# Management of Symptoms in Amyotrophic Lateral Sclerosis

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## Opinion statement

The mainstay of treatment of amyotrophic lateral sclerosis (ALS) is management of symptoms. Health care providers involved in the care of ALS patients should be armed with the most current knowledge about symptomatic management of these patients so that an aggressive approach to controlling symptoms can be undertaken at the most appropriate time. Among the important modalities is noninvasive positive pressure ventilation, which has been shown to improve not only quality of life but also survival. Similarly, clinicians should consider earlier intervention with enteral feeding. Palliative care should begin soon after ALS is diagnosed.

## Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive, degenerative disease of motor neurons. It is the most common motor neuron disease occurring in adulthood, with the mean age of onset being 58 years. Men are more affected than women, with a ratio of 3:2 [1, Class III]. The worldwide prevalence is estimated to be 600,000 to 800,000, with an incidence of approximately 200,000 per year [2, Class III].

The disease is marked by the progressive death of both upper and lower motor neurons in the brain, brainstem, and spinal cord. Atrophy of muscles accompanied by spasticity leads to weakness throughout the body, causing progressive oropharyngeal muscle dysfunction, loss of ambulatory ability, and eventual respiratory failure. Clinical presentation is variable, as is the disease course; about 50% of patients die within 3 years of symptom onset [3, Class III].

The etiology of ALS is not known. It is still considered a lethal disease, as no curative treatment has yet been identified. Although the scientific community has not given up hope that a cure may be found, the mainstay of treatment remains symptomatic management. This review discusses management of the major symptoms occurring in patients with ALS.

## SYMPTOMS

### Respiratory failure

Respiratory insufficiency and associated pulmonary complications are the most common cause of death in ALS. There have been some documented cases in which acute respiratory insufficiency was the first manifestation of the disease, but usually it is a late manifestation [4, Class III]. Progressive weakness of the diaphragm and the intercostal, accessory, and abdominal musculature causes a restrictive pattern of lung disease. Repeated episodes of aspiration and retention of secretions owing to bulbar weakness and ineffective coughing cause pulmonary microatelectasis. Breathing becomes inefficient and chronic hypoventilation ensues. The most obvious symptoms of respiratory insufficiency are dyspnea on exertion and orthopnea [5••, Class III].

The earliest indicator of respiratory insufficiency, however, may be sleep-related respiratory dysfunction in the form of frequent nocturnal arousals, unrefreshing sleep, morning headaches, excessive daytime somnolence, incapacitating fatigue, cognitive dysfunction, and vivid dreams. Weakness of the diaphragmatic muscle in ALS becomes evident during REM sleep, when it is essentially the only muscle performing the work of breathing. The supine sleep position worsens the condition, as patients with diaphragmatic weakness have more difficulty breathing while supine. For patients in whom bulbar involvement is significant, increased upper airway resistance on inspiration causes obstructive apneic episodes, further complicating sleep-related ventilatory abnormalities. Central apnea may also play a role.

Hypoventilation causing transient nocturnal hypoxemia and hypercapnia initially manifested during sleep evolves over time into chronic respiratory failure. Eventually, abnormal blood gases persist through the day, as uncorrected nocturnal hypoventilation with hypoxemia and hypercapnia causes a blunting of the normal respiratory chemoreceptor response [5••,6, Class III].

### Malnutrition

Nutrition is an independent prognostic factor for survival in ALS [7, Class III]. Malnutrition develops in 15% to 50% of patients [8, Class III]. It is usually related to a number of factors: anorexia, dysphagia, physical inability to prepare and eat food, recurrent or chronic infections, and psychological upset. Malnutrition leads to loss of muscle function, impaired immunity, and reduced tissue viability and thus perpetuates clinical deterioration [9, Class III].

### Sialorrhea

Sialorrhea is defined as excessive salivation or drooling. In the setting of ALS, sialorrhea is due to bulbar dysfunction that produces improper handling of secretions, rather than an overproduction of saliva [10, Class III].

### Pseudobulbar affect

Pseudobulbar affect, defined as pathologic lability of emotion, occurs in about 50% of ALS patients at some point during the course of their disease [11, Class III]. Pseudobulbar affect is not a mood disorder but rather a consequence of disruption in the descending prefrontal cortical fibers that normally inhibit the brainstem centers controlling motor output [12, Class III]. Patients may suddenly cry or laugh uncontrollably out of context to their prevailing mood. This emotional incontinence can be socially disabling and have a negative impact on quality of life.

### Fasciculations and muscle cramps

Fasciculations are visible contractions of small groups of muscle fibers, occurring spontaneously in resting muscle. In ALS, fasciculations are a manifestation of denervation. They are rarely the presenting complaint and often cause no concern for the patient, so they usually require no treatment.

Muscle cramps are painful contractions that begin in a portion of a muscle as a series of fasciculations and usually spread to involve the entire muscle [13, Class III]. Cramps occur in shortened muscles and are provoked by contraction of the shortened muscle.

## APPROACH TO CARE

ALS is a devastating neurodegenerative disease with a highly predictable course, so palliative care should begin at or soon after diagnosis. Because there is no curative treatment, the focus is on enabling the patient to achieve maximal function and independence at each stage of the illness by relieving the many symptoms that develop over time [14, Class III]. Control of pain, respiratory distress, anxiety, and fear is paramount. The goal of palliative care is achievement of the best possible quality of life for patients and their families [15, Class III].

# Treatment

## Management of respiratory failure

- It is important to have a high clinical index of suspicion for sleep-related ventilatory disturbance detrimentally affecting quality of life. Sleep-related respiratory abnormalities may occur out of proportion to the severity of the neuromuscular disease. Patients in whom sleep-related respiratory issues are suspected should be evaluated in a sleep laboratory using overnight polysomnography to determine the need for noninvasive positive airway pressure support [6, Class III]. These patients may begin by using ventilation only at night, but they inevitably will progress to daytime use, at first intermittently and finally continuously [16, Class III].
- Respiratory care in ALS presents challenging decisions for both the patient and physician regarding the appropriate time to initiate ventilatory support. This decision is critical given the risk of sudden death due to acute respiratory insufficiency and the consequence of ventilator dependence before advanced planning is in place. Emergency ventilation should be avoided at all costs. Counseling about ventilatory support must begin as soon as possible after diagnosis, to promote early decision making [17].

### Noninvasive positive pressure ventilation (NIPPV)

- It has been only within the past decade that noninvasive positive pressure ventilation (NIPPV) has become the mainstay of respiratory support in ALS. Invasive ventilation by tracheostomy previously was the only alter-

native. Because of the complications, difficulties, and social issues associated with invasive mechanical ventilation, the choice to pursue ventilatory support should begin with a trial of NIPPV to determine if the patient can tolerate such therapy. Patients with significant bulbar weakness who have trouble handling secretions will have the least tolerance and thus will reap the least benefit from NIPPV, but bulbar weakness should not be considered a contraindication to initiation of NIPPV [18••, Class I].

- Noninvasive ventilation, if tolerated, can help preserve the functions of oral feeding and speech, reduce the risk of respiratory infections, and reduce the burdens of cost and reliance on caregivers [19, Class III]. The decision to begin NIPPV does not sentence the patient to lifelong ventilator dependence. NIPPV can easily be withdrawn at any time, and patients who use NIPPV seem better equipped to deal with later issues involving invasive ventilation [20, Class III].
- Although death from ALS overwhelmingly results from respiratory failure (85% of cases), most patients do not receive NIPPV, suggesting that there is still much uncertainty in the medical community about the benefits offered by this therapy [21,22, Class III]. It has overwhelmingly been concluded in the literature that NIPPV improves survival for patients with ALS [16, Class III; 18••, Class I; 23,24, Class III]. Physicians may be concerned that prolongation of survival may somehow inflict further suffering upon an already disabled and distressed patient, but several studies have now shown that NIPPV not only improves survival but also dramatically improves quality of life by improving symptom control [16, Class III; 18••, Class I; 24, Class III]. In 2006, Bourke et al. [18••, Class I] were the first to conduct a randomized, controlled trial that reaffirmed that NIPPV improved survival and quality of life in NIPPV-tolerant patients as a result of improved symptom control (especially sleep-related symptoms). Taken as a whole, the estimated survival benefit conferred by these studies ranges from 5 to 20 months depending on tolerance of the therapy, a survival benefit surpassing that offered by the only neuroprotective agent on the market to date, riluzole [25,26, Class I].
- There is no clear consensus on which physiologic marker best reflects the threshold for initiation of NIPPV, nor is there consensus on the frequency with which these indices should be evaluated. After gauging a baseline respiratory status, many authors repeat testing every 2 to 3 months or when symptoms worsen. In the practice parameters set forth by the American Academy of Neurology (AAN), it is considered standard of care to introduce NIPPV when forced vital capacity (FVC) falls below 50% of the predicted value, because at this critical point respiratory symptoms become apparent. However, many suggest that this may not be the optimal time to introduce NIPPV [17]. They suggest that nocturnal oximetry, maximal inspiratory pressure (MIP), and sniff nasal inspiratory force (SNIF) may be better tests for early detection of respiratory insufficiency [27,28, Class III]. Evidence in the literature conflicts, however, as to whether earlier ventilatory support beneficially slows the progression of respiratory dysfunction in ALS or detrimentally hastens it by the deconditioning of inspiratory muscles through an unloading effect [24, Class III]. With the growing awareness of early respiratory signs and symptoms in ALS, it is certain that more prospective, controlled clinical trials are needed to objectively reach this determination [29, Class III]. If future studies can reliably show that NIPPV slows the decline in respiratory function, then ideally NIPPV should be implemented earlier.
- A combination of respiratory indices have been used to determine the need for noninvasive ventilation. Within the past several years, the

Health Care Financing Administration (HCFA) has established criteria for coverage of NIPPV under Medicare. In order for Medicare to cover the cost of NIPPV, dyspnea or symptoms consistent with sleep-related hypoventilation must be documented. Additionally, one of the following criteria must be met: $SPaO_2$ below 88% lasting at least 5 minutes during nocturnal oximetry, arterial blood gas $PCO_2$ greater than 45 mm Hg during wakefulness, FVC less than 50% of the predicted value, or maximal inspiratory pressure less than 60 cm $H_2O$. Along with the AAN practice parameters, these criteria have served as a guideline for the initiation of NIPPV in ALS [30, Class III].

### Assisted cough

- Patients can also be offered manually or mechanically assisted coughing in an effort to prevent respiratory failure due to trapped airway secretions. Coughing is a combined function of inspiratory, expiratory, and bulbar function.
- Manually assisted coughing relies heavily on the patient's ability to maintain a closed glottis after consecutive air stacking maneuvers, to create a situation of maximum insufflation capacity in the lungs so that, through cooperative effort, patient and caregiver perform an abdominal thrust to expel air forcefully enough to simulate a cough.
- Mechanically assisted coughing (MAC) is an insufflation-exsufflation device that uses higher insufflation-to-exsufflation pressures to help expel airway debris using an abdominal thrust maneuver timed to exsufflation. Along with obvious expulsion of airway debris, MAC has been shown to provide immediate results of increased vital capacity and $SpO_2$ after use. MAC use, when combined with NIPPV, can further delay progression to invasive tracheostomy ventilation [20,31, Class III].

### Tracheostomy

- Beginning invasive tracheostomy ventilation or switching to it from NIPPV should be considered only if, despite all efforts, NIPPV and MAC in combination become inadequate for maintaining alveolar ventilation, resulting in persistent desaturation to less than 95% [16,20, Class III]. This decision process should involve a detailed discussion with the patient about complications, socioeconomic issues, and the implications of being ventilator-dependent in the face of an advancing disease process ultimately causing complete paralysis and loss of communication. Patients should be armed with this information as soon as possible after diagnosis. Invasive tracheostomy ventilation prolongs survival in ALS for an average of 5 years, but quality of life in this stage is considered poor for both patient and caregivers [19,32, Class III]. Many ethical concerns surround this topic. The patient must be reassured that if the option of invasive ventilation is declined, appropriate symptomatic and palliative measures to control the discomfort of dyspnea will be implemented and may be used in conjunction with NIPPV as desired [16, Class III].

## Management of malnutrition

- Dysphagia is common in ALS and is one of the most serious symptoms for these patients [33, Class III]. There is no single test to detect dysphagia, and swallowing is difficult to assess objectively. Patients should be asked at each visit about their caloric intake and swallowing difficulties. It may be best to recommend use of a dietary log.

- As soon as symptoms of dysphagia are identified, the patient should be referred to a speech and language therapist. The therapist can determine the severity and nature of the dysphagia, suggest a prognosis for improvement, and teach swallowing techniques to reduce the risks of choking and aspiration [34, Class III].

### Enteral feeding

- ALS patients will eventually require enteral feeding. Enteral feeding in ALS depends on the presence of inadequate oral intake and diminished quality of life due to choking, rather than on the result of a swallowing study [35, Class II]. The principal aim of enteral feeding should be to improve the quality of life rather than simply to prolong life. Enteral feeding consists of percutaneous endoscopic gastrostomy (PEG), percutaneous radiologic gastrostomy (PRG), or nasogastric tube. PEG is currently the method of choice for long-term maintenance of good nutrition in ALS patients [36, Class III]. PRG has recently been shown to be safe and effective in ALS patients and may be more feasible in patients with significant ventilatory compromise [37, Class II]. To prevent obstruction, tubes with a relatively large diameter (eg, 18–22 Charrière) are recommended for PEG and PRG [38••, Class III].
- The timing of PEG placement to maximize survival and quality of life can be assessed by onset of dysphagia and corresponding weight loss. It is also important to assess respiratory function. The general recommendation for the beginning of enteral feeding is when weight loss relative to usual weight reaches a threshold of 10% [39, Class III]. A body mass index less than 18 kg/m$^2$ has been shown to be an unfavorable prognostic factor for survival after gastrostomy.
- Patients with severely compromised respiratory function have higher complication rates when they have PEG placement. The current AAN practice parameter guidelines suggest that PEG procedures should be done, if possible, before the patient's FVC drops below 50%, rather than in the preterminal stages of the disease [17].

## Management of sialorrhea and bronchial secretions

- Sialorrhea is socially disabling and should be addressed to improve quality of life and prevent the development of aspiration pneumonia. Both pharmacologic and nonpharmacologic treatment modalities can be employed [38••, Class III].

### Pharmacologic therapies

- Because of a lack of evidence in ALS, most pharmacologic therapies have stemmed from the treatment of sialorrhea in other conditions such as cerebral palsy and mental retardation. Anticholinergic medications are the mainstay of pharmacologic treatment of sialorrhea. Adverse side effects include excessively dry mouth and constipation, which can render the therapy intolerable to some patients.
- Amitriptyline is one of the most commonly used drugs. It is efficacious and low in cost. It can be given in liquid or tablet form starting at a low dose (10 mg, administered at bedtime to counter sedative effects) and titrated to 25 to 50 mg three times per day to achieve efficacy.
- Atropine, another efficacious anticholinergic agent that is less often used, is available in liquid or tablet form and is given at dosages of 300 to 600 μg two to three times daily [40, Class III]. A newer sublingual preparation of atropine has been shown to provide a statistically significant

reduction in saliva production and is recommended for ALS patients at a dose of 0.25 to 0.75 mg three times daily [41, Class III].

- Oral glycopyrrolate at 0.4 mg three times daily has demonstrated good effect with the added advantage of not crossing the blood-brain barrier [42, Class III]. More recently, glycopyrrolate in an intravenous or nebulized form was shown to be effective in a class I study involving patients with cerebral palsy or developmental disabilities [43, Class I].
- Benztropine has also been reported to be efficacious in a class I study in developmentally disabled patients [44, Class I].
- Transdermal hyoscine is another agent that has been used to relieve sialorrhea; a 1-mg patch is replaced every 3 days [40, Class III; 45, Class I].
- Trihexyphenidyl hydrochloride has also been used [46, Class III].
- Viscous mucus due to bronchial secretions can be an added problem for patients with sialorrhea. Simple hydration is beneficial. Daily β-blockers such as propranolol (10 mg) or metoprolol (50 mg), or a mucolytic such as N-acetylcysteine, can be used in conjunction with anticholinergics to reduce viscosity and aid expectoration [40, Class III]. Manually or mechanically assisted cough techniques also can be used to help clear airway secretions [31, Class III].
- Because oral anticholinergic therapy is often limited by lack of efficacy and increasing adverse effects with titration of doses, other means of controlling sialorrhea have been studied recently. Botulinum toxin A (BTX-A) injection has been shown to be relatively safe and efficacious for use in patients with sialorrhea resulting from a neurodegenerative disorder. A randomized, controlled trial by Lipp et al. [47, Class I] found that a dose of 75 mouse units (MU) BTX-A injected into each parotid gland reduced drooling by 50% compared with patients receiving a placebo. The effects of BTX-A remained stable for 1 month; partial relapse occurred within 3 months.

### Nonpharmacologic therapies

- Studies have suggested that a single low dose (7–8 Gy) of radiation to the salivary glands can be a safe and effective means of controlling salivary secretions. Because of the low dose of radiation and the limited lifespan of the patient, the development of secondary malignant neoplasia of the glands does not seem to be a concern [48, Class III].
- Surgical procedures including tympanic neurectomy, salivary gland excision, and parotid duct ligation, relocation, or photocoagulation have been performed in patients with ALS, but they are not uniformly recommended because of surgical risks [38••, Class III].

## Management of pseudobulbar affect

- Amitriptyline was first described as efficacious in a class I study involving patients with multiple sclerosis and pseudobulbar affect [49, Class I].
- Fluvoxamine and other selective serotonin reuptake inhibitors (SSRIs) have also been shown to be beneficial in decreasing episodes of lability [50, Class III; 51, Class I].
- A study by Brooks et al. [52, Class I] demonstrated convincing efficacy for the combination of dextromethorphan (30 mg) and quinidine (30 mg) twice daily in the suppression of pseudobulbar affect, with improvement in quality of life. A new formulation combining the two agents into one tablet for convenience of administration is currently in phase III trial [53, Class III]. This combination is not yet approved by the US Food and Drug Administration (FDA) and is not currently available.

## Management of muscle cramps

### Pharmacologic treatment

- Quinine sulfate is one of the oldest medications used to treat cramps. Since 1969, however, the FDA has received 665 reports of adverse events associated with quinine, including 93 deaths. Recently, the FDA warned against using quinine for treating cramps and removed unapproved quinine from the market [54]. Quinine is now approved only for the treatment of malaria.
- Other medications that have been tried for cramps are sodium-channel blocking agents such as carbamazepine and phenytoin. Their efficacy is limited and there are no randomized, placebo-controlled trials [55, Class III].
- In an open-label, unblinded trial with 30 patients, gabapentin was shown to be effective for treating muscle cramps [56, Class III].
- Botulinum toxin has been found to reduce the occurrence of calf cramps [57, Class III].
- Other treatments that have been tried are verapamil, vitamin E, and baclofen [58, Class III].

### Nonpharmacologic treatment

- Based on the observation that stretching treats acute cramps and that experimentally induced cramps do not occur in lengthened muscles, stretching is an important nonpharmacologic treatment of cramps. Nocturnal leg cramps were markedly reduced in patients instructed to stretch their calf three times daily [59, Class III]. Stretching before exercise is probably an effective method to prevent cramps during exercise.
- It is important to address dehydration or nutritional deficiencies as potential causes of cramps. Supplementation with magnesium has demonstrated marginal effects in a single placebo-controlled trial [60, Class II].

## Palliative care and end-of-life issues

- Although pain in ALS is not usual in the initial stages, 40% to 73% of patients experience pain in the later stages [61, Class III]. Management is similar to the pain management advocated for cancer patients. Opioids should be used when needed. Dyspnea occurs in approximately 50% of patients with ALS [62, Class III]. Opioids are useful in treating dyspnea. Other measures to consider are intravenous morphine or chlorpromazine.
- Dyspnea often results in anxiety attacks; short-acting anxiolytics can help relieve this symptom.
- In the final stages of the disease, it is appropriate to involve a home hospice team. A retrospective analysis of hospice chart data showed that 94% of patients with motor neuron disease were judged to be peaceful and settled at death in hospice [62, Class III]. Most patients wish to die at home and this is especially feasible when they have a supportive family environment.
- End-of-life issues should be discussed early and whenever patients make some indication that they are ready to address these issues. Physicians should discuss the options for respiratory support and advance directives soon after establishing the physician-patient relationship in caring for a patient with ALS. It is important for family members to know the patient's wishes. To the extent that they can respect the patient's right to autonomy, family members should be involved in the process. Spiritual issues may be an important consideration for patients and their families when deciding on treatment choices.

# Disclosures

No potential conflicts of interest relevant to this article were reported.

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