Management of dyspnea in advanced motor neuron diseases

Vilma Adriana Tripodoro[a] and Eduardo Luis De Vito[b]

[a]Section of Palliative Care, Institute of Medical Research Alfredo Lanari, University of Buenos Aires, Argentina and Pallium Latinoamérica and [b]Section of Pulmonary Laboratory, Institute of Medical Research Alfredo Lanari, University of Buenos Aires, Buenos Aires, Argentina

Correspondence to Vilma Adriana Tripodoro, MD, Instituto Lanari, Combatientes de Malvinas 3150, 1427 Buenos Aires, Argentina
Tel: +54 1145148701/04x191;
e-mail: vilma.tripodoro@gmail.com

Current Opinion in Supportive and Palliative Care 2008, 2:173–179

Purpose of review

Patients with amyotrophic lateral sclerosis or motor neuron disease (ALS/MND) invariably develop respiratory muscle weakness and most die from pulmonary complications. Little evidence is available that identifies optimal management approaches for caring for the dying patient. This review discusses the state of the art on dyspnea in advanced ALS/MND and its treatment.

Recent findings

Multiple observational studies have demonstrated that noninvasive positive pressure ventilation is beneficial in ALS/MND. It is a relatively safe intervention in the late stages of disease with additional survival benefits when it is started relatively early and it can improve survival. Despite guidelines related to pulmonary function testing about the use of noninvasive positive pressure ventilation, the factors, which are most closely associated with noninvasive positive pressure ventilation utilization, are dyspnea and orthopnea.

Summary

In ALS/MND, loss of function relentlessly progresses, and subsequent death occurs mostly in a predictable manner. Therefore, the end of life care is heavily influenced by the type and quality of care provided from the earliest stages. Most patients with ALS/MND develop dyspnea, agitation, anxiety and air hunger in the final phase. Noninvasive positive pressure ventilation has become the standard of care for patients with ALS/MND and advanced respiratory insufficiency. A multidisciplinary approach is strongly recommended.

Keywords

amyotrophic lateral sclerosis, dyspnea, end stage disease, motor neuron disease, noninvasive ventilation, palliative care

Curr Opin Support Palliat Care 2:173–179

1751-4258

Introduction

Amyotrophic lateral sclerosis or motor neuron disease (ALS/MND) is a devastating neurodegenerative disease with a highly predictable clinical course such that palliative care should begin at or soon after diagnosis. Respiratory symptoms especially dyspnea are common and respiratory failure remains the most common cause of death. Multiple problems require a multidisciplinary approach for both patients and families. In late stage illness, dyspnea associated with loss of respiratory capacity is used as a criterion for hospice eligibility, implying a prognosis of 6 months or less. Timing of discussion of advance directives and treatment preferences must be tailored to the individual's illness course, readiness, and imminence of respiratory crisis [1••]. The purpose of this review is to discuss the state of the art on dyspnea in advanced ALS/MND patients and its treatment.

Dyspnea, setting and management

In ALS/MND, the diaphragm and other muscles of respiration are invariably affected. There is no reliable method to predict when respiratory muscle weakness will occur [2].

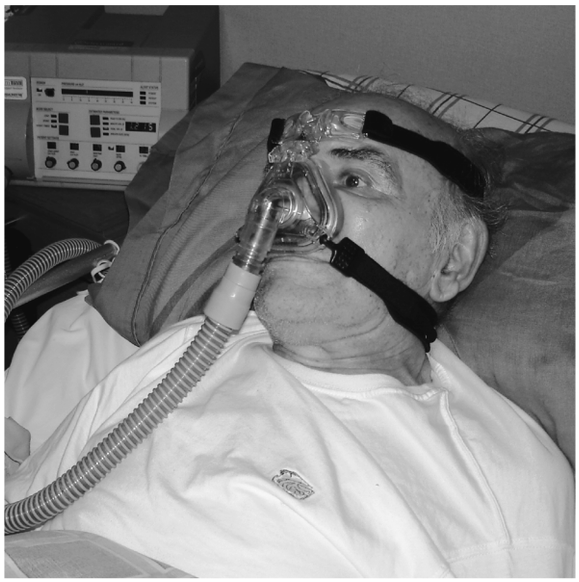
According to the American Thoracic Society, dyspnea is a term used to characterize a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. This definition considers the current understanding of the interplay between psychological, physiological, social, and behavioral factors in producing respiratory discomfort as well as the spectrum of phrases used by patients to describe their sensations [3]. 'Our ability to provide the best care possible to patients with dyspnea depends upon our capacity to break down any communication barriers between physician and patients' [4].

Most patients with ALS/MND develop dyspnea, agitation, anxiety and air hunger in the final phase of ALS/MND. Knowledge about respiratory issues in ALS/MND has grown dramatically over the last 10 years. Respiratory interventions have a greater impact on survival and quality of life (QoL) than any other treatments [2].

There are two crucial points in the respiratory management of patients with ALS/MND.

Inspiratory muscle weakness can produce shortness of breath and hypoventilation. When respiratory difficulty begins to interfere with sleep or forced vital capacity (FVC) declines substantially (usually below 50% of predicted), noninvasive positive pressure ventilation (NPPV) is usually recommended. Nearly all patients agree to try NPPV when advised to do so. There are many different NPPV interfaces; nasal masks are the most common (Fig. 1). Another popular NPPV interface is 'nasal pillow' that has two pieces, one fitting into each nostril. Many patients do well with a nasal mask, but some patients who have mouth weakness have difficulty in preventing air leakage through the mouth. Sometimes a chinstrap can prevent air leakage, but at times a full-face mask is needed [2]. Long-term and full-time NPPV are desirable and possible. Sometimes patients with severe bulbar dysfunction cannot tolerate it whereas others leave installed equipment unused. We agree with Bach's [5•] opinion that it is only when bulbar-innervated musculature becomes completely dysfunctional and the patient has lost the ability to speak, swallow food and to protect the airway from continuous saliva aspiration that the tracheostomy tube becomes necessary for survival. At this point, the patient must decide whether or not to accept this option.

Figure 1 Patient with ALS/MND using noninvasive bi-level positive pressure ventilation with nasal mask at home



Weak cough and difficulty in clearing secretions are common symptoms caused by expiratory muscle weakness, causing much distress to the patient. The proper management of secretion is a major factor in the success of NPPV. A patient's ability to cough effectively can be evaluated by measuring the peak cough flow. The difference between traditional peak expiratory flow and during cough (or check valve with the tongue) could inform about bulbar function [6]. The assisted coughing technique includes simpler methods of improving cough such as manual compression, and insufflations using resuscitation bag as well as mechanical cough assist devices. These measures can be used at home by caregivers or by a physiotherapist in hospital in the event of a respiratory tract infection.

According to our opinion, causes of dyspnea in ALS/MND patients are as follows:

(1) Dyspnea as the initial symptom in ALS/MND.
(2) Dyspnea caused by the combination of nonsevere respiratory muscle weakness and any previous lung disease.
(3) Dyspnea with exertion.
(4) Orthopnea–breathless lying flat.
(5) Dyspnea caused by progressive retained secretions and laryngospasm.
(6) Dyspnea caused by choking while eating and drinking.
(7) Dyspnea caused by retained secretions in the throat.
(8) Dyspnea related to anxiety.
(9) Progressive dyspnea in advanced ALS/MND, related to progressive and severe respiratory muscle weakness.
(10) Dyspnea in end-stage ALS/MND patients.
(11) Asynchrony patient ventilator (both during NPPV and tracheal ventilation).

Dyspnea as the initial symptom in amyotrophic lateral sclerosis or motor neuron disease

Respiratory failure is a presenting symptom of ALS/MND in only a small number of patients, and may precede clinical manifestation in voluntary motor units. Patients with respiratory failure as initial manifestation have worse prognosis than patients with spinal onset [7]. Patients with dyspnea as the initial symptom and patients with bulbar onset or both are a subset in whom early palliative care intervention is extremely crucial as it is expected that premature respiratory failure and severe bulbar-innervated musculature weakness precludes failure of NPPV. Patients who cannot use NPPV should be

informed about the terminal phase, ventilation via tracheostomy, hospice referral and palliative care. In fact, a palliative care approach should be incorporated into the care plan for patients and carers from the time of diagnosis (class III recommendation). Long-term mechanical ventilation (LTMV) can prolong survival. It can be acceptable for some patients and caregivers and in these cases can improve patients' QoL, although some patients become unable to communicate in a locked-in state [8••].

Dyspnea caused by the combination of nonsevere respiratory muscle weakness and any previous lung disease

Some patients with dyspnea have relatively preserved pulmonary functions testing. Dyspnea could be related to other respiratory or nonrespiratory disease that should be properly characterized [e.g. chronic obstructive pulmonary disease (COPD), heart failure, etc.]. According to Lechtzin [2], p_{CO_2} is highly variable in ALS/MND. In general, hypercapnia does not develop until there is advanced respiratory muscle weakness, but some patients will have hypercapnia unexpectedly, perhaps related to other conditions. As a practice guideline, it would be remarkable to address: FVC may not fall below normal limits until there is a 50% reduction in muscle strength, but clinically relevant weakness is unlikely if FVC is normal, maximal inspiratory pressure values higher than 80 cmH_2O exclude clinically relevant respiratory muscle weakness [9]. Thus, patients with resting dyspnea and normal or middle reductions in FVC and nonsevere respiratory muscle weakness must be studied for other conditions.

Dyspnea with exertion

Patients with ALS/MND can complain of dyspnea with exertion. They have a combination of advanced respiratory muscle weakness and relatively well preserved muscular limb force. Reduction of physical activity related dyspnea should be recommended.

Orthopnea: breathless lying flat

Respiratory failure due to bilateral diaphragm paralysis can occur at any time of the evolution of ALS/MND, and virtually all these patients cannot tolerate a recumbent position once lying on the bed. On the basis of the data from the ALS Care Database, the current American Academy of Neurology (AAN) guidelines for initiation of NPPV when the FVC drops below 50% are not being followed in the majority of patients. In fact, this guideline suggests modification of the existing ones to include initiation of NPPV in any patient with orthopnea [10]. In our opinion, orthopnea represents a precise indication for NPPV (in patients with relatively well-preserved bulbar function), independent of any others tests. In order to alleviate symptoms of orthopnea and nocturnal respiratory failure, patients should be ventilated overnight. Immediately following the start of NPPV, orthopnea is alleviated and after a few nights, it is expected to find a marked improvement of daytime somnolence and exertional dyspnea.

Dyspnea caused by progressive retained secretions and laryngospasm

Immobility, hypersialorrhea, and impaired swallowing all contribute to an increased risk of pulmonary infection. Occasionally, patients with prominent bulbar involvement will develop laryngospasm, which can be terrifying and often prompts emergency department visits. Fortunately, these laryngospasms usually resolve spontaneously after several minutes [2].

Good practice points for bronchial secretions have been recently published [8••]. These recommendations are mainly based on expert opinions and uncontrolled studies. However, we could identify a lack of comments on clearance of secretions and respiratory muscle aids [11]. Bach [12] reported a series of patients with ALS/MND who had relatively few respiratory complications over a period of years when they adhered to a regimen of mechanically assisted cough, NPPV and pulse-oximetry monitoring.

Dyspnea caused by choking while eating and drinking

Dysphagia associated with ALS/MND results from disturbed motility of the tongue, pharynx and esophagus. It can lead to choking and aspiration. Patients with symptomatic dysphagia or both cough and choking while eating or drinking should be informed about percutaneous endoscopic gastrostomy (PEG) whose early detection can improve survival [2]. The best treatment of choking is to prevent it. A careful evaluation of dysphagia is mandatory. Choking is a very distressing situation both for the patient and relatives; however, deaths caused by choking attacks are almost unheard of.

Dyspnea caused by retained secretions in the throat

Tenacious and thick secretions in the throat and tongue can produce discomfort and dyspnea. This situation is often under addressed. The clearing can be difficult for the patient. A portable home suction device or manual cleaning is useful for clearing the throat and tongue.

Dyspnea related to anxiety

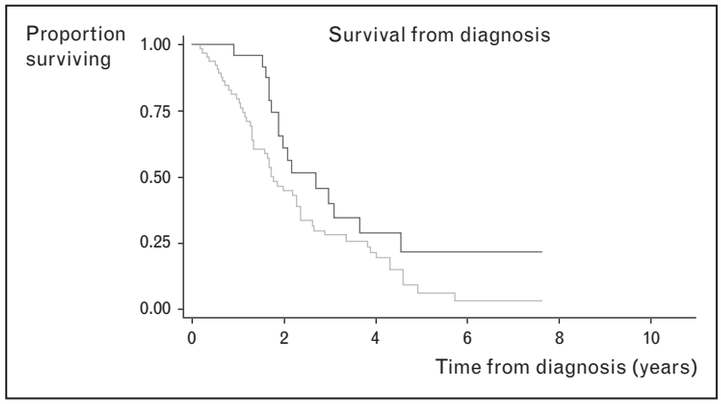
Patients' subjective experience of dyspnea is closely related to emotions and psychological control over the disease. Dyspnea is not always related to objective measures of lung function such as FVC, irrespective of limb or bulbar presentation.

Progressive dyspnea in advanced amyotrophic lateral sclerosis or motor neuron disease, related to progressive and severe respiratory muscle weakness

With progressing respiratory insufficiency, symptoms of chronic nocturnal hypoventilation may develop. Lastly,

Figure 2 Kaplan–Meier plot comparing tracheotomy-free survival from time of diagnosis between early NPPV users (upper line black) and the standard group (lower line gray). $P = 0.045$ [13••]

NPPV, noninvasive positive pressure ventilation.



dyspnea at rest dominates the clinical picture. NPPV is an efficient and cost-effective method of alleviating these symptoms in patients with appropriate control of their upper airway. In fact, NPPV has become the standard of care for patients with ALS/MND and advanced respiratory insufficiency. The AAN Practice Parameter recommends considering NPPV when the FVC falls below 50% predicted or if patients have symptomatic hypoventilation. The study from Lechtzin *et al.* [13••] showed markedly better survival from the time of diagnosis in patients who started NPPV when their upright FVC was more than 65% predicted compared with those who used NPPV at more traditional starting points (Fig. 2). Use of nocturnal NPPV has been shown to normalize daytime arterial CO_2 [13••].

The recommendation for the use of NPPV is on the basis of class II. There is general agreement that NPPV may prolong survival, and improve QoL despite disease progression [1••,13••,14–18]. Class I evidence on the effectiveness of NPPV in prolonging survival or improving QoL in ALS/MND is lacking. A randomized controlled trial is needed to establish the effect of NPPV on QoL and survival, but might be difficult to perform considering the widespread belief in the positive effect of NPPV [13••]. On the contrary Piepers *et al.* [14] advised that the reported positive effects of NPPV might be attributable to publication bias, as negative results are less likely to be published. Their search identified several studies reporting negative results or limitations of NPPV use. ALS/MND patients treated with NPPV may be different from those who are not treated, with regard to characteristics influencing survival or QoL.

The frequency of NPPV use by ALS/MND patients may differ considerably between centers and countries with cross-cultural and ethical differences [14]. NPPV may not be offered by caregivers, or accepted by patients for fear that prolonged survival at the expense of increasing disability may be undesirable. Andersen *et al.* [16] agreed with the beneficial effects of NPPV but it is underused. In spite of emerging evidence of therapeutic benefit from NPPV, only a minority of ALS/MND patients use this therapy. NPPV compliance was strongly correlated with dyspnea and orthopnea as well as with the use of other therapies including PEG tubes, augmentative speech devices, and riluzole. There was no correlation between age, race, type of insurance, FVC, duration of symptoms, ALSFRS-R questionnaire, caregiver burden or QoL with the use of NPPV. The findings may be useful in designing prospective studies to examine the factors, which might explain the underutilization of NPPV and the optimal use of this treatment [10].

The patient's advance directives and a clear plan for management of respiratory failure should be established before respiratory failure occurs [8••]. If the patient with progressive dyspnea as expression of terminal illness refuses NPPV, oxygen administration may be attempted. Oxygen should be administrated if hypoxia is present and it is expected to alleviate hypoxia-related dyspnea. Administering oxygen does not provide assistance to the weakening respiratory muscles, but gives both the patient and the doctor the false impression that appropriate treatment is being provided [19]. Dyspnea could be temporary released with fresh air on the face as well.

In ALS/MND, respiratory capacity eventually fails, even with NPPV. Patients and families are faced with deciding about LTMV intervention, and advance planning is essential to preclude unwanted emergency tracheal intubation in a crisis. With LTMV, patients eventually may reach a 'locked-in' state in which they cannot communicate at all. This may be a circumstance in which

patients would desire discontinuation of ventilation, but unless clearly specified in advance, decisions about how to proceed become highly problematic [1••]. Home LTMV is known to be an expensive labor-intensive therapy for informal caregivers and it influences the family's life style and QoL. It is well documented that caregivers of patients under home LTMV are at high risk to develop depression, burden, overload and declining health over time [20].

Further studies are required to confirm the benefits of NPPV treatment in patients with bulbar involvement, especially in the early stages [21]. A guideline for multidisciplinary care of HMV patients was proposed by Eng [17]. It recommends multidisciplinary management, respiratory care planning, starting NPPV, palliative care physician to co-ordinate the multidisciplinary team's activities, review written advanced directives regularly at least 6 monthly, discuss end-of-life care (if appropriate) and bereavement service.

Dyspnea in end-stage amyotrophic lateral sclerosis or motor neuron disease patients

On the basis of consensus among 20 ALS experts, the triggers for initiating discussion about end-of-life issues in patients with ALS/MND are [11]:

(1) The patient or family asks – or opens the door – for end-of-life information and interventions (elicited or spontaneous, verbal or nonverbal)
(2) Severe psychological, social, or spiritual distress or suffering
(3) Pain requiring high dosages of analgesic medications
(4) Dysphagia requiring feeding tube
(5) Dyspnea or symptoms of hypoventilation or a FVC of 50% predictable or less
(6) Loss of function in two body regions (regions include bulbar, arms, and legs)

Although there are few data, it has been estimated that in the USA, between 5 and 8% of ALS/MND patients are placed on LTMV, not all of them voluntarily. In the study of Rabkin *et al.* [22], the rate of LTMV was 19%, substantially more than other American reports and quite possibly an artifact of their late-stage sample; all patients had a presumed life expectancy of less than 6 months at baseline. A US study ($n = 1458$) found a rate of LTMV use of 2%, whereas in an English sample ($n = 50$) was 0 at a time when national health insurance did not cover home ventilation, and 3% in a German study ($n = 121$) [22]. In contrast, in the Japanese study, the rate of LTMV was 45%. This rate appears to be increasing, perhaps related to financial considerations (the Japanese government covers costs of LTMV), physician support for LTMV, social pressure from the Japanese ALS/MND Association, and differences in cultural attitudes about 'truth telling' and death. Historically, Japanese patients and families expected the doctor to determine treatment strategies and decisions, at least until quite recently [22]. In a German survey, 66% of patients receiving LTMV had emergency intubation, and 81% did not give informed consent for the procedure. [23].

The frequency with which withdrawal of LTMV occurs is unknown. Some patients may ultimately require palliative sedation [24]. For patients who withdraw LTMV or choose not to have it, palliation becomes the sole focus of interventions. The aim of palliative care is to maximize QoL of patients and families by relieving symptoms, providing emotional, psychological and spiritual support as needed, removing obstacles to a peaceful death, and supporting the family in bereavement [20,25,26,27••]. End-of-life decision making in patients with ALS/MND is often delayed. The most important factor in whether the ALS/MND patient decides for or against invasive measures is whether the physician addresses these issues in a timely manner. The pulmonologist can play a valuable role in end-of-life discussions [28].

The pharmacologic treatment of dyspnea could be implemented in the setting of a patient submitted to NPPV or LTMV as well as patients who refused them. Setting of ventilators should be checked at any time. The European ALS Consortium (EALSC) working group recommend for short dyspneic bouts, relieve anxiety and give lorazepam 0.5–2.5 mg sublingually for longer phases of dyspnea (>30 min), give morphine 2.5 mg orally (p.o.) or subcutaneously (s.c.). For chronic dyspnea, start with morphine 2.5 mg p.o. 4–6 times daily. For severe dyspnea, give morphine s.c. or intravenous (i.v.) infusion, start with 0.5 mg/h and titrate. If needed, add midazolam (2.5–5 mg) or diazepam for nocturnal symptom control and to relieve anxiety [8••]. Titrating the dosages against the clinical symptoms will almost never result in a life-threatening respiratory depression (class I A recommendation). For treating terminal restlessness and confusion due to hypercapnia, neuroleptics may be used (e.g. chlorpromazine 12.5 mg every 4–12 h p.o., i.v. or per rectum) [8••]. Table 1 shows recommendations for symptom management during last hours of life on or not on ventilator support.

In our view, the paper from Bach [5•] regarding the palliative care subject matter in ALS/MND and related to 'uninformed euthanasia' deserves a few considerations. In these patients, the indication of NPPV to treat hypoventilation and prolong survival is not opposed to the palliative care approach. There is not the end of a care and the beginning of another one. Both approaches should coexist. The intensity of intervention should be in harmony with the evolution and the needs of the patient and family.

Table 1 Recommendations for symptom management during last hours of life [8••]

Terminal management of patients	
On ventilatory support	Not on ventilatory support
Recommendations to the field for development	Recommendations to the field for development
Routinely assess patient's preferences for ventilatory support at successive stages of illness, provide assurance that respiratory distress will be actively managed with or without ventilatory support	Follow the same procedures mentioned before except initiate medications (such as opioids) in a more gradual fashion (around the clock if distress recurs) as there is no specific event to anticipate
Discuss when to withdraw ventilatory support and what to expect at this time; review advance directives with patients and family members	Ensure that the physician is readily accessible for adjustments of medication
Establish the basis for withdrawal of ventilation prior to initiating ventilation, discussion should include the expected manner and time course of death medications that will be used to manage symptoms possible use of sedation	Stop use of all unnecessary medications
Withdraw ventilation with a physician present; make all arrangements prior to the removal of support including discussing, planning, and implementing all cultural or religious rituals	Consider discontinuing monitoring (vital signs and oximetry)
Use parenteral medications, such as opioids and benzodiazepam, to achieve rapid sedation without paralyzing agents; once comfort has been obtained, discontinue positive expiratory pressure, followed by conversion to a T-piece in the case of tracheotomy ventilation	

Asynchrony patient ventilator (both during noninvasive positive pressure ventilation and tracheal ventilation)
Sudden agitation and dyspnea can occur at any time during NPPV or even during LTMV. Asynchrony patient ventilator is a contributor to ventilator intolerance and failure to ventilate under assisted modes. This may produce distress both for the patients and their caregivers. Ventilator settings, interfaces, secretion retention, air leaks, rebreathing, as well as emotional environment should be checked and corrected. Often pharmacological treatment should be considered.

Conclusion

Virtually all patients with ALS/MND will complain of dyspnea, which is perhaps the most distressing symptom of this devastating disease. Dyspnea can take place as first manifestation or as the result of progressive respiratory muscle weakness. Acute dyspnea related to many other circumstances can occur at any time. According to the setting, evolution and patients' preferences, the current treatment of dyspnea includes NPPV, LTMV as well as drug therapy including oxygen therapy.

A recent study from Vender *et al.* [29••] concluded that the correlation between clinically defined milestones, most importantly onset of dyspnea, and the calculated rate of decline in FVC represent obtainable and objective measurements that predict the natural course of respiratory muscle dysfunction in patients with ALS/MND and provide important prognostic information in relation to individual patient survival duration.

We found that many authors insist on the multidisciplinary management of ALS/MND. There remains no consensus on when and how end-of-life issues should be addressed. The relatively gradual progression of ALS/MND allows the patients and their families time to contemplate and participate in end-of life decisions, especially when these issues are addressed in a timely manner.

We recognized the following research recommendations related to dyspnea: to develop treatment and management protocols and algorithms for alleviation of respiratory symptoms through the end of life; to develop treatment and management protocols and algorithms on how to withdraw ventilatory support at end of life; and to undertake studies to examine how patients die in a natural setting as compared with those patients on ventilatory support.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 229).

1 •• Mitsumoto H, Rabkin JG. Palliative care for patients with amyotrophic lateral sclerosis: 'prepare for the worst and hope for the best'. JAMA 2007; 298:207–216.
Presenting the unusual case of a patient with ALS who is also a prominent neurologist specializing in ALS, the authors enumerate issues in management and palliative care applicable to ALS but also to other fatal and progressive neurologic diseases.

2 Lechtzin N. Respiratory effects of amyotrophic lateral sclerosis: problems and solutions. Respir Care 2006; 51:871–881.

3 Official Statement of the American Thoracic Society adapted by the ATS Board of Directors. Dyspnea: mechanisms, assessment, and management: a consensus statement. Am J Respir Crit Care Med 1999; 159:321–340.

4 Scano G, Stendardi L, Grazzini M. Understanding dyspnoea by its language. Eur Respir J 2005; 25:380–385.

5 • Bach JR. Palliative care becomes 'uninformed euthanasia' when patients are not offered noninvasive life preserving options. J Palliat Care 2007; 23:181–184.
The author discussed that it is time that care became 'facilitative' rather than 'palliative' for people with MND.

6 Suárez AA, Pessolano FA, Monteiro SG, *et al.* Peak flow and peak cough flow in the evaluation of expiratory muscle weakness and bulbar impairment in patients with neuromuscular disease. Am J Phys Med Rehabil 2002; 81:506–511.

7 Czapliński A, Strobel W, Gobbi C, *et al.* Respiratory failure due to bilateral diaphragm palsy as an early manifestation of ALS. Med Sci Monit 2003; 9:34–36.

8 •• Andersen PM, Borasio GD, Dengler R, *et al.,* EALSC Working Group. Good practice in the management of amyotrophic lateral sclerosis: clinical guidelines. An evidence-based review with good practice points. Amyotroph Lateral Scler 2007; 8:195–213.
The review addresses the current optimal clinical approach to ALS. The literature search is complete till December 2006. They concluded that noninvasive positive pressure ventilation improves survival and QoL but is underused in Europe.

9 Shahrizaila N, Kinnear WJ, Wills AJ. Respiratory involvement in inherited primary muscle conditions. J Neurol Neurosurg Psychiatry 2006; 77:1108–1115.

10 Jackson CE, Lovitt S, Gowda N, *et al.* Factors correlated with NPPV use in ALS. Amyotroph Lateral Scler 2006; 7:80–85.

11 Mitsumoto H, Bromberg M, Johnston W, *et al.* Promoting excellence in end-of-life care in ALS. Amyotroph Lateral Scler 2005; 6:145–154.

12 Bach JR. Amyotrophic lateral sclerosis: prolongation of life by noninvasive respiratory AIDS. Chest 2002; 122:92–98.

13 •• Lechtzin N, Scott Y, Busse AM, *et al.* Early use of noninvasive ventilation prolongs survival in subjects with ALS. Amyotroph Lateral Scler 2007; 8:185–188.
A retrospective cohort study of patients with ALS was performed comparing survival from time of diagnosis in patients who started NPPV use when their FVC was above 65% predicted (early NPPV) with patients who started NPPV when their FVC was below 65% predicted (standard NPPV). Their findings suggest that clinicians either encourage earlier use of NPPV or use more sensitive tests for respiratory muscle impairment than upright FVC.

14 Piepers S, Van den Berg JP, Kalmijn S, *et al.* Effect of noninvasive ventilation on survival, quality of life, respiratory function and cognition: a review of the literature. Amyotroph Lateral Scler 2006; 7:195–200.

15 Aboussouan LS, Khan SU, Banerjee M, *et al.* Objective measures of the efficacy of noninvasive positive-pressure ventilation in amyotrophic lateral sclerosis. Muscle Nerve 2001; 24:403–409.

16 Andersen PM, Borasio GD, Dengler R, *et al.* EFNS task force on management of amyotrophic lateral sclerosis: guidelines for diagnosing and clinical care of patients and relatives. Eur J Neurol 2005; 12:921–938.

17 Eng D. Management guidelines for motor neuron disease patients on noninvasive ventilation at home. Palliat Med 2006; 20:69–79.

18 Sívori M, Rodríguez GE, Pascansky D, *et al.* Outcome of sporadic amyotrophic lateral sclerosis treated with noninvasive ventilation and riluzole. Medicina (B Aires) 2007; 67:326–330.

19 Oppenheimer EA. Oxygen is not for hypoventilation in neuromuscular disease. Reprinted from IVUN News, Spring, 2000; 14 with permission of Gazette International Networking Institute, 4207 Lindell Blvd., #110, St. Louis, MO 63108–2915.

20 Tsara V, Serasli E, Voutsas V, *et al.* Burden and coping strategies in families of patients under noninvasive home mechanical ventilation. Respiration 2006; 73:61–67.

21 Farrero E, Prats E, Povedano M, *et al.* Survival in amyotrophic lateral sclerosis with home mechanical ventilation: the impact of systematic respiratory assessment and bulbar involvement. Chest 2005; 127:2132–2138.

22 Rabkin JG, Albert SM, Tider T, *et al.* Predictors and course of elective long-term mechanical ventilation: a prospective study of ALS patients. Amyotroph Lateral Scler 2006; 7:86–95.

23 Kaub-Wittemer D, Steinbuchel N, Wasner M, *et al.* Quality of life and psychosocial issues in ventilated patients with amyotrophic lateral sclerosis and their caregivers. J Pain Symptom Manage 2003; 26:890–896.

24 Lynn J. Serving patients who may die soon and their families: the role of hospice and other services. JAMA 2001; 285:925–932.

25 Borasio GD, Voltz R, Miller RG. Palliative care in amyotrophic lateral sclerosis. Neurol Clin 2001; 19:829–847.

26 Albert SM, Rabkin JG, Del Bene ML, *et al.* Wish to die in end-stage ALS. Neurology 2005; 65:68–74.

27 •• McPherson CJ, Wilson KG, Murray MA. Feeling like a burden to others: a systematic review focusing on the end of life. Palliat Med 2007; 21:115–128.
The study provides a systematic review of the literature, addressing self-perceived burden at the end of life. There is now a small but growing body of evidence to suggest that worry about creating a burden to others is a common and troubling concern for people who are nearing the end of their lives. This concern is referred to as 'self-perceived burden'.

28 Munroe CA, Sirdofsky MD, Kuru T, Anderson ED. End-of-life decision making in 42 patients with amyotrophic lateral sclerosis. Respir Care 2007; 52:996–999.

29 •• Vender RL, Mauger D, Walsh S, *et al.* Respiratory systems abnormalities and clinical milestones for patients with amyotrophic lateral sclerosis with emphasis upon survival. Amyotroph Lateral Scler 2007; 8:36–41.
In this study, the reported data represent results from a retrospective review of the medical records of 153 patients with ALS. The authors concluded that the correlation between clinically defined milestones, most importantly onset of dyspnea, and the calculated rate of decline in FVC represent obtainable and objective measurements that predict the natural course of respiratory muscle dysfunction in patients with ALS and provide important prognostic information in relation to individual patient survival duration.