

Non-invasive ventilation in amyotrophic lateral sclerosis

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Abstract: Non-invasive ventilation (NIV) has become an important cornerstone of symptomatic treatment in amyotrophic lateral sclerosis (ALS), improving survival and quality of life. In this review, we summarize the most important recent developments and insights, including evidence of efficacy, indication criteria and time of initiation, ventilation parameters and adaptation strategies, treatment of complicating factors, transition from NIV to invasive ventilation, termination of NIV and end-of-life management. Recent publications have questioned former conventions and guideline recommendations, especially with regard to timing and prognostic factors; therefore, a fresh look and re-evaluation of current evidence is needed.

Keywords: amyotrophic lateral sclerosis, motor neuron diseases, non-invasive ventilation

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Introduction

Amyotrophic lateral sclerosis (ALS) is characterized by degeneration of upper and lower motor neurons, leading to progressive paresis of all voluntarily innervated muscles and therefore affecting mobility, communication, swallowing, and breathing. Death occurs after a mean survival of 2–5 years,¹ usually due to respiratory failure.

Affected respiratory muscles include most notably the diaphragm, but also auxiliary respiratory muscles of the thorax and abdomen, as well as bulbar muscles which support the upper airways. Respiratory insufficiency develops slowly and leads to increased carbon dioxide partial pressure (pCO₂) in the blood; usually, first, at night during sleep; later, during the day as well. Hypercapnia causes compromising clinical symptoms such as sleep disturbances, daytime fatigue, cognitive impairment, and depression. In later stages, dyspnea and orthopnea may appear.

Non-invasive ventilation (NIV) refers to the administration of ventilatory support through the upper airways without using invasive artificial airways like endotracheal tubes or tracheostomy. It is performed using a compact breathing device with a nasal or full-face mask. It is easy to handle

and can be used at home, initially usually at night. Because of its flexible and non-invasive nature, it is usually well accepted by patients and carers. NIV uses room air, since administration of pure oxygen reduces the respiratory drive in patients with neuromuscular diseases and therefore might induce carbon dioxide narcosis.

The aim of NIV is to compensate diaphragm weakness, alleviate hypercapnic symptoms and improve patients' general condition and quality of life. Since respiratory insufficiency limits survival, NIV also prolongs life considerably in ALS. In view of its non-invasiveness and good tolerability, NIV is regarded as an essential therapeutic component in ALS.

In this review, we aim at providing a comprehensive and up-to-date summary of the current evidence of all NIV-related issues in ALS, including evidence of efficacy, indication criteria, ventilation parameters, treatment of complicating factors, and termination of NIV. In order to provide reliable recommendations, we performed an extensive literature search of all available medical reference systems, including MEDLINE (since January 1966), Cochrane Central/Cochrane Neuromuscular Disease Group Specialized

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Register, Cochrane Library, EMBASE (since January 1980), AMED (since January 1985), CINAHL plus (since January 1938), LILACS (since January 1982), OVID HealthSTAR (since January 1975), ClinicalTrials.gov (since January 1997), and International Clinical Trials Search Portal (since November 2004). We considered all clinical trials up to the date of our last search (1 May 2019) addressing the issue of NIV therapy in ALS without any further limitation, but focused on randomized controlled trials (RCTs) and recent studies within the last 5 years that affect current guideline recommendations. In this context, we also reviewed international guidelines including the European Federation of Neurological Societies (EFNS), the American Academy of Neurology, the German Society of Neurology (Deutsche Gesellschaft für Neurologie), and the UK National Institute for Health and Care Excellence (NICE). In case of lack of evidence, we gave recommendations based on our own experience.

Effects on survival and quality of life

NIV has been shown to prolong survival and improve quality of life in ALS. Since genuine placebo-controlled studies are ethically problematic today, evidence largely relies on RCTs performed more than 10 years ago. A pivotal study in 2006 by Bourke *et al.* showed that survival of patients with NIV was prolonged by 7 months in patients without severe bulbar symptoms.² However, the comparatively low number of subjects ($n = 41$) and lack of blinding have to be considered a limitation of the study as pointed out in a recent Cochrane Review that identified the abovementioned study as the only relevant RCT.³ Also, as diagnostic, technical, and healthcare conditions for ventilated patients have improved significantly over the last 12 years, it can be hypothesized that the benefit might be larger today. Accordingly, more recent retrospective studies with larger numbers of patients ($n = 929$, $n = 114$, $n = 140$) found survival benefits of 13 months,⁴ 11 months,⁵ and 15.5 months,⁶ respectively. In these studies, patients who refused NIV were taken as the control group. It has also been shown that NIV delays deterioration of respiratory function.⁷

Bourke and colleagues also found that quality of life, as measured by a general and a sleep-dependent scale, improved in patients with NIV.² The positive effect on blood-gas parameters, quality of

life, and hypercapnia-associated symptoms was reproduced convincingly in several subsequent studies. Polysomnographic studies showed an improvement of oxygen saturation, $p\text{CO}_2$, and apnea-hypopnea-index,^{8,9} leading to reduced daytime fatigue and depression,¹⁰ as well as improved sleep and quality of life.^{9,11} Patients may notice improvements already after the first night of NIV usage,⁸ and continued therapy promises long-lasting positive effects over several months,^{10,12} although they weaken over time.¹³

Importantly, while Bourke *et al.* found improvement of sleep-related quality of life in all patients, they failed to demonstrate a life-prolonging effect in patients with pronounced bulbar involvement.² Although it is unanimously accepted that NIV therapy is more complicated in bulbar patients due to hypersalivation and other aggravating factors (see below), more recent studies have shown that bulbar patients might have a prolonged survival as well.⁴

Indication criteria and timing of NIV initiation

It is generally accepted that NIV should be applied at the latest, when clinical symptoms of respiratory insufficiency are evident. However, recent studies investigated whether initiation of NIV at an earlier stage of the disease might result in greater benefits. In this context, a great variety of additional diagnostic measures such as forced vital capacity (FVC), slow vital capacity (SVC), sniff nasal inspiratory pressure (SNIP), peak cough flow (PCF), maximum inspiratory (MIP) and expiratory pressure (MEP), invasive arterial-blood-gas analysis, non-invasive oximetry, capnometry, and phrenic nerve conduction¹⁴ were suggested to improve diagnosis of early respiratory decline. A recent survey among 186 ALS specialists¹⁵ showed that FVC was the most important parameter for US practitioners to decide whether NIV was indicated, while European physicians considered the occurrence of orthopnea and dyspnea as most important. Accordingly, a recent French study showed that 90% of patients were symptomatic at NIV initiation.¹⁶ In the US, NIV prescription is also heavily influenced by insurance and financial constraints.¹⁵

The advantages of spirometric parameters are that they are easy to apply and correlate well with clinical decline in ALS.¹⁷ FVC and SVC

correlate strongly and decline similarly during disease progression.¹⁸ However, when FVC or SVC are used as the main indication criterion for NIV, one must keep in mind that results of bulbar patients who lack facial strength can be inaccurate when a mouthpiece is used.¹⁹ Also, FVC and SVC are late markers of respiratory decline and may be normal, although nocturnal hypoventilation is already present.²⁰ Recently, the measurement of diaphragm compound muscle action potential (CMAP) to phrenic nerve stimulation has been reported as a reliable method that is easy to apply. One study showed that CMAPs correlated with other respiratory parameters and were a sensitive marker of respiratory function.²¹

The EFNS guidelines recommend initiating NIV when at least one respiratory clinical symptom or one of the following criteria is present: FVC < 80%, SNIP < 40 cm H₂O, significant nocturnal desaturation, or pCO₂ > 45 mmHg (morning blood-gas measurements). However, a recent placebo-controlled study in 54 patients showed that patients with earlier NIV initiation (FVC > 80%) showed a slower subsequent decline of FVC compared with placebo.²² In this study, the patients of the placebo group received ventilation with a very low inspiratory pressure of 3 cm H₂O. Similarly, a very recent retrospective study in 194 patients found an improved survival for patients with early NIV initiation.²³

Therefore, it can be concluded that the proposed EFNS criteria, which were based on expert opinions rather than evidence, might not describe the optimal timing. Although recent studies suggest an earlier NIV initiation, they still do not provide an optimal time frame defined by diagnostic measures; therefore, additional clinical trials are needed to address these issues. Taking into account recent findings, it seems advisable to initiate NIV as soon as any abnormalities in respiratory diagnostics are evident. In our own experience and as suggested by several studies, nightly capnometry²⁴ or polygraphy²⁵ may serve as very sensitive diagnostic tools for detecting early respiratory decline. However, the potential issue of lacking compliance and adherence to NIV in asymptomatic patients must be considered and should be investigated in future studies.

Regarding respiratory monitoring before, as well as after, NIV adaptation, the EFNS guidelines

recommend using FVC on a regular basis, as it is easy to apply and universally available,²⁶ while SNIP is recommended for bulbar patients. The NICE guidelines recommend that a healthcare professional with appropriate competencies should perform respiratory function tests (oxygen saturation, FVC, and SNIP/MIP) every 2–3 months and arterial-blood-gas analysis in case of desaturation. In case of sleep-related respiratory symptoms, a nocturnal oximetry or limited sleep study is advocated.

In our own experience, a thorough anamnesis regarding respiratory symptoms already offers quite reliable information about the respiratory status and whether additional diagnostic measures are needed. We recommend conducting a nocturnal capnometry in case of potential hypercapnia-associated symptoms. Additionally, oxygen saturation, FVC, and SNIP/MIP may serve as screening and monitoring tests which are easy to apply in an outpatient setting about every 3 months. Additional diagnostic measures at home rarely add any relevant information and are not routinely done.

NIV adaptation

Ventilation masks

The important question about which masks should be used has been completely neglected in clinical studies so far. Nasal masks can be problematic in bulbar patients, since ventilation air might escape due to incomplete closure of the mouth, especially at night during sleep. On the other hand, nasal masks are generally better tolerated and allow easier communication compared with full-face masks covering mouth and nose. Both types of mask can lead to facial pressure ulcers, which may limit their application, and necessitate the use of total full-face masks that cover the whole face but have the disadvantage of greater dead space and leakage. One study showed that facial pressure ulcers cannot be prevented by protective patches.²⁷ In patients with functioning mouth muscles, daytime mouthpiece ventilation may be beneficial due to the reduced risk of facial pressure ulcers as well as enhanced speech and swallowing.²⁸

Evidence regarding the efficacy of different masks for NIV in ALS is completely missing. In our own experience, a combination of full-face-mask ventilation during the night and nasal-mask

ventilation during the day offers an acceptable approach for most patients; however, blood-gas parameters should be controlled in regular intervals, since nasal-mask ventilation during the day might be insufficient in later stages of the disease.

Ventilation parameters

Few studies so far have investigated the effect of different ventilation modes and parameters on blood gases, clinical symptoms, and survival. Ventilation parameters should be comfortable for the patient to ensure an acceptable quality of life, as well as sufficient compliance. At the same time, they should mimic physiological breathing. In our experience, stepwise adaptation of pressure values, breathing rate, and other parameters, according to the continuous feedback of the patient about his or her breathing comfort, is advisable. One study found no effect of pressure- versus volume-controlled ventilation on survival.²⁹ Assisted pressure-controlled ventilation (aPCV) is most commonly used in clinical practice, which forces a controlled breathing rhythm, but allows the patient to trigger additional breaths at any time. In addition, modern ventilation devices allow the definition of a target tidal volume and automatically adapt the inspiratory pressure accordingly within a predefined range. The defined target tidal volume should be chosen according to physiological values which equal 400–600 ml in most patients (corresponding to 8 ml/kg body weight). Tidal volumes and required inspiratory pressures usually provide a reliable overview about the ventilatory situation of each patient, although ventilation devices may display inaccurate data.³⁰

In contrast to obstructive lung diseases, ALS patients do not usually require high inspiratory pressures, nor positive end expiratory pressure (PEEP). The only study investigating the effect of PEEP in 25 ALS patients found that a PEEP of 4 cm H₂O was associated with a worse quality of sleep compared with 0 cm H₂O.³¹ Although evidence is generally low, it can be concluded that PEEP should be avoided when possible, although it might be necessary in the case of pneumonia or other pulmonary complications.

Since respiratory function declines over time, blood-gas parameters should be checked regularly, and ventilation parameters must be adapted accordingly. It has been shown that adapting NIV

parameters may reduce nocturnal desaturations, obstructive events, and improve prognosis.^{32,33}

Duration of NIV usage

So far, there are no studies investigating how often and how long NIV should be used in the early stages of respiratory insufficiency. In clinical practice, ventilation times are based upon individual needs, clinical symptoms, and diagnostic parameters, as described above. In our experience and according to the NICE guidelines, short phases of ventilation during the day under supervision of a specialized physician or therapist in hospital may help the patient to get used to the unfamiliar situation. However, recently, it has been shown that NIV can potentially be successfully adapted in a specialized outpatient setting as well.³⁴

Since early intermittent hypercapnia usually first occurs at night, the establishment of a night-time ventilation is generally regarded as a reasonable therapeutic objective in early stages of respiratory insufficiency. However, complicating factors such as hypersalivation, cognitive deficits, or panic attacks may prevent extensive ventilation times, especially in oligosymptomatic patients who do not feel the need of ventilation. In this context, it is crucial to inform the patient in detail about the long-term benefits of early NIV as outlined above, as well as establishing an optimal symptomatic treatment of NIV-impeding factors. In later stages of the disease, ventilation times naturally increase due to clinical worsening to the point of 24 h ventilation.³⁵ Regular monitoring of clinical symptoms and blood gases may help estimate whether current ventilation times are sufficient or if the patient should be advised to increase NIV usage.

Context factors

Neurobehavioral and cognitive symptoms

Although motor symptoms dominate the clinical picture, ALS is a multisystem degeneration, and nonmotor symptoms like cognitive impairment, psychiatric disorders, extrapyramidal, sensory, and autonomic symptoms are increasingly recognized.³⁶ The pathogenetic and clinical overlap between ALS and frontotemporal dementia (FTD) has been firmly established since the discovery of p-TDP43 in 2006.³⁷ Although only 5–10% of ALS patients develop frontotemporal dementia,³⁸ about 30% of patients show

neurobehavioral and cognitive abnormalities resembling FTD but do not fulfill diagnostic criteria.³⁹ Importantly, a recent study has shown that such deficits do not significantly influence the patients' decisions regarding life-prolonging measures.⁴⁰

However, although they still might benefit from NIV, it has been shown that patients with severe neurobehavioral abnormalities have reduced compliance and survival.^{41,42} NIV adaption in these patients is time consuming and requires a specialized multidisciplinary team; in some cases of advanced FTD it might not be possible at all. Since there is no effective treatment of frontotemporal deficits and since severe behavioral or cognitive deficits interfere with NIV adaptation and tolerance, it can be hypothesized that NIV in such patients should generally be applied as early as possible.

Some patients are prone to panic attacks under mask ventilation which can be treated with small amounts of opioids or benzodiazepines. The EFNS guidelines suggest treating anxiety with sublingual lorazepam or tablets in a dosage of 0.5 mg two or three times daily.²⁶ Since opioids and benzodiazepines may reduce a patient's respiratory drive, they should be applied with care. On the other hand, they may help to improve NIV tolerance and efficacy; therefore, the positive long-term effects generally outweigh the short-term concerns in our experience. Information about the functionality of the device, as well as the presence of a family member, a therapist, or physician may be helpful during the acclimatization phase.

Hypersalivation

Hypersalivation hinders mask ventilation, reduces compliance⁶ and worsens prognosis after NIV initiation.^{43,44} Although the pilot study by Bourke and colleagues could not prove a survival benefit of NIV for patients with severe bulbar involvement,² more recent studies contradict this early result.⁹ Regarding the diverging results, optimal treatment of NIV limiting symptoms in bulbar patients appears to be a crucial aspect, and it has been shown that such patients particularly benefit from a specialized multidisciplinary setting in hospital.⁴⁵

The level of evidence regarding symptomatic treatment of sialorrhea in ALS is generally low.

The EFNS guidelines recommend amitriptyline, oral or transdermal hyoscine, or sublingual atropine drops, while the NICE guidelines additionally mention glycopyrrolate, especially for patients with cognitive impairment, because of fewer central nervous side effects. Injection of botulinum toxin B in the parotid and submandibular glands has been shown to improve hypersalivation in about 80% of patients⁴⁶ and is usually applied when patients do not respond sufficiently to anticholinergic drugs. In our experience, NIV tolerance can be increased considerably in patients with hypersalivation when all available measures are considered.

Some authors recommend radiation therapy of salivary glands⁴⁷ in patients who do not respond sufficiently to medicamentous treatment, but randomized controlled studies are missing.

Viscous bronchial secretions

Thin saliva has to be distinguished from viscous bronchial secretions that affect patients with weakened coughing and may lead to panic attacks and suffocation sensations under NIV. The EFNS and NICE guidelines recommend nebulizers with saline, anticholinergic bronchodilators, or furosemide,²⁶ as well as humidification of room and ventilation air in order to reduce or dilute the mucus. Other treatment options include mucolytics like N-acetylcysteine and beta-receptor antagonists like propranolol. However, the level of evidence for mucolytic drugs is generally low, and such agents may be even harmful in patients who cannot effectively eliminate secretions. Therefore, in our experience, mucolytics should only be used in combination with mechanical insufflation–exsufflation (MI-E; ‘cough-assist’) devices.

Such devices have been shown to improve respiratory outcome parameters in ALS,^{48,49} while the addition of high-frequency oscillation does not yield any additional benefit.⁵⁰ Bulbar patients may not generate effective PCF levels under MI-E due to collapse of the upper airways during exsufflation.⁵¹ One small randomized controlled study in 40 patients found no differences regarding incidence of chest infections, quality of life, and survival between MI-E and application of a breath-stacking technique using a lung-volume recruitment bag,⁵² suggesting the latter as a low-cost alternative. MI-E may be combined with

physiotherapeutic expiration and inspiration maneuvers, such as manually assisted cough or air stacking. Several studies have shown that PCF can be improved by these measures.^{53,54}

In our experience, cough-assist devices should be used in patients with severe, tenacious secretions in order to free the upper airways before each ventilation session. This way, it is possible to increase the ventilation comfort and to extend ventilation times. Furthermore, in our experience, early education of patients and caregivers regarding airway-clearing techniques has positive effects.

Sleep apnea

Although it has been neglected in the literature for many years, sleep apnea is a common phenomenon in ALS and an important context factor of ventilation. A recent retrospective study in 250 nonventilated ALS patients found an incidence of sleep apnea of 45.6%, often combined with nocturnal hypercapnia, especially in male patients.⁵⁵ Although the pathophysiological background has not been completely understood, it is hypothesized that weakened laryngeal and pharyngeal muscles collapse and obstruct the upper airways. Recently, in a retrospective study of 179 patients, it has been shown that such obstructive events can lead to insufficient nocturnal ventilation, even under NIV, as reflected by recurring desaturations, and that patients with obstructive events have a shorter survival.³³ In that study, obstructive events were partly induced by NIV use. Accordingly, another retrospective study in a smaller group of patients found that an increased apnea/hypopnea index was associated with worse prognosis.⁵⁶

The findings above highlight the importance of detecting sleep apnea in ALS by appropriate diagnostic measures. Anamnesis, nocturnal capnometry and oximetry, morning blood gases, and SNIP⁵⁷ are diagnostic tools that are easy to apply and may point to sleep apnea and trigger further polygraphic diagnostics.

Although prospective studies are absent, current evidence suggests intensifying NIV at night in case of sleep apnea and modification of ventilation parameters to prevent upper airway obstruction. In asymptomatic ALS patients with sleep apnea and without NIV, initiation of NIV seems

justified, based on existing literature. In our experience, continuous positive airway pressure should be avoided because respiratory muscles may exhaust during further disease progression.

Percutaneous endoscopic gastrostomy and radiologically inserted gastrostomy

Because of progressive weight loss and risk of aspiration due to bulbar involvement, insertion of a percutaneous endoscopic gastrostomy (PEG) is a standard procedure in patients with ALS and may interfere with NIV adaptation. PEG insertion had formerly been regarded risky in patients with FVC < 50%,⁵⁸ and it has been shown that hypercapnia was associated with a worse prognosis after PEG placement.⁵⁹

However, recent studies have shown that PEG placement can be safely performed, even in patients with severe respiratory insufficiency.^{60–62} In this context, new mask systems have proven beneficial which feature openings for gastrostomy devices and allow PEG insertion under NIV.^{63,64} Therefore, intubation, which carries the risk that the patient cannot be extubated afterwards, can be avoided. One study showed that PEG was safe in high-risk patients who underwent insertion with reduced sedation and the option of nasal non-invasive ventilation in a semirecumbent position.⁶¹ Mechanically assisted coughing as described above has also been reported beneficial.⁶⁴ Those recent findings also imply that in patients with low FVC and indication for PEG, NIV should be adapted first, and PEG should be inserted later, after stabilization of the respiratory situation under NIV.

In recent years, radiologically inserted gastrostomy (RIG; also, percutaneous radiologic gastrostomy) has been identified as an alternative, well-tolerated method, which can also be executed using local anesthesia and NIV. A meta-analysis showed that both methods were equally safe.⁶⁵

Diaphragm pacing

Electrical diaphragm stimulation (diaphragm pacing system, DPS) refers to the endoscopic placement of several electrodes at branches of the phrenic nerve in the diaphragm, which was supposed to cause a training effect, delay atrophy of the diaphragm, as well as the need of NIV, and therefore prolong survival in ALS. Although supportive data have never been published, the

procedure was approved by the US Food and Drug Administration; since then, DPS has been applied to many ALS patients in the US and in Europe and has usually been combined with NIV.

However, in 2015, a British study showed that patients with NIV and DPS had shorter median survival [−11.5 months; 95% confidence interval 8.3–13.6 months] than patients with NIV alone.⁶⁶ Later, this result was confirmed by a French study which showed that DPS did not delay the need of NIV as compared with sham stimulation and was associated with shorter survival.⁶⁷ They also showed that >50% of patients suffered from serious adverse events related to the procedure. Therefore, DPS alone or in combination with NIV is not regarded as a valid therapy option in ALS anymore.

Complications

When adapted successfully, NIV is generally well tolerated, as it improves respiratory symptoms and quality of life as described above. Although systematic data are missing, it is generally assumed that NIV might lower the incidence of respiratory complications such as atelectasis and pneumonia due to an improved ventilation of the lung. However, respiratory complications may still occur and demand that NIV parameters and times of usage must be adapted until specific treatment measures take effect. For example, it might be necessary to increase inspiratory pressure or PEEP, or to prolong ventilation times in the case of pneumonia. In severe cases or if antibiotic treatment fails, the respiratory situation might no longer be compensated by NIV and invasive ventilation (IV) might need to be considered.

Termination of NIV

Although theoretically, NIV can be stopped at any time, it is rarely desired because the disease is chronically progressive, and NIV alleviates respiratory symptoms and improves quality of life. Therefore, termination of NIV is usually connected with either transition to IV (see transition to invasive ventilation) or palliative treatment and termination of life-prolonging measures (see end-of-life management).

Transition to invasive ventilation

There is no universally accepted guideline regarding indication criteria and the exact time when IV

should be considered. Because of its invasiveness and extreme demands of care, it is usually regarded as a late option for patients who can no longer be stabilized by NIV, or who do not tolerate it. However, in cases of severe bulbar involvement with massive secretion problems, IV may be considered earlier.

Survival can be prolonged considerably by IV,⁶⁸ which implies that patients experience far advanced stages of disease up to complete paralysis and locked-in syndrome. Many patients reject IV because they do not feel that quality of life is acceptable under such conditions. It has also been shown that patients who used NIV for more than 6 months were more likely to refuse tracheostomy.⁵

Decision making regarding life-prolonging measures in ALS is a continuous process, and patients' decisions may change over time. Patients' attitudes toward initiation and termination of life-prolonging measures also largely depend on cultural background.⁶⁹ In this context, it is very important that patients are informed in detail about the consequences of IV at a time when they are conscious and the respiratory situation is still stable because it has been shown that family members,⁷⁰ as well as inexperienced physicians,⁷¹ often underestimate quality of life of ALS patients and therefore cannot reliably estimate his or her own will. A recent study showed that the timing of end-of-life discussions varies greatly.³⁵

End-of-life management

Patients should be informed that death usually occurs peacefully as a result of carbon dioxide narcosis and that fear of suffocation is unfounded,⁵⁸ although dyspnea may occur if respiratory complications like pneumonia arise which may require hospitalization and appropriate treatment. Symptomatic treatment with opioids, benzodiazepines, and oxygen can sometimes be required to avoid or reduce dyspnea and anxiety.²⁶ Physicians experienced in palliative care are usually able to adequately manage the terminal phase of ALS in an outpatient setting. However, the option to be treated at home largely depends on the availability of adequate care facilities. During the terminal phase of the disease, NIV is usually continued in order to avoid situations of severe dyspnea.

Ventilation-dependent patients who decide to abruptly discontinue NIV or IV treatment should usually be diagnosed and treated in a hospital setting and should be supported by experienced specialists. Diagnostic procedures have to include diagnosis and differential diagnosis of depression that occurs independently from physical disability.⁷² In patients who do not tolerate ventilation-free intervals, continuous deep sedation is required.⁷³

An advance directive may help to avoid unwanted measures. It should be as specific as possible and include the patient's attitude toward NIV, IV, and PEG. Patients should be informed about the legal issues regarding withdrawal from life-prolonging measures, and assistance in formulating the advance directive should be offered.²⁶ If termination of IV is legal in the patient's country, the advance directive should include whether ventilation should be terminated under certain circumstances. Many patients define the state of complete locked-in syndrome with inability to move their eyes as the time to terminate life-prolonging measures.⁷³

Discussion and conclusion

It has been established for many years that NIV improves survival and quality of life for patients with ALS and respiratory insufficiency. Recent studies have broadened the spectrum of patients who might benefit from NIV, including patients with severe bulbar involvement. Furthermore, several studies suggest that NIV should be initiated earlier, as suggested by current guidelines, and that NIV can improve survival and respiratory decline even in asymptomatic patients with an FVC > 80%. In this context, the question, which diagnostics offer the highest sensitivity for detection of early respiratory insufficiency, is important. Recent studies using nocturnal capnometry and polygraphy have revealed that many patients even with normal FVC suffer from sleep disturbances related to recurrent oxygen desaturations and hypercapnia. In this context, the important role of sleep apnea in ALS has been increasingly recognized. These findings imply that respiratory diagnostics should be performed even in asymptomatic patients, and that NIV should be initiated as soon as early pathologic changes appear. Therefore, randomized controlled studies are needed.

Recent studies have also highlighted the importance of different context factors in terms of

successfully establishing NIV. Consequently, hypersalivation, as well as viscous bronchial secretions must be treated to facilitate effective ventilation. In this context, several recent studies have addressed the therapeutic option of MI-E. Although positive experiences are frequently reported, high-level evidence is still missing. The same applies to other symptomatic non-invasive therapies of hypersalivation and bronchial secretions in ALS.

NIV in patients with neurobehavioral abnormalities represents a challenge and should be performed in a specialized, multidisciplinary setting. Although it has been shown that such patients have a worse compliance and prognosis, current evidence does not allow the conclusion that NIV is not indicated in these cases.

It has been firmly established by several independent studies that PEG can be safely performed under NIV even in patients with severe respiratory insufficiency (FVC < 50%). In this situation, NIV should be established prior to PEG, and PEG placement should be performed under NIV, using special ventilation masks and minimal sedation. This is an important finding, since several textbooks and guidelines still mention FVC < 50% as a contraindicatory criterion. Recent studies suggest that RIG is an important, well-tolerated alternative to PEG.

A possible additional benefit of diaphragm pacing for respiratory-affected ALS patients with or without NIV has been refuted by two independent RCTs.

Evidence regarding optimal parameter settings, ventilation masks, and time intervals of NIV usage is still largely missing, and current practice largely relies on local expertise and experience as described above. The proper timing of transition from NIV to IV has been neglected by current literature so far. However, the importance of early and comprehensive patient information about life-prolonging measures and their implications, as well as the presence of a specialized multidisciplinary team is generally accepted.

Table 1 summarizes the most important guideline recommendations and the respective developments based on the most important studies within the last 5 years.

Table 1. Guideline recommendations and recent developments.

EFNS	AAN	NICE	Recent developments (level of evidence)
Initiation of NIV			
<p>Clinical signs or FVC < 80% or SNIP < 40 cm H₂O or MIP max < 60 mm H₂O or nocturnal desaturation or pCO₂ > 45 mmHg</p>	<p>Orthopnea or FVC < 50% or SNIP < 40 cm H₂O or MIP < -60 cm or nocturnal desaturation</p>	<p>FVC < 50% or FVC < 80% + orthopnea or SNIP/MIP < 40 cm H₂O or SNIP/MIP < 65 cm H₂O (men), < 40 cm H₂O (women) + orthopnea or SNIP/MIP - 10 cm H₂O over 3 months</p>	<p>Consider NIV in patients with FVC > 80% and in asymptomatic patients (Ib) Use of capnometry/polygraphy to detect early sleep disturbance (III): (1) nocturnal hypercapnia (2) nocturnal desaturation (3) sleep apnea</p>
NIV in patients with severe bulbar involvement and frontotemporal symptoms			
<p>Patients with bulbar palsy are less compliant with NIV, due in part to increased secretions NIV improves quality of life and prolongs survival in patients presenting with respiratory insufficiency, although this has not been confirmed in patients with bulbar-onset disease.</p>	<p>Bulbar involvement and executive dysfunction: possibly lower compliance with NIV Noncompliance was seen in 75% of patients with ALS and frontotemporal dysfunction No survival benefit was seen in patients with poor bulbar function</p>	<p>Before a decision is made on the use of NIV for a person with a diagnosis of FTD, the multidisciplinary team, together with the respiratory ventilation service, should carry out an assessment that includes the person's capacity to make decisions and to give consent, the severity of dementia and cognitive problems, whether the person is likely to accept treatment, whether the person is likely to achieve improvements in sleep-related symptoms or behavioral improvements, a discussion with the person's family or carers (with the person's consent if they have the capacity to give it)</p>	<p>Bulbar involvement possibly lowers compliance, but consequent symptomatic treatment of secretions can improve NIV acceptance (IV) Several retrospective studies with large numbers of subjects showed a survival benefit for bulbar patients (although less pronounced than in patients without bulbar involvement) (III) Neurobehavioral deficits in patients who do not fulfill the criteria for FTD do not significantly influence the patients' decisions regarding life-prolonging measures (III)</p>
Management of hypersalivation			
<p>Amitriptyline 10 mg 3 times a day Atropine drops 0.5–1% 3–4 × /d Glycopyrrolate Transdermal scopolamine 1.5 mg every third day Botulinum toxin A/B injected into salivary glands Irradiation of salivary glands</p>	<p>-</p>	<p>Advice on swallowing, diet, posture, positioning, oral care and suctioning Antimuscarinic medicine Glycopyrrolate Botulinum toxin A (second line)</p>	<p>-</p>
Management of tenacious bronchial secretions			
<p>N-acetylcysteine 200–400 mg/d* Beta-receptor antagonists + nebulizer (saline, anticholinergic bronchodilators, mucolytic, furosemide) Manual-assisted cough MI-E Portable home suction device Room humidifier</p>	<p>MI-E possibly effective HFCWO unproven</p>	<p>Humidification, nebulizers, carbocisteine* Manual-assisted cough Breath stacking Volume recruitment bag MI-E device</p>	<p>Growing evidence for MI-E, but still no high-class evidence studies (IV) HFCWO probably ineffective (IV)</p>

(Continued)

Table 1. (Continued)

EFNS	AAN	NICE	Recent developments (level of evidence)
PEG and respiratory function/NIV			
To minimize risks, PEG should be performed before vital capacity falls below 50% of predicted NIV during PEG procedure may be feasible in patients with respiratory impairment	FVC > 50%: low risk FVC 30–50%: moderate risk FVC < 30%: high risk The risk of PEG placement increased when the FVC declined below 50% of predicted	–	PEG insertion under NIV is safe, even in patients with FVC < 50% (III) Establish NIV prior to PEG, use NIV during PEG placement, use minimal sedation (IV)
Diaphragm pacing			
The use of diaphragmatic pacing or respiratory exercises in ALS is not established	–	–	Diaphragm pacing is contraindicated in ALS (Ib)
Indication criteria of IV/transition from NIV to IV			
Severe bulbar weakness or NIV intolerance or declines NIV: propose invasive mechanical ventilation IV has a major impact upon caregivers and should be initiated only after informed discussion Unplanned (emergency) IV should be avoided through an early discussion of end-of-life issues, coordination with palliative care teams and appropriate advance directives	NIV not tolerated: further education regarding documented benefits; evaluate reasons for noncompliance; reintroduce NIV; if not successful: hospice referral for palliative care or IV Unable to maintain pO ₂ > 90%, pCO ₂ < 50mmHg or unable to manage secretions: IV IV may be considered to preserve quality of life in patients with ALS who want long-term ventilatory support	–	–
Termination of NIV/IV, end-of-life management			
Discuss the options for respiratory support and end-of-life issues if the patient has dyspnea, other symptoms of hypoventilation or an FVC < 50% Rediscuss the patient's preferences for life-sustaining treatment every 6 months Treatment of dyspnea: opioids alone or in combination with benzodiazepines if anxiety is present Use oxygen only if hypoxia is present	–	If a person on continuous NIV wishes to stop treatment, seek advice from healthcare professionals who have knowledge and experience of stopping NIV	If termination of IV is legal in the patient's country, the advance directive should include whether ventilation should be terminated under certain circumstances, since the patient will eventually lose the ability to communicate (IV)
*In our experience, mucolytic drugs are usually ineffective and may even be harmful if not combined with MI-E. AAN, American Academy of Neurology; ALS, amyotrophic lateral sclerosis; EFNS, European Federation of Neurological Societies; FTD, frontotemporal dementia; FVC, forced vital capacity; HFCWO, high-frequency chest-wall oscillation; IV, invasive ventilation; (IV), class IV evidence; MI-E, mechanical insufflation-exsufflation; MIP, maximal inspiratory pressure; NICE, National Institute for Health and Care Excellence; NIV, non-invasive ventilation, pCO ₂ , carbon dioxide partial pressure; pO ₂ , oxygen partial pressure; PEG, percutaneous endoscopic gastrostomy; SNIP, sniff nasal inspiratory pressure.			

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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