AMERICAN THORACIC SOCIETY DOCUMENTS

Long-Term Noninvasive Ventilation in Chronic Stable Hypercapnic Chronic Obstructive Pulmonary Disease

An Official American Thoracic Society Clinical Practice Guideline: Executive Summary

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Background: Noninvasive ventilation (NIV) is used for patients with chronic obstructive pulmonary disease (COPD) and chronic hypercapnia. However, evidence for clinical efficacy and optimal management of therapy is limited.

Target Audience: Patients with COPD, clinicians who care for them, and policy makers.

Methods: We summarized evidence addressing five PICO (patients, intervention, comparator, and outcome) questions. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach was used to evaluate the certainty in evidence and generate actionable recommendations. Recommendations were formulated by a panel of pulmonary and sleep physicians, respiratory therapists, and methodologists using the Evidence-to-Decision framework.

Recommendations: *1*) We suggest the use of nocturnal NIV in addition to usual care for patients with chronic stable hypercapnic COPD (conditional recommendation, moderate certainty); *2*) we suggest that patients with chronic stable hypercapnic COPD undergo screening for obstructive sleep apnea before initiation of long-term NIV (conditional recommendation, very low certainty); *3*) we suggest not initiating long-term NIV during an admission for acute-on-chronic hypercapnic respiratory failure, favoring instead reassessment for NIV at 2–4 weeks after resolution (conditional recommendation, low certainty); *4*) we suggest not using an in-laboratory overnight polysomnogram to titrate NIV in patients with chronic stable hypercapnic COPD who are initiating NIV (conditional recommendation, very low certainty); and *5*) we suggest NIV with targeted normalization of Pa_{CO_2} in patients with hypercapnic COPD on long-term NIV (conditional recommendation, low certainty).

Conclusions: This expert panel provides evidence-based recommendations addressing the use of NIV in patients with COPD and chronic stable hypercapnic respiratory failure.

Keywords: chronic obstructive pulmonary disease; hypercapnic respiratory failure; noninvasive ventilation

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Summary of Recommendations

For patients with chronic ($FEV_1/FVC < 0.70$; resting $Pa_{CO_2} > 45$ mm Hg; not during exacerbation) hypercapnic respiratory failure due to chronic obstructive pulmonary disease (COPD):

1. We **suggest** the use of nocturnal noninvasive ventilation (NIV) in addition to usual care for patients with chronic stable hypercapnic COPD (conditional recommendation, moderate certainty).
2. We **suggest** that patients with chronic stable hypercapnic COPD undergo screening for obstructive sleep apnea before initiation of long-term NIV (conditional recommendation, very low certainty).
3. We suggest **not** initiating long-term NIV during an admission for acute-on-chronic hypercapnic respiratory failure, favoring instead reassessment for NIV at 2–4 weeks after resolution (conditional recommendation, low certainty).
4. We suggest **not using** an in-laboratory overnight polysomnogram (PSG) to titrate NIV in patients with chronic stable hypercapnic COPD who are initiating NIV (conditional recommendation, very low certainty).
5. We **suggest** NIV with targeted normalization of Pa_{CO_2} in patients with hypercapnic COPD on long-term NIV (conditional recommendation, low certainty).

Introduction

Since the development of NIV, there has been interest in its use for the treatment of patients with COPD and chronic stable hypercapnia. During acute exacerbations with ventilatory failure, NIV is frequently used because it has been shown to improve survival (reviewed in Reference 1). However, there have been fewer studies addressing the use of chronic domiciliary, nocturnal NIV for stable hypercapnic COPD.

In stable patients with COPD and chronic hypercapnia (defined as $FEV_1/FVC < 0.70$; resting $Pa_{CO_2} > 45$ mm Hg; not during exacerbation), long-term NIV has the potential to improve physiological parameters (e.g., lung function or gas exchange), clinical symptoms (e.g., functional capacity, dyspnea, quality of life [QOL], and sleep quality) and patient-centered outcomes (e.g., hospital readmission and survival). The purpose of this clinical practice guideline is to summarize the available evidence and provide actionable recommendations addressing *1*) patients with COPD, especially potential subgroups who might benefit from NIV therapy; *2*) the ideal timing and location (e.g., hospital or sleep laboratory vs. home) for NIV initiation; and *3*) the identification of optimal modes and settings for chronic NIV therapy.

Methods

The guideline was developed according to the policies and procedures of the American Thoracic Society (ATS); the methods are described in detail in the full-length version of the guideline.

Results

Question 1: Should long-term nocturnal NIV versus usual care be used for chronic stable outpatients with hypercapnic COPD?

Recommendation. We suggest the use of nocturnal NIV in addition to usual care for patients with chronic stable hypercapnic COPD (conditional recommendation, moderate certainty).

Summary of the evidence. Thirteen randomized controlled trials (RCTs) were included in the analysis, with follow-up ranging from 3 to 12 months. There was some variation in the standard of care provided to the control group in the included studies. Although most trials compared NIV as an addition to oxygen therapy, two compared nocturnal NIV with exercise training with exercise training alone (2, 3), and in one study, not all patients received oxygen therapy in the control arm (4).

All 13 studies reported mortality, but in 5 studies, the effect of NIV on mortality was not able to be estimated because of an absence of events in either group. In the remaining eight studies, mortality risk was reduced by 14% in the NIV group compared with those receiving usual care (relative risk, 0.86; 95% confidence interval [CI], 0.58 to 1.27; low certainty). Patients receiving NIV had a decrease in hospitalizations (mean difference [MD], 1.26 fewer; 95% CI, 2.59 fewer to 0.08 more hospitalizations; low certainty), improved QOL, and improvement in dyspnea compared with standard of care.

Improvements in awake gas exchange favored NIV, although the magnitude of effect was small and of questionable clinical importance. No significant difference in

lung function as measured by FEV_1 was seen, nor was any significant difference seen in sleep efficiency assessed by questionnaire. Six-minute-walk distance was higher with NIV (MD, 32 m; 95% CI, 10.8–53.3 m; moderate certainty).

There was a 10-fold increase in the risk of discomfort, skin breakdown, and rash in the NIV group when compared with standard of care. No serious adverse events such as hypotension or pneumothorax were reported in any of the trials included in our analyses.

Rationale for the recommendation. Overall, the balance between desirable and undesirable effects of NIV in this patient population probably favors NIV. Although the amount of certainty around these outcomes is low, the panel was impressed with the consistency of the direction of effect in favor of improvement in dyspnea and QOL scores in the NIV group.

The panel recognized that the implementation of resources and cost of NIV may be significant barriers to the widespread acceptance of NIV in patients with stable hypercapnic COPD. It was judged that the costs of treating patients with stable hypercapnic COPD with NIV were moderate. It was noted that there would likely be a high upfront cost in initiating NIV, and many of the studies included frequent follow-ups with personnel who called or interacted with the study subjects weekly or biweekly. Many clinical services may not have the resources to provide such intensive follow-up, even in the short term, which might be important to achieving high adherence and improved outcomes.

There are also costs to the patients, as many insurers may not cover NIV or copayments may be too high for patients to afford. Overall, despite the initial costs, NIV may be cost-effective in many settings (5). Patients may have difficulty accepting NIV because of claustrophobia or dyssynchrony. This difficulty is reflected in the variations in adherence seen in the studies; some patients may choose to discontinue NIV, particularly if there are problems with the interface. The panel recognized that this recommendation could impact health equity. Access to experts in both pulmonary and sleep medicine is increasingly rare, especially in rural and nonacademic centers. Training in sleep medicine has also changed in recent years, with more trainees entering sleep fellowships without pulmonary training. Similarly, pulmonary training programs may not provide adequate education to trainees regarding home NIV. Access to respiratory therapists with sleep and/or home ventilation training is also necessary to ensure a patient's success with mask fittings and NIV acceptance. The panel judged, however, that if the infrastructure is in place, providing NIV in patients with stable hypercapnic COPD is feasible in many settings.

Unanswered questions and research priorities. First, research is needed into which patients (i.e., phenotypes) would be expected to benefit the most from NIV therapy. Second, the mechanism by which NIV appears to improve outcomes remains unclear, although it may include respiratory muscle rest, reduction in hyperinflation, and improvement in $\dot{V}/\dot{Q}$ matching. A better understanding of the contribution of these components would allow clinicians to better target and titrate therapy. Third, major questions remain regarding how exactly (mode, settings, monitoring, titration) to implement and follow patients on long-term NIV therapy. Finally, further data examining important patient outcomes and cost-effectiveness (in less intensive, real-world settings) are needed to improve the certainty of evidence informing the recommendation.

Question 2: Should patients with chronic stable hypercapnic COPD undergo assessment for sleep apnea (i.e., overlap syndrome) before initiation of long-term NIV?

Recommendation. We suggest that patients with chronic stable hypercapnic COPD undergo screening for obstructive sleep apnea (OSA) before initiation of long-term NIV (conditional recommendation, very low certainty).

Summary of the evidence. The panel identified several studies that suggest that identification and treatment of OSA with continuous positive airway pressure (CPAP) in patients with COPD improves outcomes. However, these data were not from RCTs, nor were they from studies of patients with hypercapnic COPD initiating or already on NIV (6–10).

No trials comparing an OSA screening strategy versus no OSA screening strategy in patients with stable hypercapnic COPD were identified. Similarly, there was no evidence evaluating the consequences of identifying (or failing to identify) OSA in patients who are already receiving long-term NIV for COPD. The panel noted that most trials evaluating NIV in COPD excluded patients with OSA and/or high body mass index, thus precluding subgroup analysis. Therefore, the panel chose to proceed with a GRADE (Grading of Recommendations, Assessment, Development and Evaluation)–supported two-step approach to develop this recommendation, first evaluating anticipated test accuracy and second evaluating the anticipated impact of test results on patient-important outcomes (11).

Two studies have evaluated the diagnostic accuracy of OSA screening tools in patients with COPD (12, 13). These two small studies have demonstrated that OSA-screening-test characteristics in patients with COPD are consistent with those seen in patients without COPD, although the estimates are imprecise because of the small sample sizes. The panel therefore chose to use indirect estimates from the population without COPD, for which there were substantially more data (and therefore more precise estimates) available, acknowledging that the indirect estimate would increase our uncertainty in the effects (14). As the reported prevalence of OSA in patients with COPD varies, we evaluated the accuracy of screening tests while assuming the need to identify severe OSA (apnea–hypopnea index $>$ 30 events/h), assuming a 10% prevalence.

Desirable and undesirable consequences. The panel discussed the potential desirable and undesirable consequences for screening in the context of two OSA screening tools, the STOP-BANG (Snoring, Tiredness, Observed Apnea, Pressure, BMI, Age, Neck size, Gender) Questionnaire (SBQ; sensitive but not specific) and the Epworth Sleepiness Scale (less sensitive and not specific).

Patients who screen positive and have OSA (true-positive results) will likely go on to receive further diagnostic sleep testing to evaluate for OSA. If OSA is found to be the major contributor to the patient's respiratory failure, the patient may require CPAP alone, rather than the more costly and challenging-to-implement NIV. Alternatively, knowledge of OSA diagnosis may result in better titration of NIV (e.g., higher expiratory positive airway

pressure [EPAP]) that may result in better outcomes due to fewer obstructive events. Finally, adherence to therapy might be improved if patients and clinicians were aware that they had two indications for NIV. These effects would not be seen in the absence of OSA screening. Patients who screen positive and do not have OSA (false-positive results) may undergo unnecessary diagnostic sleep testing (a one-time event) and will still receive NIV to treat their COPD.

Patients who screen negative and do not have OSA (true-negative results) will likely receive NIV and avoid further diagnostic sleep testing. Patients who screen negative but actually have OSA (false-negative results) may not receive diagnostic sleep testing to diagnose OSA and thus may not have their OSA fully treated using NIV alone with standard settings for hypoventilation (e.g., EPAP of 5 cm of water). However, some patients with false-negative results may receive NIV when all they require is CPAP to treat their OSA. These effects would also occur in the absence of screening.

Rationale for the recommendation. The panel judged that the greatest benefit to screening would be in patients ultimately determined to have COPD–OSA overlap (true-positive results), as this might lead to better titration of settings to address OSA and might focus clinicians on OSA and/or obesity as contributors to hypoventilation rather than COPD alone. The panel judged that patients with true-negative or false-negative screen results would not be adversely or beneficially affected by screening, as a negative screen result would not change management compared with no screening being performed. False-positive screen results would have some negative effects (unnecessary costs and time of confirmatory testing of OSA using a sleep study); however, these are likely of minimal consequence, as they are part of a singular event. Furthermore, the burden of sleep testing may vary depending on whether a full in-hospital or clinic-based PSG is done, versus a less-burdensome home sleep study.

Use of a sensitive test such as the SBQ will pick up most of these patients and may result in improved management. On the other hand, the high number of patients with false-positive results will result in an increased number of diagnostic sleep tests, most of which will be negative. These were judged by the panel to be of minor consequence to patients. Use of a less sensitive and also not specific screening instrument such as the Epworth Sleepiness Scale would also result in false-positive test results but would miss nearly half of the patients with severe OSA who would benefit from having properly diagnosed OSA. Weighing these considerations, together with the minimal cost and burden of screening using the SBQ, the panel judged that the benefits of screening using a highly sensitive test (e.g., the SBQ) probably outweighs the harms in a population with a severe OSA prevalence around 10%. Patients with COPD and overweight (body mass index $\geqslant 25$ kg/m^2) and cardiovascular disease appear to be at particularly high risk of overlap syndrome, and these characteristics may prompt consideration of OSA screening before initiating long-term NIV, although patients without these characteristics can also have concomitant OSA (13).

Unanswered questions and research priorities. COPD–OSA overlap was identified by the panel as an area of research priority, given the increasing recognition that a high proportion of patients with severe COPD receiving long-term NIV may also have OSA. Specific research topics identified include OSA-screening-tool test characteristics, specifically in patients with COPD; effects of screening for OSA in COPD (impact of testing on management decisions, clinical effects, financial costs, cost-effectiveness, etc.); identifying which patients with COPD are most at risk of OSA and therefore those most likely to benefit from screening and management of overlap syndrome; and phenotypes of sleep changes in overlap syndrome (e.g., apneas vs. hypopneas) and whether or not these phenotypes require different management strategies.

Question 3: Should long-term NIV be initiated in patients hospitalized with a COPD exacerbation associated with acute-on-chronic respiratory failure?

Recommendation. We suggest not using in-hospital initiation of long-term NIV after an episode of acute-on-chronic hypercapnic respiratory failure, favoring instead reassessment for NIV at 2–4 weeks after resolution (conditional recommendation, low certainty).

Summary of the evidence. We identified four RCTs evaluating the use of long-term NIV after an episode of acute hypercapnic respiratory failure. Pooled data suggest that there are no major differences in mortality, exacerbations, the need for hospitalization, changes in dyspnea, QOL, or exercise tolerance measured with 6-minute-walk distance when using NIV.

As this analysis was driven by two large RCTs, the RESCUE (Respiratory Support in COPD after Acute Exacerbation) trial (15) and the HOT-HMV (Home Oxygen Therapy–Home Mechanical Ventilation) trial (16), some detail of these trials is important. In RESCUE, 201 patients with COPD admitted to the hospital with acute hypercapnic respiratory failure who had persistent hypercapnia more than 48 hours after ventilatory support were randomly assigned to NIV or to no NIV. At 1 year, although there was improvement in both daytime and nocturnal hypercapnia, there was no improvement in mortality, frequency of exacerbation, or time to hospital readmission or death. In HOT-HMV, 116 patients with severe COPD who received NIV during acute hypercapnic respiratory failure and who remained hypercapnic (defined as $Pa_{CO_2} > 53$ mm Hg) 2–4 weeks afterward were randomly assigned to long-term NIV (HMV) with HOT or to HOT alone. At 1 year, there was no significant difference in 12-month mortality between the groups (28% for HOT + HMV vs. 32% for HOT), although there was some crossover to NIV in the HOT-only arm. However, there were fewer exacerbations (3.8 exacerbations/yr with HOT + HMV vs. 5.1 exacerbations/yr in HOT-only arm). In both studies, there was a minimal and temporary impact of NIV intervention on general QOL assessments, making definitive conclusions on the impact of NIV on QOL metrics in patients with COPD difficult.

Rationale for the recommendation. Patients with COPD and frequent hospitalizations might be expected to benefit from NIV, and inpatient hospitalization might provide a convenient clinical pathway to initiate NIV. Although the pooled evidence might suggest a possible benefit in starting NIV in patients who remain hypercapnic after an episode of acute hypercapnic respiratory failure, the RESCUE trial, the largest of the included trials, suggests that initiation of NIV in the hospital directly after termination of NIV for acute hypercapnic respiratory failure does

not improve patient-important outcomes. Indeed, these trials are complementary in that many (nearly 21%, and the largest reason for exclusion) potential HOT-HMV patients who were hypercapnic at hospital discharge were no longer hypercapnic 2–4 weeks later. These data suggest that initiation too early may result in many patients receiving long-term NIV unnecessarily. The panel also noted that the theoretical benefits of starting NIV earlier (reducing early readmission or recurrent exacerbation) were not supported by the data from the HOT-HMV trial, which demonstrated a larger effect size than the trials that initiated long-term NIV during an admission for acute-on-chronic hypercapnic respiratory failure. Lastly, there might be potential convenience to initiating NIV during an admission for acute-on-chronic hypercapnic respiratory failure, including availability of trained staff and equipment, but it might further prolong hospitalization to acclimatize to NIV.

Patients with known or suspected OSA were excluded from many of these studies. These recommendations would not apply to those who remain persistently hypercapnic and cannot be "weaned" from NIV in the hospital.

Unanswered questions and research priorities. There are no studies examining which hospitalized patients will have resolution of hypercapnia versus those who will not, nor has the time course of resolution after an acute exacerbation of COPD been thoroughly examined. Thus, the ideal time to evaluate (or reassess) appropriateness of NIV is not known. Long-term studies with extended follow-up are needed to see whether differential outcomes are maintained after prolonged outpatient therapy, including outcomes such as exacerbations, rehospitalizations, and QOL. Finally, there are no data regarding cost-effectiveness in the United States, although on the basis of costs in the United Kingdom, the use of long-term NIV is likely to be commensurate with other therapies considered to be cost-effective (17).

Question 4: Should long-term NIV settings be determined by an in-laboratory overnight PSG in patients with chronic stable hypercapnic COPD?

Recommendation. We suggest not using an in-laboratory overnight PSG to titrate NIV in patients with chronic stable hypercapnic COPD who are initiating NIV (conditional recommendation, very low certainty).

Summary of the evidence. Two small RCTs have examined the initiation of NIV using in-laboratory PSG titration versus an alternative method. Pooled data from both studies showed no difference in NIV adherence, QOL at 3 months, or Pa_{CO_2} amounts at 3 months.

Rationale for the recommendation. In theory, in-laboratory overnight titration might be useful to optimize NIV settings and/or provide a setting to introduce patients to NIV. For example, higher amounts of EPAP may be adjusted to maintain upper-airway patency and minimize patient–ventilator asynchrony. Some laboratories also have the ability to monitor transcutaneous CO_2 concentrations, so that titration could occur over the night and target near-normal CO_2 concentrations. Or, CO_2 measurements taken at night or during sleep may be more sensitive for nocturnal hypoventilation than daytime arterial blood gases and could be used to assess the efficacy of ventilation over time (18). The presence of a registered polysomnographic technician could also introduce NIV and the interface to the patient, possibly resulting in higher adherence.

However, possible concerns include the cost of in-laboratory testing and the delay in therapy that such testing would entail. Although measurement of CO_2 concentrations might have value in these patients (*see* question 5 below), few sleep laboratories currently measure CO_2 concentrations or have developed clear titration protocols for NIV on the basis of the overnight amounts. Furthermore, it is not clear if it is desirable, or even safe, to achieve normocapnia in a single night, and aggressive titration can result in glottic closure rather than increased ventilation (19, 20). Substantial education and training would be needed for sleep physicians and technicians. Multiple studies examining positive airway pressure adherence for the treatment of OSA have not demonstrated lower adherence in the absence of in-laboratory titration. Most NIV devices now provide information that might be used to titrate settings over time (e.g., residual apnea–hypopnea index) and, increasingly, incorporate algorithms for the automatic determination of EPAP (21–23). Similarly, daytime measurements of CO_2 concentrations could be used as surrogates for nocturnal changes over time. Finally, in-laboratory titration could always be pursued later for subjects experiencing difficulties with therapy or those with known COPD–OSA overlap.

Unanswered questions and research priorities. Many basic questions remain about the optimal mode and settings used for NIV in COPD and how such settings should be modified over time to maximize effectiveness and adherence. The ideal time course for change in CO_2 is not known (i.e., should the goal be to change Pa_{CO_2} in a single night or over many weeks?). Whether clinicians should attempt to decrease Pa_{CO_2} using a specific mode of NIV, by attempting larger V_Ts or with a more rapid respiratory rate, is not known. Finally, nearly all research studies of NIV in chronic stable hypercapnic COPD exclude those who are at risk for OSA or those with known OSA. Yet, in clinical practice, many patients with COPD will also have OSA.

Question 5: Should NIV with targeted normalization of Pa_{CO_2} amounts versus NIV without targeting normal Pa_{CO_2} amounts be used for long-term NIV in patients with COPD?

Recommendation. We suggest NIV with targeted normalization of Pa_{CO_2} in patients with hypercapnic COPD on long-term NIV (conditional recommendation, low certainty).

Summary of the evidence. There has been no direct comparison of these two similar but distinct modes of titration of NIV with regard to long-term outcomes (e.g., mortality). Nor have there been smaller homogenous studies that lend themselves to a meta-analytic approach. The available indirect data are from generally small physiological studies in which patients already on NIV were placed on settings designed to reduce Pa_{CO_2} for minutes to weeks at a time and then crossed over to less intense settings in random order, and outcomes include change in CO_2 concentrations, patient comfort, and NIV adherence. Pooled data from these studies demonstrate greater reductions in Pa_{CO_2} amounts when NIV is specifically targeting CO_2 clearance (MD, 4.9 mm Hg lower; 95% CI, 7.4 to 2.4 mm Hg lower; low certainty), and Pa_{O_2} increased by 3.4 mm Hg (2.4 mm Hg lower to 9.2 mm Hg higher,

low certainty). There were no significant differences in QOL or adherence.

In addition to these physiological studies directly comparing high- versus low-intensity NIV, the panel also considered subgroup analysis of all available studies of NIV in stable hypercapnic COPD (from PICO [patients, intervention, comparator, and outcome] question 1). As part of this subgroup analysis, we compared RCTs that targeted normalization of Pa_{CO_2} (high intensity) to studies that did not specifically target Pa_{CO_2} (low intensity). This analysis did not demonstrate any credible subgroup effect, with similar clinical outcomes seen in both groups. In part, this might be because the difference in Pa_{CO_2} between high- versus low-intensity NIV was relatively modest at 2.8 mm Hg. However, it should be noted that sleep amounts of Pa_{CO_2} were not always measured and might show larger differences.

Rationale for the recommendation. Our analysis did not demonstrate any effect on mortality when using targeted Pa_{CO_2} reduction with NIV in patients with stable hypercapnic COPD, although the certainty of evidence was low or very low for all outcomes, with no direct head-to-head trials. Pa_{CO_2} amounts tend to decrease only modestly with therapy; thus, the benefits of a further reduction in Pa_{CO_2} are unclear, and it is uncertain whether any potential benefit of NIV is mediated directly through lowered Pa_{CO_2} amounts or whether Pa_{CO_2} is a marker of other benefits from NIV (e.g., intrinsic muscle work of breathing).

In the absence of strong data favoring high-intensity NIV, the primary concerns were cost and other practical considerations related to measurement and monitoring of CO_2. Costs associated with targeted Pa_{CO_2} reduction are not insignificant, although, given that both targeted reduction and no targeted reduction achieved lower Pa_{CO_2}, monitoring of Pa_{CO_2} need not be aggressive. A commonly voiced concern with Pa_{CO_2}-targeted NIV is adherence related to higher pressures required to normalize Pa_{CO_2}. However, adherence to NIV has been similar to that for low-intensity settings in two studies (24, 25) and slightly greater with high-intensity NIV in one study (26). Thus, the use of Pa_{CO_2}-targeted NIV is probably feasible and acceptable to key stakeholders, allowing for a clear target to guide the use and titration of NIV.

Unanswered questions and research priorities. Further research is needed to define optimal Pa_{CO_2} reduction (to normal amounts or a different threshold), the speed at which Pa_{CO_2} should be reduced, and whether benefits of NIV occur in all patients with COPD and hypercapnia or whether there are specific subgroups that benefit most. As noted above, the optimal modes and settings used to reduce CO_2 need further study. In addition, titration with less invasive forms of CO_2 monitoring, such as transcutaneous or venous blood gases, should also be evaluated. Possible additional harms of NIV with targeted normalization of Pa_{CO_2} that require further investigation include its impact on hemodynamics, especially in patients with COPD and cardiac comorbidities. For example, Duiverman and colleagues (24) reported individual reductions in $\dot{Q}$ with high-intensity NIV in patients with heart failure.

Discussion

What Others Are Saying

The European Respiratory Society (ERS) recently published the results of a task force examining the broad issue of home NIV for stable hypercapnic COPD (27). Several PICO questions were similar to our questions and resulted in similar conclusions (i.e., conditional recommendation for NIV and for attempts to target reductions in Pa_{CO_2}). However, one notable difference was the timing of NIV initiation, with the ERS guideline suggesting initiation of NIV shortly after hospitalization for an acute exacerbation of COPD if hypercapnia persists. No specific time frame was provided, and reassessment 2–4 weeks after the initial episode "could be considered," although we do suggest reassessment at 2–4 weeks before consideration of long-term therapy. The ERS task force considered various modes and settings for delivery of NIV, but we remain agnostic, given the paucity of data in this regard. Another difference was our consideration of OSA before the initiation of NIV, which may reflect higher rates of obesity in the United States than in Europe (28) and thus a greater likelihood of encountering OSA. Overall, the ATS and ERS statements complement each other and provide assurance about the validity of the recommendations made in them.

Putting It All Together

It is exciting to consider NIV as additional therapy for those with hypercapnic COPD; however, there are many issues to consider.

First, appropriate patient selection remains critical. We emphasize that the patients in the studies reviewed here were selected because they had severe chronic stable hypercapnic COPD, and subjects with severe obesity or known OSA were excluded. In clinical practice, there are likely patients who have unrecognized concomitant OSA (so-called overlap syndrome) who might be treated with CPAP rather than NIV. Although data are lacking, Resta and colleagues (29) have demonstrated hypercapnia with relatively preserved lung function in patients with OSA–COPD compared with patients with COPD alone, a finding that may help clinicians recognize those patients. Although use of NIV, properly titrated, for these patients will not clearly cause harm, there are additional costs with NIV, and the emphasis of treatment might differ on the basis of the underlying diagnosis. Alternatively, many clinicians do not routinely measure arterial blood gases in clinic or use other surrogate measures such as transcutaneous CO_2 monitoring. As a result, it is possible that many patients who should be considered for NIV will not be included. Our recommendations have generally tried to limit the use of NIV to patients with persistent hypercapnia from COPD alone. Unfortunately, COPD is often clinically diagnosed in patients with overweight and obesity; clinicians need to be aware of alternate diagnoses such as obesity hypoventilation (30).

Second, there are implementation barriers to consider with these recommendations. Not all pulmonologists, nor all sleep physicians, are comfortable with NIV. Education will be needed for clinicians, respiratory therapists, and registered polysomnographic technicians who will be expected to evaluate, study, and potentially titrate NIV for subjects in the sleep laboratory. Such education should include knowledge of supplemental oxygen, measurement of transcutaneous CO_2, positive-pressure ventilation modes, and interfaces. Furthermore, initiation of NIV in clinical practice will be very different from initiation in research. For example, in the recent study by Duiverman and colleagues (23), initiation in the hospital

occurred over 7 days, on average (range, 4–15 d). Finally, adherence to this therapy will require additional efforts.

Third, clearly more data are needed to guide the desired goals of therapy, specifically regarding how aggressively clinicians should target Pa_{CO_2}. Is a greater reduction always better? Might there be tradeoffs with adherence with increasing pressures (or improvements with adherence with more respiratory support)? What are the dangers of too-rapid normalization of Pa_{CO_2}? In addition, if Pa_{CO_2} is a rational target for therapy, what will be the best mode and settings to achieve such a reduction?

Fourth, the panel noted that there were several regulatory and payor considerations (at least in the United States) related to the ability to obtain home NIV for COPD (reviewed in Reference 31). The Centers for Medicare and Medicaid Services requires the following testing and evaluation elements to consider NIV therapy: arterial blood gas, overnight oximetry, and evaluation for OSA (although formal testing is not required). Although these tests alone may be difficult to accomplish, successful completion will only confirm eligibility for a respiratory assist device that will not have a backup rate; many of the studies above, and particularly those targeting Pa_{CO_2} reductions, used devices capable of providing a backup rate. Paradoxically, it may be easier to qualify a patient for a more expensive home ventilator (32). Should more definitive evidence suggest mortality or other hard outcome benefits, an easier approval process for the needed therapy will be required.

Finally, given the cost and expertise needed to provide NIV for patients with stable hypercapnic COPD, there is potential for worsening of healthcare disparities. This is especially likely in rural and underserved regions, where important comorbidities (obesity, OSA) are likely to coexist. ■

This official clinical practice guideline was prepared by an *ad hoc* subcommittee of the ATS Assembly on Sleep and Respiratory Neurobiology.

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