

# Slowing Disease Progression in Amyotrophic Lateral Sclerosis: A Review of Guidelines and Current and Emerging Therapies

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## HIGHLIGHTS

- › Overview of Current and Emerging Therapies for Amyotrophic Lateral Sclerosis
- › The Role of Managed Care Professionals in Improving Care for Patients With ALS
- › CE Sample Posttest

# Slowing Disease Progression in Amyotrophic Lateral Sclerosis: A Review of Guidelines and Current and Emerging Therapies

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## Intended Audience

Pharmacists and managed care professionals

## Activity Overview

ALS remains a devastating diagnosis that presages a rapid decline in motor functioning and often leads to death within 2 to 5 years. Two FDA-approved treatments are currently marketed that stem the decline temporarily, and guidelines strictly recommend these therapies be used and implemented into therapy as soon as possible. However, neither offer a cure and despite this progress, the disease ravages the ability of patients with ALS to function as they lose their ability to walk, swallow, sometimes think, and, eventually, breathe. With the advent of targeted therapies and growing knowledge about the disease, several discoveries are at last offering a glimpse into a more hopeful future for patients with this rare condition. It is imperative managed care professionals review the current treatment landscape and guidelines and the potential of emerging therapies to change the landscape.

## Statement of Educational Need

More than 5000 Americans receive a diagnosis of ALS each year, and an estimated 20,000 Americans are living with the disease. ALS poses a clinical and economic burden, with a grim prognosis and requirement for high level of care. Continuing education on the current and emerging therapies and burden of ALS will allow managed care professionals to provide quality care and medication access to patients.

## Educational Objectives

Upon completion of this activity, participants should be able to:

- Examine the disease burden of amyotrophic lateral sclerosis (ALS) from population and patient perspectives.
- Differentiate the mechanisms of action and clinical data for currently approved treatments in ALS.
- Characterize disease targets and investigational drugs in ALS research.
- Explore utilization management considerations in ALS, including best practices and emerging therapies.

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## Slowing Disease Progression in Amyotrophic Lateral Sclerosis: A Review of Guidelines and Current and Emerging Therapies

### OVERVIEW

Through this supplement to *The American Journal of Managed Care*<sup>®</sup>, managed care professionals will increase their knowledge of the burden of amyotrophic lateral sclerosis and the treatment landscape.

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# Overview of Current and Emerging Therapies for Amyotrophic Lateral Sclerosis

Jack J. Chen, PharmD, BCPS, BCGP, FASCP, FCCP

## Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by the loss of cortical and spinal motor neurons, leading to weakness, muscle atrophy, and, in a substantial number of patients, cognitive impairment.<sup>1,2</sup> A strong association between frontotemporal dementia (FTD) and ALS is now recognized, with between 20% and 50% of those with the disease developing FTD.<sup>3</sup> Most patients die of respiratory failure within 2 to 5 years of onset. There is no cure and just 2 drugs are approved for the disease, each of which can slow progression somewhat in selected patients.<sup>2</sup>

The majority of patients are diagnosed with sporadic ALS, whereas about 10% are diagnosed with the familial form of the disease. In both familial and sporadic forms of ALS, the symptoms are the same. In the United States, men are almost twice as likely as women to develop the sporadic form. Sporadic ALS is diagnosed at an average age of 55 years, but the familial form of the disease may manifest much earlier.<sup>4</sup> More than 5000 patients in the United States receive a diagnosis of ALS each year, and an estimated 20,000 are living with the disease. The overall prevalence in the United States is approximately 5 per 100,000 individuals.<sup>4,5</sup>

## Etiology and Presentation

The greatest risk factors for ALS are age and family history, with numerous genetic aberrations now identified. Since the first ALS genetic mutation was identified in 1993, more than 120 are now known to contribute to the disease.<sup>4</sup> Several other potential risk factors have been investigated, including exposure to pesticides, chemicals, and heavy metals; military service; athleticism; smoking; and viruses.<sup>6</sup>

The disease has a heterogenous presentation and is a diagnosis of exclusion, which can lead to diagnostic delays of up to 1 year (Table 1).<sup>7</sup> This, in turn, delays initiation of therapies that may improve symptoms and slow disease progression. Diagnosis combines clinical examination, nerve conduction studies and electromyography, and laboratory tests, and is typically made using the revised El Escorial criteria (Table 2).<sup>7,8</sup>

Patients with older age, bulbar-onset, early respiratory dysfunction, and a lower score on the Revised Amyotrophic Lateral Sclerosis

## ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a devastating, fatal neuromuscular disease. Most patients die within 2 to 5 years of diagnosis. The disease stems from death of upper and lower motor neurons leading to degeneration of motor pathways and the paralytic effects of the disease. The economic cost of the disease is not clear, with estimates ranging from about \$64,000 per year to \$200,000. Two drugs, riluzole and edaravone, are currently FDA approved for the treatment of ALS, and each provides modest benefits in mortality and/or function. Recent developments in the understanding of the underlying pathophysiologic processes that contribute to ALS have led to the development of numerous investigational therapies, with several now in phase 3 trials. This article highlights the oral tyrosine kinase inhibitor masitinib; the antisense drug tofersen; the humanized monoclonal antibody C5 complement inhibitor ravulizumab-cwvz; and mesenchymal stem cell (MSC)-neurotrophic factor (NTF) cells, a proprietary platform that induces autologous bone marrow-derived MSCs to secrete high levels of NTFs.

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For author information and disclosures, see end of text.

**TABLE 1.** Phenotypes of ALS<sup>7</sup>

Limb-onset ALS	About 70% of patients present with this form, which involves both upper and lower motor neuron dysfunction.
Bulbar-onset ALS	About 25% of patients present with this form, which manifests with swallowing and speech difficulties, with limb involvement occurring later in the disease.
Primary lateral sclerosis	This type is marked by slower progression, less weight loss, and only lower motor neuron signs in the first few years of the disease, although patients eventually develop upper motor neuron involvement. At that point, this type is called upper motor neuron-dominant ALS. Patients do, however, have a better prognosis than those with the more typical presentation of ALS.
Progressive muscular atrophy (PMA)	There is some debate as to whether this form is ALS. It initially involves lower motor neuron impairment, but eventually progresses to clinical signs of upper motor neuron involvement, at which point it is called lower motor neuron ALS. Autopsies find that 50%-66% of patients with PMA have corticospinal tract involvement.
ALS-plus syndrome	This type is diagnosed in patients with additional symptoms beyond upper and lower motor neuron involvement, including dementia, extrapyramidal manifestations, autonomic dysfunction, ocular motility disturbance, and/or sensory loss.

ALS, amyotrophic lateral sclerosis.

**TABLE 2.** Revised El Escorial Criteria<sup>7,8</sup>

The diagnosis of ALS requires:

- Clinical, electrophysical, or neuropathologic evidence of lower motor neuron degeneration
- Clinical, electrophysical, or neuropathologic evidence of upper motor neuron degeneration
- Evidence of progressive spread of symptoms or signs within a region or to other regions

Combined with the absence of:

- Electrophysiologic or pathologic evidence of other disease processes that might explain the patient's motor neuron degeneration
- Neuroimaging evidence of other diseases that might explain the observed clinical and electrophysiologic signs

ALS, amyotrophic lateral sclerosis.

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Functional Rating Scale (ALSFRS-R) have a poorer prognosis. Younger patients and patients with limb-onset or delayed diagnosis typically have a longer survival.<sup>3</sup> No matter the presentation, patients with ALS will need assistance with activities of daily living shortly after diagnosis and require more acute medical interventions and hospitalizations as the disease progresses. A person with ALS may regain motor function but these ALS reversals are rare and fewer than 1% retain improvement for 12 months or longer.<sup>9,10</sup>

## Pathophysiology of ALS

The pathologic hallmark of ALS is the death of upper and lower motor neurons, leading to degeneration of motor pathways. Although the pathogenic mechanism underlying motor neuron death in ALS remains unclear, protein aggregates in the affected neurons proliferate as the disease progresses, contributing to further damage, with the protein TDP43 found in the cytoplasm of affected neurons in 97% of cases.<sup>11</sup> Each ALS subtype is marked, however, by varied protein deposits.<sup>4</sup> The motor neurons that control ocular, bowel, and bladder function are initially spared until the later stages of the disease.<sup>12</sup>

Since 1980, more than 80 randomized controlled trials (RCTs) on ALS have been published and just 2 drugs, riluzole and edaravone, have emerged as FDA-approved therapies for the disease. Reasons for the negative results of RCTs include an incomplete understanding of ALS pathogenic mechanisms, clinical heterogeneity of ALS progression, shortcomings of study design, and pharmacogenetic interactions. In terms of pathogenic mechanisms, it is generally accepted that several damaging processes trigger motor neuron degeneration. These include protein misfolding and aggregation, oxidative stress, mitochondrial dysfunction, RNA processing impairment, neurofilament aggregation, loss of axonal transport, disruption of the neuromuscular junction, and axon demyelination.<sup>13,14</sup> Several potentially disease-modifying drugs are currently under investigation and build on past RCT failures with new research insights.<sup>13</sup>

## Burden of ALS

Medical costs for patients newly diagnosed with ALS in the United States are substantial and increase rapidly with each disability milestone.<sup>15</sup> Care of patients with ALS is intensive and requires a team of medical professionals, special equipment, and support for assistance with activities of daily living. The associated costs are significant and include direct medical costs, nonmedical costs, and loss of household income (eg, reduced employment of both the patient and/or family caregivers). Compared with other degenerative neuromuscular diseases (eg, Duchenne muscular dystrophy, myotonic muscular dystrophy, spinal muscular atrophy), ALS is the costliest for medical, nonmedical, and indirect costs.<sup>12</sup> An analysis of the economic costs of ALS in the United States published in 2014 estimated the per patient per year cost at \$63,693 (\$31,121 in direct

medical costs). Of the direct medical costs, outpatient care was the largest cost driver, including hospital outpatient visits, physician visits, and physical and occupational therapy. The mean annual prescription medication cost was \$2473, which, in this author's experience, likely reflects costs for symptomatic medications. The study authors do not provide disaggregated data for medication costs, so it is unknown how much of the \$2473 includes the cost of riluzole.<sup>16</sup>

Ventilator and wheelchair use were the main drivers for family out-of-pocket payments. Overall, this amounted to an annual cost to the healthcare system of between \$256 million and \$433 million.<sup>17</sup> The authors noted that interventions to slow disease progression, reduce care requirements, and keep patients walking for longer could significantly lessen costs. An analysis published in 2012 estimated \$502 million (2010 dollars) in annual direct medical costs (inpatient acute or long-term hospitalization, outpatient costs, durable medical equipment, and prescription medication); \$287 million in nonmedical costs (home or motor vehicle purchase or modifications; professional home care; costs of food, supplements, travel, and training the family or others incurred); and \$236 million in indirect costs (household income loss) using moderate prevalence estimates, making ALS the most expensive among the major neuromuscular diseases.<sup>18</sup>

The disease also takes a tremendous toll on the patient's family, who provide the bulk of caregiving, sometimes up to 15 hours a day for an average of 47 hours a week.<sup>19</sup> Most are female and most are caring for their partner. The physical, emotional, and financial effects of caregiving can lead to significant declines in the caregiver's own health.<sup>20</sup>

## Management of ALS

The American Academy of Neurology (AAN) 2009 practice parameters for the management of ALS were reaffirmed in January 2020. They noted that multidisciplinary clinics improve patient outcomes and, where available, encourage referral. Such teams should include a physician, physical therapist, occupational therapist, speech pathologist, dietitian, social worker, respiratory therapist, and nurse case manager.<sup>21</sup>

Study results find that patients treated in ALS clinics are more likely to use percutaneous endoscopic gastrostomy (PEG) and noninvasive ventilation (NIV). Patients receive more aids and appliances and have a higher quality of life, with even a single visit to a multidisciplinary clinic providing benefits. Patients also have fewer hospital admissions and longer mean survival.<sup>2</sup> One 5-year study concluded the use of multidisciplinary clinics reduced overall mortality by 47% and 1-year mortality by 29.7%.<sup>22</sup> However, results of studies show that patients in these clinics tend to be younger and have longer symptom duration than the general population, suggesting some referral bias.<sup>21</sup>

Although beyond the scope of this article, a mainstay of treatment is to manage symptoms as the disease progresses and provide palliative care.<sup>7</sup> This includes medical management for painful muscle spasms, hypersalivation, pseudobulbar affect (which can affect up to half of patients with ALS), cognitive impairment, and depression; as well as the use of adaptive aid devices and medical interventions, such as ventilation (invasive or noninvasive) and PEG. Guidelines also recommend that clinicians talk with patients and their families about palliative care and end-of-life decisions. However, the AAN 2009 guidelines also highlight the underutilization of many therapies, particularly PEG and NIV.<sup>2,21</sup>

## FDA-Approved Treatments for ALS

### Riluzole

The FDA approved the glutamate antagonist riluzole in 1995 as the first treatment for ALS. The approval was based on 2 studies demonstrating a modest survival benefit of about 2 to 3 months.<sup>23</sup> Subsequent analyses and modeling suggest a slightly longer benefit of 6 to 7 months, while a *Cochrane* review of 4 randomized clinical trials suggests it increases the likelihood of an additional year of survival by 9%.<sup>24,25</sup> Real-world evidence from patient databases suggests an even greater improvement, with survival benefits ranging from 6 to 21 months.<sup>2,25</sup>

Riluzole exerts an inhibitory action on glutamate release, inactivating sodium channels and interfering with downstream events resulting from transmitter binding at excitatory amino acid receptors.<sup>23</sup> Guidelines from the AAN recommend its use upon diagnosis.<sup>2</sup> It is available in oral and liquid forms.<sup>26,27</sup>

The effect of riluzole on mortality was first evaluated in a study of 155 patients randomized to 100 mg/day of riluzole or placebo. The riluzole group demonstrated a significantly higher 12-month survival compared with placebo (74% vs 58%;  $P = .014$ ), with an even greater benefit for patients with bulbar-onset disease (73% vs 35%;  $P = .014$ ). One-year survival in patients with limb-onset disease was 74% compared with 64% in patients receiving placebo ( $P = .17$ ).<sup>28</sup>

The riluzole group also demonstrated less muscle strength deterioration. However, the therapeutic effect decreased between 12 and 21 months (the end of the placebo-controlled period). Adverse effects (AEs) included asthenia, spasticity, and mild aminotransferase level increases. A significantly higher drug-related withdrawal rate among the study group was also observed.<sup>28</sup>

A larger follow-up trial of 959 patients with fewer than 5 years of probable or clinically diagnosed ALS used tracheostomy-free status or death as end points. Patients received 50, 100, or 200 mg/day of riluzole or placebo and were followed for 1 year. An analysis conducted at a median 18 months follow-up found that 57% of patients in the riluzole group versus 50% of those in the placebo group demonstrated survival without tracheostomy (adjusted relative risk [RR], 0.65; 95% CI, 0.50-0.85), but there was no significant difference in functional measures or mortality.<sup>29</sup>

## Edaravone

Edaravone is an antioxidant and free radical scavenger that has been shown to reduce excess oxidative stress and cell death.<sup>7,12</sup> However, its exact mechanism of action in ALS remains unknown.<sup>23,30</sup> It is administered as 60 mg intravenously (IV) over a 1-hour infusion daily for 14 days followed by a 14-day drug-free period initially. Subsequent dosing is done in cycles of daily dosing for 10 days of 14-day periods, again followed by 14-day drug-free periods.<sup>31</sup>

The phase 3 trials for edaravone used change in ALSFRS-R score as the primary outcome. An initial 24-week trial randomized 206 participants with ALS with a disease duration of 3 years who lived independently and had forced vital capacity (FVC) of at least 70%.<sup>32</sup> There was no significant change on ALSFRS-R in the edaravone versus placebo groups in the overall population, although a post hoc analysis showed a significant improvement in function based on the ALSFRS-R in those who scored 2 or more on all items of the instrument, had an FVC of at least 80% at baseline, and a disease duration of at most 2 years.<sup>33</sup> However, the authors wrote, “there is no indication that edaravone might be effective in a wider population of patients with ALS who do not meet the criteria.”<sup>33</sup>

A second trial enrolled individuals who met the criteria of those demonstrating a benefit in the first study. A clinically significant smaller decline in function at 24 weeks occurred in the intervention group (−5.01 vs −7.50, difference 2.49; 95% CI, 0.99–3.98;  $P = .0013$ ) versus the placebo group, with a 33% slower decline in function and improvement based on the ALS assessment questionnaire (ALSAQ-40).<sup>31</sup>

A post hoc analysis of an open-label follow-up of 65 edaravone-treated patients and 58 placebo-treated patients who then received edaravone for 24 weeks showed continued benefit out to 48 weeks in the 93 patients who completed the follow-up. Patients who switched from placebo to edaravone demonstrated a 34% lower functional decline than projected for those who would have remained on placebo through week 48 (−10.9 vs −13.0;  $P < .0001$ ) based on the ALSFRS-R. There was also a 38% difference in disease progression in those who received the drug for 48 consecutive weeks compared with the projected decline in the placebo group (−8.0 vs −13.0;  $P < .0001$ ). The most frequent AEs were injection-site contusion, gait disturbance, and headache.<sup>34</sup>

The results of edaravone in a real-world setting are mixed. A retrospective study of 22 patients treated with edaravone and 71 untreated patients with similar baseline demographic and clinical characteristics—albeit shorter disease duration in the treated patients—found similar ALSFRS-R, muscle strength, and respiratory function between the groups 6 months after the baseline visit.<sup>35</sup>

An Italian retrospective study of 243 patients who received a median treatment period of 6.4 months (median 3 cycles) with edaravone found good adherence and a good safety profile, but no significant difference in ALSFRS-R or FVC percentage scores

at 6 months.<sup>36</sup> Another retrospective analysis of 167 patients with ALS who had been using edaravone for at least 3 months (median 332 days per patient) found an average improvement in ALSFRS-R score of −0.62 units per month. However, no information about the baseline characteristics of these patients was provided.<sup>37</sup>

Perhaps the longest-term data comes out of Japan, where edaravone was approved in 2015. A retrospective, single-center study analysis of 27 patients treated with edaravone and 30 not treated between 2010 and 2016 found significant reductions in ALSFRS-R score from baseline to 6 months in the treated group, with significantly improved levels of serum creatinine, a possible marker for ALS severity, and improved survival.<sup>38</sup>

As stated previously, the FDA has approved 2 drugs for treatment of ALS to date, regardless of whether patients have sporadic or familial ALS. Overall, treatment with riluzole can be expected to delay time to death or time to tracheostomy for patients with ALS by about 3 months.<sup>25</sup> Treatment with edaravone preserves function and delays motor deterioration, specifically when initiated in patients with early disease (ie, those with functionality retained in most activities of daily living). To circumvent IV administration challenges and to provide an alternative route of administration, a novel oral suspension formulation of edaravone is undergoing phase 3 investigation (ClinicalTrials.gov Identifier: NCT04165824) for safety and efficacy in ALS.<sup>39</sup>

## Investigational Treatments

Clinical research into new treatments for ALS is plagued by difficulties in study design and questions over the appropriateness of primary and secondary interactions. Research and clinical trial guidelines published in 2019 may rectify some of those challenges.<sup>11,40</sup> One hundred forty key members of the ALS community, including researchers, clinicians, patient representatives, and regulatory agencies, revised the Airlie House guidelines to provide consensus on design and implementation of clinical trials in 9 areas<sup>40</sup>:

1. Preclinical studies
2. Biological and phenotypic heterogeneity
3. Outcome measures
4. Therapeutic and symptomatic interventions
5. Recruitment and retention
6. Biomarkers
7. Clinical trial phases
8. Beyond traditional trial designs
9. Statistical considerations

Additionally, the FDA has issued guidance to assist industry sponsors in the clinical development of drugs and biological products for the treatment of ALS. Specifically, the guidance addresses the FDA’s current thinking regarding the clinical development

program and clinical trial designs for drugs to support an indication for the treatment of ALS.<sup>41</sup>

Pharmacogenetic interactions with investigational compounds create another issue, as not taking genetic information into account may mask evidence of response to treatment or be an unrecognized source of bias, and it is suggested to account for genetic polymorphisms in clinical studies.<sup>41</sup> For example, genetic variants, such as the expanded hexanucleotide repeats in *C9orf72* and mutations in superoxide dismutase 1 (*SOD1*), are more prevalent in familial ALS cases. Carriers of the *C9orf72* repeat expansion have been associated with greater functional decline, and thus they may have an altered response to investigational compounds.<sup>42</sup>

Nonetheless, the greater understanding of the pathophysiology and genetic underpinnings of ALS has led to the development of numerous compounds targeting various pathways, including oxidative stress, excitotoxicity, mitochondrial dysfunction, neuroinflammation, apoptosis, nucleocytoplasmic transport, DNA damage, and RNA splicing/metabolism, among others. Additionally, clinical studies are underway to investigate the impact of treatments on an array of molecular biomarkers (REFINE ALS study, ClinicalTrials.gov Identifier: NCT04259255); however, it is beyond the scope of this article to discuss all investigational compounds. Four compounds ready for phase 3 clinical trial investigation are highlighted in the following paragraphs.

### Masitinib

The oral tyrosine kinase inhibitor masitinib targets microglia, macrophage, and mast cell activity in the central and peripheral nervous systems to provide a neuroprotective effect. It was investigated in a phase 2/3 study evaluating its use in combination with riluzole in 394 patients. Participants were randomized to riluzole plus placebo or riluzole plus masitinib (4.5 or 3.0 mg/kg/day) over a 48-week treatment period. Enrolled patients must have had disease duration fewer than 3 years from their first ALS symptom, an FVC of at least 60%, and received a stable dose of riluzole 100 mg/day for at least 30 days prior to baseline. The primary efficacy population (ie, "normal progressors" receiving riluzole and masitinib 4.5 mg/kg/day vs riluzole and placebo) comprised 105 and 113 patients, respectively, of which 99 and 102 were assessable at study end.<sup>43</sup>

The combination treatment demonstrated a statistically and clinically meaningful 27% slowing of ALSFRS-R deterioration over the 48 weeks (between group difference in ALSFRS-R of 3.39;  $P = .016$ ). Patients on the combination therapy also demonstrated a 29% lower decline in quality of life (ALSAQ-40 score,  $P = .008$ ) and 22% less respiratory deterioration ( $-26.45$  FVC vs  $-33.99$  FVC;  $P = .03$ ). A time-to-event analysis showed that patients on masitinib had a 25% delay in disease progression (20 vs 16 months,  $P = .016$ ). The greatest treatment-related benefits occurred in patients with lower baseline disease severity.<sup>43</sup>

Rates of AEs in patients receiving the lower dose of masitinib were similar to those on placebo (22% vs 17%, respectively). However, serious AEs occurred in 29% of those in the 4.5-mg dose group. In the 4.5-mg and 3.0-mg group, 16.3% and 16.0% of patients, respectively, discontinued the study drug compared with 9% in the placebo arm. The most common AEs in the masitinib group (>5%) versus placebo were maculopapular rash and peripheral edema.<sup>43</sup> A phase 3 randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov Identifier: NCT03127267) with a planned enrollment of 495 patients is underway and will compare the efficacy and safety of combination treatment with masitinib and riluzole to that of riluzole monotherapy.<sup>44</sup>

### Tofersen

Tofersen is an antisense oligonucleotide being investigated for treatment of ALS caused by mutations in the *SOD1* gene, which occurs in up to 2% of ALS cases. The mechanisms by which mutations in the *SOD1* gene cause degeneration of motor neurons is not fully understood, but an overproduction of toxic *SOD1* protein is a leading mechanism. Tofersen is designed to reduce the synthesis of *SOD1* protein.<sup>45,46</sup>

A phase 1/2 trial in 50 patients with ALS and *SOD1* mutations who received varying doses of tofersen or placebo via a lumbar intrathecal injection over 3 months found that those assigned to the highest dose ( $n = 10$ ; 100 mg) demonstrated a 36% reduction from baseline of the protein in their spinal fluid compared with 3% for those who received placebo ( $n = 12$ ). Patients treated with tofersen also scored better on the exploratory outcome of ALSFRS-R (breathing capacity, muscle strength, and function), with an average 1.19-point decline on activity function versus 5.63-point decline on placebo. The most common AEs were mild to moderate headache, procedural pain, post lumbar puncture syndrome, and falls.<sup>47</sup> Cerebrospinal fluid pleocytosis was also observed in tofersen-treated individuals, but the clinical significance remains unknown.<sup>46</sup> The safety and efficacy of tofersen are being evaluated in a phase 3, randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov Identifier, NCT02623699) and its long-term extension study (NCT03070119).<sup>45</sup>

### Ravulizumab-cwvz

Ravulizumab-cwvz is a long-acting humanized monoclonal antibody that blocks terminal complement C5 activation and is designed to reduce neuroinflammation. It is FDA approved as a treatment for atypical hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria and is now in a phase 3 randomized clinical trial for ALS.<sup>11</sup>

The CHAMPION-ALS study (ClinicalTrials.gov Identifier: NCT04248465) is enrolling approximately 350 adults with sporadic or familial ALS with disease onset within the prior 3 years, a slow vital capacity of at least 65% predicted, and no respiratory support dependence. Participants will be randomized to receive either

ravulizumab-cwvz or placebo (and may continue receiving their existing standard of care treatment) for 50 weeks, followed by a 2-year, open-label extension phase in which all patients will receive ravulizumab-cwvz. The primary end point is the change in ALSFRS-R score from baseline. Secondary end points include ventilation assistance-free survival and respiratory capacity.<sup>48</sup>

## Mesenchymal stem cell (MSC)-neurotrophic factor (NTF) cells

NurOwn is an autologous bone marrow-derived MSC platform that expands and induces the cells to secrete high levels of NTFs (MSC-NTF) to promote the growth of nerve tissue and improve neuroprotective function. The compound is delivered via intramuscular or intrathecal injection.<sup>49</sup>

A phase 2 safety and efficacy study randomized 48 patients with an ALSFRS-R of at least 30, slow vital capacity at least 65% of the predicted normal value, and symptom duration between 1 and 2 years. The trial met its primary end point of demonstrated safety, with all serious AEs that developed after treatment began related to the disease not the treatment.<sup>50</sup>

There was a significant improvement in the ALSFRS-R slope at 2 and 4 weeks post transplant in the MSC-NTF group (+1.7 and +0.6 points, respectively), but no statistically significant benefit after 4 weeks. The rapid progressors subgroup demonstrated an even greater improvement at 2 and 4 weeks (+3.3 vs -1.3,  $P = .021$ ; and +2.0 vs -0.1,  $P = 0.033$ , respectively) with a continued trend for improvement throughout the remainder of the trial.<sup>50</sup>

Biomarker changes also indicated a positive response to treatment with increases in neuroprotective and anti-inflammatory biomarkers and significant decreases in inflammatory biomarkers, suggesting the treatment successfully moderated neuroinflammation. Response rates slowed towards the end of the follow-up period, signifying a need for repeated treatments in order to maintain a therapeutic benefit.<sup>50</sup>

NurOwn recently completed enrollment ( $N = 261$ ) of a randomized, double-blind, placebo-controlled phase 3 trial (ClinicalTrials.gov Identifier: NCT03280056) assessing the safety and effectiveness of a series of 3 intrathecal injections administered at 2-month intervals. Primary end point is patient score on the ALSFRS-R. Secondary end points are biomarker assessment, including cell-secreted NTFs, inflammatory factors, and changes in blood and cerebrospinal fluid. The study is slated to be complete in late 2020.<sup>51</sup>

## Conclusions

ALS is a motor neuron disease associated with early death due to respiratory failure. Treatment with riluzole or edaravone has demonstrated some prolonged survival and/or function. However, additional pharmacologic therapies are needed and several compounds are in clinical trials to evaluate disease-modifying and/or functional benefits. ■

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# The Role of Managed Care Professionals in Improving Care for Patients With ALS

Winston Wong, PharmD

## Economic Burden of Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) represents a significant economic burden in the United States, which may or may not be realized by managed care organizations. A moderate estimate in 2010 suggested the total economic burden of ALS was just over \$1 billion. Although this number may not seem large when compared with total healthcare expenditures, it is important to note that the overall prevalence was about 20,000 at the time, with an annual incidence rate of 5000.<sup>1-3</sup> This incidence rate is about 2 cases for every 1,000,000 people and is increasing each year.<sup>4</sup> If ALS were to reach incidence numbers similar to other chronic diseases, the total economic burden would be much higher and more significant. Disease characteristics that may affect costs of care include age of onset (40-75 years old) and average time of survival after diagnosis, which is currently just 2 to 5 years, with 20% of patients with ALS living longer than 5 years, 10% living 10 years, and 5% living 20 or more years.<sup>1-5</sup> Along with the increasing incidence rate per year, physicians have noted an increasing number of younger patients with ALS.<sup>4</sup> Unfortunately, this disease has no known cure and shows a rapid and progressively worsening disease state. As disability scores increase, so do costs associated with overall care.<sup>1</sup>

Current disease-modifying medication therapy focuses on the delay of disease progression. Other treatments are available to provide supportive care for sequelae of disease that can include cognitive and behavior changes, pseudobulbar affect (PBA, defined as sudden outbursts of laughter and/or crying), difficulty communicating, spasticity, pain, nutrition, and mobility.<sup>6</sup>

When considering the total cost of care for ALS, it is important to include not only the cost of medications but also costs under the medical benefit, such as institutional and ambulatory services, professional services, durable medical equipment (DME), and other ancillary services. In one retrospective claims analysis conducted from 2008 to 2015 of the Truven Health Analytics MarketScan Database, the top 3 drivers of ALS costs were inpatient care, surgery, and prescriptions. One consideration is this was before the FDA approval of edaravone in 2017, which would have increased prescription drug costs. In this same study, the estimated total cost of care

## ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a debilitating disease of progressively worsening physical function. The direct medical, direct nonmedical, and indirect costs of care for these patients is significant, and annual costs can be around \$70,000 on average. Major drivers of cost can include hospitalizations, in-home care, nutrition, physical and occupational therapy, and medication interventions. Beyond the monetary costs, patients also endure a decreased quality of life, which may also burden caregivers and family members. Appropriate utilization management by managed care organizations and support for the multidisciplinary care team approach can help to ensure appropriate care, with a goal of optimizing clinical outcomes and potentially delaying disease progression. Although ALS has no cure, progressive gene therapy is currently being investigated and may offer promise. Thus, gene therapy may necessitate the need for novel and creative approaches to cost-management strategies in the future.

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per member per month (PMPM) was \$3460 compared with \$486 for an average adult patient aged 16 years and older.<sup>7</sup> One limitation with the current studies evaluating the cost of ALS is the limited amount of patient data. Another annual cost estimate for the total cost of care in 2015 was around \$70,000, which is approximately \$5833 PMPM.<sup>3</sup> However, it should be noted the cost of care will vary greatly between patients due to heterogeneity of patient treatment plans.

In a case study of 1 patient with ALS, cost data were collected over 10 years (2001-2010). The total cost of care over 10 years was \$1,433,992, of which 85% was paid by third-party payers, 9% paid by the patient, and 6% paid by charities. For this patient, the 3 main drivers of total costs were in-home care (46.7%), ventilation (14.8%), and in-hospital expenses (8.0%). Medications accounted for just 1.7% of the total cost of care. It bears noting, however, that this patient did not take riluzole. Use of riluzole and/or edaravone (approved after this case study) would have substantially increased the cost of medications in this case study.<sup>8</sup>

The American Academy of Neurology (AAN) developed quality measures in 1999 to address gaps in care and ensure proper utilization of evidence-based therapies for patients with ALS, which were updated in 2009.<sup>9,10</sup> A summary of these quality measures is outlined in [Table 1](#).<sup>9,10</sup>

The following sections will review the direct medical costs (eg, healthcare utilization, physical therapy, pharmacotherapy), direct nonmedical costs (eg, DME, vehicle and home modifications), and indirect costs (eg, quality of life, caregiver and family burden). Each patient has a unique clinical presentation with a variable rate of disease progression as well as a different perspective on what quality of life means.<sup>11</sup> These factors would drastically alter the total cost of care for each patient. Therefore, estimations of total cost of care will vary greatly between each patient.

## Direct Medical Costs

Healthcare utilization costs include provider visits, hospitalizations, long-term care, nutrition, pharmacotherapy, and hospice.<sup>12-18</sup> For a

**TABLE 1.** Quality Measures and Potential Cost Items<sup>9,10</sup>

Quality measure	Description	Examples of potential cost items
Multidisciplinary care team	Development of care coordination to serve patients with ALS updated at least annually	Transportation to ALS Association Certified Centers of Excellence
Disease-modifying pharmacotherapy	Provider should discuss disease-modifying therapy (ie, riluzole, edaravone <sup>a</sup> ) at least annually with patient	Initiation of riluzole and/or edaravone therapy
Cognitive and behavioral screening	Patients should be screened at least annually for cognitive impairment	Additional provider visits and testing
Symptomatic pharmacotherapy	Provider should discuss with patient treatment of ALS sequelae, such as pseudobulbar affect, and other related symptoms	Initiation of therapy, such as dextromethorphan/quinidine (20 mg/10 mg)
Respiratory function and referral	Patients should be evaluated at least every 3 months regarding respiratory function and referred to pulmonary function	Additional provider visits and testing
Noninvasive ventilation for respiratory insufficiency	Patients with ALS and respiratory insufficiency should be consulted on noninvasive respiratory support at least annually	Initiation of noninvasive respiratory support
Sequelae from dysphagia	Patients should be screened at least every 3 months for dysphagia, weight loss, and impaired nutrition	Additional provider visits and testing
Nutritional support	Patients with dysphagia, weight loss, or impaired nutrition offered nutritional support through PEG tube or another gastrostomy	PEG tube placement, nutritional consultation, and support
Communication support	Patients with difficulty speaking or writing should be offered a referral to a speech language pathologist for assessment	Additional provider visits and testing
End-of-life planning	Assistance with end-of-life care should be offered at least annually	Invasive ventilation, hospice
Fall assessment	Patient should be assessed for number of falls within the past 12 months	Cane, walker, wheelchair, motorized wheelchair, patient lift, hospital bed, and home and vehicle modifications

ALS, amyotrophic lateral sclerosis; PEG, percutaneous endoscopic gastrostomy.

<sup>a</sup>Edaravone was not in the 2009 American Academy of Neurology ALS Quality Measures.

**TABLE 2.** Currently Available Pharmacotherapy for ALS and Dosing<sup>21-24</sup>

Medication name	Dosing
Riluzole tablets	50 mg PO/PFT BID
Riluzole oral solution	50 mg PO/PFT BID (5 mg/mL)
Riluzole oral film	50 mg PO BID
Edaravone IV solution	<b>Loading dose:</b> 60 mg IV daily for 14 days, followed by 14 days off <b>Maintenance dose (28-day cycles):</b> 60 mg IV daily for 10 days of a 14-day period, followed by 14 days off

ALS, amyotrophic lateral sclerosis; IV, intravenous; PO/PFT, oral or per feeding tube.

patient with ALS, hospitalizations can be a result of loss of respiratory function, pneumonia, nutrition, or other consequences of decreased physical functioning. In a 2010 study of Medicare patients with ALS, estimated costs were \$13,324 for inpatient care and \$10,745 for outpatient care (eg, physician office visits, occupational/physical therapy).<sup>1</sup> Appropriate care coordination and multidisciplinary care teams may help to optimize care to decrease unnecessary medical costs and hospitalizations. Managed care organizations need to recognize that current disease-modifying treatment options are not cures, and the goal of treatment is to delay or slow disease progression. Thus, disease progression is inevitable and seeking inpatient care may not be avoidable.

Besides direct hospitalization costs, treatment of sequelae of ALS progression may also require treatment. For example, PBA is a known sequela of ALS. This condition is characterized by uncontrollable laughter and crying and may affect the patient's quality of life. Treatment for PBA is limited as there is only 1 FDA-approved medication indicated for the treatment of symptoms. Dextromethorphan hydrobromide/quinidine sulfate (20 mg/10 mg) capsule has been shown in clinical trials to significantly decrease the number of laughing and crying episodes from baseline. Managed care organizations must recognize that this medication is indicated for any patient with PBA, which includes ALS and other mild cognitive impairment conditions.<sup>19</sup>

Pain and spasticity are common as ALS progresses, developing as secondary complications of musculoskeletal dysfunction due to limited mobility or loss of range of motion. Many patients with ALS report pain even in the early stages of their disease. Spasticity may compromise gait and manual dexterity and may lead to the development of painful joint contractures. The treatment of associated pain and spasticity is multimodal and includes nonpharmacologic (eg, massage, stretching, positioning, use of appropriate bed/chair/lift) and pharmacologic therapies (eg, muscle relaxants, laxatives, benzodiazepines). Risks of pharmacologic therapy should be weighed against potential benefits. Consultation and referral to

physical therapy may offer patients a higher quality of life without the added adverse reactions, such as sedation. Increased sedation in patients with ALS may potentially increase risk of respiratory insufficiency.<sup>20</sup> Decreased motor function can also lead to reduced ability or complete inability to eat, which can lead to malnutrition or need of enteral nutrition in later stages of the disease.<sup>11</sup>

Nutritional needs for patients are a significant contributor to total cost of care. In 2001, it was estimated that alternative nutritional maintenance was about \$7300 per year. This does not include other ancillary needs or complications of enteral nutrition (eg, PEG surgery), and overall cost is undoubtedly higher today than it was in 2001.<sup>14</sup>

Although there are other direct medical costs that can be considered, one other significant cost associated with care is pharmaceutical treatment options. Current disease-modifying pharmacotherapeutic options for management of ALS are riluzole and edaravone. As previously noted, these treatment options neither reverse disease progression nor represent a cure, but they may help to slow disease progression. For more than 2 decades, riluzole oral tablets were the only disease-modifying therapy available for ALS. Riluzole is currently available as a generic tablet and a brand only oral solution. Most recently, an oral film formulation has been FDA approved for the treatment of ALS, but has not yet been launched into the market. Edaravone was approved for the treatment of ALS in 2017.<sup>3,21-25</sup>

**Table 2**<sup>21-24</sup> outlines the currently approved FDA pharmacotherapy options for ALS. It must be noted that edaravone starts with a loading dose of 60 mg daily for 14 days, followed by 14 days off. This is followed by 60 mg daily for 10 days of a 14-day period, followed by 14 days off.<sup>18,24</sup>

## Direct Nonmedical Costs

Direct nonmedical costs include costs paid by payers or the patient that are not directly related to medical services or care. This includes DME, such as hospital beds, walkers, wheelchairs, and ventilation.<sup>26-30</sup> Less obvious costs include patient lifts and electronic eye gaze devices that allow speech through a patient's eye movements.<sup>13,31</sup>

There appears to be a direct correlation to the staging of the disease and the amount of direct nonmedical costs. Although there are multiple proposed staging methodologies for ALS, there is no accepted gold standard.<sup>5,27,32,33</sup> One system that is suggested is outlined here:

- Stage 1: Symptom onset involvement of 1 region (defined by origin of onset: bulbar, upper limb, lower limb, diaphragmatic region)
- Stage 2: Symptomatic involvement of a second region
- Stage 3: Symptomatic involvement of a third region
- Stage 4: Nutritional or respiratory failure (terminal)
- Stage 5: Death

The disease stage can also be defined by the amount of aid needed to ambulate, such as moving from a cane or walker to a wheelchair or moving from noninvasive ventilation (NIV) to invasive mechanical ventilation.<sup>5,30</sup> In one retrospective study of Centers for Medicare & Medicaid Services (CMS) Limited Data Set, patients were evaluated on the cost and time from ALS diagnosis to each milestone. A total of 1687 patients who had a diagnosis of ALS for at least 6 months prediagnosis were identified. These milestones (M1-M6) as well as the average time (months) and cost of ALS treatment from diagnosis to milestones are summarized in **Table 3**.<sup>34</sup>

The study also found that for patients with at least 12 months postdiagnosis data (n = 956) the average total cost of treatment was higher in patients with ALS compared with a matched control group (\$34,475 vs \$32,165;  $P < .01$ ). Compared with the matched control group, patients with ALS also had higher utilization of healthcare resources, which included physician office visits (96.5% vs 91%), outpatient hospital visits (91.3% vs 80.1%), and at least 1 DME claim (65.4% vs 52.4%; all  $P < .01$ ). Study results showed decline in physical function is progressive, and milestones may occur concurrently or in rapid succession.<sup>34</sup>

The origin of ALS symptoms, limb versus bulbar, may play a role in how quickly a patient progresses. In one study, patients with ALS that originated in the lower extremities (limb onset) progressed to walking aids at a faster rate compared with bulbar (head/neck) or upper extremity onset. Those who required a PEG tube sooner more likely had a bulbar onset of ALS symptoms. However, this study found that regardless of where the initial onset of symptoms occurred, many patients required the full array of DME (ie, cane, walker, PEG, wheelchair, NIV, ankle-foot orthosis) and nonmedical interventions for 60% to 80% of the entirety of their ALS disease duration. The study authors concluded that these DME and interventions will likely be needed in the second half of ALS progression, which averages about 15 months after diagnosis.<sup>30</sup> The highest cost noted was a customized power wheelchair, which in 2008 was estimated to be about \$27,800.<sup>26,30</sup> Other significant costs were PEG tube placement (\$2000), NIV machine (\$3000), and equipment installed in the home, such as lift chair (\$900), stair lift (\$2000), and vertical lift (\$4000).<sup>30</sup>

In terminal patients, invasive ventilation may be warranted instead of NIV.<sup>29</sup> NIV can be provided through a mask by a bi-level intermittent positive airway pressure (BiPAP) machine; invasive ventilation is given through a tracheostomy.<sup>1,14</sup> Both noninvasive and invasive ventilation have been shown to prolong life in patients with ALS, but there is a significant cost incurred with invasive ventilation. Therapy that may delay time to tracheostomy or disease progression (ie, riluzole, edaravone) represents an opportunity for potential cost-savings. In one case study, total cost of ventilation over 10 years for a patient was \$212,430. Other intangible costs that may be incurred by patients are costs of back-up batteries and

**TABLE 3.** Average Time and Cost of ALS from Diagnosis to Milestone<sup>34</sup>

Milestone	Months to milestone	Cost to milestone
M1: Canes/walkers/wheelchairs	9.4	\$46,576
M2: Artificial nutrition	9.6	\$58,767
M3: Noninvasive/invasive ventilation	7.5	\$47,793
M4: Speech-generating devices	11.2	\$47,707
M5: Hospice	14.1	\$70,544
M6: Death	14.8	\$78,764

ALS, amyotrophic lateral sclerosis.

generators in case of a power outage and increased utilization of in-home care to ensure around-the-clock monitoring for respiratory function.<sup>8</sup> Other apparatus that may be required by some patients who have lost the ability to communicate verbally or in writing are augmented communication devices. These can range from \$38 for a visual eye blink board to more than \$30,000 for an ALS-specific computer system to track eye movement.<sup>13</sup>

### Indirect Costs: Quality of Life and Caregiver and Family Burden

ALS is not only a disease of healthcare resource utilization costs but also of significant cost not related to treatment. There are significant impacts upon the loss of productivity, work, and quality of life for patients as well as the burden on their immediate family and caregivers.<sup>1,5,8,16,35</sup>

Caregivers have described their first-hand experiences of providing care to patients with ALS, and the concept of First Half or Second Half method of communicating, which refers to the first or second half of the alphabet. As described earlier, many patients in the advance stages of ALS lose the ability to communicate, and their only way to do so is through their eye movements. To spell out words, each letter would have to be painstakingly spelled out by gesturing with their eyes. To save time and effort, it is easier to split the alphabet in half. Caregivers also talk about having to lubricate and close their patient's eyes at night so they do not dry out, constantly suctioning fluid out of the tracheostomy, worrying if the ventilator battery will last if there is a power outage, and considering the ethical dilemmas of death with dignity and religious beliefs.

Calculating loss of income from work is difficult to determine. Although patients with ALS will decline physically, mental acuity does not diminish. In one estimate, a family would have an average income loss of \$19,217 per year, with a personal indirect cost of \$14,682. This will vary depending on the amount of care needed as well as who provides care to that family member.<sup>1</sup> Other costs besides loss of income include increased cost of in-home care, especially in patients with ventilator needs. The total annual cost

for supporting a mechanically ventilated (invasive ventilation) patient can be \$18,965 on average, whereas costs for those on NIV are around \$5650 and costs for those with no ventilators may be \$1653.<sup>1</sup>

Additional costs of care can include retrofitting a vehicle for a patient, providing for power wheelchair transportation, and making house renovations, such as bigger entryways, support tracks for patient lifts, accessible bathrooms, and specialized hospital beds to decrease the risk of bed sores and other sequelae of being bedridden. In previously reported cases, the cost of an accessible van was between \$30,000 and \$36,000.<sup>8</sup>

In addition to the indirect costs, ALS has a significant and profound psychosocial impact on patients and caregivers.<sup>1,16,27,35,36</sup> Increased disability and decreased quality of life associated with advanced stages of ALS have been correlated to worsening depression and anxiety scores.<sup>27</sup> This intangible human cost is difficult to quantify; however, it is arguably one of the largest costs ALS imposes on a patient and the patient's family. With ALS, it is inevitable that a patient has to face their mortality. Where it is legal, death with dignity laws have allowed patients with certain diseases the right to end their own life. It is not a decision taken lightly and has many legal procedures that must occur prior to implementation. However, for patients with ALS, death with dignity is a choice that many explore. In one study, patients with ALS in the state of Washington had the highest proportion of death with dignity compared with other diagnoses.<sup>36</sup> With this decision comes many other dilemmas, such as conflicts with religious beliefs and family member wishes. As a note for managed care pharmacists, federal funding may not be used for services or medications under death with dignity.<sup>37</sup>

## Utilization Management Considerations

### Goal of Therapy

Both riluzole and edaravone are disease-modifying medications that do not result in a cure or reversal of disease progression. They are 2 different compounds with a mechanism of action in ALS that is still not well defined. The inclusion criteria and primary end points evaluated in pivotal trials also differed between riluzole and edaravone, though both agents were FDA approved for all patients with ALS. In the pivotal trials, riluzole significantly reduced the median time to tracheostomy or death (primary outcome) by 60 to 90 days in patients with ALS. However, there was no significant difference in muscle strength and neurological function.<sup>21</sup>

On the other hand, edaravone was studied in a slightly different population and with a different primary outcome. In pivotal trials, patients must have 2 years or fewer of a definite or probable diagnosis of ALS based on the El Escorial revised criteria, normal respiratory function (forced vital capacity  $\geq 80\%$ ), and mostly retained functionality of daily living as defined by a score of 2 or more on all components of the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R), meaning these patients were

early in their ALS disease course. It is important to note that at the time of study start, 90% of patients were on riluzole and could continue riluzole. The primary outcome in this study was the change (negative change indicating decreased functionality) in ALSFRS-R from baseline to week 24. At week 24, compared with placebo, patients on edaravone had significantly higher (though still decreased) ALSFRS-R scores ( $-5.01$  vs  $-7.50$ ), representing a 33% less worsening of function.<sup>27</sup> Many have debated on what change in ALSFRS-R is considered clinically meaningful. In one survey of ALS clinicians, a decrease in ALSFRS-R score of 4 was considered clinically meaningful.<sup>38</sup> Although edaravone decreased amount of functional decline, it did not stop or reverse the course of the disease through a 1-year follow-up.

## Medical versus Pharmacy Benefit

Patients with ALS are qualified for Medicare benefits as soon as Social Security Disability Insurance payments start, which is approximately 5 months after a patient is deemed disabled.<sup>39</sup> The difficulty for most patients is that prior to an official diagnosis of ALS there may be several months of differential diagnostic testing and evaluation that can increase both payer and patient costs.<sup>12</sup>

Medicare benefits include Part A (hospital), Part B (outpatient), Part C (Medicare Advantage), and Part D (prescription drug coverage). Medicare regulations require Part D formularies to have at least 2 drugs in each drug category or class (eg, U.S. Pharmacopeia, American Hospital Formulary Service, or custom). In most scenarios, riluzole will be managed under the Part D benefit, whereas edaravone will be covered under the Part B benefit because it is an intravenous infusion. However, there may be an instance where edaravone is given as a home infusion and billed as a Part D drug benefit.<sup>40</sup> Each managed care organization is different, and internal policies should be followed in determining Part B or Part D determinations; however, there are opportunities for managed care organizations to potentially save money by promoting administration in a home setting as opposed to an institutional ambulatory setting. Part C Medicare Advantage plans will have the Part B versus Part D distinction for coverage as well as the possibility of integrated utilization management across the medical and pharmacy benefits.

## Formulary Considerations for Riluzole and Edaravone

Because the riluzole tablets have been on the market for decades and are generically available, most health plans will not feel the need to implement strict utilization management criteria. If a prior authorization is imposed, it may require only attestation of an ALS diagnosis. Riluzole is also available as a branded oral suspension (approved in 2018) and a film (approved in 2019).<sup>21-23</sup> Though the riluzole film has been approved, it is currently not commercially available.<sup>25</sup> Managed care organizations should consider limiting

utilization of these branded formulations to patients who are unable to tolerate swallowing whole oral tablets. Authorization criteria should include documentation of a previous trial of generic riluzole tablets (step therapy) and attestation of the patient being unable to administer or tolerate oral tablets.

Edaravone, approved in 2017, is a novel pharmacologic agent that was first approved for use in Japan in 2001 to facilitate the recovery from cerebrovascular accidents. It was then studied in Japan in 2011 for ALS, resulting in an approval in 2015. Initial trials of edaravone in the general ALS population in the United States failed to show any benefit. However, further dissection of the general ALS population indicated a benefit when used early in patients with ALS, leading to the pivotal trial of edaravone in early-stage ALS and its FDA approval.

It is important to note that, to date, there have been no head-to-head trials comparing the safety and efficacy of riluzole with edaravone. Claims of superiority of one agent over the other cannot be made. In fact, most patients in the edaravone clinical trials were taking riluzole and were allowed to continue taking their riluzole. Because coverage will default to the medical benefit, medical policy and precertification process will be used to manage edaravone utilization. The level of enforcement of the medical policy and precertification process will differ with each managed care organization. Medication policy and precertification criteria will largely mirror inclusion criteria from the pivotal trial, including a definite or probable diagnosis of ALS of no more than 2 years and, for the most part, normal physical and respiratory function.<sup>24</sup> This would exclude many current patients with ALS who are beyond 2 years or whose disease has progressed to a stage where physical and respiratory function parameters do not satisfy the pivotal trial inclusion criteria.

## Best Practices

The ALS Association and the Muscular Dystrophy Association (MDA) are 2 national nonprofit organizations focused on ALS. Both the ALS Association and the MDA collaborate with physicians and researchers to certify clinics.<sup>41,42</sup>

There is limited evidence to suggest that multidisciplinary care can directly lower patient cost.<sup>43-45</sup> One study did suggest that earlier referral to multidisciplinary care may decrease cost but may not decrease time to ALS diagnosis.<sup>44</sup> Regardless, formation of a multidisciplinary team is still an accepted quality measure of the AAN. If possible, patients should seek either an ALS Association Certified Treatment Center of Excellence or a Recognized Treatment Center to ensure optimal care.<sup>9,45</sup>

There should be little disagreement that care for patients with ALS—especially in the late stages—can be complex. Managed care organizations need to embrace and support the use of a multidisciplinary approach, integrating their care coordination capability to ensure the most cost-effective use of resources. Managed care

pharmacists should play an integral and proactive role in the treatment and management of these patients to ensure utilization of appropriate medications. As new therapies are developed, pharmacists may have to facilitate patient enrollment into clinical trials at ALS Association Certified Treatment Centers of Excellence.<sup>42</sup>

## Future Considerations

In September 2019, the FDA released a guidance on the development of clinical trials for ALS. The guidance suggests that trials not exclude patients with ALS based on characteristics such as age or disease stage unless scientifically necessary. This is an attempt to include a broader patient population in ALS trials. In addition, the FDA suggests primary end points should focus on patient-oriented outcomes, such as physical function, respiratory function, and mortality. It also acknowledges the potential for gene therapy as an option for ALS.<sup>46</sup>

Biologic therapy and gene therapy are currently being explored for use in ALS.<sup>47-49</sup> Gene therapies are still early in development, but the early research shows promise. Current gene therapy research is focused on patients with ALS with mutations in superoxide dismutase 1 (*SOD1*) or *C9orf72* genes. These mutations may lead to types of familial ALS, which accounts for approximately 10% of the ALS population.<sup>47-49</sup> The vector utilized to target these genes is derived from the adeno-associated virus (AAV), the same vector that is being used for a recently approved gene therapy for another motor neuron disease, spinal muscular atrophy (SMA), called onasemnogene abeparvovec-xioi (Zolgensma). This gene target, along with a viable vector derived from AAV, gives some promise to a potential cure for ALS.<sup>50</sup>

Clinically, a cure for ALS would be nothing short of miraculous, but it does create a difficult situation for managed care organizations. Onasemnogene abeparvovec-xioi has set the pricing precedent for gene therapies. There is a strong possibility that managed care organizations will again be faced with balancing the cost of care with the clinical outcome in an attempt to determine the overall cost-effectiveness proposition. One way to evaluate treatment options in ultrarare and catastrophic conditions is through the use of a cost-effectiveness threshold (CET), which is the maximum cost at which the treatment is deemed to be cost-effective and the cost is justified. The CET evaluation framework was developed and executed by the Institute for Clinical and Economic Review (ICER) and is utilized by many evaluating organizations globally.<sup>48</sup> The ICER is an independent research organization that objectively reviews both clinical and financial aspects of medications and other healthcare tools. This organization is considered a leading monitor for drug pricing and evaluates how drugs should be priced to reflect the benefit.<sup>50</sup>

The CET is usually calculated through an incremental cost-effectiveness ratio, which is a ratio of difference in cost between

2 possible interventions, divided by the difference in the effect, which is calculated based upon the number of years life is extended by with a quality-of-life modifier. This cost-effectiveness ratio is usually presented as a dollar amount for quality-adjusted life-year (QALY) gained. For normal health conditions, the CET has been described as \$50,000 to \$150,000 per QALY. Although there is no definitive CET for ultrarare conditions, the consensus range is between \$175,000 and \$500,000 per QALY for ultraorphan drugs. For example, a recently approved drug for SMA, nusinersen (Spinraza), has a ratio of more than \$375,000 per QALY gained. Although this does not pass the upper limit of the CET of \$500,000 per QALY, it is still an expensive agent that could be debated as not cost-effective.<sup>48</sup>

In order to provide policymakers with a broad view of cost-effectiveness, the ICER included the cost per life-year-gained (LYG) in conjunction with the cost per QALY. The difference between QALY and LYG is that the QALY calculation includes a utility measurement of quality of life and duration of life extension. The cost per LYG approach values any life extension with no regard to the quality of life. Hence, in treatments for which the impact to quality of life is minimal but which are associated with a significant extension of life, the cost per LYG may appear more favorable compared with the cost per QALY.<sup>50</sup>

A pharmacoeconomic review of edaravone by the Canadian Agency for Drugs and Technologies in Health (CADTH) estimated that the incremental cost-effectiveness ratio for edaravone was \$1,440,786 (CAD) for patients with mild ALS.<sup>51</sup> Some have questioned whether the ICER evaluation framework is broad enough to take into account those parameters upon which a value cannot be placed. One article points out that the current cost-effective evaluation methodology is only useful when the information available to drive the treatment decision process is similar between the physician and the evaluation tool.<sup>52</sup> In other words, is the evaluation tool including the same level of information in the evaluation as the physician is using when making a treatment decision? Unfortunately, this does not usually occur. The physician will usually have more clinical and psychosocial information available to make the treatment decision, as opposed to what the payer or the evaluation tool assumes or takes into account to determine the value of the treatment. The ability to place a cost value upon these real-world decision parameters simply does not exist. A second point the author makes is that although best practices can be identified and endorsed, there will be clinical presentations where the best therapeutic options may not be the best practice but rather be in the best interest of the patient.<sup>52</sup> These points highlight that coverage criteria fit most patients but not all. Therefore, managed care organizations should take into consideration provider judgment when making utilization management decisions.

In an attempt to blunt the impact of these high-cost therapies, managed care organizations are actively seeking creative ways to

provide coverage for these medications while not financially overburdening the entity that holds the financial risk. Manufacturers acknowledge that the costs of these curative treatments are not easily managed. In a pilot venture, the New Drug Development ParadigmS (NEWDIGS), a Massachusetts Institute of Technology-based group, is exploring new payment methodologies. This collaboration comprises payers, manufacturers, and other stakeholders. One of the features being investigated is a performance-based annuity payment model, which spreads out payments to the manufacturer over time, similar to a traditional mortgage. One payment model suggests a mobility of payments, so if a patient switches health plans, the new health plan is responsible for continued payments to the manufacturer.<sup>53,54</sup> Managed care organizations may need to be creative in the future of payment models for these ultrarare and expensive curative therapies, if approved.

## Conclusions

Managed care organizations have the difficult task of balancing clinical outcomes with the cost of care. Therefore, it is incumbent upon the organization to responsibly implement utilization management strategies to ensure appropriate use for medication treatment options for ALS. Although the current treatment options will cross the line of pharmacy versus the medical benefits, coverage determinations should take into account the clinical presentation with respect to the total cost of care as well as any psychosocial parameters in an effort to delay disease progression. Managed care organizations need to be supportive of the use of multidisciplinary care teams providing care to and supporting patients with ALS as well as initiate pharmacotherapy interventions earlier in the disease course to potentially provide optimal benefit. As gene therapy continues to be developed, innovative cost-containment strategies should be explored to manage the cost of care for patients with ALS. ■

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# Slowing Disease Progression in Amyotrophic Lateral Sclerosis: A Review of Guidelines and Current and Emerging Therapies

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## Sample of Online Posttest

Choose the best answer for each of the following:

1. **Most patients with amyotrophic lateral sclerosis (ALS) die within how many years of symptom onset?**
  - A. 1 to 3
  - B. 2 to 5
  - C. 3 to 6
  - D. 4 to 7
2. **What is the mechanism of action of riluzole?**
  - A. Glutamate inhibitor
  - B. Antioxidant and free radical scavenger
  - C. Neuroprotectivity by targeted inflammatory proteins
  - D. Reduction of superoxide dismutase 1 (SOD1) protein production
3. **Caregiving for a patient with ALS by family averages how many hours per week?**
  - A. 12
  - B. 26
  - C. 31
  - D. 47
4. **In clinical trials, which study drug demonstrated significant slowing of ALS severity and quality of life reductions over a 48-week time period in patients?**
  - A. Tofersen
  - B. Ravulizumab
  - C. Masitinib
  - D. NurOwn
5. **Which statement is true regarding currently available pharmacologic therapy for ALS?**
  - A. Approved riluzole formulations include tablets, oral solutions, and an oral film.
  - B. Edaravone can be self-administered through subcutaneous administration.
  - C. Disease-modifying therapy can reverse ALS disease progression.
  - D. Edaravone has been FDA approved for more than 20 years.
6. **Which of the following was not an inclusion criterion for study participants in edaravone pivotal trials?**
  - A. A definite or probable diagnosis of ALS based on the El Escorial revised criteria
  - B. Respiratory function (forced vital capacity  $\geq$ 80%)
  - C. Patient newly diagnosed with ALS at most 1 year prior to study initiation
  - D. Retained functionality of daily living as defined by a score of 2 or more on all components of the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R)
7. **Which of the following is an investigational drug designed to reduce the synthesis of the SOD1 protein?**
  - A. Ravulizumab-cwvz
  - B. Tofersen
  - C. NurOwn
  - D. Riluzole

- 8. Which part of Medicare would edaravone intravenous solution fall under?**
- A. Medicare Part B only
  - B. Medicare Part D only
  - C. Medicare Part B mainly, but may be under Medicare Part D in some rare circumstances
  - D. Medicare Part D mainly, but may be under Medicare Part B in some rare circumstances
- 9. VK is a 62-year-old woman who received a diagnosis of limb-onset ALS 3 months ago. VK will soon start on edaravone. Which of the following is true?**
- A. Edaravone is initially administered daily for 14 days followed by a 14-day drug-free period.
  - B. VK is not eligible for pharmacologic treatment as her disease has not progressed enough to warrant treatment.
  - C. VK must undergo genetic testing prior to initiating edaravone.
  - D. Edaravone has not been shown to have any effect on disease progression.
- 10. In a retrospective analysis of the Centers for Medicare & Medicaid Services Limited Data Set, which of the following observations regarding patients with newly diagnosed ALS and matched controls is true?**
- A. Costs were similar between patients with newly diagnosed ALS and matched controls due to slowed progression of disease.
  - B. Patients with newly diagnosed ALS had significantly higher all-cause costs compared with matched controls.
  - C. Compared with matched controls, patients with newly diagnosed ALS were more likely to have a physician office visit but less likely to have an outpatient hospital visit.
  - D. The most costly milestone for patients with newly diagnosed ALS was noninvasive/invasive ventilation.

SAMPLE  
POSTTEST



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