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.

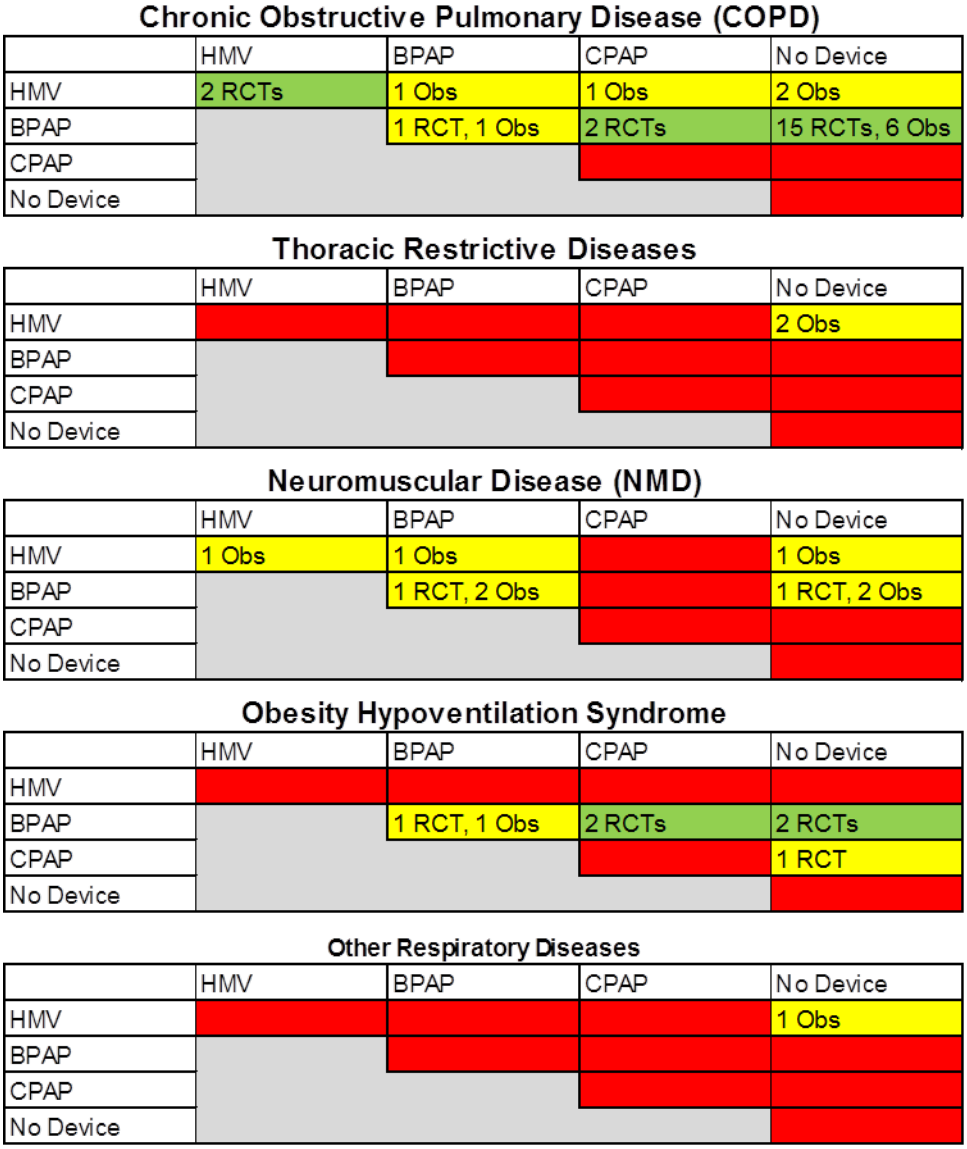

Figure legend: HMV: home mechanical ventilation; BPAP: bi-level positive airway pressure, CPAP: continuous positive airway pressure; RCT: randomized controlled trial; Obs: observational study. The colored cell shows the number of RCTs and observational studies for the comparisons between devices. Red 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.