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

An Official American Thoracic Society Clinical Practice Guideline

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This official clinical practice guideline of the American Thoracic Society was approved May 2020

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

COPD is a major cause of morbidity and mortality in the world and is the fourth leading cause of death in the United States (1, 2). Despite progress in the treatment of symptoms and prevention of acute exacerbations, few advances have been made to ameliorate disease progression or decrease mortality (3). To date, the only therapeutic interventions known to reduce mortality in COPD are smoking cessation and long-term treatment with continuous supplemental oxygen for patients who have severe hypoxemia at rest (4).

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 5). However, there have been fewer studies addressing the use of chronic domiciliary, nocturnal NIV for stable hypercapnic COPD. Most older studies were small and/or used modest driving pressures (6) in an attempt to normalize gas exchange, improve symptoms, and reduce morbidity and mortality. More recently, however, interest in the use of NIV in chronic hypercapnic COPD has been renewed with studies of so-called "high-intensity" NIV, which refers to inspiratory pressures higher than those used in most previous randomized controlled trials (RCTs) as well as controlled ventilation with higher-than-baseline respiratory rates to maximally reduce the Pa_{CO_2} (7–10).

Thus, 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

Panel Composition

The project was proposed by the chair and co-chairs (M.M., M.B.D., and R.L.O.) through the American Thoracic Society (ATS) Sleep and Respiratory Neurobiology Assembly and was approved by the ATS Board of Directors. The chair and co-chairs identified potential panelists on the basis of their expertise in sleep-disordered

breathing and COPD. The panel consisted of 12 physicians and 2 respiratory therapists with expertise in the field of domiciliary NIV and/or COPD and 2 clinician–methodologists with experience in evidence synthesis and guideline development using GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology. The ATS also recruited two patient partners who did not participate in further development of the recommendations to participate in question selection and outcome prioritization. The panel met regularly through conference calls and met in person at the yearly ATS International Conferences.

Conflict-of-Interest Policy

Industry relationships and other potential conflicts of interest were disclosed and managed in accordance with the policies and procedures of the ATS (available at https://www.thoracic.org/about/governance/ethics-and-coi/coi-principles.php). Briefly, all potential panelists disclosed their conflicts of interest to the ATS. Panelists determined to have no substantial conflicts of interest were "approved without limitation," whereas those with potential conflicts of interest that were considered manageable were "approved with management," allowing participation in discussions about the evidence but not in the formulation of recommendations related to their conflicts of interest. Potential panelists whose conflicts of interest were deemed not manageable were disqualified.

Question Generation

The panel chairs developed an initial list of questions, which was discussed in detail by panel members considering the importance, availability of evidence, and patient perspectives before final selection and wording of questions. The panel prioritized five PICO (patients, intervention, comparator, and outcome) questions for the guideline to address.

Prioritization of Outcomes

Following the standard GRADE guidance, the panel rated each outcome for their perceived importance to a patient with COPD on a scale of 1–9, with mean scores of 7–9 indicating a "critical" outcome, mean scores of 4–6 indicating an "important but not critical" outcome, and scores of 1–3 indicating an outcome that was "not important." (11) In general, outcomes deemed critical should be most informative to the panel in generating recommendations. The panel identified 11 key outcomes that would take priority in guideline decision-making for all PICO questions: dyspnea, hospitalizations, mortality, 6-minute-walk distance (6MWD), serum CO_2 and O_2, QOL, FEV_1, FVC, sleep efficiency, and minor side effects.

Literature Search and Study Selection

With the assistance of a medical librarian, the two methodologists conducted literature searches for each PICO question. We searched Medline, Embase, Cochrane CENTRAL (Central Register of Controlled Trials), CINAHL (Cumulative Index to Nursing and Allied Health Literature), and Web of Science from inception to April 2019 for English-language observational studies and RCTs addressing the PICO questions of interest. If existing systematic reviews addressing the PICO questions were available, these searches and reviews were updated to include the latest evidence (12–14). The two methodologists screened all potential citations identified by the search independently in duplicate to identify all relevant studies to include in the quantitative evidence summaries.

Evidence Summary and Critical Appraisal of Included Studies

The methodologists extracted data and imported them into RevMan version 5.3 software (Cochrane) for meta-analysis. We used DerSimonian and Laird random-effects models to conduct all meta-analyses (15). Study weights were generated using the inverse-variance method. We present results of all analyses using relative risks (RRs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes, both with 95% confidence intervals (CIs). We assessed risk of bias (RoB) independently and in duplicate for each outcome of individual studies using the Cochrane RoB tool that classifies RoB as "low," "high," or "unclear" for each of the following domains: sequence generation, allocation sequence concealment, blinding, selective outcome reporting, and other bias. We rated the overall RoB as the highest risk attributed to any criterion.

With input from the panel chairs, the methodologists developed an evidence profile for each PICO. Following GRADE principles, the certainty of evidence for each outcome was judged to be "high," "moderate," "low," or "very low." In accordance with GRADE, the certainty of evidence for each outcome was originally set as high if it originated from RCTs and low if it originated from observational data. We subsequently downgraded the quality of the evidence by one or two degrees if results from individual studies had a serious or very serious RoB (16), there were serious inconsistencies in the results across studies (17), the evidence was indirect (18), the data were imprecise (19), or publication bias was believed to be likely.

Generation of Clinical Recommendations for PICO Questions

The direction and strength of recommendations was decided by consensus at an in-person panel meeting. With the assistance of the methodologists, the chairs led the panel in developing recommendations for each PICO question by working through the GRADE Evidence-to-Decision (EtD) framework, which considers the quality of evidence, balance of desirable and undesirable effects, assumptions of patient values and preferences, resource use, health equity, acceptability of an intervention, and feasibility of implementation (20, 21). For question 2 (obstructive sleep apnea [OSA] screening), we used the GRADE EtD framework for diagnostic tests (22). Following GRADE guidance, each recommendation was designated as "strong" or "conditional," using the phrasing "we recommend" for strong recommendations and "we suggest" for conditional recommendations (23).

Manuscript Preparation

After the generation of recommendations, the panel divided up into working groups for manuscript preparation. For each PICO question, we summarized the recommendation, provided a narrative summary of the evidence (highlighting the largest and most relevant clinical trials for each PICO question), discussed issues raised as part of the EtD framework, and provided a justification for the final recommendation considering the above, together with implementation considerations and future research directions. Each PICO summary was reviewed by the individual working

group and then synthesized by the chairs and methodologists.

Editing and feedback on the manuscript were conducted electronically and were coordinated by the panel chairs. The final wording of all recommendations and justifications was agreed on by the entire panel and submitted to ATS for review and approval. The guideline underwent anonymous peer review by content experts and a methodologist. After multiple cycles of review and revision, the guideline was reviewed and approved by a multidisciplinary board of directors.

How to Use These Guidelines

Patient preferences, available resources, technical expertise, and clinical circumstances vary widely across clinical practice settings. Thus, alongside each recommendation, we also summarize evidence limitations, panel judgments made when moving from evidence to decisions, subgroup considerations, and implementation concerns. These summaries will allow patients, clinicians, policy makers, and other healthcare stakeholders to make rational, evidence-based decisions with regard to the use of long-term NIV in COPD, which are relevant to their local setting. In Table 1, we provide a high-level summary of how these guidelines can be applied (24, 25). For additional information, including the complete evidence summaries and EtD frameworks, *see* the online supplement. The guideline will be reviewed by the ATS 3 years after publication, and whether an update is necessary will be determined.

For evidence summaries (including forest plots from meta-analyses) and EtD tables for each PICO question, *see* the online supplement.

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).

Background. Currently, COPD has been diagnosed in over 15 million adults in the United States. The most severe of these have hypercapnia, which has been associated with increased dyspnea, decreased QOL, more frequent hospitalizations, and increased mortality (26, 27). Despite progress in the treatment of symptoms and prevention of acute exacerbations, few advances have been made to ameliorate disease progression or reduce mortality in this population. Since the development of positive-pressure NIV, there has been interest in its use for the treatment of patients with COPD and hypercapnia. However, clinical heterogeneity and variability in NIV protocols employed in available studies have led to a lack of consensus, variable practice, and no clear direction related to its use in this population with COPD.

Summary of the evidence. Thirteen RCTs from the search were included in the analysis for this question. Follow-up for these trials ranged 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 (28, 29), and in one study, not all patients received oxygen therapy in the control arm (9).

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 (RR, 0.86; 95% CI, 0.58 to 1.27; low certainty). Patients receiving NIV had a decrease in hospitalizations (MD, 1.26 fewer; 95% CI, 2.59 fewer to 0.08 more hospitalizations; low certainty), improved QOL (standard MD [SMD], 0.48; 95% CI, 0.09 to 0.88; low certainty) and improvement in dyspnea (SMD, −0.51; 95% CI, −0.95 to −0.06; moderate certainty) compared with standard of care.

Improvements in awake gas exchange favored NIV, although the magnitude of

Table 1. Application of Guideline Recommendations for Different Stakeholders

	Strong Recommendation = We Recommend	Conditional Recommendation = We Suggest
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices are likely to be appropriate for different patients and therapy should be tailored to the individual patient's circumstances. Those circumstances may include the patient's or family's values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations, including for use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

These guidelines were created using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) Working Group criteria (24).

effect was small and of questionable clinical importance. The use of NIV reduced awake Pa_{CO_2} (MD, 3.49 mm Hg lower; 95% CI, 1.3–5.67 mm Hg lower; moderate certainty) compared with standard care; however, this effect varied greatly across the studies. In one study, a mean rise of 7.3 mm Hg was noted (30), whereas in another, the mean Pa_{CO_2} with NIV fell by 18 mm Hg compared with standard care (31). Use of NIV increased awake Pa_{O_2} (MD, 3.1 mm Hg; 95% CI, 1.45–4.74; moderate certainty).

No significant difference in lung function as measured by FEV_1 was seen between NIV and standard care (FEV_1: SMD, 0.07; 95% CI, −0.14 to 0.27; FVC: SMD, 0.10; 95% CI, −0.06 to 0.26; both low certainty). There was also no difference in sleep efficiency between NIV and standard care (low certainty), although sleep questionnaires rather than objective measures (i.e., PSG) were used to rate sleep quality. The 6MWD was higher with NIV (MD, 32 m; 95% CI, 10.8–53.3 m; moderate certainty).

Four studies provided data around adverse events associated with NIV compared with usual care. One study (32) reported an increase in discomfort and skin breakdown with NIV, whereas two studies (9, 33) reported skin rashes associated with the NIV mask. Overall, 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. Desirable effects of NIV included possible reductions in mortality and hospital admissions, improved QOL, reduced dyspnea, and improvements in functional capacity, awake blood gases, and 6MWD. The use of NIV appeared to have little impact on subjective sleep quality, and the harms reported were generally minor and related to the interface. However, the panel acknowledged that the amount of certainty around these outcomes is low because of RoB from lack of blinding and imprecision. Nevertheless, 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. These benefits would likely outweigh the inconveniences of using a mask overnight. However, it was recognized that attention to mask fit and comfort is paramount to minimize harms.

The severity of baseline hypercapnia and lung disease, mode of ventilation, and pressure settings used varied considerably among studies. In addition, management of the control groups also differed with respect to the use of oxygen therapy and whether the comparator included exercise training or not. This clinical heterogeneity may have contributed to the imprecision of the data.

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 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 and expertise to provide such intensive follow-up, even in the short term, which might be important to achieving high adherence and, thus, 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 (34). 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. The panel identified many areas for future investigation related to this question. 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 (although we have attempted to address these with other PICO questions) regarding how exactly (mode, settings, monitoring, and 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 OSA before initiation of long-term NIV (conditional recommendation, very low certainty).

Background. Among the populations with COPD, COPD–OSA prevalence estimates vary widely, from 0.5% in individuals with generally mild COPD (SHHS [Sleep Heart Health Study]) to 39% in a U.S. veteran population (again, with milder disease) and up to 65% in a pulmonary rehabilitation population with moderate COPD and some severe COPD (mean FEV_1, 42%; 39% on long-term oxygen therapy) Thus, in particular, the true prevalence of COPD–OSA is not known in those with severe COPD (i.e., those most likely to qualify for NIV) (35–37). Alternatively, in one recent single-center trial of those initiating NIV, home polygraphy (which might underestimate OSA severity) found only about 5% of subjects to have an

apnea–hypopnea index > 15/h (38). Flenley (39) has considered "the overlap syndrome" to have important clinical and therapeutic implications, which were different from the presentation and management of each underlying disorder. Indeed, several studies have shown that those with COPD and OSA have more profound nocturnal oxygen desaturations and sleep disturbances compared with those with either disease alone (35). Thus, we aimed to compare the effect of an OSA screening strategy versus no OSA screening strategy on proposed outcomes in patients with stable hypercapnic COPD.

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 (40–44). We did find ongoing trials evaluating the treatment of OSA–COPD overlap syndrome, including those examining the use of CPAP (clinicaltrials.gov identifier NCT 03647462), NIV (clinicaltrials.gov identifiers NCT 03184714 and NCT 02363413), and CPAP versus NIV (clinicaltrials.gov identifier NCT 03766542); however, these results were not reported in time for inclusion in this guideline.

No trials comparing an OSA screening strategy with 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 (BMI), thus precluding subgroup analysis. Therefore, the panel chose to proceed with a GRADE-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 (45).

Two studies have evaluated the diagnostic accuracy of OSA screening tools in patients with COPD (46, 47). 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. These pooled estimates of screening test characteristics were adapted from Chiu and colleagues (48), who used a random-effects bivariate analysis (49) including 108 studies and a total of 47,989 participants with suspected OSA. The panel recognized that test accuracy may vary in the population with COPD, particularly in patients with comorbidities such as congestive heart failure, who often report less daytime sleepiness (50). As the reported prevalence of OSA in patients with COPD varies, we evaluated the accuracy of screening tests across the low (10%), middle (30%), and high (60%) prevalences described in the literature (36, 51). As accurate identification of severe OSA (apnea–hypopnea index > 30 events/h) was identified by the panel as the clinical priority, the data below represent the screening characteristics for detecting severe OSA, with an estimated overall 10% prevalence. The overall certainty of test accuracy was judged to be low because of heterogeneity and indirectness, as the screening tests have not been extensively validated in people with COPD.

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 (ESS; less sensitive and not specific). Assuming a prevalence of severe OSA of 10%, application of these screening tools to 100 people with COPD would yield the following:

The SBQ would yield a pooled sensitivity of 0.93 (95% CI, 0.89–0.95) and a pooled specificity of 0.35 (95% CI, 0.28–0.44; low certainty) and would result in 9 true-positive screen results, 1 false-negative screen result, 32 true-negative screen results, and 58 false-positive screen results.

The ESS would yield a pooled sensitivity of 0.58 (95% CI, 0.48–0.67; low certainty) and a pooled specificity of 0.60 (95% CI, 0.53–0.68) and would result in 6 true-positive, 4 false-negative, 54 true-negative, and 36 false-positive screen results.

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. This would also occur in the absence of screening. 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 (vs. a less-burdensome home sleep study).

The panel made this suggestion on the basis of the anticipated benefits of successfully identifying patients with severe OSA, as this may result in optimal management of their respiratory disease, including choice of CPAP versus NIV, better titration of EPAP, and weaning or discontinuation of inhalers if it is recognized that OSA and obesity hypoventilation syndrome contribute to hypercapnia and are treated. Use of a sensitive test such as the SBQ will pick up most of these patients (9 out of 10 per 100 patients) and may result in improved management. On the other hand, the high number of patients with false-positive results (58 out of 90 per 100 patients) 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, as described above.

Use of a specific screening instrument such as ESS would also result in false-positive test results (36 of 90 patients) but would miss nearly half of the patients with severe OSA who would benefit from having properly diagnosed OSA (6 of 10). 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 outweigh the harms in a population with a severe OSA prevalence around 10%. Patients with COPD and overweight (BMI $\geq$ 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 (47).

Although this recommendation may also apply to sensitive OSA screening questionnaires other than the SBQ, it should be noted that less sensitive and more specific screening tests have differing test characteristics, and the desirable and undesirable consequences of using these tests may differ from those used in the panel's deliberations. In particular, screening tests with high specificity and lower sensitivity (such as the ESS) may not perform well in patients with COPD (47). Similarly, this recommendation would not apply in settings where the prevalence of OSA in patients with COPD is either extremely high or extremely low.

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 most likely to benefit from screening and management of overlap syndrome; phenotypes of sleep changes in overlap syndrome (e.g., apneas vs. hypopneas) and whether or not these phenotypes require different management strategies; and the natural history of overlap syndrome, as it is currently unclear how it differs from OSA or COPD alone.

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).

Background. COPD exacerbations are a key cause of morbidity and mortality and place a considerable burden on healthcare systems. Unfortunately, patients often do not recover to the baseline amount of lung function or degree of symptoms, and COPD exacerbations are therefore an important contributor to worse outcomes, including lung-function decline, poorer QOL, and increased risk of death (52, 53). After discharge, 60–80% of the patients are readmitted within 1 year, and 30–49% die within this first year after their hospital admission for an acute COPD exacerbation (54). These disappointing outcomes raised the question of whether long-term NIV should be provided to patients admitted to the hospital with an exacerbation of COPD.

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 (RR, 0.92; 95% CI, 0.67 to 1.25; low certainty), exacerbations (MD, 0.3 fewer; 95% CI, 1.17 fewer to 0.57 more; low certainty), the need for hospitalization (RR, 0.61; 95% CI, 0.30 to 1.24; very low certainty), changes in dyspnea (MD, 0.8 points lower; 95% CI, 2.17 points lower to 0.58 points higher; low certainty), QOL (MD, 2.89 points higher; 95% CI, 1.03 points lower to 6.8 points higher; low certainty), or exercise tolerance measured with 6MWD (MD, 8.64 m lower; 95% CI, 209 m lower to 192 m higher; very low certainty) when using NIV. There was a significant reduction in Pa_{CO_2} (MD, 3.41 mm Hg lower; 95% CI, 4.09 to 2.73 mm Hg lower; moderate certainty), but there was no improvement in Pa_{O_2} (MD, 1.53 mm Hg lower; 95% CI, 4.24 mm Hg lower to 1.17 mm Hg higher; very low certainty) or FEV_1 (SMD, 0.36 SD; 95% CI, -0.74 to 0.03; low certainty).

As this analysis was driven by two large RCTs, the RESCUE (Respiratory Support in COPD after Acute Exacerbation) trial (Struik and colleagues [55]) and the HOT-HMV (Home Oxygen Therapy–Home Mechanical Ventilation) trial (Murphy and colleagues [56]), 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).

HOT-HMV and RESCUE assessed QOL with general (health-related QOL) and respiratory-specific (Severe Respiratory Insufficiency Questionnaire, St. George's Respiratory Questionnaire [SGRQ]) assessment tools. In both the HOT-HMV and the RESCUE study, there was a minimal and temporary impact of NIV intervention on general QOL assessment. Similarly, there was no sustained impact on respiratory-specific QOL scores. The limited available data from these studies make a definitive conclusion regarding the impact of NIV on QOL metrics difficult to assess when initiated after a severe COPD exacerbation. The minimal impact of NIV in these studies may reflect prior observations that respiratory-specific health-related QOL questionnaires are driven so substantially by COPD factors (FEV_1 and exacerbations) that improvements in comorbid disease control (such as through interventions like NIV) may not be sufficient to impact respiratory-specific QOL outcomes. This is supported by other studies showing that comorbidities like congestive heart failure, diabetes mellitus, and venous thromboembolism do not contribute to SGRQ scores, and improving comorbidity control is therefore not expected to substantially impact SGRQ scores (57, 58). Moreover, additional multidisciplinary management after COPD exacerbation may influence the impact of NIV initiation on QOL metrics. It is also possible that the side effects or burdens of NIV offset potential improvements in QOL. The current data in this area limit meaningful conclusions on the impact of NIV on QOL outcomes after COPD exacerbations.

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. In fact, more recent data suggest that home initiation of NIV leads to similar outcomes yet is less costly (38). Given all of the above concerns, the panel made a conditional recommendation against 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.

Patients with known or suspected OSA were excluded from many of these studies and should be considered separately, as reviewed above in PICO question 2. These recommendations would not apply to those who remain persistently hypercapnic and cannot be "weaned" from NIV in the hospital. In such patients, in-hospital continuation and transition to long-term NIV may be required.

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 (59).

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).

Background. There is little guidance about how to initiate NIV in patients with COPD. Trials outside the United States sometimes adjust settings over time (e.g., 1–2 wk) while patients are hospitalized (8). Initiation in a sleep laboratory might allow for acclimatization to equipment and might provide additional education from sleep technicians. Conversely, PSG and real-time Pa_{CO_2} measurement tools constitute a limited resource in most settings.

Summary of the evidence. Two RCTs have examined the initiation of NIV using in-laboratory PSG titration versus an alternative method. Hannan and colleagues (60) predominantly included patients with neuromuscular disease being initiated on NIV using daytime titration followed by a sham PSG comparator. Patout and colleagues (61) examined patients with COPD and OSA, using a nurse-led titration protocol as the comparator, but there were only seven patients in each arm. The study by Hannan and colleagues (60) demonstrated no effect on mortality (RR, 0.32; 95% CI, 0.01 to −7.61), NIV asynchrony as measured by the patient–ventilator asynchrony index (MD, −15.3; 95% CI, −59 to 28 points), or adverse effects as measured with a sleep apnea QOL questionnaire (MD, 0.5; 95% CI, −1.75 to 2.8 points). Pooled data from both studies showed no difference in NIV adherence (−45 min; 95% CI, −202 to 112 min; very low certainty), QOL at 3 months

as measured with the Severe Respiratory Insufficiency Questionnaire (MD, 0.6 points higher with in-laboratory titration; 95% CI, −4.2 to 5.4 points; very low certainty), or Pa_{CO_2} amounts at 3 months (MD, 1.39 mm Hg; 95% CI, −4.3 to 7.1; very low certainty).

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 (62). 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 concentrations. 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 (63, 64). 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. The panel also noted that most NIV devices would provide information that might be used to titrate settings over time (e.g., residual apnea–hypopnea index) and that, increasingly, NIV devices incorporate algorithms for the automatic determination of EPAP (65, 66). 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. Alternatively, in-laboratory titration could be reserved for certain patients (e.g., those with known COPD–OSA overlap).

Duiverman and colleagues (38) recently published an RCT of home and telemedicine versus in-hospital initiation of NIV. They found no difference in CO_2 reduction or QOL at 6 months. Although there were differences in NIV settings early on, these differences were not statistically significant after 6 months, suggesting the feasibility (and need) to adjust settings over time. Finally, adherence was good in both groups but better in the home-initiation group.

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 and will likely need higher EPAP settings.

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).

Background. A variety of different approaches to NIV have been used over the years in studies of patients with hypercapnic COPD, including different equipment, ventilation modes and settings, and therapeutic targets (e.g., symptoms and patient adherence). Given that stable hypercapnia is characterized by persistent elevation in Pa_{CO_2}, one target for NIV has been adjustment of therapy on the basis of Pa_{CO_2}. More recently, several studies have used so-called high-intensity NIV, which refers to high inspiratory pressures as well as higher-than-baseline respiratory rates to reduce Pa_{CO_2} (7–9). However, the impact of normalization of Pa_{CO_2} is not known.

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 that have been studied to date 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 (low certainty) or adherence (low certainty).

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 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 and would include the possible need for hospital admission to titrate initial settings, increased follow-up clinic visits, and arterial or transcutaneous blood-gas testing, all of which are potentially not needed when using low-intensity NIV that does not target Pa_{CO_2} amounts. Overall, the marginal "cost" to stakeholders is probably small. 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 (67, 68) and slightly greater with high-intensity NIV in one study (7). 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), define the speed at which Pa_{CO_2} should be reduced, and determine whether benefits of NIV occur in all patients with COPD and hypercapnia or whether there are specific subgroups that benefit most. In addition, the relationship between nighttime Pa_{CO_2} and daytime Pa_{CO_2} should be further evaluated to determine which is a better target to direct titration. 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 (67) 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 (69). 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." As discussed above, we do suggest reassessment at 2–4 weeks before consideration of long-term therapy. Although the ERS task force considered various modes and settings for delivery of NIV, 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 (70) 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

Few interventions have been shown to improve morbidity and mortality in COPD. Thus, it is exciting to consider NIV as additional therapy for those with hypercapnic COPD. Nevertheless, 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 (71) 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 misdiagnosed in patients with overweight and obesity; clinicians need to be aware of alternate diagnoses such as obesity hypoventilation (72).

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 its initiation in research. For example, in the recent study by Duiverman and colleagues (38), 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 a 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 73). 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 (74). 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.

The strengths of the current work include an expert panel including leaders in the field, strict conflict-of-interest management, an *a priori* set of questions and outcome prioritization, librarian support, a comprehensive search of the literature, and application of GRADE to assess certainty in evidence and develop recommendations using the EtD process. Thus, the panel has gathered all relevant information to comment on patient- and provider-relevant outcomes. Although the panel did include patients with COPD when considering relevant outcomes, one limitation is that we could have included more patients or maintained involvement of patients throughout the guideline-development process. Other limitations relate to the paucity of direct data for some of our PICO questions and heterogeneity in pooled analyses, which ultimately led to low or very low certainty of evidence for many of our PICO questions. Finally, there are as yet few cost-effectiveness data, particularly in the United States, and this limited our ability to include these considerations in the recommendation deliberations with any degree of certainty.

Future Research

Specific research topics are reviewed for each PICO question above. As can be seen, there are a number of questions that will require several different approaches to answer. For example, studies of relatively short duration might be useful to compare modes and settings of ventilation. A modest number of longitudinal studies of those with acute exacerbation of COPD would be useful to help address gaps in knowledge regarding resolution versus persistence of elevated Pa_{CO_2}. However, larger and longer-duration studies will be needed to assess the efficacy of NIV both on hard outcomes and also on patient-centered metrics. A recurring theme was the need for more generalizable studies (i.e., less restrictive patient inclusion criteria, such as including concomitant OSA) and more real-world studies to better assess the impact of NIV distinct from the effects of frequent assessments and interactions with healthcare providers that take place during research.

Conclusions

On the basis of the evidence to date, we suggest long-term nocturnal NIV for chronic stable hypercapnic COPD. Research is needed to better determine the benefits and optimal management of such patients. Barriers to implementation will require attention from physicians as well as payors and other stakeholders. ■

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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patent 10,315,002 for a ventilator with integrated oxygen production and U.S. patent 10,245,406 for a ventilator with integrated oxygen production. B.C. served on an advisory committee for Chiesi, GlaxoSmithKline, Pulmonx, and Sanofi; as a consultant for AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Menarini, and Sanofi; and as a speaker for Novartis; and received research support from AstraZeneca. D.R.H. served on an advisory committee for Ventec Life Support; served as a consultant for Philips Respironics and Ventec Life Support; received author royalties from Jones and Bartlett, McGraw-Hill, and UpToDate; received other transfers of value from American Board of Internal Medicine Pulmonary Disease Board; and served as an editor-in-chief of Respiratory Care and as such is an employee of Daedalus Enterprises. J.A.O. served on an advisory committee for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Mylan, Sunovion, Theravance, and Verona; served as a consultant for Reckitt Benckiser; and served as a consultant for the following law firms: Beasley Allen, Garrison Law, Levy Konigsberg, and Wallace and Graham. J.E.O. received research support from an ATS Foundation/ResMed partnered grant. A.J.P. served as a speaker for Philips Respironics and ResMed; and received other transfers for value from Fisher and Paykel. N.M.P. received research support from ResMed. P.J.W. served as consultant for Air Liquide; received research support from Goedegebuure, Philips Respironics, ResMed, Vital Air, and VIVISOL; and received personal fees from Philips Respironics and ResMed. M.M., J.M.C., S.L.K., S.O., S.R., B.R., and S.Y.-Y. reported no relationships with relevant commercial interests.

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