Washington University School of Medicine

Digital Commons@Becker

Open Access Publications

2020

Top ten tips palliative care clinicians should know about amyotrophic lateral sclerosis

Elyse A. Everett

Washington University School of Medicine in St. Louis

Elizabeth Pedowitz

Icahn School of Medicine at Mount Sinai

Samuel Maiser

Hennepin Healthcare

Joss Cohen

Cedars-Sinai Medical Center, Los Angeles

Jessica Besbris

Cedars-Sinai Medical Center, Los Angeles

See next page for additional authors

Follow this and additional works at: https://digitalcommons.wustl.edu/open_access_pubs

Please let us know how this document benefits you.

Recommended Citation

Everett, Elyse A.; Pedowitz, Elizabeth; Maiser, Samuel; Cohen, Joss; Besbris, Jessica; Mehta, Ambereen K.; Chi, Luqi; and Jones, Christopher A., "Top ten tips palliative care clinicians should know about amyotrophic lateral sclerosis." *Journal of Palliative Medicine*. 23, 6. 842 - 847. (2020).
https://digitalcommons.wustl.edu/open_access_pubs/9455

This Open Access Publication is brought to you for free and open access by Digital Commons@Becker. It has been accepted for inclusion in Open Access Publications by an authorized administrator of Digital Commons@Becker. For more information, please contact vanam@wustl.edu.

Authors

Elyse A. Everett, Elizabeth Pedowitz, Samuel Maiser, Joss Cohen, Jessica Besbris, Ambereen K. Mehta, Luqi Chi, and Christopher A. Jones

Top Ten Tips Palliative Care Clinicians Should Know About Amyotrophic Lateral Sclerosis

Elyse A. Everett, MD, MOT,¹ Elizabeth Pedowitz, MD,² Samuel Maiser, MD,³ Joss Cohen, MD,⁴
Jessica Besbris, MD,^{4,5} Ambereen K. Mehta, MD, MPH,⁶
Luqi Chi, MD, MSCE,⁷ and Christopher A. Jones, MD, MBA⁸

Abstract

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive and fatal neurodegenerative disorder with enormous palliative care (PC) needs that begin at the time of diagnosis. Although it is an uncommon disease, clinicians who work in PC or hospice are likely to encounter ALS somewhat frequently given the needs of patients with ALS with regard to psychosocial support, symptom management, advance care planning (ACP), caregiver support, and end-of-life care. As such, PC clinicians should be familiar with the basic principles of ALS symptoms, treatments, disease course, and issues around ACP. This article, written by a team of neurologists and PC physicians, seeks to provide PC clinicians with tips to improve their comfort and skills caring for patients with ALS and their families.

Keywords: ALS; amyotrophic lateral sclerosis; hospice; palliative care; symptom control

Introduction

AMYOTROPHIC LATERAL SCLEROSIS (ALS) is a progressive neurodegenerative disorder that causes severe weakness, respiratory failure, and a host of other debilitating symptoms. ALS is a devastating disease that is uniformly fatal, generally within years of diagnosis.¹ Palliative care (PC) needs in ALS start essentially at the time of diagnosis (psychosocial support and symptom management), evolve over the course of the illness (advance care planning [ACP] and caregiver support), and intensify nearing the end of life (hospice care and bereavement support).² Patients with ALS are best cared for in multidisciplinary ALS clinics that typically include neurologists, pulmonologists, nurses, physical and occupational therapists, respiratory therapists, speech language pathologists (SLP), social workers, and nutritionists.³

Society guidelines for the treatment of ALS advocate the inclusion of PC in ALS care.^{4,5} Primary PC provided by neurologists is ideal, given that almost all patients with ALS will be under the care of a neurologist, but this can be severely limited owing to neurologists' limited PC training⁶ and clinical time constraints. Specialist PC clinicians, on the contrary, may be

uncomfortable with the management of patients with ALS because of the relative rarity of this disease and its unique symptom management techniques, disease-directed treatment options, and disease trajectory. Given that many patients with ALS will end up being seen by PC or hospice at some point in their disease course, it is important that all clinicians who care for those with serious illness have an understanding of the varied symptoms and management options, expected disease progression, and distinctive end-of-life considerations in ALS. In this article, 10 tips that physicians involved in the care of patients with ALS consider important for PC clinicians to know about this illness are provided.

Tip 1: There Are Two FDA-Approved Disease-Modifying Medications for ALS that Provide Modest Benefit over Placebo

Riluzole was approved in 1995 after a landmark trial showed that it offered a two- to three-month survival benefit over placebo; there are little data on how it affects the quality of life (QoL).^{7,8} Riluzole is a glutamate antagonist that is taken orally twice daily. The main adverse effects include

¹John T. Milliken Department of Medicine, Washington University in St. Louis, St. Louis, Missouri, USA.

²Department of Neurology, Icahn School of Medicine at Mount Sinai, New York, New York, USA.

³Department of Neurology, Hennepin Healthcare, Minneapolis, Minnesota, USA.

Departments of ⁴Neurology and ⁵Supportive Care Medicine, Cedars-Sinai Medical Center, Los Angeles, California, USA.

⁶Department of Medicine, University of California, Los Angeles, California, USA.

⁷Department of Neurology, Washington University in St. Louis, St. Louis, Missouri, USA.

⁸Department of Medicine, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA.

Accepted January 29, 2020.

hepatotoxicity, fatigue, and gastrointestinal effects (nausea, anorexia, and indigestion). The cost is ~\$1,000 per month.

Edaravone was approved in 2017 after a landmark trial showed that it slowed the rate of functional neurologic decline by ~33% in a select subset of patients with low severity of illness and had some positive effect on QoL.⁹ Edaravone is a free radical scavenger administered through intravenous infusion (four-week cycle with two weeks on and two weeks off) using a port or peripherally inserted central catheter at home or in an infusion center. The adverse effects include headache, constipation, gait disturbances, and respiratory changes.^{9–11} There are data supporting its efficacy up to 12 months, although the benefit is unclear past that point. The cost is ~\$145,500 per year.

As with many medications for life-limiting illnesses, timing of discontinuation is unclear. For riluzole, there is conflicting evidence regarding the survival benefit in advanced stages of the disease, and some studies suggest it may even be harmful when used in advanced stages.^{12–14} There is no consensus, but common considerations for discontinuation include advanced stage (tracheostomy placement or hospice enrollment), medication side effects, and patient wish to avoid life-prolonging treatments. Deciding when to stop edaravone is challenging given the limited data on its long-term effect, but discontinuation frequently happens naturally owing to patient preference, physician recommendation, insurance denials, or hospice election.

Tip 2: Clinicians Hesitate to Apply Existing Prognostication Models to Individual Patients Given the Heterogeneous Nature of ALS

Although ALS is uniformly fatal, extreme variability exists within the disease course because of the notable phenotypic variability of initial presentation, progression, and survival. The general median survival time from symptom onset to death ranges from 20 to 48 months, although 10% of patients go on to survive longer than 10 years.^{1,15} Bulbar-onset ALS has an even worse prognosis than the more common limb-onset ALS, with a median survival of 2 years (greater than 10-year survival of only 3%).¹⁵

Several demographic and clinical factors correlate with longer or shorter prognosis. Age is a strong predictor of mortality; those with symptom onset before age 40 are more likely to live longer (>10 years) than those with symptom onset after age 80 (median survival 2 years).¹ Those who have concomitant frontotemporal dementia have a worse prognosis. Most studies have found no difference between sporadic and familial ALS in outcomes, although mutations in SOD1 and genetic expansion of C9orf72 have been associated with shorter survival.^{1,16}

Diagnostic delay has been found to be a favorable indicator as a shorter onset between symptom onset and diagnosis likely indicates more aggressive disease. Although there are diagnostic models that combine certain variables (weight loss, forced vital capacity [FVC] change, functional capacity decline, etc.) to predict time from symptom onset to either death or respiratory insufficiency,^{16,17} physicians still hesitate to give predictions to individual patients as survival times can vary widely from months to over a decade. Overall, older age, bulbar onset, and shorter diagnostic delay have the strongest correlation with a poor prognosis.

Tip 3: There Is a Recognized Need for Early and Regular Advance Care Planning Conversations for Patients with ALS and Patients and Families Generally Welcome These Discussions

ACP for patients with ALS is unique given the predictable progression, lack of cure, and variety of symptoms that may limit patient ability to participate meaningfully in complex conversations at advanced disease stages. Cognitive impairment is common in ALS and can influence decision-making capacity. Pseudobulbar affect (PBA), dysarthria, and behavioral changes make communication difficult even if patients maintain decision-making capacity.^{18,19}

ACP in ALS should start early, especially in cases of delayed diagnosis and rapidly progressive disease, and should continue throughout the disease course as treatment preferences often change with symptom progression. Many clinicians worry that patients and families may feel that discussions about ACP happen too early, although framing ACP as a “normal part of practice that is done with all patients” can eliminate that concern. A “planning for the worst” approach has not been shown to diminish hope or patient engagement. Studies have instead shown that patients and families welcome the opportunity to discuss what to expect as the disease progresses.²⁰

The most common components of ACP conversations in ALS include code status, risks and benefits of life-sustaining interventions (tracheostomy and gastrostomy tube [G-tube]), and identifying a surrogate decision maker. It is important to address intubation preference with the added education that chronic respiratory failure may make safe extubation difficult even in reversible illnesses like pneumonia, thereby forcing a tracheostomy decision. Documentation of these decisions is often done through advance directives (ADs) and, in some states, Provider Orders for Life-Sustaining Treatment (POLST). ALS-specific ADs are novel and currently being studied.^{20,21} ACP should also include an exploration of patient values focused on what gives their life meaning and purpose. This knowledge helps patients and physician choose the medical interventions that have the best chance to offer meaningful outcomes as defined by the patient.

Tip 4: Noninvasive Ventilation Can Improve Both Quantity and Quality of Life for Patients with ALS, but Oxygen Alone Should Never Be Used for Dyspnea

Respiratory failure in ALS develops because of respiratory muscle weakness.²² Symptoms of respiratory insufficiency include dyspnea, orthopnea, sleep disruption, morning headaches, and fatigue. Respiratory insufficiency typically begins with nocturnal hypoventilation followed by daytime hypoventilation as weakness progresses. Noninvasive ventilation (NIV) is used to provide external respiratory support in those with respiratory insufficiency.²³ NIV has been shown to prolong survival and improve QoL in patients with ALS who can tolerate it,²⁴ with earlier initiation providing more benefit.^{25–27} Methods to improve patient comfort and compliance with NIV include proper mask fittings, alternative mask types, adjusting settings according to efficacy data and comfort, and the concurrent use of dyspnea/anxiety medications.

NIV mode and settings should be carefully selected by a physician familiar with neuromuscular disease and NIV. Conventional NIV such as bilevel positive airway pressure (BiPAP) can be used, but owing to rapid progression of

weakness, BiPAP settings must be adjusted frequently to maintain adequate respiratory support. This can be mitigated by newer devices that offer volume-targeted pressure support modes, including those that automatically adjust pressure values to achieve targeted tidal volumes (average volume assured pressure support or AVAPS). A significant barrier in the past, some home ventilators now have batteries that allow more freedom outside the home for when NIV is used during awake time. Before entering hospice, patients may be required to transition from a home ventilator to a less expensive BiPAP machine; assistance should be sought from someone knowledgeable in NIV. Oxygen cannot be used to improve dyspnea in patients with ALS and should never be used as a replacement for NIV, as the problem in ALS-associated respiratory failure is hypoventilation with hypercapnia rather than hypoxia.

Tip 5: Not All Patients Benefit from Gastrostomy Tubes

Most patients with ALS develop dysphagia at some point in their disease. This can lead to effortful mealtimes, weight loss, malnutrition, and choking. Loss of appetite and inability to feed oneself may also contribute to decreased oral intake.²⁸ It is important to have early consultation with an SLP at the first sign of impaired chewing or swallowing. The SLP can recommend safe swallowing techniques and modifications of food and liquid consistencies if needed. High-calorie and high-protein nutritional supplements are often recommended.⁵ Depending on the severity of dysphagia and rate of weight loss, the placement of a G-tube may be considered. It is important for patients to understand that enteral feeding does not have to replace oral feeding and can be used to supplement oral intake.²⁸

There are no randomized controlled trials (RCTs) comparing survival in those with and without G-tubes, and there is no high-quality evidence on whether enteral nutrition affects QoL in patients with ALS.^{5,28,29} The optimal timing of G-tube placement is controversial with neurology academy ALS guidelines recommending placement when FVC is >50% of predicted to reduce peri-procedural risk.^{5,28} Risks of G-tube placement include laryngeal spasm, infection, hemorrhage, failure to place, and death as a result of respiratory arrest.

Given the paucity of data surrounding G-tube use in ALS and difficulty in predicting the risks and benefits in individual patients, emphasis should be placed on shared decision making. Relevant concerns to discuss with patients include how burdensome eating is, the weight loss curve, and their preferences on surgical interventions and artificial nutrition.

Tip 6: Tracheostomy Is Often the Hardest Care Decision in ALS

As the muscles of respiration weaken, patients are initially managed on NIV. There may come a point when this will no longer provide adequate ventilation and patients become increasingly symptomatic. At this point, the patient must decide between invasive ventilation with tracheostomy or aggressive symptom management through hospice, often causing patients to feel like they are choosing whether to live or die. In western countries, a minority of patients with ALS undergo tracheostomy (up to ~15%).³⁰

Patients who elect tracheostomy do so to prolong their life, although median survival following tracheostomy can range from eight months to three years with the majority dying within one to two years.^{30,31} Survival is significantly shorter for patients older than age 60.³² Patients with tracheostomies can have an acceptable QoL with depression rates similar to controls,³¹ but very little is known about the burden on caregivers. Patients with ALS who have tracheostomies require 24-hour care at home or in long-term care facilities. This level of care can create high physical, emotional, and financial demands on families and caregivers.

In addition to describing the amount of care needed for these patients, it is important to clearly define “endpoints” before tracheostomy placement. These endpoints are used to identify the time when life prolongation is no longer acceptable to the patient and invasive ventilation should be discontinued. For many, loss of ability to communicate is a commonly chosen endpoint, so previous knowledge of their wishes is necessary. The choice to undergo tracheostomy is an incredibly complex decision, which should be a shared decision among the patient, family, and physician.

Tip 7: There Are Multiple Causes of Pain/Discomfort in ALS that Are Amenable to Different Treatments

Pain is a common but often underappreciated symptom of ALS that can interfere with daily functioning and affect QoL.³³ There are multiple causes of pain and discomfort including cramps, spasticity, neuropathic pain, joint pain, and pressure sores. Clinicians must be familiar with identifying the different types of pain and various treatment strategies (Table 1). There is a lack of high-quality data for treatment of pain in ALS.

Muscle cramps (sudden, involuntary muscle contractions) are one of the most common causes of pain in ALS.³⁴ Quinine sulfate had traditionally been used but is no longer recommended because of safety concerns.⁴ A small RCT found that mexiletine, a sodium channel-blocking antiarrhythmic, reduces the frequency and severity of cramps.³⁵ Although no high-quality data exists, baclofen, magnesium, vitamin E, gabapentin, and benzodiazepines are commonly used and may be helpful. A daily stretching program can also help alleviate these symptoms.

Spasticity (velocity-dependent increase in muscle tone) is common in ALS, contributes to loss of voluntary movement, and can be painful.³⁶ Clinical practice guidelines recommend physical therapy to maintain range of movement and prevent contractures and consideration of oral therapy with baclofen or tizanidine or intrathecal baclofen if spasticity is severe.⁵ It is important to monitor for systemic side effects of oral antispasticity medications as generalized weakness and sedation can be debilitating. Low-dose botulinum toxin injections may be helpful but require high-level expertise.³⁷

Skin breakdown, pressure sores, and joint pain related to immobility are other possible sources of pain and should be monitored. There are special mattresses, pillows, and custom-fitted wheelchairs to help prevent these, and frequent repositioning and range of motion exercises are important. Joint pain can be treated with acetaminophen and nonsteroidal anti-inflammatory drugs. Pain may become severe enough to warrant careful treatment with low-dose opiates when refractory to other agents.

TABLE 1. PAIN ETIOLOGIES AND TREATMENTS

Type of Pain	Medications	Nonmedication Options
Cramps	Baclofen Mexiletine Gabapentin Benzodiazepines Magnesium Antiepileptic drugs (levetiracetam or carbamazepine) Vitamin E	Stretching Massage
Spasticity	Baclofen (oral or intrathecal) Tizanidine Benzodiazepines Antiepileptic drugs (levetiracetam or carbamazepine) Dantrolene Carbidopa/levodopa Botulinum toxin injections	Physical therapy Stretching Neutral-position splints for hands and ankles to reduce joint contractures
Neuropathic pain	Gabapentin Pregabalin Tricyclic antidepressants	
Pressure sores		Special mattresses, pillows, custom-fitted wheelchairs Frequent repositioning
Unspecified pain (joint, etc)	Acetaminophen Nonsteroidal anti-inflammatory drugs Opiates Antiepileptic drugs Tetrahydrocannabinol and cannabidiol	Physical therapy Massage Warm and cold compresses Acupuncture

Tip 8: Nonmotor Symptoms Like Fatigue, Excessive Secretions, and Cognitive Changes are Common in ALS and Can Be Treatable

Nonmotor symptoms of ALS commonly occur and can be just as disabling as the motor symptoms. High-quality data for the treatment of these symptoms is limited.

Fatigue is one of the most prevalent complaints and can be difficult to treat, leading to impaired QoL.³⁸ The etiology of fatigue is multifactorial including muscle weakness, pain, respiratory insufficiency, and decreased caloric intake.³⁹ Early recognition and management of treatable comorbidities are key to improving fatigue. Treatment can entail both pharmacological therapy with modafinil, methylphenidate, or amantadine and biopsychosocial modalities including energy conservation, setting expectations, and relaxation techniques.

Excess secretions are one of the most disabling nonmotor symptoms of ALS and can lead to exacerbation of dysarthria and respiratory failure, aspiration, and psychosocial distress.⁴⁰ Anterior secretions (drooling) are differentiated from posterior secretions (thick mucus leading to congestion) as treatment of these two entities is distinct. Anterior secretions can be treated with suctioning and anticholinergics such as amitriptyline, atropine drops, glycopyrrrolate, and scopolamine patches. If refractory, botulinum toxin injections or irradiation to the salivary glands can be considered.⁴⁰ Posterior secretions are more difficult to manage but can be treated with hydration, guaifenesin, and cough assist machines.

PBA, reflexive outbursts of excessive or inappropriate laughter or crying, affects 20–50% of patients with ALS, is distressing to the patient and family, and can be easily misdiagnosed as depression. PBA can be managed with the

combination drug dextromethorphan and quinidine; selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) can be trialed as well.⁴

ALS is associated with a range of psychological and cognitive disturbances.^{41–43} Up to 50% of patients with ALS have evidence of cognitive impairment and 15% meet criteria for frontotemporal dementia. Frontotemporal dysfunction includes issues with executive function, language, apathy, loss of empathy, and disinhibition.

Tip 9: Patients and Families with ALS Carry a Host of Psychosocial Needs Specific to This Illness

ALS confers a substantial psychosocial burden on patients and families with studies indicating that psychosocial factors may play a greater role in QoL than physical factors like weakness.⁴⁴ Patients with ALS often experience diagnostic delays, enduring a year or more of potentially unnecessary procedures or treatments, only to ultimately learn they have a relentlessly progressive disease with limited treatments and no cure, requiring immediate adjustment of their expectations for their lives.

With an average age at diagnosis of 55 years, these patients may be primary earners or parents of young children. Worsening physical debility may require spouses and children to step into new financial or caregiver roles that may lead to a significant shift in relationship dynamics.⁴⁵ The demands on caregivers increase as the disease progresses. Because of increasing physical and financial dependence, patients often express worry about being a burden to family members; this concern has been found to be particularly prevalent when considering tracheostomy⁴⁵ and may influence decision

making regarding this intervention. The gradual loss of physical ability and communication skills often leads to social isolation, which may contribute to low mood or reduced QoL. Diagnosis with a life-threatening illness may lead to spiritual distress, increasing the need for spiritual support as well.

Despite these factors, low rates of depression have been reported in ALS, although commonly used depression scales may not be best suited to detect depression in this illness.⁴⁶ When present, depression appears to be linked to shorter survival times, controlling for age and disease severity.⁴⁷ Higher perceived social support and confidence in the patient's own coping potential may predict less depressed mood, and studies have demonstrated the importance of social networks, family support, and technological aid devices.⁴⁶ Given the substantial influence of psychosocial wellbeing on QoL, experts advocate a holistic approach incorporating psychosocial and spiritual support into clinical care⁴⁵ with acknowledgment that support needs may differ between patients and their family members.

Tip 10: Although They Fear a Death from Suffocation, Most Patients with ALS Die Peacefully in the Location of Their Preference

The cause of death in most patients with ALS is respiratory failure.²² The most common clinical scenario is an acute deterioration in respiratory status followed by death within a day or so.^{48,49} Consequently, a significant portion of people with ALS fear that they are going to “choke” or “suffocate” to death, which can provoke anxiety and depression and a wish and/or request to die.⁵⁰ Fortunately, the majority of patients with ALS die peacefully⁴⁸ and in the location of their choosing,⁵¹ be it at home or in an inpatient hospice unit. The most common symptoms experienced by patients with ALS at the end of life are dyspnea, anxiety, pain/discomfort, and insomnia,^{48,51} which if assessed for can be adequately controlled with opiates, benzodiazepines, and other medications. Many patients choose to discontinue use of NIV or invasive ventilation at the end of life,⁵¹ especially if they feel it is keeping them alive in an unwanted state or prolonging their death. Patients with ALS should be informed during routine visits that while their likely cause of death will be respiratory related, it is very uncommon for people to choke or suffocate to death and their death will most likely be peaceful. Their concerns about end-of-life should be queried and they should be reassured that their terminal symptoms can nearly always be controlled.

Conclusion

ALS is a rapidly progressive and widely symptomatic neurodegenerative condition that is always fatal and causes significant amounts of suffering to patients and their caregivers. PC clinicians should be familiar with the expected disease course, symptoms and treatments, common ACP decisions, and end-of-life care for ALS to provide the best possible care to those with this devastating disease.

Funding Information

No funding was received.

Author Disclosure Statement

No competing financial interests exist.

References

- Chio A, Logroscino G, Hardman O, et al.: Prognostic factors in ALS: A critical review. *Amyotroph Lateral Scler* 2009;10:310–323.
- Oliver D: Palliative care in motor neurone disease: Where are we now? *Palliat Care* 2019;12:1–14.
- Traynor BJ, Alexander M, Corr B, et al.: Effect of a multidisciplinary amyotrophic lateral sclerosis (ALS) clinic on ALS survival: A population based study, 1996–2000. *J Neurol Neurosurg Psychiatry* 2003;74:1258–1261.
- Miller RG, Jackson CE, Kasarskis EJ, et al.: Practice Parameter update: The care of the patient with amyotrophic lateral sclerosis: Multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review). *Neurology* 2009;73:1227–1233.
- Andersen PM, Abrahams S, Borasio GD, et al.: EFNS guidelines on the Clinical Management of Amyotrophic Lateral Sclerosis (MALS)—Revised report of an EFNS task force. *Eur J Neurol* 2012;19:360–375.
- Brizzi K, Creutzfeldt CJ: Neuropalliative care: A practical guide for the neurologist. *Semin Neurol* 2018;38:569–575.
- Bensimon G, Lacomblez L, Meininger V: A controlled trial of riluzole in amyotrophic lateral sclerosis. *ALS/Riluzole Study Group. N Engl J Med* 1994;330:585–591.
- Miller RG, Mitchell JD, Moore DH: Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). *Cochrane Database Syst Rev* 2012;3:CD001447.
- Abe K, Aoki M, Tsuji S, et al.: Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: A randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2017;16:505–512.
- Abe K, Itoyama Y, Sobue G, et al.: Confirmatory double-blind, parallel group, placebo-controlled study of efficacy and safety of edaravone (MCI-186) in amyotrophic lateral sclerosis patients. *Amyotroph Lateral Scler Frontotemporal Degener* 2014;15:610–617.
- Writing Group on Behalf of the Edaravone (MCI-186) ALS 19 Study Group: Open-label 24-week extension study of edaravone (MCI-186) in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener* 2017;18(suppl1):55–63.
- Traynor B, Alexander M, Corr B, et al.: An outcome study of riluzole in amyotrophic lateral sclerosis: A population-based study in Ireland, 1996–2000. *J Neurol* 2003;250:473–479.
- Bensimon G, Lacomblez L, Delumeau JC, et al.: A study of riluzole in the treatment of advanced stage or elderly patients with amyotrophic lateral sclerosis. *J Neurol* 2002;249:609–615.
- Fang T, Al Khleifat A, Meurgey JH, et al.: Stage at which riluzole treatment prolongs survival in patients with amyotrophic lateral sclerosis: A retrospective analysis of data from a dose-ranging study. *Lancet Neurol* 2018;17:416–422.
- Chio A, Calvo A, Moglia C, et al.: Phenotypic heterogeneity of ALS: A population-based study. *J Neurol Neurosurg Psychiatry* 2011;82:740–746.
- Westeneng HJ, Debray TPA, Visser AE, et al.: Prognosis for patients with amyotrophic lateral sclerosis: Development and validation of a personalized prediction model. *Lancet Neurol* 2018;17:423–433.

17. Ackrivo J, Hansen-Flaschen J, Wileyto EP, et al.: Development of prognostic model of respiratory insufficiency or death in ALS. *Eur Respir J* 2019;53:1802237.
18. Connolly S, Galvin M, Hardiman O: End-of-life management in patients with amyotrophic lateral sclerosis. *Lancet Neurol* 2015;14:435–442.
19. Kiernan MC: Palliative care in amyotrophic lateral sclerosis. *Lancet Neurol* 2015;14:347–348.
20. Levi BH, Simmons Z, Hanna C, et al.: Advance care planning for patients with amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener* 2017;18:388–396.
21. Benditt JO, Smith TS, Tonelli MR: Empowering the individual with ALS at the end-of-life: Disease-specific advance care planning. *Muscle Nerve* 2001;24:1706–1709.
22. Gil J, Funalot B, Verschueren A, et al.: Causes of death among French patients with amyotrophic lateral sclerosis: A prospective study. *Eur J Neurol* 2008;15:1245–1251.
23. Clinical indications for noninvasive positive pressure ventilation in chronic respiratory failure due to restrictive lung disease, COPD, and nocturnal hypoventilation—A consensus conference report. *Chest* 1999;116:521–534.
24. Bourke SC, Tomlinson M, Williams TL, et al.: Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: A randomised controlled trial. *Lancet Neurol* 2006;5:140–147.
25. Ward S, Chatwin M, Heather S, et al.: Randomised controlled trial of non-invasive ventilation (NIV) for nocturnal hypoventilation in neuromuscular and chest wall disease patients with daytime normocapnia. *Thorax* 2005;60:1019–1024.
26. Orlikowski D, Prigent H, Quera Salva MA, et al.: Prognostic value of nocturnal hypoventilation in neuromuscular patients. *Neuromuscul Disord* 2017;27:326–330.
27. Vitacca M, Montini A, Lunetta C, et al.: Impact of an early respiratory care programme with non-invasive ventilation adaptation in patients with amyotrophic lateral sclerosis. *Eur J Neurol* 2018;25:556–e33.
28. Miller RG, Jackson CE, Kasarskis EJ, et al.: Practice Parameter update: The care of the patient with amyotrophic lateral sclerosis: Drug, nutritional, and respiratory therapies (an evidence-based review). *Neurology* 2009;73:1218–1226.
29. Katzberg HD, Benatar M: Enteral tube feeding for amyotrophic lateral sclerosis/motor neuron disease. *Cochrane Database Syst Rev* 2011;1:CD004030.
30. Chio A, Calvo A, Ghiglione P, et al.: Tracheostomy in amyotrophic lateral sclerosis: A 10-year population-based study in Italy. *J Neurol Neurosurg Psychiatry* 2010;81:1141–1143.
31. Vianello A, Arcaro G, Palmieri A, et al.: Survival and quality of life after tracheostomy for acute respiratory failure in patients with amyotrophic lateral sclerosis. *J Crit Care* 2011;26:329.e7–e14.
32. Atsuta N, Watanabe H, Ito M, et al.: Age at onset influences on wide-range clinical features of sporadic amyotrophic lateral sclerosis. *J Neurol Sci* 2009;276:163–169.
33. Chio A, Mora G, Lauria G: Pain in amyotrophic lateral sclerosis. *Lancet Neurol* 2017;16:144–157.
34. Ng L, Khan F, Young CA, et al.: Symptomatic treatments for amyotrophic lateral sclerosis/motor neuron disease. *Cochrane Database Syst Rev* 2017;1:CD011776.
35. Oskarsson B, Moore D, Mozaffar T, et al.: Mexiletine for muscle cramps in ALS: A randomized double-blind cross-over trial. *Muscle Nerve* 2018;58:42–48.
36. Ashworth NL, Satkunam LE, Deforge D: Treatment for spasticity in amyotrophic lateral sclerosis/motor neuron disease. *Cochrane Database Syst Rev* 2012;2:CD004156.
37. Marvulli R, Megna M, Citraro A, et al.: Botulinum toxin type A and physiotherapy in spasticity of the lower limbs due to amyotrophic lateral sclerosis. *Toxins* 2019;11:381.
38. Abraham A, Drory V: Fatigue in motor neuron diseases. *Neuromuscul Disord* 2012;22 Suppl 3:S198–S202.
39. Nicholson K, Murphy A, McDonnell E, et al.: Improving symptom management for people with amyotrophic lateral sclerosis. *Muscle Nerve* 2018;57:20–24.
40. Garuit G, Rao F, Ribuffo V, Sansone V: Sialorrhea in patients with ALS: Current treatment options. *Degener Neurol Neuromuscul Dis* 2019;9:19–26.
41. Zucchi E, Ticozzi N, Mandrioli J: Psychiatric symptoms in amyotrophic lateral sclerosis: Beyond a motor neuron disorder. *Front Neurosci* 2019;13:175.
42. Ringholz G, Appel S, Bradshaw M, et al.: Prevalence and patterns of cognitive impairment in sporadic ALS. *Neurology* 2005;65:586–590.
43. Roos E, Mariosa D, Ingre C, et al.: Depression in amyotrophic lateral sclerosis. *Neurology* 2016;86:2271–2277.
44. Clarke S, Hickey A, O'Boyle C, et al.: Assessing individual quality of life in amyotrophic lateral sclerosis. *Qual Life Res* 2001;10:149–158.
45. McLeod JE, Clarke DM: A review of psychosocial aspects of motor neurone disease. *J Neurol Sci* 2007;258:4–10.
46. Matuz T, Birbaumer N, Hautzinger M, et al.: Psychosocial adjustment to ALS: A longitudinal study. *Front Psychol* 2015;6:1197.
47. McDonald ER, Wiedenfeld SA, Hillel A, et al.: Survival in amyotrophic lateral sclerosis: The role of psychological factors. *Arch Neurol* 1994;51:17–23.
48. Neudert C, Oliver D, Wasner M, et al.: The course of the terminal phase in patients with amyotrophic lateral sclerosis. *J Neurol* 2001;248:612–616.
49. O'Brien T, Kelly M, Saunders C: Motor neurone disease: A hospice perspective. *BMJ* 1992;304:471–473.
50. Maessen M, Veldink JH, van den Berg LH, et al.: Requests for euthanasia: Origin of suffering in ALS, heart failure, and cancer patients. *J Neurol* 2010;257:1192–1198.
51. Ganzini L, Johnston WS, Silveira MJ: The final month of life in patients with ALS. *Neurology* 2002;59:428–431.

Address correspondence to:

Elyse A. Everett, MD, MOT
 Division of Palliative Medicine
 Washington University School of Medicine
 Mid Campus Center
 4590 Children's Place, Suite 6519
 St. Louis, MO 63110
 USA

E-mail: aufmane@wustl.edu