

Amyotrophic Lateral Sclerosis: An Update for 2018

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Abstract

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease affecting motor neurons and other neuronal cells, leading to severe disability and eventually death from ventilatory failure. It has a prevalence of 5 in 100,000, with an incidence of 1.7 per 100,000, reflecting short average survival. The pathogenesis is incompletely understood, but defects of RNA processing and protein clearance may be fundamental. Repeat expansions in the chromosome 9 open reading frame 72 gene (*C9orf72*) are the most common known genetic cause of ALS and are seen in approximately 40% of patients with a family history and approximately 10% of those without. No environmental risk factors are proved to be causative, but many have been proposed, including military service. The diagnosis of ALS rests on a history of painless progressive weakness coupled with examination findings of upper and lower motor dysfunction. No diagnostic test is yet available, but electromyography and genetic tests can support the diagnosis. Care for patients is best provided by a multidisciplinary team, and most interventions are directed at managing symptoms. Two medications with modest benefits have Food and Drug Administration approval for the treatment of ALS: riluzole, a glutamate receptor antagonist, and, new in 2017, edaravone, a free radical scavenger. Many other encouraging treatment strategies are being explored in clinical trials for ALS; herein we review stem cell and antisense oligonucleotide gene therapies.

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder that, by definition, affects lower and upper motor neurons. In the United States, the disease is often referred to as Lou Gehrig's disease after the New York Yankee baseball player who was diagnosed as having ALS in 1939 at Mayo Clinic. In addition to motor neurons, neurons in the frontal cortex and other neuroanatomical regions may also be affected. This review covers our current understanding of the disease process, its epidemiology, the current standard of care, a new Food and Drug Administration (FDA)–approved therapy, and select potential future therapies.

BACKGROUND

Amyotrophic lateral sclerosis was described in 1869 by the great French neurologist Charcot as a neurodegenerative disorder that affects lower and upper motor neurons (Figure 1).¹ Loss of lower motor neurons, which extend from the spinal cord to the muscles, leads to muscle weakness, wasting, cramps, and fasciculations. These lower motor neuron features

contribute to mortality more so than the features caused by the loss of upper motor neurons in the brain, which include spasticity, clumsiness, brisk reflexes, and functional limitations. It is now appreciated that extramotor systems are also involved in ALS, albeit to varying degrees. For example, some patients develop neuronal loss in the frontotemporal cortex, with approximately half of all patients experiencing cognitive and behavioral signs or symptoms. The recognition of extramotor involvement in ALS, which was previously overlooked, has improved clinical care and provided new insight into the pathogenesis of ALS.

EPIDEMIOLOGY

The US National ALS Registry Act was enacted in 2008 by Congress to gather and organize information about who gets ALS and its potential causes; such data have now been collected for 6 years. This unique program, administered by the Agency for Toxic Substances and Disease Registry, captures information from 4 national administrative databases (the Centers for Medicare and Medicaid Services,

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ARTICLE HIGHLIGHTS

- No diagnostic test for amyotrophic lateral sclerosis (ALS) is yet available.
- The prevalence of ALS in the United States is 5 in 100,000.
- Care for ALS is best delivered through a multidisciplinary ALS clinic.
- A new intravenous medication, edaravone, was approved for the treatment of ALS in 2017.
- Edaravone slows disease progression by 33% (measured by the ALS Functional Rating Scale-Revised) in a very select population of patients with ALS.

the Veterans Health Administration, and the Veterans Benefits Administration), and also lets people self-identify as patients with ALS and provide additional information through a voluntary online enrollment system. The program has substantially added to our overall knowledge about the epidemiology of ALS, and it estimates an ALS prevalence rate in the United States of 5 cases per 100,000 population for 2013, the last year for which published data are available.² This is consistent with most previous estimates, including one for Olmsted County in Minnesota, where an average annual incidence rate of 1.7 cases per 100,000 people was seen.³ According to population-based studies, the median survival of patients with ALS is 2 to 3 years from symptom onset, with death typically resulting from ventilatory failure. Amyotrophic lateral sclerosis is more common in men than in women by a factor of 1.5, and the rate of disease progression may be more rapid in patients with an older age at onset, a bulbar site of onset, cognitive impairment, and certain genotypes.⁴ Regarding the latter, approximately 10% of ALS is familial and caused by a genetic mutation that is usually inherited in a mendelian autosomal dominant manner. A hexanucleotide G₄C₂ repeat expansion in the chromosome 9 open reading frame 72 gene (*C9orf72*) is the most common known genetic cause of ALS, accounting for 30% to 40% of familial ALS, and it also causes frontotemporal dementia (FTD).^{5,6} Whereas the normal range of G₄C₂ repeats is generally considered to be 30 or fewer, patients with either ALS or FTD

may carry several hundreds or thousands of repeats. Of note, *C9orf72* repeat expansions are frequently associated with cognitive and behavioral changes. Together with the *C9orf72* repeat expansion, mutations in genes encoding copper-zinc superoxide dismutase (SOD1), transactive response DNA-binding protein 43 (TDP-43), and fused in sarcoma (FUS) account for more than 50% of the familial ALS cases, and another 30 or so genes have been identified as possibly causing ALS, increasing the risk of developing ALS, or hastening disease progression. For example, the Ala4Val variant in the *SOD1* gene causes a highly aggressive disease phenotype, and mutations in *FUS* are associated with a younger onset of disease and rapid disease progression. It has also been suggested that some genetic variants influence the response to therapy and may, thus, lead the way to precision medicine for ALS.⁷

Although our understanding of the genetic basis of ALS is continually expanding, our knowledge of other risk factors is less advanced. Given that genetic causes for ALS are determined at conception but ALS develops most often in adulthood, other factors, such as time and environmental exposures, must underpin or influence disease susceptibility. The relationships among genetic risk, environmental factors, and disease phenotype, however, remain largely unknown. One reason for this is that environmental risk factors for ALS have proved difficult to identify, in part because exposure to such factors can change over time and may not be accurately recorded. Nonetheless, although there are currently no known environmental risk factors that irrefutably link to ALS, suspected risk factors include smoking, athletic propensity or activity, military service, β -N-methylamino-L-alanine, head trauma, electromagnetic fields, agricultural chemicals, and exposure to lead and other heavy metals.⁸ Overall, the gene-time-environment model suggests that the development of ALS is a multi-step process in which genetic defects are but 1 of several steps eventually leading to ALS.⁴

PATHOGENESIS

Although the pathogenesis of ALS remains largely unknown, neuropathologic features and gene mutations associated with ALS

have shed important light on the etiology of the disease. Indeed, we have dramatically advanced our understanding of the pathogenesis of ALS in the past decade, which has led to optimism in the field. A common feature of many neurodegenerative diseases characterized by neuronal dysfunction and eventual cell death is the accumulation of proteinaceous aggregates in cells throughout the nervous system. A protein called TDP-43 is the primary component of such aggregates in most ALS cases, including cases caused by *C9orf72* repeat expansions.^{9,10} Notably, mutations in *TARDBP*, the gene that encodes the TDP-43 protein, have been discovered in sporadic and familial ALS, providing a direct link between TDP-43 abnormalities and neurodegeneration.¹¹⁻²¹ How these abnormalities in TDP-43 cause neuronal loss is not yet definitely known but is likely to involve a combination of events. The TDP-43 inclusions may themselves be toxic, and they may also harm neurons by sequestering TDP-43 and preventing it from performing its usual functions in cells.^{22,23}

Transactive response DNA-binding protein 43 is an RNA-binding protein with more than 6000 RNA targets in the brain; combined with its role in multiple steps of RNA processing, this suggests that disrupted RNA metabolism contributes to ALS pathogenesis. Further supporting this notion is the fact that mutations in *FUS*, *heterogeneous nuclear ribonucleoproteins A1 and A2B1*, *TATA-box binding protein associated factor 15*, and *TIA1*, which also encode RNA-binding proteins, are implicated in the causation of ALS.²⁴ Through functions performed in both the nucleus and the cytoplasm, these RNA-binding proteins determine the fate of RNA transcripts from their maturation to their degradation. One such critical function is the recruitment of messenger RNA (mRNA) transcripts into stress granules formed on cellular stress; this facilitates cell survival by silencing mRNAs not needed to cope with the stress while allowing the optimal translation of mRNAs that are.²⁵ Stress granules are membraneless, cytoplasmic organelles composed of mRNAs, translation initiation factors, 40S ribosomes, and RNA-binding proteins.²⁶ Once the stressful event has subsided, stress granules disassemble. However, perturbations in TDP-43, *FUS*, *TIA1*, and related RNA-binding proteins can impair

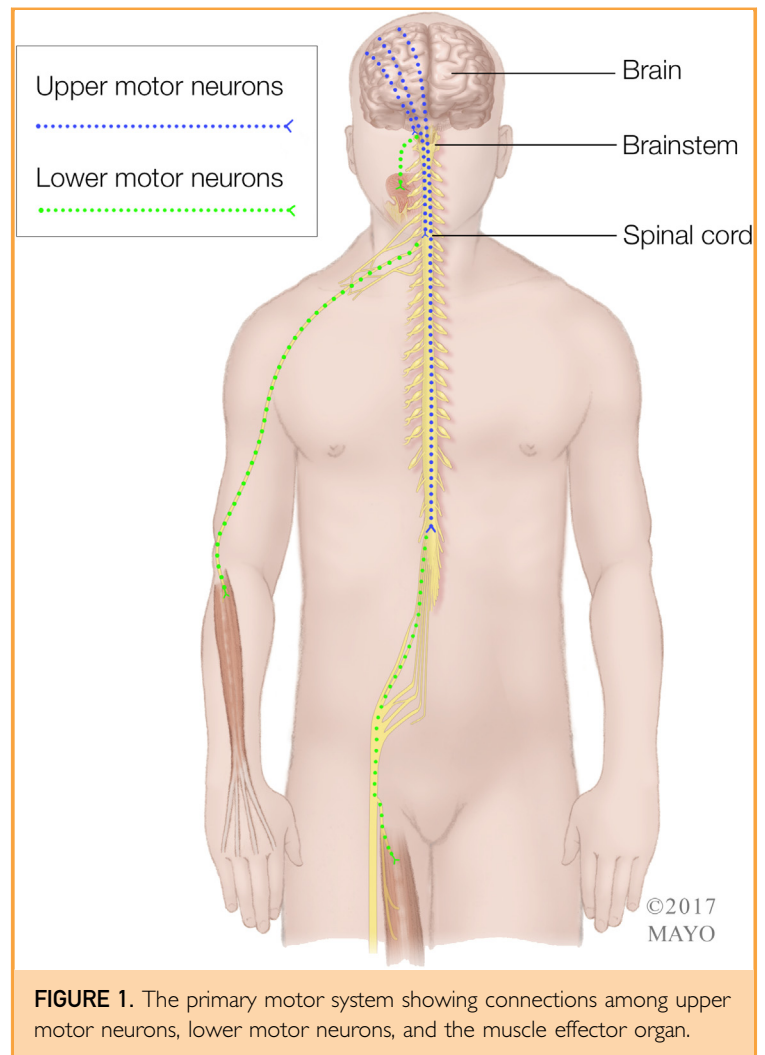


FIGURE 1. The primary motor system showing connections among upper motor neurons, lower motor neurons, and the muscle effector organ.

proper stress granule dynamics and thus prevent a proper stress response. For example, *TIA1* mutations delay stress granule disassembly after stress and promote the accumulation of stress granules that harbor TDP-43.²⁴ Indeed, it bears mentioning that the localization of TDP-43 and related RNA-binding proteins to stress granules may further promote their aggregation and the disruption of neuronal homeostasis. Of interest, in patients with ALS caused by *C9orf72* repeat expansions, TDP-43 pathology is accompanied by other hallmark features that are also believed to contribute to impaired RNA metabolism and stress granule dysregulation. One such feature is the accumulation of repeat-containing RNA transcribed from *C9orf72* repeat expansions, which binds to various RNA-binding proteins and, in so

TABLE. Diseases Commonly Considered in the Differential Diagnosis of Amyotrophic Lateral Sclerosis

Region/involvement	Upper motor neuron suspect findings	Lower motor neuron suspect findings
Bulbar	Brainstem lesion (stroke, multiple sclerosis, tumor)	Brainstem lesion (stroke, multiple sclerosis, tumor), neuromuscular junction disorder (myasthenia gravis, muscle-specific tyrosine kinase myasthenia), bulbosacral muscular atrophy
Cervical	Cervical myelopathy	Multifocal motor neuropathy, cervical radiculopathy
Lumbosacral	Thoracic myelopathy	Lumbosacral radiculopathy

doing, can impair their function. Furthermore, a variety of aggregation-prone proteins of repeating dipeptides are produced from *C9orf72* repeat expansions, and 2 of these—poly(GR) and poly(PR)—trigger stress granule formation or impair their dynamics.²⁷⁻³⁰

In addition to defects in RNA metabolism, impaired protein metabolism is thought to contribute to ALS pathogenesis.³¹ Indeed, mutations in genes involved in protein clearance, such as charged multivesicular body protein 2B, optineurin, sequestosome 1, valosin-containing protein, TANK-binding kinase 1, and ubiquilin 2, cause ALS or FTD.³²⁻³⁹ There exists 2 major protein degradation pathways in cells: the ubiquitin proteasome system, which degrades short-lived, soluble proteins, and the autophagy-lysosome pathway, which degrades relatively long-lived proteins, misfolded and aggregated proteins, and organelles. Defects in these degradation systems may not only contribute to the aberrant accumulation of TDP-43, FUS, or SOD1 but also further compound the problem by failing to clear stress granules and, thus, promote the aggregation of these proteins.⁴⁰ In turn, the protein aggregates are proposed to inhibit protein degradation pathways and to sequester RNA and other proteins required for proper cellular function. In addition, in *C9orf72*-associated ALS, dipeptide repeat proteins also bind proteins involved in key cellular pathways and adversely affect protein translation and degradation.^{41,42}

Many additional pathologic mechanisms have been implicated in various steps of the neurodegenerative process of ALS, including mitochondrial dysfunction, oxidative damage, excitotoxicity, inflammation, and defects in intracellular and nucleocytoplasmic transport.⁴³ Further adding to the complexity of the disease is that ALS is not only a disorder

of neurons, but also involves, and possibly even requires, other cell types, including astrocytes, microglia, macrophages, and potentially oligodendrocytes.⁴⁴⁻⁴⁷ Also of note, for most patients with ALS, the disease has a focal site of onset that then spreads along neuroanatomical pathways, possibly suggesting a prion-like transmission to susceptible tissues.^{48,49}

Finally, the concept of ALS as a single disease has also been challenged. As described herein, there are many genetic variants and perhaps environmental risk factors that can lead to the overlapping clinical phenotypes of upper motor neuron disease, lower motor neuron disease, and even FTD, which are likely to cause ALS through both common and distinct pathologic mechanisms. Indeed, it has been speculated that many clinical trials in ALS have failed, at least in part, due to potential differences in underlying pathophysiologic mechanisms among patients with ALS. A better understanding of the molecular underpinnings of the various putative forms of ALS and the development of representative preclinical models are expected to facilitate endeavors to identify effective treatments for ALS.

CLINICAL CARE

Amyotrophic lateral sclerosis remains a disease without a specific diagnostic test. A clinical diagnosis of ALS is based on a history of progressive, painless weakness, and examination findings of both upper and lower motor neuron dysfunction. The initial symptoms of ALS vary among patients depending on the degree of upper and lower motor neuron involvement and which regions of the body are involved. Where the neurologic deficits manifest dictates which other diseases may produce the observed symptoms and, thus,

informs the differential diagnostic evaluation. Clinical presentations can range from a spastic pattern of speech caused by upper motor neuron loss to a foot drop caused by lower motor neuron loss, with numerous permutations in between (diseases commonly worth considering are listed in the [Table](#)). The diagnosis may, therefore, be uncertain initially, and only with the development of additional features can the diagnosis be established with greater certainty. The appropriate exclusion of other diseases in the differential diagnosis is paramount, and electrophysiologic evaluations (electromyography and nerve conduction studies) are often the most important tests to help establish a diagnosis, but neuroimaging and serologic studies can also be of great value and are indicated in most cases. Spinal fluid analysis and nerve and muscle biopsies are tests that only rarely need to be used to exclude specific diseases in the differential diagnosis.

The standard of care for ALS is delineated in the 2009 American Academy of Neurology practice parameter, and several other organizations provide guidance, including the 2012 European Federation of the Neurological Societies Task Force and the United Kingdom's National Institute for Health and Care Excellence, with its more recent 2016 guidelines for ALS care.⁵⁰⁻⁵³ There exist differences among the guidelines accounting for new evidence and data that emerged since their respective publication, and there are also methodological differences. For example, the American practice parameter is more stringent and avoids making recommendations if high-quality evidence is lacking, whereas the other guidance documents provide expert-based recommendations. Another difference is the scope of the guidance, and the National Institute for Health and Care Excellence guideline, which is more encompassing, recommends that physicians make prompt referrals to Neurology before patient diagnosis, and subsequently emphasizes integration with primary care providers (general practitioners). All recommendations focus on a multidisciplinary approach for the care of patients with ALS; this has proved to be effective, but this model of care may not be fully reimbursed in the United States.^{54,55} Telemedicine is emerging as a complement to the current center-based care model.⁵⁶

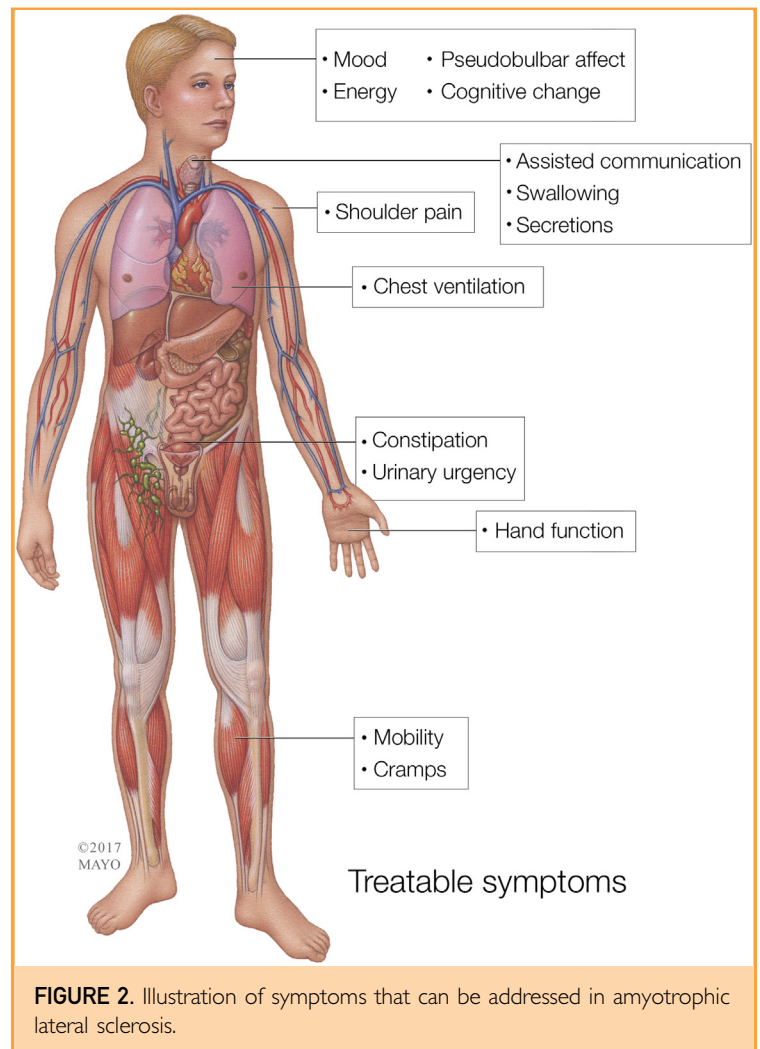


FIGURE 2. Illustration of symptoms that can be addressed in amyotrophic lateral sclerosis.

Until recently, disease-modifying therapies for ALS have been limited to riluzole, a glutamate release inhibitor approved for the treatment of ALS in 1995. The drug is generally well-tolerated, but has a limited potency. A survival benefit of approximately 3 months was noted in clinical trials.^{57,58} No effect on function or quality of life was discernible. Attempts at identifying subgroups of patients more likely to benefit from riluzole treatment have been made.⁵⁹ Many patients use complementary and alternative therapies exemplified by vitamins and nutritional supplements.⁶⁰ Some supplements have scientific rationale, but there is insufficient clinical trial evidence to substantiate such claims. Counseling to avoid the use of dangerous treatments is advisable.

With the limited potency of disease-modifying agents, management instead centers on addressing symptoms (Figure 2). This includes cognitive and behavioral evaluations given that thinking and behavioral symptoms are increasingly recognized in patients with ALS, and this can impact disease course, symptom management, and decision making throughout the illness.⁶¹ Clinical interventions are more difficult for patients with cognitive impairment to accept, but special strategies, such as additional education and recurrent reminders, may help improve compliance. Unfortunately, no medications for cognitive and behavioral dysfunction are of clear benefit, including cholinesterase inhibitors, which are used in amnesic dementia.

Approximately 25% to 50% of patients with ALS develop pseudobulbar affect.⁶² This neurologic condition, also known more descriptively as *inappropriate emotional expression disorder*, is characterized by a tendency to cry or laugh uncontrollably or out of proportion to the experienced emotion.⁶³ These outbursts may be mood incongruent, with sadness manifesting as laughter, or joy manifesting as crying. Several medications, including a combination of dextromethorphan and quinidine, can be effective in controlling the symptom.⁶⁴ This combination was FDA approved for the treatment of pseudobulbar affect in 2010. An ALS diagnosis is a major psychological stressor, and although depression and anxiety are not necessarily more common in the ALS population compared with the general population, depression and hopelessness are likely negative prognostic factors for ALS and should, thus, be treated if present.^{65,66} Counseling and peer support groups for patients and caregivers are often valued. Fatigue is another common symptom that has been treated successfully with stimulants, and contributing respiratory problems should be addressed.⁶⁷ Although ALS is thought to be painless, nonneuropathic pain is experienced by most patients.⁶⁸ Pain is often due to secondary joint and back issues and needs to be managed according to its origin. Muscle cramps affect most patients with ALS and can be painful. Mexiletine is emerging as a possible treatment and as an alternative to quinine, which is no longer recommended by the FDA for clinical use.⁶⁹⁻⁷¹

Ventilatory failure is the leading cause of death in patients with ALS. Pulmonary function testing, nocturnal pulse oximetry, and reported symptoms can help gauge the progression of breathing weakness. Assisted ventilation, typically with noninvasive bilevel positive airway pressure settings, can substantially prolong life and also help improve quality of life.^{72,73} The trend in recent years has been to use volume-controlled modes instead of pressure control based on the notion and emerging evidence that this is better tolerated and more effective.^{74,75} These modes of ventilation can be delivered by machines with differing complexity. The US Centers for Medicare and Medicaid Services cover the necessary respiratory therapy support only for more complex devices and also do not require as extensive documentation for more advanced devices. Noninvasive ventilation often eventually fails, thus necessitating a decision about proceeding with an invasive interface (eg, tracheostomy). Only a small minority of patients with ALS in the United States select this option, with physician and caregiver preferences likely being important factors in this decision.⁷⁶ Both patients and caregivers should be provided with information regarding the consequences of invasive ventilation to allow them to make educated decisions based on their own needs and goals. Not implementing timely tracheostomy can lead to a preventable death, and an emergency tracheostomy performed without a good understanding of the long-term outcome can also have negative consequences. Strategies to maintain lung compliance and help airway clearance are also recommended.⁷⁷ Drugs known to reduce respiratory drive, such as opiates and benzodiazepines, should be avoided, if possible, until the terminal stage of the disease. Phrenic nerve stimulators, also known as diaphragm pacers, are not effective in ALS.^{78,79} Loss of voice function can artificially be compensated for with speech-generating devices and less complex writing boards.

Impaired swallowing can lead to aspiration and poor nutrition. Amyotrophic lateral sclerosis leads to increased calorie needs, and weight loss correlates with shorter survival.^{80,81} Low vitamin D levels are seen in ALS, but recent studies suggest that vitamin D is not an independent prognostic marker.^{82,83} Safe swallowing techniques and diet modifications can prolong functional independence. Gastrostomy

placement is the standard accepted treatment to ensure adequate nutrition, but it may or may not prolong survival or be beneficial outside of providing a way to deliver nutrition, hydration, and medications.^{84,85} For patients on continuous ventilatory support it would seem likely that gastrostomy feeding is required to achieve the full benefit of the ventilatory treatment. Sialorrhea (hypersalivation) due to impaired swallowing can be managed with anticholinergic medications, salivary gland botulinum toxin injections, or radiotherapy.^{86,87} Suction machines can be used to remove oral and pharyngeal secretions. Thick secretions can be liquefied with hydration, oral mucolytics, or nebulized acetylcysteine.

Many devices can be used to preserve functional independence; some of the most commonly prescribed devices are ankle-foot braces, walkers, wheelchairs, hospital beds, toileting equipment, and lifts.⁸⁸ Physical and occupational therapy can maximize the benefit of equipment and provide range of motion and exercise programs to retain function and minimize pain. Spasticity is an upper motor neuron symptom that can cause pain and limit function, but occasionally it provides a degree of functional benefit by allowing patients to do pivot transfers or other activities where a stiff limb is more useful than a flaccid one. Baclofen and other oral muscle relaxers are the mainstay of treatment, but botulinum toxin injections and, for the rare patient, implanted baclofen pumps are also useful.⁸⁹ Constipation is a frequent problem in ALS; bowel regimen strategies, such as fluid, fiber, and laxative drugs, help manage the symptom.⁹⁰ Urinary urgency is another symptom that can be managed with anticholinergics and intravesical botulinum toxin.⁹⁰ It is unclear whether these latter symptoms are purely secondary to immobility or are due to ALS involvement of the autonomic nervous system.⁹⁰

The patients' individual goals of care are important, and treatment plans should be tailored with these goals in mind and using interventions acceptable to the patient. Most patients with ALS will die of their ALS, and many will have questions regarding this process. Should the patient want this type of information, factual and compassionate information regarding the dying process can help demystify it and reduce anxiety. For most patients, death

can be described as peaceful, and terminal anxiety and shortness of breath are controlled with oxygen, opiates, and benzodiazepines.⁹¹ Information regarding hospice care and how terminal symptoms can be effectively managed should be provided when appropriate. Patients often have questions regarding physician-assisted suicide, which is now legal in many states. This remains a complex ethical and legal question, but the acceptance of active suicide as an appropriate option to death from untreated ventilatory weakness is growing. Most patients with ALS do not use this option even in states where it is legal, and a small minority of patients with ALS do commit suicide even without physician assistance.⁹² Cognitive impairment accompanied by difficulties making decisions and grasping complex problems can make these types of discussions even more difficult.

NEWLY APPROVED THERAPY

Edaravone is an intravenous drug for the treatment of ALS that was approved by the FDA in May 2017, approximately 2 years after its approval for the treatment of ALS in Japan and South Korea. As of December 2017, the drug has not been filed for approval in Europe, and the European ALS investigators in the European Network to Cure ALS recommend additional studies before a European approval.⁹³

Edaravone was first approved in Japan in 2001 for the treatment of cerebrovascular accidents, and it has been dosed in more than 1.7 million patients. The use of this drug, a free radical scavenger, was subsequently assessed for other neurologic disorders, including ALS, in several clinical trials. In one trial, 139 patients with ALS were randomized 1:1 to receive active or control intervention over a 6-month duration.⁹⁴ This short duration did not allow for the assessment of an effect on survival, and neither was one seen in this study. The selection criteria were also narrow and somewhat innovative with the purpose of enriching for patient groups that seemed to perform better in a previous study.⁹⁵ The main inclusion criteria were age 20 to 75 years, a Japan ALS Severity Classification of grade 1 or 2 (no to mild disability), scores of at least 2 points on all 12 items of the ALS Functional Rating Scale-Revised (ALSFRS-R), forced vital capacity of 80% or more, definite or probable ALS according to the revised El Escorial criteria,

and disease duration of 2 years or less. In addition, during a 12-week lead-in phase, patients had to lose 1 to 4 points on the ALSFRS-R before being randomized. It is estimated that approximately 1 in 20 patients with ALS followed at an ALS clinic would meet these enrollment criteria, which has raised questions regarding the generalizability of the results. Nevertheless, the results were rather remarkable, showing a slowing in the decline of the ALSFRS-R score by 33% over the 6 months. The ALS quality-of-life measures also tracked accordingly showing a significantly slower decline. Respiratory measures trended in the same direction but did not reach statistical significance.

Edaravone is delivered by intravenous infusions in cycles consisting of daily dosing for 2 weeks followed by a 2-week drug-free period. Subsequent infusion cycles allow interruptions over the weekend. The drug's half-life is approximately 4.5 to 6.0 hours, suggesting that a more frequent dosing schedule could be more beneficial. Most patients in the studies were taking concomitant riluzole, and the 2 medications can be used together. The drug's safety profile is favorable, with more patients in the placebo arm having significant adverse events compared with patients receiving drug in the Japanese trial; this has also been observed in the author's clinical experience in the United States to date. Allergic reactions, including anaphylaxis, are the most severe reported reactions. Edaravone does not have any listed drug interactions, and its dosing is not recommended to be adjusted for moderate kidney or liver dysfunction. The cost of the medication and the frequent infusions has further increased the cost of ALS care in the United States. Many insurance companies and the Veterans Health Administration limit the coverage of the drug and do not provide coverage for all patients with ALS. As part of its approval of edaravone, the FDA has requested additional studies to assess the effect of more frequent and higher dosing.⁹⁶ Edaravone is also being developed in oral form, which would circumvent the major hurdles with its administration.

FUTURE THERAPIES

Currently, there are many trials of varying phases in ALS. The severity of the medical

need, lack of highly effective therapies, rapid disease course, engaged patient community, and well-developed research infrastructure are likely factors contributing to this. The lack of biomarkers of the disease is likely the most limiting factor for treatment development at this time, but many approaches are being explored to rectify this deficiency.

Stem Cells

During the past few years, there has been considerable excitement about stem cell–based therapies for ALS and other neurodegenerative diseases. Stem cell therapeutics are now in phase 1, 2, and even 3 clinical trials and use a variety of cell types. Current stem cell approaches are primarily designed to help protect surviving motor neurons via paracrine effects (neuroprotection); they are not designed to replace dead motor neurons.

Mesenchymal stromal cells (MSCs) are primarily being used as an autologous stem cell therapy for ALS due to their ability to secrete neurotrophic factors and modulate the immune system, 2 mechanisms shown to slow disease course in animal models. The MSCs naturally arise from pericytes in several tissue types (fat, connective tissue, bone marrow, dental pulp) and are thought to mediate tissue healing while also being able to differentiate into bone, cartilage, and fat.^{97,98} The MSCs are isolated from fat or bone marrow biopsies, expanded in vitro, and then injected into the thecal space via lumbar puncture (with or without simultaneous intravenous or intramuscular injections) or directly intraspinally.⁹⁹⁻¹⁰² Some groups have also developed conditioned media that increases the MSCs' neurotrophic factor secretion, and others are using genetic editing strategies to increase the secretion of specific factors.^{103,104} Overall, the safety profile of MSC therapies has been good, and the lack of required concomitant immunosuppression has been considered a benefit. Although none of these early-phase studies have been powered to prove efficacy, there have been reports of subjective benefits and case studies that suggest that a subset of patients may respond to therapy.^{99,105} A phase 3 clinical trial was recently started using intrathecal delivery of autologous MSCs overexpressing neurotrophic factors.¹⁰⁶

Another stem cell strategy uses neuroglial-lineage precursors to treat ALS. With this

approach, stem cell lines have been developed from fetal neural tissue, which are then injected directly into the anterior horn of the spinal cord.^{107,108} Because the cells are allogeneic, immunosuppression is required to prevent transplant rejection. Phase 1 and 2 clinical trials have been completed using stem cells obtained from human fetus spinal tissue.¹⁰⁹ Although not powered for efficacy, there seemed to be modest benefit in a subset of patients, and larger multicenter trials are being planned. Phase 1 and 2 studies using similar strategies are beginning at other centers in the United States.^{107,110,111}

Other Agents

At present, many agents are being investigated for the treatment of ALS. One agent, the tyrosine kinase inhibitor masitinib, was filed for approval in Europe after positive yet unpublished studies.^{112,113} The purported effect of the drug would be in the range of riluzole or edaravone. Additional studies may be required to validate the results before any approvals are granted.

The knowledge that genetic variants cause ALS provides putative targets for therapy even in the absence of a definitive understanding of the pathologic mechanisms initiated by the mutated gene. Directly altering the expression of the mutated gene may mitigate critical steps in the development of disease. In a phase 1 clinical trial, intrathecal delivery of antisense oligonucleotides designed to inhibit *SOD1* expression were found to be well-tolerated by patients with *SOD1* familial ALS, and a second trial is ongoing.¹¹⁴ Likewise, the discovery of *C9orf72* repeat expansions as a cause of ALS uncovered a therapeutic strategy for this more common form of ALS. As mentioned previously herein, many of the adverse events resulting from this mutation are believed to arise from the accumulation of repeat-containing RNA transcribed from the *C9orf72* repeat expansion. For example, these RNA transcripts aberrantly interact with RNA-binding proteins and also serve as templates for the synthesis of dipeptide repeat proteins, several of which are toxic in *in vitro* and *in vivo* models. Consequently, antisense oligonucleotides that target these repeat-containing transcripts and cause their degradation are being developed as a potential therapy. This

strategy has mitigated many of the adverse events associated with repeat RNA in mouse models of *C9orf72*-associated ALS.^{115,116}

CONCLUSION

Amyotrophic lateral sclerosis remains a fatal neurodegenerative disease destroying the primary motor system, and it also often affects neuroanatomical regions involved in cognition and behavior. Identifiable genetic causes, which are potential drug targets, are responsible for a portion of sporadic cases and most cases with a positive family history, admittedly leaving most cases without a clearly defined etiology. Nevertheless, significant advances have been made in elucidating the pathogenesis of ALS. With an increased understanding of these pathologic mechanisms, we hope to be informed of the environmental factors that may play an important role. Two medications, riluzole and the recently approved edaravone, have proved effective for the treatment of ALS, but more treatments are needed. Current treatment strategies are otherwise largely palliative, aiming to provide better life quality and longer survival, with assisted ventilation being the single most powerful approach. With a better understanding of the underlying genetic causes and the pathogenesis of ALS, many novel treatment approaches are in development, hopefully leading to more effective treatments in the near future.

Abbreviations and Acronyms: ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS Functional Rating Scale-Revised; *C9orf72* = chromosome 9 open reading frame 72; FDA = Food and Drug Administration; FTD = frontotemporal dementia; FUS = fused in sarcoma; mRNA = messenger RNA; MSC = mesenchymal stromal cell; *SOD1* = copper-zinc superoxide dismutase; TDP-43 = transactive response DNA-binding protein 43

Potential Competing Interests: B Oskarsson serves as a consultant for FlexPharma and has provided consultations to Biogen regarding SMA. The rest of the authors report no competing interests.

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