Evidence Summary

Background and Objectives

Chronic respiratory failure is a common medical condition characterized by the inability to maintain normal oxygen ($PaO_2 \geq 60$mmHg) and/or carbon dioxide ($PaCO_2 \leq 45$mmHg) 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 ($PaCO_2$ ranging from >45 to >56mmHg), pH>7.35, FEV1 <50% of normal, and/or hypoxia (PaO_2 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 $PaCO2 \geq 45mmHg$) 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

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