Invited Review

Amyotrophic Lateral Sclerosis and Palliative Care: Where We Are and the Road Ahead

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AMYOTROPHIC LATERAL SCLEROSIS AND PALLIATIVE CARE: WHERE WE ARE, AND THE ROAD AHEAD

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EDUCATIONAL OBJECTIVES  Upon completion of this journal review, the reader will acquire skills to:

1. Determine the mechanisms, incidence and impact of pain in patients with amyotrophic lateral sclerosis (ALS) and to describe effective pharmacologic and non-pharmacologic treatment strategies.

2. Evaluate the prevalence of depression and other mood disorders (including pseudobulbar affect and fatigue) in patients with ALS, possible mechanisms involved, and treatment strategies.

3. Compare and characterize the incidence, impact, and mechanisms of sialorrhea (along with rating scales used) in patients with ALS including effective pharmacologic and non-pharmacologic treatment strategies.

4. Describe and characterize the incidence, impact, and mechanisms of respiratory failure in patients with ALS.

5. Recognize and appreciate the complicated decision making process that patients with ALS and their family members experience when confronted with palliative care issues.

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ABSTRACT: Patients with amyotrophic lateral sclerosis (ALS) have high symptom burdens, including pain, fatigue, dyspnea, and salivation, and they must make difficult decisions about the use of life-prolonging therapies, such as long-term mechanical ventilation. The impact of ALS is also felt by family caregivers who often struggle to meet the heavy physical, financial, and emotional demands associated with the illness. Expert multidisciplinary care may improve both quality and length of life of patients with ALS. However, although advances have been made in the treatment of some symptoms, others, including pain management, remain poorly studied. Involvement of palliative care specialists as part of the ALS multidisciplinary team is recommended, as we continue to work toward improving the quality of life for patients and their families.

Amyotrophic lateral sclerosis (ALS) is a progressive, incurable neuromuscular disorder with an incidence of about 2 per 100,000 person-years. Patients with ALS have high symptom burdens, including pain, fatigue, dyspnea, and salivation. The emotional and spiritual challenges to these patients are also profound and include loss of independence, declining ability to communicate, and demoralization. They must make difficult decisions about the use of life-prolonging therapies; such decisions are in many ways more complex than those faced by other patients with life-limiting illnesses. The impact of this disease is also felt by family caregivers who often struggle to meet the heavy physical, financial, and emotional demands associated with the functional decline that is the hallmark of ALS.

Riluzole, which may prolong survival by 3–6 months, is currently the only disease-modifying agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of ALS. By definition, much of the care provided to ALS patients is palliative in nature, which involves helping patients and families cope with the symptoms of the disease, improving quality of life and functional status, and helping them make decisions about goals of care.2,3 The purpose of this study is to review the data on management of common ALS-related symptoms, examine issues related to decision-making about the use life-prolonging technology, and assess the role of palliative care specialists in the treatment of ALS patients across the spectrum of the disease.

PAIN
Incidence and Impact. ALS patients have pain from a variety of causes, some of which are incompletely understood. Muscle atrophy and weakness may result in postural imbalance and cause pain in the muscles and joints as they compensate for more affected areas. Loss of the muscle mass ensheathing bones and joints can lead to more pressure and pain. Small discomforts, which might be relieved by position changes, become magnified when patients cannot move or turn, and these become even worse if patients have difficulty communicating their needs to caregivers.4 Pain from muscle cramping and spasticity is also common.5 The reported incidence of pain has been shown to vary from 19% to 80%,4,8 and both incidence and severity tend to increase as the disease progresses.10 Ganzini et al. interviewed 100 ALS patients about their symptoms, suffering, and quality of life and found that uncontrolled pain was fairly common. The median physical pain score as reported by the patients was 2 on a scale of 1–6; however, 19% rated their pain as ≥4. Patients with more pain were likely to report more suffering from their disease. In the final month of life, caregivers reported that their loved ones experienced increasing pain: on average, they rated a 4 on the 1–6 scale, with 30% of caregivers indicating a score of ≥5.5

Treatment. Recommendations for the treatment of pain in ALS patients are based on expert opinion because virtually no clinical trials have been done for the management of this symptom. The 1999 AAN ALS practice parameter noted the lack of evidence in this area.11 A 2009 update of this parameter failed to identify any controlled studies on this topic during the intervening years.12 Similarly, a Cochrane Review of drug treatment for ALS-related pain in 2008 indicated no randomized, or quasi-randomized studies of pain and no well-designed...
 observational studies of the efficacy of medications to treat pain. Position changes, padding of painful areas, and stretching and massaging of stiff limbs are non-pharmacological methods commonly used to decrease musculoskeletal pain, cramping, and stiffness. No data exist to support these practices. Expert recommendations for drug treatment of ALS pain suggest starting with non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and physiotherapy, and using opioids if these are ineffective. Several studies have addressed the issue of painful muscle cramping and spasticity, which are sometimes treated as separate topics from other types of pain in ALS. Baclofen, dantrolene, quinine, diazepam, gabapentin, and tizanidine have been commonly prescribed for these symptoms in ALS, much as they are used in multiple sclerosis and cerebral palsy. The FDA has issued a warning about the use of quinine due to safety concerns. Tizanidine may have efficacy in the treatment of spasticity in multiple sclerosis. A clinical trial of gabapentin for the primary treatment of ALS measured pain and muscle cramping as a secondary outcome. No symptomatic or functional benefits were noted. One double-blind study of oral baclofen for ALS-related spasticity done in 1979 failed to show benefit; however, a case series of intrathecal baclofen pumps in 8 ALS patients with severe spasticity-related pain reported that 6 of the 8 (75%) patients had significant pain relief, and 3 had complete resolution of pain. The average reduction in pain scale was 54% after placement of the pump. The value of exercise in the treatment of spasticity in ALS patients is unclear. One study of a personalized exercise program in the treatment of ALS-related spasticity showed benefit at 3 months, but this was not statistically significant.

MOOD DISORDERS IN ALS
Incidence and Impact. Difficulties in diagnosing depression in patients with chronic medical conditions are well known. Many common depression rating scales (such as the Beck Depression Inventory and the Hamilton Depression Rating Scale) include somatic markers of depression. Tools relying on these symptoms may overestimate the prevalence of depression in ALS patients for whom insomnia, fatigue, appetite, and weight loss are part of their underlying medical illness. On the other hand, clinicians may underestimate depression in the belief that a depressed mood is an inevitable reaction to being diagnosed with a life-threatening illness, a misapprehension that is at odds with careful studies. Given these difficulties it is not surprising that the prevalence of depression in ALS has been reported to be as low as 8% and as high as 75%. Studies using the ALS Depression Inventory (ADI-12), an ALS-specific depression rating scale, have indicated rates of clinically significant depression ranging from 28% to 48%.

Physical symptoms can be mistaken for depression in ALS, but they may also be a cause of mood disorders. Dyspnea in late-stage ALS can cause anxiety and depression may be associated with uncontrolled pain or other physical symptoms. Furthermore, ALS patients may experience profound fatigue due to insomnia, medication, and worsening respiratory function, and this symptom is associated with anhedonia and depressed mood.

Depression must also be distinguished from pseudobulbar affect. Pseudobulbar affect (PBA), or emotional lability, consists of episodes of laughing and crying, which are uncontrollable, stereotyped, and sometimes inappropriate in the context of the situation. In comparison to depressed patients, those with PBA have crying episodes that are excessive compared with the underlying emotion. PBA occurs in up to 50% of ALS patients.

Finally, the existential despair some patients feel in the face of their illness may be poorly described by the word depression. Despairing patients are not just depressed; they experience an overwhelming sense of demoralization, hopelessness, and loss of meaning in the face of their mortality. This feeling of despair is seen more often in patients who feel that they are a burden to their caregivers. Despairing patients are more likely to consider assisted suicide than others with ALS.

Treatment. The most recent AAN practice parameter notes that there are no controlled trials on the treatment of depression or anxiety in ALS, although at least one study suggested that depression is treatable even in the end stages of this illness. Choice of antidepressant should be tailored to the patient’s symptoms. Tricyclic antidepressants can be used for sialorrhea as well as mood, although the doses required for antidepressant effect are associated with an increased side effect profile compared with other medications. Patients who have anxiety or insomnia may benefit from an antidepressant that promotes sleep (such as amitryptiline, trazodone, or mirtazapine). Ritalin and modafinal are medications that have been used to treat fatigue in cancer and multiple sclerosis and may act as antidepressants as well. Modafinal may improve fatigue in ALS, although its efficacy as an antidepressant in this context is not known. PBA has been shown to respond to treatment with a variety of antidepressants, although most studies have been done in patients whose PBA was the result of multiple sclerosis.
(MS), stroke, or other brain injuries not related to ALS. A fixed combination of dextromethorphan and quinidine has been shown to be effective in ALS-related PBA. This formulation has been approved by the FDA and is marketed in the USA under the trade name Nuedexta.

**SIALORRHEA**

**Incidence and Impact.** About 50% of ALS patients experience significant sialorrhea; 20% have moderate to severe symptoms. In normal adults 1–1.5 liters of saliva are secreted daily, mainly by the parotid and submandibular glands. ALS patients may have sialorrhea due to inability to manage their saliva, decreased ability to swallow, and difficulties in maintaining head posture and closing the mouth. Patients with marked sialorrhea may have diminished quality of life due to aspiration of saliva, which leads to coughing and choking. They may have trouble sleeping due to worsening aspiration in the recumbent position, and increased difficulty using non-invasive positive pressure ventilation (NIPPV). Saliva can cause facial irritation and skin breakdown. Finally, excessive drooling can be embarrassing, leading patients to avoid social interaction.

Several sialorrhea scales have been developed. Some of these scales are quantitative, measuring volume of saliva flow. Others measure the amount of saliva more qualitatively, such as the saliva subjection of the revised ALS Functional Rating Scale (ALSFRS-R), or the impact of sialorrhea on quality of life and ability to function, such as the Drooling Impact Scale and the Global Impression of Change Scale. Objective measures of saliva volume are not sufficient to assess the impact of sialorrhea treatments on quality of life, because interventions that decrease sialorrhea may have unacceptable side effects. In the clinical setting, use of the ALSFRS-R or a quality-of-life (QOL) scale are likely to be sufficient to evaluate the need for intervention and to document response to treatment.

**Treatment.** Non-pharmacological means of treating sialorrhea include positioning and suctioning. A variety of anti-cholinergic medications are used to treat sialorrhea, including glycopyrrolate, amitriptyline, atropine, hyoscyamine, and transdermal scopolamine. Most of the evidence regarding use of these drugs is based on research done in non-ALS patient populations, including children with developmental delays and patients with head and neck cancer; however, data from the National ALS Patient CARE database suggest that about 70% of patients treated with these medications receive some benefit. Side effects of anticholinergic medications include sedation and delirium, which are especially common in elderly patients. Furthermore, the medications may cause thickening of mucous secretions in the lungs and throat, which for some patients is worse than sialorrhea. Cough assist devices and guaifenesin may increase the ability of patients to mobilize secretions and thus improve tolerability of anticholinergic drugs.

For patients who do not respond to anticholinergic agents or who have unacceptable side effects, some data support the use of botulinum toxin injected into the parotid and submandibular glands for patients with ALS and other conditions, such as Parkinson disease. Although earlier studies have raised concerns about possible side effects, including worsening of dysphagia and chewing difficulties, no significant adverse effects were reported in more recent studies, in which injections were done under electromyographic guidance.

Low-dose radiation has also been used to treat ALS patients who have severe sialorrhea. In case reports, 8-Gy radiation in one dose seemed as effective in producing clinical benefit as higher doses. Potential side effects include thickened secretions, radiation dermatitis (which should be minimal at this low dose of radiation), and sore throat.

**DYSPNEA AND RESPIRATORY FAILURE**

**Incidence and Impact.** As ALS progresses, most patients will have worsening shortness of breath. For patients who do not elect to use long-term mechanical ventilation (LTMV), worsening dyspnea has been cited as a cause of suffering in 56–82% in the last month of life. Severe dyspnea is associated with increased anxiety and insomnia, which are common in ALS and a cause of distress for both patients and caregivers. Fear of this symptom has been cited by patients who have requested assisted suicide.

**Treatment.** Non-invasive positive pressure ventilation (NIPPV) has been shown in many studies to improve life expectancy and QOL in patients with a forced vital capacity (FVC) of <50%. Patients who use NIPPV live an average of several months longer than those who do not. In addition, they may have less dyspnea, daytime fatigue, and insomnia. These benefits may persist even as the disease continues to progress.

Despite benefits in both quality and quantity of life, many patients do not use NIPPV. One study indicated that only about 9% of patients with an FVC of <40% predicted were using NIPPV support. Although these numbers increased in the years after the publication of the ALS practice parameter in 1999 (from 9% to 21%), use of NIPPV remains far below recommended levels. The reasons for this are unclear; however, in the ALS CARE study group report, about half of patients with an FVC of <40% who were not using NIPPV were offered this intervention but refused or did
not tolerate it. Patients with loss of bulbar tone or severe sialorrhea may have reduced tolerance for NIPPV. Those with ALS-related frontotemporal lobar dementia (FTLD) are less likely to comply with NIPPV. Patients who are more severely orthopneic or dyspneic may also be more likely to comply with NIPPV.

For patients who refuse NIPPV or whose symptoms are otherwise incompletely controlled, opioids, especially morphine, are often recommended for the treatment of severe dyspnea. Morphine has been shown to be safe and effective in dyspnea related to cancer, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and other life-limiting illnesses, and use of morphine, even in patients with respiratory failure, does not seem to hasten death. Although clinicians may be concerned about the possibility of morphine causing respiratory depression in this patient population, one study of 6 dyspneic ALS patients indicated that morphine administration resulted in symptomatic improvement and decreased respiratory rate without decreased oxygenation or increased PCO2. Appropriate use of opioids to treat dyspnea in ALS patients is therefore likely to be safe, as long as clinicians follow the “sedation precedes respiratory depression” rule. This clinical rule states that opioids will tend to produce sedation prior to decreasing respiratory drive and that serial assessment of level of consciousness can help clinicians avoid dangerous doses of opioids.

Patients who elect to receive LTMV generally do not suffer from dyspnea. If they choose to be withdrawn from ventilatory support they should be medicated appropriately with sedatives and opioids to prevent severe air hunger and suffering during the process.

**DECISION-MAKING IN ALS**

Patients with ALS and their families face difficult choices as the disease progresses. Although ALS is incurable, it is different in some respects from other life-limiting illnesses. Patients whose cancer is incurable may still have many therapeutic options to treat their disease. Many choose to undergo treatments that may prolong life for only a few months. On the other hand, if their disease does not respond to treatment, cardiopulmonary resuscitation (CPR) and mechanical ventilation (MV) are usually ineffective to prevent death from progression of their underlying malignancy, and the nature of the disease is such that long-term survival on MV is rarely an option. ALS patients have far fewer choices for treatment of the underlying illness. However, when they develop life-threatening respiratory failure, LTMV can prolong life for more than 10 years. Patients who intend to prolong their life in this manner must remain ventilated, and will continue to have disease progression. ALS patients and their families must therefore contemplate not whether their life can be prolonged, but whether life prolonged in this way is worth living. In fact, the use of LTMV by ALS patients is rare in this country (<10% of patients); it is much more common in other countries, such as Japan. Increased rates of LTMV in Japan have been attributed to a culture in which physicians and family members traditionally take the lead in decision-making and are expected to do everything possible to prolong the life of the patient. The fact that the Japanese government covers all costs of home mechanical ventilation may play a role as well.

Historically, many ALS patients on LTMV have been intubated without prior consideration of their wishes. Because patients may undergo a progressive decline in the ability to communicate due to dysarthria and ALS-related FTLD, early discussion is crucial. This is especially true because, once intubated, most ALS patients cannot be weaned from ventilatory support and would need to make the more difficult decision about whether to discontinue MV. Physicians may fear that discussing end-of-life care would lead patients to feel anxious or hopeless, and for this reason many avoid introducing the topic, waiting until the patient broaches the issue. However, studies show that ALS patients want and need information, are open to discussing their options, and believe that the physician should initiate the conversation. In 1996, a study of 75 ALS patients on LTMV showed that most were intubated emergently and were ill-prepared to make an informed decision at the time of initiation of MV. One fourth of the patients were unaware of the inevitability of respiratory failure, and less than half had discussed wishes regarding life support with their doctors. This situation seems to have improved, and more recent data suggest that ALS patients may have such discussions with their doctors at a rate higher than patients with advanced cancer.

How can we help patients with ALS and their families make decisions about life-prolonging interventions? Educational materials about LTMV are available, but the value of various tools in providing education about choices and/or helping decision-making has not been studied. Patients’ decisions regarding LTMV in ALS have been shown to also correlate with concerns about the burden of care placed on family members. LTMV at home is much more acceptable to patients than LTMV in a facility, in practice, however, home ventilation is an option only for those with the financial and social resources to have 24-hour, highly skilled care. For this reason,
educational materials and discussions with clinicians should include realistic information about topics such as insurance coverage and caregiving issues that affect the feasibility of home LTMV. Finally, because the decision to initiate LTMV also correlates strongly with the attitude of the physician who discusses this issue, care should be taken to ensure that educational materials provide a variety of perspectives on this choice.

In addition to educational materials specifically designed for ALS patients, a variety of advance medical directives are available to the general population. These documents allow patients to state, in advance of incapacity, their wishes for CPR, MV, and other forms of life support, such as gastrostomy tubes. Most advance directives also allow patients to name a surrogate decision-maker. Because even patients who desire LTMV may want withdrawal of ventilatory support if a "locked-in" state or cognitive decline occurs, documentation of these wishes beforehand is crucial, and advance medical directives can be very useful for this purpose. However, these documents tend to be quite general, do not address the specific issues ALS patients face, and may not be sufficient by themselves to guide patients and families.

The decision to withdraw MV in the patient receiving LTMV is extremely challenging. When the patient is unable to communicate and has not clearly documented his or her choices in advance, there may be conflict about whether withdrawal is in accordance with the patient’s wishes, with or without ventilation. Although no data exist on how best to guide these decisions, consultation with ethics and/or palliative care services may help ensure that all aspects of this decision have been considered. Support should be offered to family members and staff.

**ALS AND PALLIATIVE CARE**

Since the publication of the ALS practice parameter in 1999, increased utilization of multidisciplinary clinics has improved quality of life for many ALS patients. However, many patients continue to suffer from uncontrolled symptoms and struggle to make decisions about life-prolonging therapies. Although research has provided new options for treatment of some symptoms, others, such as ALS-related pain, remain poorly understood.

Palliative care is a medical specialty that focuses on symptom management and medical decision-making for patients who are facing life-limiting illnesses. Early involvement of palliative care services into ALS care has been suggested as a method for improving symptom control and quality of life for ALS patients and their families across the trajectory of this illness. This approach has shown benefits in the care of cancer patients. In the USA and elsewhere, however, palliative care specialists have generally been involved with ALS patients only during the terminal phases of their disease, when hospice care is contemplated or when decisions about withholding or withdrawing LTMV are being made. Inclusion of palliative care as part of a multidisciplinary team approach would be one way to integrate care across the continuum of the illness.

How might this change benefit ALS patients? Although not every patient with ALS needs palliative care involvement at initial diagnosis, those with increasing symptoms might benefit from this intervention. Neurologists and palliative care physicians both have experience in treating the type of symptoms facing patients with ALS, but they have slightly different areas of expertise. Neurologists are likely to be more familiar with the treatment of salivary, PBA, and spasticity, which are common in the patient populations they treat. Palliative care physicians may be more comfortable with management of pain and dyspnea, and especially with the use of opioids and benzodiazepine medications for these conditions, due to their treatment of cancer patients. Combining these perspectives may provide more attention to the full range of symptoms ALS patients face at every phase of their illness, and help address the well-documented suffering associated with this disease.

As a palliative care physician, I will note that there are challenges to working with patients in the ALS clinic. In working with cancer patients whose symptoms are poorly controlled, our team will often see patients every few weeks. ALS patients, however, often come from long distances to be seen in the ALS specialty clinic, and are usually seen in such a clinic only every 3–6 months. Infrequent visits are the norm for several reasons: as the disease progresses it becomes more difficult to transport the patient and, unlike chemotherapy, riluzole therapy does not require frequent visits for monitoring or administration. Active management of symptoms like pain or dyspnea and gauging response to treatment in a timely manner are more challenging for this reason. The use of telemedicine may be one way to overcome this structural barrier.

As the illness progresses, physical symptoms of the disease intensify. Psychological distress in ALS patients and their caregivers also increases. Decisions about gastrostomy tube placement and the use of MV must be made. Coordinated care, providing aggressive symptom management, and support for decision-making all become critical, and integration of palliative care into the multidisciplinary team approach may be especially beneficial at this point. For patients choosing to forgo LTMV, palliative care clinicians working as part of the ALS multidisciplinary team could facilitate the appropriate and timely utilization of hospice.
services. As noted by others, difficulties in accessing hospice care are common for ALS patients. Hospice eligibility criteria are strict, requiring patients to have a life expectancy of 6 months or less, whereas the functional decline and intense caregiving needs of ALS patients is such that they might benefit from these services for far longer than that 6-month time-frame. The per-diem rate structure for hospice care makes provision of necessary equipment, such as power wheelchairs (with an average cost of $26,404), prohibitive, and lack of familiarity with modalities like NIPPV may lead hospices to refuse ALS patients who utilize them. Hospices, possibly having limited experience with ALS patients, often need education about their care, and the ALS team may benefit from a better understanding of hospice services. Palliative care physicians working with the ALS team may help to bridge this divide. This collaboration may also help improve the quality of the care ALS patients receive once they are admitted to hospice by enhancing communication between hospice agencies and the ALS team. Finally, palliative care clinicians and ALS providers should work together to advocate for needed changes in the hospice Medicare benefit so that it more adequately meets the patient’s needs.

In addition to clinical collaboration, further improvements in the QOL of ALS patients and their families will require ongoing research. Palliative care physicians, whose research is focused on end-of-life decision-making and the management of symptoms like pain and dyspnea in other patient populations, have a common agenda with the neurologists, pulmonologists, and other members of the core ALS team. Research informed by the differing yet complementary perspectives of these professionals will be beneficial in increasing the evidence base about issues that remain sparsely studied even 10 years after the publication of the first ALS practice parameter and may help in continuing to improve treatment of this illness.

REFERENCES

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