acute care facility
LTOT	Long-term oxygen therapy
m	meters
mbad	megabar
MHRA	Medicines and Healthcare Products Regulatory Agency
MIP	Maximal inspiratory pressure
Mbar	Megabar
mL	Milliliters

mmHg	Millimeters of mercury
NA	Not Available
NIPPV	Non-invasive positive pressure ventilation
NIV	Non-invasive ventilation
NMD	Neuromuscular diseases
NOS	Not otherwise specified
OHS	Obesity hypoventilation syndrome
OR	Odds ratio
PaCO2	Partial pressure of arterial carbon dioxide
PaO2	Partial pressure of arterial oxygen
PCF	Peak cough flow
PEEP	Positive end expiratory pressure
pH	Potential of hydrogen
PICOTS	Population, interventions, comparisons, outcomes, timing, and setting
Pimax	Maximal inspiratory mouth pressures
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSG	Polysomnogram
PtcCO2/TcCO2	Pressure of transcutaneous carbon dioxide
QoL	Quality of life
RAD	Respiratory assist device
RCT	Randomized controlled trial
S	Spontaneous mode
SaO2	Arterial blood oxygen saturation
SF-36	Medical Outcomes Study Questionnaire Short Form
SMD	Standardized mean difference
SNP	Sniff nasal pressure
SOE	Strength of evidence
ST	Spontaneous/timed breath mode
ST90	Sleep time with oxygen saturation below 90%
TRD	Thoracic restrictive diseases
VAPS	Volume assured pressure support
VC	Vital capacity
WMD	Weighted mean difference

Noninvasive Positive Pressure Ventilation in the Home: Addendum

Justification:

This is an addendum to the technology assessment report titled Noninvasive Positive Pressure Ventilation in the Home. This addendum is required to update the findings of the original report because of an updated literature search using the same search criteria (original report search was on June 26, 2018 and the updated search was on November 6, 2019) and some other minor changes due to a journal peer review and editorial process.

The updates in this amendment include updated results for Key Question 1 (Initiation Criteria for COPD), Key Question 2 (Device Effectiveness for COPD), and Key Question 3 (Device Effectiveness for COPD). The addendum included outcomes for NIPPV (BPAP and HMV combined) and post hoc subgroup analyses based on study design (RCTs vs. observational studies).

Initiation Criteria for COPD (KQ1):

Two additional studies which described criteria for initiation of BPAP devices in patients with COPD were identified.[1, 2] The criteria used for initiation of BPAP are listed in Table 1. These criteria were generally similar to those in the original report.

Table 1. Updated results for initiation criteria for patients with COPD

Author, Year, Study Design	Device/mode	Patient characteristics to start or continue device	Laboratory characteristics to start or continue device	Device titration
Duiverman, 2019[1] RCT	BPAP ST started in the hospital BPAP ST started in the home using telemedicine	-COPD (FEV1<50%) -Stable (no AECOPD in prior 4 weeks)	-PaCO2 >6.0 kPa (45 mmHg) -pH >7.35 (daytime, room air)	Settings adjusted to achieve normocapnia during the night or at least a reduction in nocturnal mean PtCo2 of 20% compared with the first night of spontaneous breathing. Initiation period ended once the patient could sleep 6 consecutive hours with the ventilator and the gas exchange goals were achieved.
Satici, 2018 [2] Observational	BPAP S Treatment adherent (≥4 hours per day on ≥70% of days) BPAP S Treatment non-adherent	-COPD -Prescribed home NIPPV for 6 months -PaCO2 >55mmHg or PaCO2 50-55mmHg and nocturnal desaturation (<88% for at least 5 min) or -2 hospitalizations in 1 year	-PaCO2 >55mmHg or PaCO2 50-55mmHg and nocturnal desaturation (<88% for at least 5 min) or 2 hospitalizations in 1 year	NR

BPAP: Bilevel Positive Airway Pressure, COPD: chronic obstructive pulmonary disease, ST: spontaneous/timed breath mode, S: spontaneous mode, AECOPD: acute exacerbation of chronic obstructive pulmonary disease, FEV1: Forced expiratory volume in one second, kPa: kilopascal, mmHg: millimeters of mercury (pressure), NIPPV: Noninvasive positive pressure Ventilation,

PaO2: partial pressure of arterial oxygen, PaCO2: partial pressure of arterial carbon dioxide, pH: potential of hydrogen, PtCO2: pressure of transcutaneous carbon dioxide

Risk of bias ratings for the two additional studies are listed in Tables 3 and 4.

Table 3. Updated risk of bias for randomized controlled trials (Cochrane ROB tool)

Author, Year	Sequence Generation	Allocation Concealment	Blinding of Participants Personnel	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias	Overall RoB
Duiverman, 2019[1]	Unclear	Unclear	High ROB	High ROB	High ROB	Low ROB	Low ROB	High ROB

ROB: Risk of Bias

Table 4. Updated risk of bias for observational studies (Newcastle-Ottawa Quality Assessment Scale)

Author, Year	Representativeness of the Study Population	Ascertainment of Exposure	Assessment of Outcome	Adequate Followup	Conflict of Interest	Overall RoB
Satici,2018 [2]	High ROB	Low ROB	Low ROB	Low ROB	Low ROB	Moderate ROB

ROB: Risk of Bias

Device Effectiveness for COPD (KQ2):

For NIPPV (combined BPAP or HMV), the major effectiveness outcomes (mortality, need for intubation, quality of life, hospital admission) are listed in Table 5.

Table 5. Major effectiveness outcomes with SOE (NIPPV vs. no device in COPD patients)

Outcome	Conclusion	Overall Evidence Strength (Direction of Effect)
Mortality	OR*: 0.65; 95% CI: 0.48 to 0.88	Moderate (reduction with NIPPV)
Need for intubation	OR*: 0.34; 95% CI: 0.14 to 0.83	Moderate (reduction with NIPPV)
Quality of life (higher score represents better outcome)	SMD*: 0.16, 95% CI: -0.06 to 0.32	Insufficient
Number of hospital admissions	Rate Ratio*: 0.75; 95% CI: 0.52 to 1.10	Low (no change with NIPPV)

NIPPV: noninvasive positive pressure ventilation; SOE: strength of evidence; COPD: chronic obstructive pulmonary disease; OR: odds ratio; SMD: standardized mean difference. *: Pooled effect size from meta-analysis

The results of the post hoc subgroup analyses for study design (RCTs vs. observational studies) are found in Table 6.

Table 6. Post-hoc subgroup analyses of study design on primary outcomes (NIPPV compared with no device)

Outcome	Study Design	Findings(95% CI)	I^2
Mortality	8 RCTs (985 patients)[3,4,5,6,7, 8,9,10,11]	OR=0.72(0.49 to 1.05)	26.9%
	7 Observational studies (613 patients)[12,13,14,15,16,17,18]	OR=0.58(0.35 to 0.96)	31.9%
Need for Intubation	1 RCT (52 patients)[5]	OR=0.48(0.04 to 5.64)	N/A
	2 Observational studies (215 patients)[15,18]	OR=0.32(0.12 to 0.83)	0.0%
Number of all-cause hospital admissions	3 RCTs (243 patients)[5,6,10]	Rate ratio=0.92(0.67 to 1.26)	35.3%
	3 Observational studies (176 patients)[14,17,18]	Rate ratio=0.65(0.40 to 1.06)	53.0%
Quality of life (higher score represents worse outcome)	6 RCTs (467 patients)[7, 8,19,9,20,21,11]	SMD=0.15(-0.12 to 0.42)	56.5%
	1 Observational study (49 patients)[18]	SMD=0.97(0.36 to 1.58)	N/A

NIPPV: noninvasive positive pressure ventilation; RD: risk difference; OR: odds ratio; SMD: standardized mean difference; RCT: randomized clinical trial

Effectiveness outcomes for the two additional studies which were identified are found in Table 7.

Table 7. Updated effectiveness outcomes in patients with COPD who used home NIPPV (compared with other NIPPV devices or device settings)

Comparison	Outcome	Study Design	Findings	Overall Evidence Strength (Direction of Effect)
BPAP S Treatment adherent (≥4 hours per day on ≥70% of days) vs. BPAP S Treatment non-adherent	Number of all-cause hospital admissions	1 Observational study,[2] 54 patients	0.4 vs. 1.0 (p<0.01)	Low (reduction with BPAP S Treatment adherent)
	Number of ICU admissions	1 Observational study,[2] 54 patients	0.6 vs. 1.2 (p=0.37)	N/A
BPAP ST started in the home using telemedicine vs. BPAP ST started in the hospital	Mortality	1 RCT,[1] 67 patients	6.06% vs. 2.94%; RD: 0.03, 95% CI:-0.07 to 0.13; OR: 2.13; 95% CI: 0.18 to 24.67; I^2=N/A	Insufficient
	Quality of life (Severe Respiratory Insufficiency Questionnaire Summary Score, higher score represents better outcome)	1 RCT,[1] 67 patients	WMD: -1.20; 95% CI: -9.92 to 7.52; I^2=N/A	Insufficient
	Dyspnea (Medical research council scale, higher score represents worse outcome)	1 RCT, [1] 67 patients	WMD: 0.10; 95% CI: -0.50 to 0.70; I^2=N/A	N/A
	6-minute walk distance test (meters)	1 RC, [1] 67 patients	WMD: -19.00; 95% CI: -64.60 to 29.60; I^2=N/A	N/A
	Number of all-cause hospital admissions	1 RCT, [1] 67 patients	WMD: -0.10; 95% CI: -0.60 to 0.40; I^2=N/A	Insufficient
	Number of exacerbations	1 RCT, [1] 67 patients	No significant difference between the two groups	N/A

AECOPD: acute exacerbation of chronic obstructive pulmonary disease, BPAP: bi-level positive airway pressure, CI: confidence interval, COPD: chronic obstructive pulmonary disease, CPAP: continuous positive airway pressure, HMV: home mechanical ventilation, N/A: not applicable, NOS: not otherwise specified, OR: odds ratio, RCT: randomized controlled trial, RD: risk difference; ST: spontaneous/timed mode, WMD: weighted mean difference

In addition, the following changes were made: In patients with COPD, BPAP compared with no device was associated with fewer patients with hospital admissions but no difference in the total number of hospital admissions (Rate Ratio=0.91, 95% CI: 0.71 to 1.17) and quality of life (SMD=0.16, 95% CI: -0.03 to 0.39). In patients with stable COPD, NIPPV compared with no device was associated with no difference in the total number of hospital admissions (Rate Ratio=0.84, 95% CI: 0.59 to 1.18). In patients with COPD and recent exacerbation, NIPPV compared with no device was associated with no difference in mortality (OR=0.66, 95% CI: 0.41 to 1.06), but was associated with fewer hospital admissions (RR=0.59, 95% CI: 0.43 to 0.81).

NIPPV may be associated with improved quality of life in patients with higher PaCO2 compared with patients with lower PaCO2 (PaCO2 ≥ 52 mmHg: SMD=0.18; 95% CI: -0.05 to

0.40 vs. PaCO2 ≥50 to 51: SMD=0.97; 95% CI: 0.36 to 1.58 vs. PaCO2 ≥45 to 49: SMD= -0.06; 95% CI: -0.28 to 0.17).

Device Characteristics for COPD (KQ3):

Two additional studies which described device characteristics for patients with COPD were identified. [1, 2] The device characteristics are listed in Table 8. These device characteristics were generally similar to those in the original report.

Table 8. Updated equipment parameters for patients with COPD.

Author, Year, Study Design	Device/mode	Model (Manufacturer; Location of Manufacturer)	Device Characteristics	Prescribed Usage (frequency and duration)	Actual Usage
Duiverman, 2019 [1] RCT	BPAP ST started in the hospital	BPAP BiPAP A30; Philips Respironics (FDA approved 510(k) clearance) BiPAP A40; Philips Respironics (FDA approved 510(k) clearance)	IPAP, EPAP, rate	NR	-7.5 ± 2.0 hours/day -IPAP: 25.7 ± 3.4 cm H2O -EPAP: 6.0 ± 1.3 cm H2O -Rate: 15.4 ± 3.0 breaths/minute
	BPAP ST started in the home using telemedicine				-8.2 ± 1.7 hours/day -IPAP: 23.6 ± 2.3 cm H2O -EPAP: 4.6 ± 0.9 cm H2O -Rate: 13.9 ± 2.0 breaths/minute
Satici, 2018 [2] Observational	BPAP S Treatment adherent (≥4 hours per day on ≥70% of days)	NR	IPAP, EPAP	NR	-8.3± 4.0 hours/day -IPAP: 22.3 ± 3.9 cm H2O -EPAP: 8.3 ± 1.5 cm H2O
	BPAP S Treatment non-adherent				-2.1± 2.0 hours/day -IPAP: 20.9 ± 3.5 cm H2O -EPAP: 7.7 ± 1.6 cm H2O

COPD: chronic obstructive pulmonary disease; RCT: randomized controlled trial; BPAP: Bilevel Positive Airway Pressure; S: spontaneous mode; ST: spontaneous/timed mode; cmH2O: centimeters of water (pressure); NR not reported; IPAP: inspiratory positive airway pressure; EPAP: expiratory positive airway pressure.

References

1. Duiverman ML, Vonk JM, Bladder G, et al. Home initiation of chronic non-invasive ventilation in COPD patients with chronic hypercapnic respiratory failure: a randomised controlled trial. Thorax. 2019 Sep 4. doi: 10.1136/thoraxjnl-2019-213303. PMID: 31484786.
2. Satici C, Arpinar Yigitbas B, Seker B, et al. Does Adherence to Domiciliary NIMV Decrease the Subsequent Hospitalizations Rates and Cost for Patients Diagnosed with COPD? Copd. 2018 Jun;15(3):303-9. doi: 10.1080/15412555.2018.1500532. PMID: 30188219.
3. Murphy PB, Rehal S, Arbane G, et al. Effect of Home Noninvasive Ventilation With Oxygen Therapy vs Oxygen Therapy Alone on Hospital Readmission or Death After an Acute COPD Exacerbation: A Randomized Clinical Trial. Jama. 2017 06 06;317(21):2177-86. doi: https://dx.doi.org/10.1001/jama.2017.4451. PMID: 28528348.
4. Struik F, Sprooten R, Kerstjens H, et al. Nocturnal non-invasive ventilation in COPD patients with prolonged hypercapnia after ventilatory support for acute respiratory failure: a randomised, controlled, parallel-group study. Thorax. 2014:thoraxjnl-2014-205126.
5. Casanova C, Celli BR, Tost L, et al. Long-term controlled trial of nocturnal nasal positive pressure ventilation in patients with severe COPD. Chest. 2000 Dec;118(6):1582-90. PMID: 11115443.
6. Clini E, Sturani C, Rossi A, et al. The Italian multicentre study on noninvasive ventilation in chronic obstructive pulmonary disease patients. European Respiratory Journal. 2002;20(3):529-38.
7. Duiverman ML, Wempe JB, Bladder G, et al. Two-year home-based nocturnal noninvasive ventilation added to rehabilitation in chronic obstructive pulmonary disease patients: a randomized controlled trial. Respir Res. 2011 Aug 23;12:112. doi: https://dx.doi.org/10.1186/1465-9921-12-112. PMID: 21861914.
8. Duiverman ML, Wempe JB, Bladder G, et al. Nocturnal non-invasive ventilation in addition to rehabilitation in hypercapnic patients with COPD. Thorax. 2008 Dec;63(12):1052-7. PMID: 18710905.
9. Kohnlein T, Windisch W, Kohler D, et al. Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial. Lancet Respir Med. 2014 Sep;2(9):698-705. PMID: 25066329.
10. McEvoy RD, Pierce RJ, Hillman D, et al. Nocturnal non-invasive nasal ventilation in stable hypercapnic COPD: a randomised controlled trial. Thorax. 2009 Jul;64(7):561-6. PMID: 19213769.
11. Zhou L, Li X, Guan L, et al. Home noninvasive positive pressure ventilation with built-in software in stable hypercapnic COPD: A short-term prospective, multicenter, randomized, controlled trial. International Journal of COPD. 2017 27 Apr;12:1279-86. doi: http://dx.doi.org/10.2147/COPD.S127540. PMID: 615975404.
12. Budweiser S, Hitzl A, Jörres R, et al. Impact of noninvasive home ventilation on long-term survival in chronic hypercapnic COPD: a prospective observational study. International journal of clinical practice. 2007;61(9):1516-22.
13. Clini E, Sturani C, Porta R, et al. Outcome of COPD patients performing nocturnal non-invasive mechanical ventilation. Respiratory medicine. 1998 Oct;92(10):1215-22. PMID: 9926152.

14. Clini E, Vitacca M, Foglio K, et al. Long-term home care programmes may reduce hospital admissions in COPD with chronic hypercapnia. European Respiratory Journal. 1996 Aug;9(8):1605-10. PMID: 8866580.
15. Galli JA, Krahnke JS, James Mamary A, et al. Home non-invasive ventilation use following acute hypercapnic respiratory failure in COPD. Respiratory medicine. 2014 May;108(5):722-8. doi: https://dx.doi.org/10.1016/j.rmed.2014.03.006. PMID: 24702885.
16. Heinemann F, Budweiser S, Jörres RA, et al. The role of non-invasive home mechanical ventilation in patients with chronic obstructive pulmonary disease requiring prolonged weaning. Respirology. 2011;16(8):1273-80.
17. Paone G, Conti V, Biondi-Zoccai G, et al. Long-term home noninvasive mechanical ventilation increases systemic inflammatory response in chronic obstructive pulmonary disease: a prospective observational study. Mediators Inflamm. 2014;2014:503145. doi: https://dx.doi.org/10.1155/2014/503145. PMID: 24976687.
18. Tsolaki V, Pastaka C, Karetsi E, et al. One-year non-invasive ventilation in chronic hypercapnic COPD: effect on quality of life. Respiratory medicine. 2008 Jun;102(6):904-11. PMID: 18280131.
19. Garrod R, Mikelsons C, Paul EA, et al. Randomized controlled trial of domiciliary noninvasive positive pressure ventilation and physical training in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2000 Oct;162(4 Pt 1):1335-41. doi: https://dx.doi.org/10.1164/ajrccm.162.4.9912029. PMID: 11029341.
20. Marquez-Martin E, Ruiz FO, Ramos PC, et al. Randomized trial of non-invasive ventilation combined with exercise training in patients with chronic hypercapnic failure due to chronic obstructive pulmonary disease. Respiratory medicine. 2014 Dec;108(12):1741-51. PMID: 25456710.
21. Oscroft NS, Quinnell TG, Shneerson JM, et al. The effects of withdrawing long-term nocturnal non-invasive ventilation in COPD patients. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2010;7(2):111-6.