

Current Landscape of Treatment Options for Patients With Amyotrophic Lateral Sclerosis (ALS)

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Ask the average American what they know about “ALS” and they may remember people taking the Ice Bucket Challenge¹ or wistfully recall New York Yankee Lou Gehrig declaring he was “the luckiest man on the face of the earth” during his July 4, 1939, appearance at Yankee Stadium.² They may recall that Stephen Hawking, who died in 2018, incredibly lived with the disease for 55 years.³ But ask about the disease “amyotrophic lateral sclerosis” and most people will probably admit to not knowing much more than it being a debilitating disease—and they’re right.

While there is much that remains unknown about this rare neurodegenerative disease for which there currently is no cure,⁴ here’s what is known at a high level:



Among neurodegenerative disorders, **ALS is usually the most rapidly fatal**⁵



Patients typically succumb to ALS within 2 to 5 years of the first symptoms; only about 10% survive longer than 10 years^{4,6}



The time needed to arrive at a diagnosis of ALS **can account for a significant proportion of the total duration of illness**⁷



Death is usually the result of **respiratory failure**⁸

Understanding of the history and pathology of ALS

In 1869, French neurologist Jean-Martin Charcot was the first to describe the symptoms that define ALS. Charcot identified a relationship between the anatomy of the spinal cord and the pattern of weakness in affected individuals, noting the distinction between patients whose lesions of the anterior horn of the spinal cord resulted in weakness with muscle atrophy, whereas those who manifested damage to only the lateral columns of the spinal cord had no atrophy.⁹ Using his research method that combined anatomical and clinical data, Charcot is credited with establishing neurology as a separate area of medical specialty and moving the study of neurologic diseases, such as ALS, forward.⁹

ALS is also known as *maladie de Charcot* in France and motor neuron disease (MND) in the United Kingdom and elsewhere.¹⁰ By any name, ALS is a relentlessly progressive orphan disease caused by the degeneration and death of specialized nerve cells in the human brain (upper motor neurons [UMNs]) and in the brain stem and spinal cord (lower motor neurons [LMNs]). UMNs transport motor information from the cerebral cortex to the brain stem and spinal cord; from there, LMNs extend from the brain stem and spinal cord to the skeletal muscles to govern voluntary movements and muscle control.^{11,13}

When the UMNs and LMNs degenerate and die, affected individuals develop muscle spasticity from UMN loss and weakness and atrophy (wasting) from the loss of LMNs.^{12,14} When the brain can no longer initiate and control muscle movement, people may lose the ability to move, talk, swallow, and breathe, which, in the late stages of ALS, can lead to eventual paralysis and death.^{4,11}

Digging deeper into the pathophysiology of ALS

Neuronal death can be triggered via multiple pathways,⁵ and many of these pathways can both cause and exacerbate endoplasmic reticulum (ER) stress and mitochondrial dysfunction (FIGURE 1). Some of these pathways include

- **Glutamate excitotoxicity.** Excessive glutamate induces the generation of reactive oxygen species in motor neurons, leading to oxidative stress, mitochondrial dysfunction, and neuronal death, while the excessive influx of sodium and calcium results in aberrant calcium homeostasis^{5,15,16}
- **Defects in protein folding and degradation.** The resulting formation of protein aggregates and generation of misfolded proteins lead to oxidative stress, mitochondrial dysfunction, and neuronal death⁵
- **Disturbances in ribonucleic acid (RNA) metabolism and nucleocytoplasmic transport.** Resulting defects in nucleocytoplasmic transport of proteins such as TAR DNA-binding protein 43 (*TDP-43*) and *FUS* trigger ER stress and neuronal death^{5,16,17}
- **Oxidative stress.** Genetic mutations leading to protein aggregation, RNA dysregulation, and lipid peroxidation can lead to oxidative stress mediated by the direct interaction of ALS-associated proteins with mitochondria, leading to the increased formation of reactive oxygen species (ROS) and ROS-induced damage to mitochondrial DNA, proteins, and lipids that triggers neuronal death^{5,16,18}
- **Axonal transport defects.** Certain mutations can lead to abnormalities in proteins involved in axonal transport, mitochondrial dysfunction, and the dysfunction of axonal transport systems that triggers axonal degeneration^{5,12}
- **ER/mitochondrial dysfunction.** Individually, continued ER stress triggers neuronal death by activation of downstream mechanisms while neuronal death can also be directly triggered by the mitochondrial (intrinsic) apoptosis pathway.^{18,19} Together, the interaction of impaired ER and mitochondria at mitochondria-associated membranes (MAMs) may also result in various pathological pathways that ultimately result in motor neuron dysfunction and axonal degeneration^{20,21}

Identifying the types and classes of ALS

Between 5% and 10% of all ALS cases are familial, most commonly inherited through a mutated gene passed from one parent to a child.¹⁴

Approximately 90% of all ALS cases are sporadic, meaning that there is no family history of ALS, and the etiology of the disease is unknown.¹⁴

While more than 30 genetic variants have been associated with an increased risk of ALS, research has shown that pathogenic mutations in ALS are commonly found in the *C9orf72*, superoxide dismutase 1 (*SOD1*), TAR DNA-binding protein (*TARDBP*), and fused in sarcoma (*FUS*) genes. These mutations are more common in familial ALS, but can also be found in sporadic ALS.^{4,12,22,23}

A number of environmental risk factors have also been associated with ALS, including but not limited to military service, smoking, heavy metal exposure, and pesticide exposure.¹⁴

The onset of classic ALS is generally classified as 1 of 2 forms based on the first symptoms observed:

- **Spinal or limb onset** is the most common presentation, which occurs in approximately 70%-80% of patients who initially experience fine-motor disturbances and weakness or paralysis in the arms and legs^{7,23,24}
- **Bulbar onset** occurs in roughly 25% of patients with ALS. Here, the oropharyngeal muscles used for speaking and swallowing are initially affected, causing patients to slur their words, have impaired tongue movements, and have difficulty swallowing. In the early stages of bulbar onset ALS, the muscles of the head, face, and neck become weak before muscles in other parts of the body^{7,13,23,25}

A rare disease with considerable burden

Despite its classification as an orphan disease, ALS is the most common neurodegenerative disorder of middle age, with an average onset at age 55 years old.¹⁴ Both the incidence and prevalence have been

shown to increase with age, with the greatest rates among persons aged 60 years or older.^{14,26}

The ALS Association states that every 90 minutes, someone is diagnosed with ALS and a person with ALS dies from the disease.²⁷ In the United States, approximately 5600 individuals are diagnosed with ALS annually, and there are as many as 28,500 Americans currently affected. Based on 2014 data, the incidence rate was an estimated 5 cases of ALS per 100,000 Americans.^{24,28,29}

ALS is a heterogeneous disease, affecting people of all races and ethnicities.²⁶ Men are up to twice as likely as to develop sporadic ALS as women, while the ratio among those with familial ALS is closer to 1:1.¹⁴

The economic burden of ALS

The total cost per patient with ALS has been shown to be greater than that of many other neurologic diseases, including dementia, Parkinson's disease, and stroke.¹

Medical costs for patients with ALS are significant and increase rapidly and substantially with each disability milestone.³⁰ A systematic review of relevant articles citing "ALS," "MND," "cost," or "economics" published between January 2001 and January 2015 found that the standardized annual direct cost per patient (out-of-pocket proportion) was close to \$53,500.¹

Patient and caregiver burdens of ALS

The systematic review found that two major contributors to additional burden in ALS were the loss of patient and caregiver income and necessary home modifications.¹

- Patients who lost their jobs due to ALS-related disability had an average annual income loss of \$30,000¹
- Family members, the most common caregivers for patients with ALS,⁷ reported an additional loss of nearly \$17,000 due to their caregiver responsibilities¹

Studies have shown that caregiving demands can be extensive. In moderate to severe cases, the daily time estimates range from an average of 9.5 to more than 14 hours.³¹ In addition to lost income, caregivers also face physical, psychological, emotional, and social challenges to their health and well-being; this is most severe for caregivers of patients with ALS and frontotemporal dementia (FTD). Caregiver stress has been shown to lead to adverse outcomes, psychological distress, and increased overall burden.^{1,7,32,33}

Disease progression in ALS

Amotrophic lateral sclerosis is a disease with highly variable clinical features and prognosis,^{11,34} making the diagnosis quite challenging (see **Symptoms of ALS, right**).

As symptoms progress, patients experience increasing disability and most ultimately require assistance with activities of daily living.³⁵

Time to diagnosis can be critical

Exploratory study findings noted a mean time from symptom onset to diagnosis with ALS of approximately 19 months and a median of 12 months.^{7,14} Given that ALS is typically fatal in patients within 2 to 5 years of symptom onset, delays in diagnosis can account for a significant proportion of a patient's total illness duration and can^{4,7}

- Prevent patients from starting treatment earlier in the disease that can help alleviate symptoms, enhance quality of life, and extend survival. These include pharmacotherapies and referrals to multidisciplinary clinics^{7,36}
- Preclude patients from enrolling in clinical trials early in their disease, a time when they could have a greater potential to benefit from experimental therapies^{7,36}
- Delay the timely introduction and use of a variety of assistive devices that can help the patient in their current stage of disease—from walkers and motorized wheelchairs to text-to-speech, speech-to-text, and voice-banking technologies to noninvasive ventilators and cough-assist devices³⁷
- Result often in multiple misdiagnoses that incur unnecessary diagnostic testing and inappropriate medical treatments or surgical procedures^{36,38}

SYMPTOMS OF ALS

Initially, patients with ALS may present with either predominantly UMN or LMN symptoms; however, both UMN and LMN symptoms eventually appear in most.^{12,24}

- UMN symptoms include hyperreflexia, spasticity, and loss of dexterity
- LMN symptoms include cramps, muscle atrophy, and fasciculations



Symptoms seen in spinal/limb ALS include muscle twitching, cramping, stiffness, weakness, and atrophy.²³



Symptoms seen in bulbar ALS include weakness and/or atrophy of muscles of the jaw, face, palate, tongue, and larynx, resulting in slurred speech (dysarthria) and difficulty chewing or swallowing (dysphagia).^{23,39,40}



Pseudobulbar affect can also occur in patients with ALS and may include episodes of uncontrolled laughing or crying.¹²



Cognitive and behavioral dysfunction are not uncommon in ALS. More than half of patients with ALS have been found to have cognitive dysfunction by detailed neuropsychological testing, and in nearly 15% it is severe enough to meet the criteria for FTD. FTD can also be characterized by changes in behavior such as apathy, impulsivity, and loss of insight and judgment.^{12,41}

FIGURE 1: The Pathophysiology of ALS



Figure adapted from: Kiernan MC et al. *Nat Rev Neurol*. 2021;17(2):104-118.
mRNA=messenger ribonucleic acid.

At present, there is no single definitive diagnostic test for, and no specific radiological or serological markers of, ALS.^{5,23} Because there is considerable variability in a patient's disease presentation, neurologists typically base a diagnosis of ALS on their interpretation of the patient's clinical data, including^{4,7,11,23}

- History of symptoms and neurological examination
- Electromyography results to confirm the extent of denervation
- Laboratory tests and scans (CT, MRI) to exclude reversible disorders that may resemble or mimic ALS

Criteria to classify and measure disease progression

The clinical variability of ALS has led to the need for thoughtful clinical trial design, including enrichment strategies that select a more homogenous population to allow the demonstration of clinical efficacy in the shortest period of time.⁴²

Many trials in ALS utilize some type of enrichment, either by prognostic factors, biomarkers, or established diagnostic classifications. The revised El Escorial criteria are a diagnostic classification often used to enrich ALS clinical trial populations. They classify ALS patients into 3 categories—"possible," "probable," and "definite"—based on whether ALS-associated symptoms are present in 1, 2, 3, or 4 body regions. Presence of ALS in 1 region is considered clinically "possible," in 2 regions is considered clinically "probable," and in 3 or 4 regions is considered clinically "definite."^{12,42}

The El Escorial criteria is more a measure of the spread of the disease than the certainty of the disease; for example, almost all ALS patients with so-called "possible" ALS indeed have ALS and will progress

to "definite" ALS. All categories can have the clinical diagnosis of, and be under management for, ALS. For this reason, the El Escorial criteria are often used in clinical research, but are not recommended for use in clinical practice. The more recently developed Gold Coast criteria do away with the "possible," "probable," and "definite" categories in favor of more simplified criteria that better reflect clinical practice.^{12,43,44}

The primary measure used in clinical trials and clinical practice to estimate the severity, rate of progression, and prognosis in people with ALS is the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R).⁴⁵

The ALSFRS-R is a validated, patient-reported, clinician-administered measure of a patient's function and disability in ALS using loss of function as a marker for disease severity and disease progression.⁴⁶

ALSFRS-R tracks the progression of 12 items, broken down into 4 domains. Each item is rated on a scale of 0 to 4, wherein 4 represents normal function and 0 represents complete loss of function (FIGURE 2).⁴⁵ ALSFRS-R scoring starts at 48 (normal function in all 12 items).

Each 1-point decrease on the ALSFRS-R represents lost capability in performing activities fundamental to daily life, such as the ability to write legibly, feed and dress on one's own, or walk without assistance.⁴⁷

Patients who experience a 2-point difference in 1 item can experience meaningful loss of function in multiple activities of daily living (TABLE 1).⁴⁷

To date, the ALSFRS-R is the most widely applied rating scale in clinical trials and is used in many clinical practices on an ongoing basis.⁴⁵

FIGURE 2: ALSFRS-R Items⁴⁷

BULBAR			FINE MOTOR		
Speech  1	Salivation  2	Swallowing  3	Handwriting  4	Cutting food  5	Dressing and hygiene  6
GROSS MOTOR			BREATHING		
Turning in bed  7	Walking  8	Climbing stairs  9	Dyspnea  10	Orthopnea  11	Respiratory insufficiency  12

Figure adapted from Cedarbaum JM et al. *J Neurol Sci.* 1999;169(1-2):13-21.

TABLE 1: Level of Functional Loss in Patients Who Experience a 2-Point Difference in 1 Item of the ALSFRS-R⁴⁷

Item	2-point difference
Speech	Normal speech vs speech intelligible with repeating
Walking	Normal walking vs needs assistance while walking
Dressing and hygiene	Normal functioning vs needs some assistance intermittently and may need to modify some clothing
Cutting food and handling utensils	Normal eating vs needs some help
Respiratory insufficiency	No assistance to breathe vs continuous use of biphasic positive airway pressure (BiPAP) at night

Treatment options for ALS remain limited

Despite years of research, there is currently no treatment that cures patients with ALS. Rather, the mainstay of ALS disease management is focused on timely intervention to effectively manage symptoms, optimize function, and help ensure quality of life.^{1,14}

The American Academy of Neurology recommends adaptive treatment approaches directed at the clinical repercussions of ALS, which include⁴⁸

- **Noninvasive ventilation (NIV):** Positive pressure ventilation delivered through a mask or similar device, vs the more invasive endotracheal tube or tracheostomy, to treat respiratory insufficiency, lengthen survival, and slow the decline of forced vital capacity (FVC)^{35,49}
- **Percutaneous endoscopic gastrostomy (PEG):** Enteral nutritional feeding to stabilize weight loss in patients with dysphagia³⁵
- **Mechanical insufflation/exsufflation (MIE):** Devices that clear secretions in patients with reduced peak cough flow, particularly during an acute respiratory infection^{12,37}

There are currently only 2 commercially available pharmacologic therapies in the US indicated for the treatment of ALS: riluzole and edaravone; yet, the ClinicalTrials.gov website listed 76 active Phase 2 or 3 trials as of October 2021.^{5,50}

Riluzole was the first to enter the market, approved by the US Food and Drug Administration (FDA) in 1995 for the treatment of ALS. An oral medication taken twice daily, the mechanism of action (MOA) in patients with ALS is unknown.⁵¹

- While riluzole studies demonstrated improved survival, they did not show a benefit in the measures of muscle strength and neurological function
- The most common adverse reactions in the riluzole-treated clinical trial patients (in at least 5% of patients and more frequently than in the placebo group) were asthenia (19% vs 12%), nausea (16% vs 11%), decreased lung function (10% vs 9%), hypertension (5% vs 4%), and abdominal pain (5% vs 4%)

Edaravone received its FDA approval for the treatment of ALS in May 2017. Edaravone is administered via intravenous infusion daily for 14 days, followed by a 14-day drug-free period. Subsequent treatment cycles are daily dosing 10 days out of the next 14 days, followed by 14-day drug-free periods.⁵²

- Similar to riluzole, the MOA in patients with ALS is unknown
- Results of a 6-month randomized, placebo-controlled, double-blind study conducted in Japanese patients with ALS showed that disease progression in edaravone-treated patients was significantly less compared to placebo, based on the reduction in ALSFRS-R scores from baseline
- The most common adverse reactions that occurred in ≥10% of edaravone-treated clinical trial patients were contusion, gait disturbance, and headache

A pipeline of late-stage therapeutic options may expand treatment options for patients with ALS

As of November 2021, a number of therapies were currently in Phase 3 trials while others published Phase 3 study results (TABLE 2).

HEALEY ALS Platform Trial

The Healey & AMG Center for ALS at Massachusetts General Hospital and NEALS lead the HEALEY ALS Platform Trial designed as a perpetual platform trial to evaluate multiple potential treatments for ALS simultaneously. The platform features a single Master Protocol that will dictate the conduct of the trial.^{53,54}

In November 2021, enrollment was completed for the first 3 investigational therapies for ALS (NCT04297683)⁵³:

- Zilucoplan, a small macrocyclic peptide inhibitor of complement component 5
- Verdiperstat, an oral myeloperoxidase inhibitor
- CNM-Au8, a cellular energetic nanotherapeutic

TABLE 2: Phase 3 ALS Therapies in the US Pipeline

Compound name	Trial sponsor	Route of administration	Phase	Status/estimated study completion
HEALEY ALS Platform Trial ^{53,54}	The Healey & AMG Center for ALS at Massachusetts General Hospital and NEALS	Varies	2,3 (NCT04297683)	
ION363 (jacifusen) ^{55,56}	Ionis	Lumbar intrathecal	3 (NCT04768972)	Recruiting March 2024
NurOwn (MSC-NTF cells) ^{57,58}	BrainStorm Cell Therapeutics	Intrathecal	3 (NCT03280056)	Completed October 2020
Reldesemtiv ^{59,61}	Cytokinetics	Oral	3 (NCT04944784) 2 (NCT03160898)	Recruiting March 2024 Completed March 2019
Tofersen (BIIB067) ^{62,64}	Biogen	Intrathecal	3 (NCT02623699) 3 (NCT03070119)	Completed July 2021 Active June 2024
AMX0035 (PB/TURSO) ⁶⁵⁻⁶⁷ (sodium phenylbutyrate and taurursodiol acid)	Amylyx Pharmaceuticals	Oral	3 (NCT05021536) 2 (NCT03127514)	Recruiting March 2024 Completed November 2019

MSC-NTF=meseenchymal stromal cells secreting neurotrophic factors; NEALS=the Northeast ALS Consortium.

ION363 (jacifusen)

ION363 is a form of antisense therapy that targets messenger ribonucleic acid (mRNA) to treat a rare genetic form of ALS caused by confirmed mutations in the *FUS* gene. In April 2021, Ionis began the FUSION Phase 3 safety and efficacy trial (NCT04768972) with a goal of treating up to 64 patients worldwide and an estimated completion in March 2024. The primary outcomes will be the measure of functional change in the ALSFRS-R, time to needing additional medications due to deterioration, and time to living free of ventilation.^{55,56}

NurOwn

NurOwn therapy is a cell-therapeutic approach featuring mesenchymal stem cells derived from adult bone marrow induced to secrete high levels of neurotrophic factors (MSC-NTF). The primary outcome of the BCT-002 Phase 3 clinical trial (NCT03280056) was a responder analysis based on change in disease progression through week 28,

determined by the rate of change in ALSFRS-R per month using linear regression. In December 2021, results of the study were published, showing that it did not reach statistical significance on the primary endpoint.⁶⁸

Reldesemtiv

Reldesemtiv is a next-generation fast skeletal muscle troponin activator that expects to slow the decline of muscle function by binding to the troponin complex and slowing the rate of calcium release from the troponin complex, a regulatory protein that plays an essential role in the contraction of fast skeletal muscle fibers. The primary efficacy endpoint of the Phase 3 COURAGE-ALS trial (NCT04944784) will be the change from baseline in the ALSFRS-R total score at 24 weeks. Recruiting began in August 2021 with an estimated completion in March 2024.^{59,61}

Tofersen (BIIB067)

Tofersen, an investigational antisense therapy, is designed to specifically bind to *SOD1* mRNA, target

the protein for destruction, and prevent additional protein production in order to slow the progression of ALS. In March 2019, Biogen began the Phase 3 VALOR trial (NCT02623699), the primary outcome of which was the change from baseline in the ALSFRS-R at 28 weeks. On October 17, 2021, Biogen announced that the trial missed its primary endpoint of slowing decline on the ALSFRS-R at week 28.^{64,69}

AMX0035 (PB/TURSO)

This investigational therapy is a fixed-dose coformulation of 2 active compounds, sodium phenylbutyrate (PB) and taurursodiol (TURSO).^{66,70} AMX0035 (PB/TURSO) was studied in the CENTAUR Phase 2 multicenter study in adults with ALS that encompassed a 6-month randomized placebo-controlled phase and an open-label long-term follow-up phase. The primary objectives were to determine the safety and tolerability of AMX0035 (PB/TURSO) and to measure the change in ALSFRS-R slope over treatment duration. AMX0035 (PB/TURSO) met the study's primary outcomes, and in December 2021, Amylyx Pharmaceuticals announced that the FDA accepted for review its new drug application for priority review with a PDUFA date of June 29, 2022.^{66,71}

Summary

By whatever name people know ALS, patients with this rare neurodegenerative disease often experience a rapid functional decline in their abilities to move, talk, swallow, and breathe.^{4,10,12} With no established cure, ALS is frequently fatal within 2 to 5 years of when patients first experience symptoms.^{4,13}

The subtle onset of symptoms and variability in disease presentation often result in delayed diagnosis or misdiagnosis, whereby patients may spend one-third of their disease course searching for confirmation of the diagnosis of ALS.^{6,72}

The emotional and psychological burden to patients and their caregivers is significant and compounded by the economic burden of lost income and rising medical costs as the disease progresses.^{1,29,32}

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