CME CREDIT *EDUCATIONAL OBJECTIVE:* Readers will recommend appropriate forms of noninvasive positive pressure ventilation to appropriate candidates

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Noninvasive positive pressure ventilation for stable outpatients: CPAP and beyond

ABSTRACT

Noninvasive positive pressure ventilation (NIPPV) has been used in outpatients with sleep apnea, sleep disorders associated with heart failure, restrictive pulmonary diseases (subsuming neuromuscular diseases and thoracic cage deformities), severe stable chronic obstructive pulmonary disease, and the obesity-hypoventilation syndrome. NIPPV in these settings has resulted in significant physiologic benefits, improved quality of life, and in some cases longer survival. We discuss the modes of NIPPV, current indications, and potential benefits.

KEY POINTS

In sleep apnea, NIPPV has both short-term benefits such as improved daytime alertness and reduced fatigue, and long-term benefits such as a reduced cardiovascular risk.

The potential development of complex sleep apnea with NIPPV may be managed by using lower pressures, by continued treatment (more than half of cases improve over time), and by advanced options such as adaptive servo-ventilation.

In patients with concomitant obstructive sleep apnea and congestive heart failure, NIPPV, particularly bilevel positive airway pressure, improves blood pressure and left ventricular function, though it is not clear whether it has a survival benefit.

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Noninvasive positive pressure ventilation (NIPPV) is any form of positive ventilatory support applied without an endotracheal tube, including continuous positive airway pressure (CPAP).[1] The role of NIPPV in acute care has been discussed in an earlier review in the *Cleveland Clinic Journal of Medicine*.[2]

NIPPV is also used at night in outpatients with stable chronic conditions, first used in the 1980s in the treatment of obstructive sleep apnea[3] and neuromuscular diseases,[4] and since then in several other conditions including sleep disorders associated with congestive heart failure (including sleep apnea and the Cheyne-Stokes respiration-central sleep apnea syndrome), chronic obstructive pulmonary disease (COPD), and the obesity-hypoventilation syndrome.

In this review, we discuss the different types of NIPPV, the specific conditions in which they can be used, and the indications, recommendations, and evidence supporting the efficacy of NIPPV in outpatients.

THE TYPES OF NIPPV AND THEIR USES

Although the conditions for which different types of NIPPV can be used overlap significantly, each type has general indications and different goals of treatment. This section begins with types of NIPPV that are predominantly used to treat sleep-disordered breathing, and then proceeds to those predominantly used for conditions associated with hypoventilation and hypercapnia.

Continuous positive airway pressure

CPAP, currently the most widely used form of NIPPV, applies a constant level of positive pressure at the airway opening during spontaneous breathing.

CPAP is commonly used to treat obstructive sleep-disordered breathing, with the goals of improving daytime sleepiness and reducing cardiovascular risk. It has also been used to treat sleep-disordered breathing associated with congestive heart failure.

CPAP's role in the support of ventilation is limited and indirect. For instance, it has been used in the obesity-hypoventilation syndrome and in the "overlap" syndrome (in which both sleep apnea and COPD coexist). However, its benefits in those conditions are probably derived in large part from correction of underlying obstructive sleep apnea.

The mechanisms of action of CPAP include:

- Preventing intermittent narrowing and collapse of the airway in patients with obstructive sleep apnea-hypopnea syndrome by acting as a pneumatic splint during sleep[3,5,6]
- Counteracting auto-positive end-expiratory pressure, thereby reducing respiratory muscle load, reducing the work of breathing, and lowering daytime $Paco_2$ in patients with coexistent COPD and obstructive sleep apnea-hypopnea syndrome (the overlap syndrome)[7–9]
- Improving lung function (particularly the functional residual capacity) and daytime gas exchange in obstructive sleep apnea-hypopnea syndrome [10]
- Improving left ventricular systolic function in patients with heart failure coexisting with obstructive sleep apnea-hypopnea syndrome.[11,12]

Bilevel PAP is commonly used in conditions associated with hypoventilation

Auto-CPAP is delivered via a self-titrating CPAP device, which uses algorithms to detect variations in the degree of obstruction and consequently adjusts the pressure level to restore normal breathing. Auto-CPAP therefore compensates for factors that modify the upper airway collapsibility, such as body posture during sleep, stage of sleep, use of alcohol, and drugs that affect upper airway muscle tone.[13]

Although one of the premises of using auto-CPAP is that it improves the patient's satisfaction and compliance, several studies found it to be no more effective than fixed CPAP for treating obstructive sleep apnea-hypopnea syndrome.[14–16] Current guidelines of the American Academy of Sleep Medicine do not recommend self-titrating CPAP devices to diagnose obstructive sleep apnea or to treat patients with cardiopulmonary disorders or other conditions in which nocturnal desaturation may be unrelated to obstructive events.[17]

Adaptive servo-ventilation

Adaptive servo-ventilation was developed for Cheyne-Stokes respiration-central sleep apnea syndrome in patients with congestive heart failure, who may have periods of crescendo-decrescendo change in tidal volume (Cheyne-Stokes respiration) with possible intercalated episodes of central apnea or hypopnea. It is also applied in patients with the complex sleep apnea syndrome.

Adaptive servo-ventilation devices are usually set at an expiratory positive airway pressure (EPAP) level sufficient to control obstructive sleep apnea. The device then automatically adjusts the pressure support for each inspiration, within a prespecified range, to maintain a moving-target ventilation set at 90% of the patient's recent average ventilation. The aim is to stabilize breathing and reduce respiratory alkalosis, which can trigger apnea reentry cycles.[18]

Bilevel positive airway pressure

Bilevel positive airway pressure (bilevel PAP) can be of use in sleep-disordered breathing (including cases associated with congestive heart failure), but it is predominantly applied in conditions associated with hypoventilation.

Bilevel PAP devices deliver a higher pressure during inspiration (inspiratory positive airway pressure, or IPAP) and a lower pressure during expiration (EPAP). The gradient between IPAP and EPAP is of key importance in maintaining alveolar ventilation and reducing $Paco_2$. The IPAP acts as pressure support to augment the patient's effort, maintain adequate alveolar ventilation, unload respiratory muscles, decrease the work of breathing, and control obstructive hypopnea, whereas EPAP is set to maintain upper airway patency, control obstructive apnea, improve functional re-

TABLE 1

Types of noninvasive positive pressure ventilation

CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP)

Applications: obstructive sleep apnea; congestive heart failure with coexisting obstructive sleep apnea; obesity-hypoventilation syndrome with coexisting obstructive sleep apnea

Setup requirements: CPAP level

Advantages: simple to use, relatively inexpensive

Disadvantages: minimal or no ventilation support; preset pressures may not address variability in obstructive sleep apnea, severity with sleep stages, and positional changes

AUTO-CPAP

Applications: obstructive sleep apnea; congestive heart failure with coexisting obstructive sleep apnea; obesity-hypoventilation syndrome with coexisting obstructive sleep apnea

Setup requirements: range of allowable CPAP levels

Advantages: reduces number of titration studies; self-adjusting to adapt to variability in obstructive sleep apnea with sleep stages and positional changes; may be useful for patients with ongoing weight loss, such as after bariatric surgery

Disadvantages: more expensive than fixed CPAP; may not be effective for patients with cardiopulmonary disorders or other conditions in which nocturnal desaturation may be unrelated to obstructive events

ADAPTIVE SERVO-VENTILATION

Applications: congestive heart failure; central sleep apnea; complex sleep apnea syndrome

Setup requirements: maximum and minimum inspiratory pressures; end-expiratory pressure

Advantages: adapts pressure to maintain more consistency of respiration over time

Disadvantages: more expensive than other modes; may worsen ventilation in disease with chronic ventilator insufficiency, such as severe COPD and restrictive thoracic disorders

BILEVEL POSITIVE AIRWAY PRESSURE (BILEVEL PAP) WITHOUT BACKUP RATE

Applications: obstructive sleep apnea with CPAP intolerance; obstructive sleep apnea with central sleep apnea; restrictive thoracic disorders; severe chronic obstructive pulmonary disease; obesity-hypoventilation syndrome with coexisting obstructive sleep apnea and residual hypoventilation despite CPAP

Setup requirements: inspiratory and expiratory positive airway pressures

Advantages: promotes alveolar ventilation; unloads respiratory muscles; decreases the work of breathing; controls obstructive hypopneas

Disadvantages: more expensive than CPAP; may generate central apnea

BILEVEL PAP WITH BACKUP RATE

Applications: central sleep apnea; complex sleep apnea syndrome; worsening restrictive disorder

Setup requirements: inspiratory and expiratory positive airway pressures; backup rate; ratio of inspiratory time to expiratory time

Advantages: provides mandatory respiratory support during central or pseudocentral apneas

Disadvantages: more expensive than conventional bilevel positive airway pressure; may generate central apnea

AVERAGE VOLUME-ASSURED PRESSURE SUPPORT

Applications: obesity-hypoventilation syndrome; neuromuscular disease; chronic obstructive pulmonary disease

Setup requirements: target tidal volume (8 mL/kg of ideal weight); inspiratory positive airway pressure limits; respiratory rate

Advantages: ensures a delivered tidal volume; compensates for disease progression

Disadvantages: more expensive than other modes

sidual capacity, and prevent microatelectasis.

Although there is no evidence that bilevel PAP is better adhered to or more effective than CPAP, current guidelines propose it as an option for patients who require high pressures to control obstructive sleep apnea-hypopnea syndrome or for those who cannot tolerate exhaling against a high fixed CPAP pressure.[19]

TABLE 2

Medicare requirements to qualify for a respiratory assist device

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Noninvasive positive pressure ventilation (NIPPV) without backup rate:

$Paco_2 \geq 52$ mm Hg [a]
and
O_2 saturation ≤ 88% for ≥ 5 minutes (≥ 2 hours of recording on ambulatory nocturnal sleep oximetry) while on the higher of 2 L per minute of O_2 or prescribed FiO_2
and
Obstructive sleep apnea and CPAP treatment have been considered and ruled out by facility-based nocturnal polysomnography

NIPPV with backup rate, any time after use without backup rate:

$Paco_2 \geq 7$ mm Hg greater than the original qualifying result
and
O_2 saturation ≤ 88% for ≥ 5 minutes (≥ 2 hours of recording on facility-based nocturnal polysomnography) while on NIPPV without backup rate and apnea-hypopnea index < 5
and
An FEV_1/FVC ratio < 70% or FEV_1 < 50%

NIPPV with backup rate, no sooner than 61 days after use without backup rate:

$Paco_2$ still ≥ 52 mm Hg
and
O_2 saturation ≤ 88% for ≥ 5 minutes (≥ 2 hours of recording on ambulatory nocturnal sleep oximetry) while on the higher of 2 liters per minute of O_2 or prescribed FiO_2

RESTRICTIVE THORACIC DISORDERS: PROGRESSIVE NEUROMUSCULAR DISEASE OR SEVERE THORACIC CAGE ABNORMALITIES

NIPPV with or without backup rate:

$Paco_2 \geq 45$ mm Hg
or
O_2 saturation ≤ 88% for ≥ 5 minutes (≥ 2 hours of recording on ambulatory nocturnal sleep oximetry) while on prescribed FiO_2
or (for neuromuscular diseases only):
Minimum inspiratory pressure < 60 cm H_2O
or
FVC < 50% of predicted; COPD not contributing to the limitation

CENTRAL SLEEP APNEA OR COMPLEX SLEEP APNEA SYNDROME

NIPPV with or without backup rate:

All of the following on facility-based nocturnal polysomnography: apnea-hypopnea index > 5, central events > 50% of total, central events ≥ 5 per hour, excessive daytime sleepiness or disrupted sleep
and
Significant improvement on NIPPV and prescribed FiO_2

OBSTRUCTIVE SLEEP APNEA

Continuous positive airway pressure:

Apnea-hypopnea index/respiratory disturbance index ≥ 15 (minimum 30 events)
or
Apnea-hypopnea index/respiratory disturbance index 5–14 with symptoms or cardiovascular risks [b]

NIPPV without backup rate:

Above criteria and CPAP proven ineffective on polysomography or at home

HYPOVENTILATION SYNDROME

NIPPV without backup rate:

Awake $Paco_2 \geq 45$ mm Hg
and
$Paco_2 \geq 7$ mm Hg greater during sleep or upon awakening (on prescribed FiO_2)
or
O_2 saturation ≤ 88% for ≥ 5 minutes (≥ 2 hours of recording on facility-based nocturnal polysomonography) with an apnea-hypopnea index < 5

NIPPV with backup rate:

Awake $Paco_2$ on prescribed FiO_2 up ≥ 7 mm Hg from initial qualifying $Paco_2$, despite using NIPPV without backup rate
or
O_2 saturation ≤ 88% for ≥ 5 minutes (≥ 2 hours of recording on facility-based nocturnal polysomnography), while on NIPPV without backup, and an apnea-hypopnea index < 5
and
An FEV_1/FVC ratio ≥ 70% and an $FEV_1 \geq 50\%$ of predicted

[a] Arterial blood gas measurements done while the patient is awake and breathing the prescribed FiO_2

[b] Excessive daytime sleepiness, impaired cognition, mood disorders, insomnia; or hypertension, ischemic heart disease, or history of stroke

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Other, more-common uses of bilevel PAP are to treat coexisting central sleep apnea or hypoventilation,[19] the obesity-hypoventilation syndrome with residual alveolar hypoventilation despite CPAP and control of concomitant obstructive sleep apnea-hypopnea syndrome,[5,20] severe stable COPD with significant nocturnal hypoventilation and daytime hypercarbia,[21] and restrictive pulmonary diseases.[21]

Although the patient should be able to maintain spontaneous breathing on bilevel PAP, a backup rate option can be set for those whose ventilation during sleep may be significantly impaired (eg, those with neuromuscular diseases, complex sleep apnea, central apnea in congestive heart failure, or obesity-hypoventilation syndrome) (**TABLE 1, TABLE 2**).[22,23] However, one important paradoxical consideration is that both CPAP and bilevel PAP (with or without a backup rate) promote ventilation and have the potential of dropping the carbon dioxide level below a hypocapnic apneic threshold during sleep, thereby triggering central apnea and the complex sleep apnea syndrome.[24]

Average volume-assured pressure support

Average volume-assured pressure support is directed mainly at patients with chronic hypoventilation such as those with obesity-hypoventilation syndrome, neuromuscular diseases, and COPD. In this mode, a target tidal volume is set, and the device adjusts the pressure support to reach that set tidal volume. The advantage is that it guarantees a delivered tidal volume despite variability in patient effort, airway resistance, and lung or chest wall compliance. A particular potential benefit is that it may adapt to disease progression, as may occur in patients with progressive neuromuscular disorders.

CONDITIONS IN WHICH NOCTURNAL NIPPV IS USED IN OUTPATIENTS

Obstructive sleep apnea-hypopnea syndrome

Obstructive sleep apnea-hypopnea syndrome is estimated to affect 2% of women and 4% of men.[25] It is characterized by recurrent episodes of partial (hypopnea) or complete (apnea) upper airway obstruction during sleep despite ongoing inspiratory efforts, with associated episodes of arousal or desaturation or both. Corresponding symptoms include excessive daytime sleepiness, choking and gasping during sleep, recurrent awakenings from sleep, unrefreshing sleep, daytime fatigue, and impaired concentration that is not explained by other factors.[26]

Current understanding of the pathophysiology of obstructive sleep apnea implicates an impairment in the balance between factors that promote collapsibility of the airway (including obesity and anatomic issues such as the volume of the soft-tissue structures surrounding the upper airway) and the compensatory neuromuscular response.[27,28]

Long-standing obstructive sleep apnea-hypopnea syndrome has been linked in prospective studies to the development of hypertension,[29–31] coronary artery disease,[32,33] increased coagulation,[34,35] and stroke or death from any cause.[36,37] It is also associated with a greater rate and severity of motor vehicular accidents,[38] greater health care utilization, impaired work performance, and occupational injuries.[39]

Strong evidence exists that NIPPV (most commonly CPAP) is beneficial in obstructive sleep apnea-hypopnea syndrome, improving sleep quality, sleepiness, cognitive impairment, and quality of life,[40,41] decreasing motor vehicle accidents,[42] lowering blood pressure,[43,44] and decreasing the rates of myocardial infarction,[32] stroke,[32] and death.[45]

CPAP and bilevel PAP paradoxically can cause central apnea by lowering the blood CO_2 level

The American Academy of Sleep Medicine recommends CPAP as an optional adjunctive therapy to lower blood pressure in patients with obstructive sleep apnea-hypopnea syndrome with concomitant hypertension.[19] This is supported by a recent study that suggested that CPAP may have additional benefits on blood pressure in a subgroup of patients with uncontrolled hypertension while on antihypertensive medications.[46] Indications with Medicare guidelines for reimbursement of CPAP devices are summarized in **TABLE 2**.

Complex sleep apnea syndrome

The complex sleep apnea syndrome is characterized by the emergence of significant central sleep apnea or Cheyne-Stokes respiration after obstructive events have been brought under

control with NIPPV in patients who initially appear to have obstructive sleep apnea-hypopnea syndrome. A retrospective study of patients with the complex sleep apnea syndrome who continued their NIPPV use until a subsequent polysomnographic study and NIPPV titration showed that the syndrome may resolve spontaneously, but that 46% of patients had a persistently elevated apnea-hypopnea index with central apnea activity.[47]

Restoration of upper airway patency by CPAP and dysregulation or delayed adaptation of chemosensitive ventilatory control to a changing $Paco_2$ level may be a key pathophysiologic mechanism of the complex sleep apnea syndrome.[48] In this mechanism, increased ventilation from restored airway patency and from an increase in the slope of the ventilatory response may intermittently draw the $Paco_2$ to below the hypocapnic apneic threshold and trigger episodes of central apnea.[48]

The ideal NIPPV device for use in the complex sleep apnea syndrome should be able to provide enough pressure to resolve the obstructive sleep apnea-hypopnea syndrome while maintaining proper ventilatory support during central apnea episodes without fluctuations of $Paco_2$, which could further worsen the dysregulated ventilatory control. Currently, adaptive servo-ventilation appears to be superior to bilevel PAP and CPAP in the management of the complex sleep apnea syndrome.[49,50]

Obstructive sleep apnea has been linked to hypertension, coronary disease, hypercoagulation, stroke, and death

Sleep disturbances associated with cardiac dysfunction

There are specific indications for NIPPV modes in the setting of respiratory sleep disturbances associated with heart failure.

Obstructive sleep apnea in congestive heart failure. The prevalence of obstructive sleep apnea in patients with impaired left ventricular ejection fraction is 11% to 53%.[51] Obstructive sleep apnea-hypopnea syndrome can worsen congestive heart failure by causing a periodic increase in negative intrathoracic pressure from breathing against an occluded airway, by raising arterial blood pressure, and causing tachycardia from sympathetic nervous system stimulation from hypoxia, hypercarbia, and arousals.[52,53] Both heart failure and sleep apnea contribute in an additive manner to the increased sympathetic nervous activity.[54]

Fortunately, treatment with CPAP has been found to reduce systolic blood pressure and improve left ventricular systolic function in medically treated patients with heart failure and coexisting obstructive sleep apnea.[11,12] Furthermore, in a randomized trial in patients with stable congestive heart failure and newly diagnosed obstructive sleep apnea-hypopnea syndrome, a greater improvement in cardiac function was observed in patients on bilevel PAP than in those on CPAP.[55] The authors speculated that bilevel PAP might provide more unloading of the respiratory muscles, reduce the work of breathing more, and result in less positive intrathoracic pressure than with CPAP, and that the higher intrathoracic pressure with CPAP could reduce the left ventricular ejection fraction in patients with low filling pressures (pulmonary capillary wedge pressure < 12 mm Hg) and low baseline left ventricular ejection fractions (< 30%).[55]

Whether these interventions reduce the mortality rate is uncertain. In a prospective nonrandomized study, 9 (24%) of 37 patients who had heart failure with untreated obstructive sleep apnea died, compared with no deaths in 14 treated patients ($P = .07$).[56]

Cheyne-Stokes respiration with central sleep apnea in congestive heart failure. A related but different situation is central apnea associated with congestive heart failure.

There are several pathophysiologic mechanisms of Cheyne-Stokes respiration with central sleep apnea. Specifically, the elevation of left ventricular filling pressures, end-diastolic volumes, and pulmonary congestion generate hyperventilation, chronic hypocapnia, and increased chemoreceptor responsiveness, which contribute to the development of central apnea by promoting a decrease in the $Paco_2$ during sleep to below the hypocapnic apneic threshold.[57,58] Additionally, an increase in circulation time may result in periodicity of breathing and hyperpnea.[59] Obstructive events can then occur at the end of the central events corresponding with the nadir of the inspiratory drive.[60,61]

The Canadian Continuous Positive Airway Pressure for Patients With Central Sleep Apnea and Heart Failure (CANPAP) trial, a randomized trial of CPAP in this clinical

setting, showed that compared with optimal medical therapy alone, CPAP plus optimal medical therapy improved the ejection fraction, reduced central sleep apnea, improved nocturnal oxygenation, and improved the 6-minute walking distance, but without a survival benefit.[62] The disappointing survival results from CANPAP have to be interpreted in the context that CPAP may have failed to control the central apnea in some patients, such that the mean apnea-hypopnea index in treated patients (19 events/hour) remained above the entry criterion for recruitment (15 events/hour). In a post hoc analysis of this study, the heart-transplantation-free survival rate was significantly greater in the subgroup of patients in whom CPAP effectively suppressed central sleep apnea (< 15 events/hour).[63]

Other NIPPV modes such as bilevel PAP with backup rate and adaptive servo-ventilation have been shown in some studies to be superior to CPAP in controlling respiratory events, with adaptive servo-ventilation being the most effective in controlling central, mixed, and complex sleep apnea in this setting.[49,50] Whether more effective resolution of obstructive and central events with these treatment modes translates into improved mortality rates and transplantation-free survival rates remains to be determined.

Obesity-hypoventilation syndrome

Obesity-hypoventilation syndrome refers to daytime hypercapnia ($Paco_2$ > 45 mm Hg) in obese people when no other cause of hypoventilation is present.

The prevalence of obesity-hypoventilation syndrome among patients with obstructive sleep apnea-hypopnea syndrome is 20% to 30% and is greater in extremely obese patients (body mass index > 40 kg/m^2).[64] However, about 10% of patients with obesity-hypoventilation syndrome do not have obstructive sleep apnea-hypopnea syndrome.[64] Additionally, nocturnal hypoxemia and diurnal hypercapnia persist in about 40% of patients with obesity-hypoventilation syndrome after CPAP eliminates their sleep apnea.[65] Therefore, factors other than sleep apnea contribute to the development of obesity-hypoventilation syndrome, and in a meta-analysis, factors associated with daytime hypercapnia included, in addition to body mass index and the apnea-hypopnea index, mean overnight oxygen saturation and severity of restrictive pulmonary function.[66] Predictors of success with CPAP include better spirometric findings, a higher apnea-hypopnea index, and adequate oxygenation.[67,68]

Bilevel PAP therapy can be tried in patients in whom CPAP by itself fails. In a study of patients with obesity-hypoventilation syndrome in whom initial CPAP treatment failed, average volume-assured pressure support lowered $Paco_2$ compared to bilevel PAP alone, but did not further improve oxygenation, sleep quality, or quality of life.[69]

Restrictive pulmonary diseases

Neuromuscular diseases and thoracic cage abnormalities. Noninvasive ventilation has been used in patients with progressive neuromuscular disorders or severe thoracic cage abnormalities, with recognized benefits including an improved survival rate and improved quality of life.[70,71] However, NIPPV is used in only 9% of patients with amyotrophic lateral sclerosis when clearly indicated.[72] The indications and Medicare guidelines for reimbursement of NIPPV (with or without a backup rate) in this setting are shown in TABLE 2.

Potential contraindications to starting NIPPV in this population include upper airway obstruction, failure to clear secretions despite optimal noninvasive support, inability to achieve a mask fit, and intolerance of the intervention.[73,74]

The mechanisms of benefit of NIPPV in these settings include improvements in daytime blood gas levels (including hypercapnia[75]), a reduction in the oxygen cost of breathing,[76] an increase in the ventilatory response to carbon dioxide,[75] and improved lung compliance.[77]

Adaptive servo-ventilation appears to be superior to bilevel PAP and CPAP for complex sleep apnea syndrome

Chronic hypercapnic failure due to severe COPD

The use of NIPPV in chronic COPD is less well established than in patients with exacerbations of COPD,[78] and limitations in its use are reflected in the more stringent Medicare indications for NIPPV in this setting (TABLE 2).

A particular subset of patients with stable COPD who may benefit from NIPPV includes

those with daytime hypercapnia and superimposed nocturnal hypoventilation.[78] The potential benefits of NIPPV in these patients include improved daytime and nocturnal gas exchange, increased sleep duration, and improved quality of life.[78] Additionally, a recent randomized controlled trial of NIPPV plus long-term oxygen therapy compared with oxygen therapy alone in patients with severe COPD and a $Paco_2$ greater than 46 mm Hg demonstrated a survival benefit in favor of adding NIPPV (hazard ratio 0.6).[79]

However, that study also found no reduction in hospitalization rates, an apparent worsening in general and mental health (as reflected on the 36-Item Short Form Health Survey or SF-36, a quality-of-life questionnaire), as well as increased confusion and bewilderment (reflected on the Profile of Mood States scale).[79] These potentially deleterious effects may explain why adherence to NIPPV is low in patients with stable COPD: only 37% to 57% of patients continued to use it in several reported studies.[79–81]

A level of inspiratory pressure support that is insufficient to reduce hypercapnia may account for the low adherence rate and worsened quality of life in such patients. For instance, in a randomized trial,[82] compared with low-intensity NIPPV (mean IPAP 14 cm H_2O, backup rate 8 per minute), settings that aimed to maximally reduce $Paco_2$ (mean IPAP 29 cm H_2O with a backup rate of 17.5 per minute) increased the daily use of NIPPV by 3.6 hours/day and improved exercise-related dyspnea, daytime $Paco_2$, forced expiratory volume in 1 second (FEV_1), vital capacity, and health-related quality of life.

The overlap syndrome was first described by Flenley in 1985 as a combination of chronic respiratory disease (more generally limited to COPD) and obstructive sleep apnea-hypopnea syndrome.[83] Epidemiologic studies do not consistently show a higher incidence of obstructive sleep apnea-hypopnea syndrome in patients with COPD, but the exaggerated oxygen desaturation during sleep in patients with this combination increases the risk of hypoxemia, hypercapnia, and pulmonary hypertension.[84] In addition, there was evidence of higher risks of death and of hospitalization for COPD in patients with the overlap syndrome.[85] NIPPV is the main treatment for obstructive sleep apnea-hypopnea syndrome with or without COPD.

A recent study by Marin et al[85] showed that CPAP was associated with improved survival and decreased hospitalization in patients with the overlap syndrome. However, polysomnography or nocturnal oximetry while on NIPPV alone must be done, as additional nocturnal oxygen therapy may be warranted when significant chronic respiratory illness coexists with sleep apnea.

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