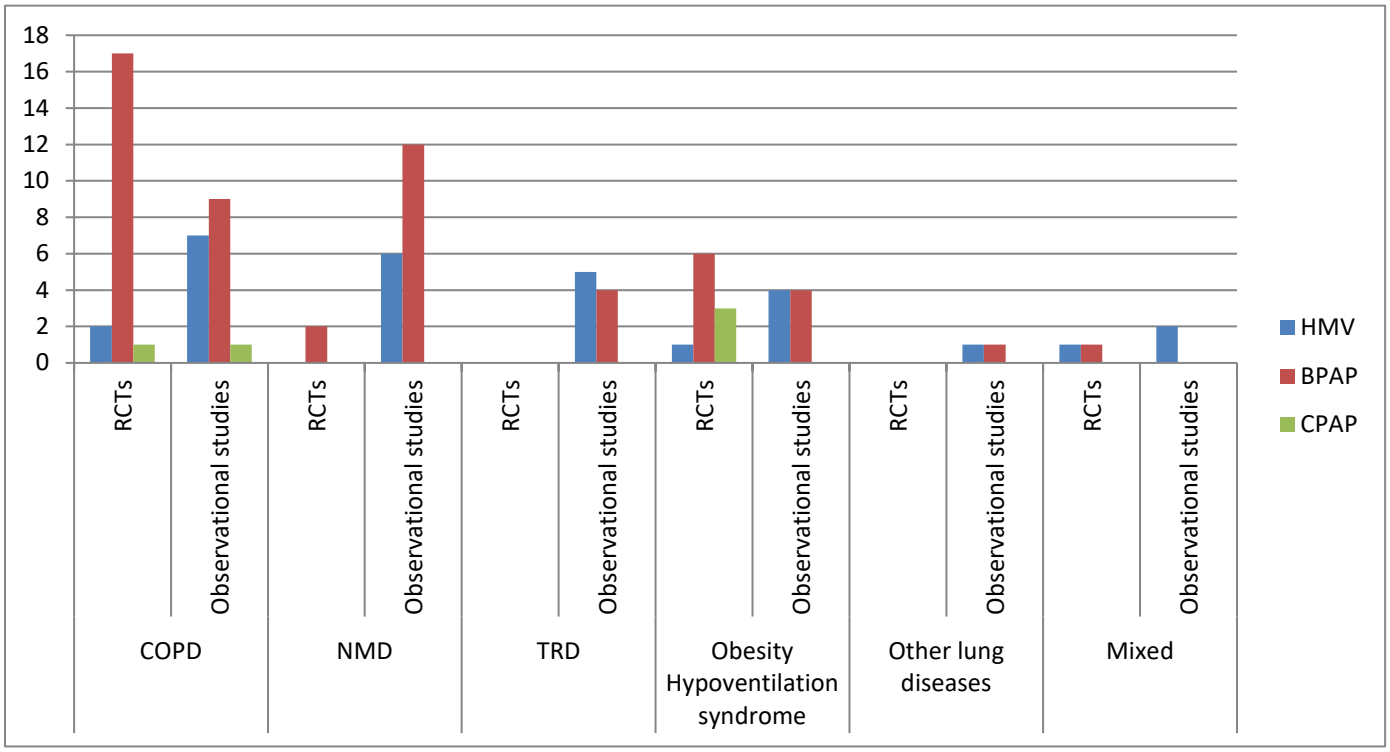
Results

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 $PaCO_2 \geq 45$mmHg
- Nocturnal hypercapnia with $PaCO_2 \geq 50$mmHg
- Daytime normocapnia with a rise in $PTcCO_2$ 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:

- $PaCO_2 \geq 45$ mm Hg
- Nocturnal oximetry demonstrating oxygen saturation $\leq 88\%$ for 5 consecutive minutes
- For progressive neuromuscular disease, maximal inspiratory pressures < 60 cmH_2O 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 $PaCO_2 > 6$ kPa or patients with $PaCO_2 \leq 6$ 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 ($PaO_2 < 80$ mmHg, $SpO_2 <95\%$). 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 cmH_2O or PImax<40 cmH_2O. 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 $PaCO_2 \geq 45$mmHg
- nocturnal hypercapnia with $PaCO_2 \geq 50$mmHg
- daytime normocapnia with a rise in $PTcCO_2$ 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.