JAMA | Review

Amyotrophic Lateral Sclerosis
A Review

John Ravits, MD; Dominic Ferrey, MD; Betul Gundogdu, MD; Wali Qayoumi, MD; Chelsea Zale, DO

IMPORTANCE Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive weakness due to degeneration of upper motor neurons in the brain and lower motor neurons in the brainstem and spinal cord. It affects approximately 25 000 individuals in the United States.

OBSERVATIONS Amyotrophic lateral sclerosis is characterized by progressive painless muscle weakness that typically begins in a focal region of the body, such as limb muscle weakness causing hand weakness or foot drop (65%), cranial muscle weakness causing speech or swallowing problems (20%-25%), or axial muscle weakness causing bent posture (5%-10%), and spreads to other body regions over time. The disease usually manifests with dysfunction indicative of both upper motor neurons (causing muscle stiffness and spasticity) and lower motor neurons (causing weakness, fasciculations, atrophy, and flaccidity). After onset, weakness spreads through the musculature and typically causes death due to respiratory muscle weakness. Among people with ALS, approximately 85% have sporadic ALS, which is not associated with known environmental or genetic factors, and 15% have familial ALS. Amyotrophic lateral sclerosis is diagnosed based on clinical features, which can be supported by results of electromyography. More than 60 genes have been associated with ALS, and most are autosomal dominant. Pathogenic variants in chromosome 9 open reading frame 72 (*C9orf72*) are found in 40% of all familial ALS cases, and pathogenic variants in superoxide dismutase 1 (*SOD1*) are found in 20% of patients with familial ALS. Patients with ALS survive a mean of 3 to 5 years after diagnosis, and there are currently no curative therapies. Clinical care primarily focuses on symptom management and quality of life. Three US Food and Drug Administration (FDA)–approved disease-modifying therapies are available in the United States. Riluzole and edaravone are oral medications that slow ALS progression by up to 2 to 4 months, and tofersen is an intrathecally administered gene therapy for patients with *SOD1* gene variants. Specialized multidisciplinary teams, comprising neurologists, nurses, therapists, dietitians, and social workers, are associated with improved survival (4-7 months) and quality of life.

CONCLUSIONS AND RELEVANCE Amyotrophic lateral sclerosis is a progressive and fatal neurodegenerative disorder of upper and lower motor neurons. No curative therapies exist. Two oral medications, riluzole and edaravone, are approved by the FDA and modestly decrease disease progression in sporadic ALS. Tofersen, an intrathecally administered gene-based therapy, is also FDA approved and slows disease progression in patients with *SOD1* pathogenic gene variants.

Multimedia

CME at jamacmelookup.com

Author Affiliations: ALS Clinical and Translational Research Programs, Department of Neurosciences, School of Medicine, University of California, San Diego, La Jolla.

Corresponding Author: John Ravits, MD, Altman Clinical Translational Institute, University of California, San Diego, 9452 Medical Center Dr, Ste 2W-108, La Jolla, CA 92037 (jravits@health.ucsd.edu).

JAMA. doi:10.1001/jama.2026.6385
Published online May 11, 2026.

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Downloaded from jamanetwork.com by Dominican Republic | Access Provided by JAMA, Rui Costa on 05/12/2026

Amyotrophic lateral sclerosis (ALS) is an adult-onset neurodegenerative disorder characterized by progressive muscle weakness due to degeneration of both upper motor neurons (UMNs) in the brain and lower motor neurons (LMNs) in the brainstem and spinal cord. The disease is fatal in most patients within 3 to 5 years after diagnosis. Amyotrophic lateral sclerosis is also called Lou Gehrig disease in the United States because Lou Gehrig, who retired from Major League Baseball at age 36 years, died in 1941 due to ALS. The disease is a challenging diagnosis for patients and families because of the progressive nature of the condition and the lack of highly effective therapies.[1] It is associated with an annual per-patient cost of approximately $32 000 to $78 000. National annual costs in the United States, excluding medications, range from $1 billion to $1.4 billion for equipment, respiratory support, nutrition, home care, and hospitalization.[2] This Review summarizes current evidence regarding the diagnosis and treatment of ALS.

Methods

A PubMed literature search restricted to the English language was performed using the primary Medical Subject Headings terms *amyotrophic lateral sclerosis* and *motor neuron disease*. Literature was searched from January 1, 2015, to March 16, 2026. We included additional references according to our knowledge of the literature. Of 462 articles identified, 86 were included, consisting of 16 clinical trials; 5 meta-analyses, systematic reviews, or both; 10 systematic reviews; 9 guidelines; 9 review articles; 16 cross-sectional observational studies; and 21 analyses of selected topics.

Discussion

Epidemiology and Risk Factors

Amyotrophic lateral sclerosis is the most common motor neuron disease in adults and the third most common neurodegenerative disease worldwide. The annual global incidence is 1.5 to 2.5 cases per 100 000 individuals, and the prevalence is 4 to 6 cases per 100 000. In the United States, approximately 25 000 people have ALS, and its incidence increased by approximately 13% from 1990 to 2021.[3] The incidence of ALS increases after age 40 years and peaks between ages 55 and 75 years. The male to female ratio is approximately 1.2:1 to 1.5:1 for sporadic ALS (sALS) and 1:1 for familial ALS (fALS), which has an autosomal-dominant inheritance.[4] In addition to risk factors of older age, male sex, and family history,[5] people with military experience have higher rates of ALS for unclear reasons.[6]

Clinical Presentation

The most typical symptom of ALS is focal muscle weakness, typically unilateral initially, that spreads to other muscle groups over time (**Box**; **Table 1**).[7-9] Approximately 60% to 65% of patients have weakness originating in muscles of the upper or lower limbs, often presenting as hand weakness or foot drop. Twenty percent to 25% of patients have a bulbar onset, characterized by weakness of the tongue, pharyngeal, and facial muscles, causing speech and swallowing difficulties. Five percent to 10% of patients present with weakness in the abdominal or trunk muscles, which is associated with stooped posture, and approximately 1% to 5% present with respiratory failure. Typically, ALS causes weakness that spreads throughout the body during months to years.[7]

Box. Frequently Asked Questions

What are the typical initial symptoms of amyotrophic lateral sclerosis?
Initial symptoms of amyotrophic lateral sclerosis (ALS) typically consist of subtle, painless neurologic difficulties, such as drop foot, difficulty using hands to manipulate keys or utensils, difficulty lifting suitcases into the overhead bin on airplanes, and slurred speech. These symptoms are progressive and usually worsen during several months.

How is ALS diagnosed?
Amyotrophic lateral sclerosis is diagnosed according to clinical findings of motor deficits that have characteristics of both upper and lower motor neuron involvement, such as an arm with weakness, atrophy, and fasciculation (indicative of lower motor neuron involvement), and hyperactive reflexes (indicative of upper motor neuron involvement). Imaging—for example, brain or cervical magnetic resonance imaging—can exclude other diagnoses, such as a tumor or spinal cord compression. Electrodiagnostic tests identify dysfunction of lower motor neurons, which is characterized by changes of denervation and reinnervations, and exclude other neuromuscular disorders, such as myopathy or neuromuscular junction disorders or nerve compression.

How is ALS treated?
Primary treatment is supportive care, provided by experienced multidisciplinary care teams that typically include neurologists, nurse coordinators, physical therapists, speech therapists, occupational therapists, respiratory therapists, and nutritional care and social workers. These multidisciplinary teams often coordinate care with pulmonologists, as well as palliative care and primary care clinicians. US Food and Drug Administration–approved treatments include riluzole and edaravone, which are oral medications that slow disease progression by approximately 2 to 6 months in patients with sporadic ALS, and tofersen, an intrathecally administered gene therapy for patients with *SOD1* variant familial ALS.

Physical Examination Findings

Patients with ALS have both UMN and LMN involvement.[8] Characteristics of UMN involvement include slowing of fine, skilled movements, such as rapid finger or foot tapping; increased muscle tone; muscle spasticity; and pathologic reflexes, including hyperreflexia and the jaw reflex. Characteristics of LMN involvement include weakness of the involved muscle, muscle atrophy, fasciculations, decreased muscle tone, flaccidity, and hyporeflexia. Amyotrophic lateral sclerosis variants include progressive muscular atrophy, characterized by LMN dysfunction, and primary lateral sclerosis,[10] characterized by UMN dysfunction (Table 1).

Other Features of ALS

At diagnosis, approximately 10% to 15% of patients have evidence of cognitive and behavioral dysfunction, such as inappropriate sociability, apathy, or deterioration in language, and meet diagnostic criteria for frontotemporal dementia.[11] If formal psychometric neuropsychological testing is performed, mild cognitive and behavioral dysfunction may be observed in up to 50% of patients with ALS.[12,13] Up to 40% of patients develop emotional lability, termed

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.
Downloaded from jamanetwork.com by Dominican Republic | Access Provided by JAMA, Rui Costa on 05/12/2026

Table 1. Typical Presentations of ALS

Category	Subtype	Prevalence of all patients with ALS, %	Typical presentation	Differential diagnosis	Survival, y
Typical presentation	Spinal-onset ALS	≈65	Progressive muscle weakness and wasting in 1 limb, later spreading to other regions; UMN signs (spasticity, hyperreflexia, pathologic reflexes) and LMN signs (atrophy, fasciculations, hyporeflexia) are present	Cervical myelopathy, including dural arteriovenous fistula MMN Diabetic polyradiculopathy MG and myasthenic syndrome	3-5
	Bulbar-onset ALS	≈30	Early symptoms include dysarthria, dysphagia, tongue weakness, and nasal or slurred speech; weakness later extends to limb and respiratory muscles	MG and myasthenic syndrome XSBMA Stroke Facial-onset sensory and motor neuronopathy	2-3
Respiratory onset	NA	≈5	Early dyspnea, orthopnea, or sleep-related breathing problems typically appear first, followed by limb and bulbar weakness	MG and rarely myasthenic syndrome Pompe disease Phrenic neuropathy	1.5-2.5
Predominant LMN variants	Progressive muscular atrophy	5-10	Muscle weakness, wasting, fasciculations, and reduced reflexes, without clear UMN signs in the early course	XSBMA Spinal muscular atrophy type 4 CIDP Diabetic polyradiculopathy Motor neuropathy Inclusion body myopathy Postpolio syndrome Benign cramp-fasciculation syndromes Tay-Sachs disease MG and myasthenic syndrome	≥5
	Flail arm syndrome	≈10	Progressive weakness and wasting in the arms, often beginning proximally in the shoulder and becoming symmetric; deficits in the lower limbs and bulbar region appear later	Monomelic amyotrophy (Hirayama disease) MMN Brachial plexopathy	4-6
	Flail leg syndrome	5	Progressive flaccid weakness and wasting in the legs, often beginning distally and becoming increasingly symmetric; deficits in the upper limbs and bulbar region; occur later	Lumbar radiculopathy Diabetic polyradiculopathy Polyneuropathy	4-6
Predominant UMN variants	PLS	1-5	Muscle weakness with clear UMN signs (spasticity, hyperreflexia, slowed and effortful movements); impaired fine motor control, and gait disturbance; few or no LMN signs	PSP HSP MS	>10 (variable)
	Mill syndrome, hemiplegic ALS	≈1	Slowly progressive hemiparesis with UMN signs, including spasticity, hyperreflexia, and weakness limited predominantly to one side of the body for extended periods	Stroke HSP PSP	Variable
Extramotor problems (ALS-plus syndromes)	Cognitive dysfunction	10-15	ALS with impairments, such as apathy, disinhibition, loss of empathy, compulsive or ritualized behaviors, and impaired executive function	Frontotemporal dementia PSP Lewy body dementia Alzheimer disease Corticobasal degeneration	Shorter (≈2-4)
	Extrapyramidal features	1-5	ALS with parkinsonism, such as bradykinesia, rigidity, resting tremor, and postural instability	Parkinson disease and related variants PSP MSA Pallido-nigro-luysian degeneration. Hexosaminidase A deficiency	Shorter survival (≈3)
	Cerebellar degeneration	1-5	ALS with gait ataxia, dysmetria, dysarthria, and oculomotor abnormalities	Spinocerebellar ataxias MSA	Shorter survival (≈3-5)
	Sensory impairments	1-5	ALS sensory impairment: loss of proprioception, other sensory modalities, or sensory ataxia	CIDP Paraneoplastic neuropathy APBD HTLV-1 myelopathy Adrenomyeloneuropathy	Variable
	Neurogenic bladder dysfunction	10-40	ALS with bladder control issues, more common in PLS; orthostatic hypotension, erectile dysfunction, or abnormal sweating	MS MSA APBD	Variable

Abbreviations: ALS, amyotrophic lateral sclerosis; APBD, adult polyglucosan body disease; CIDP, chronic inflammatory demyelinating polyneuropathy; HSP, hereditary spastic paraparesis; HTLV, human T-lymphotropic virus; LMN, lower motor neuron; MG, myasthenia gravis; MMN, multifocal motor neuropathy; MS, multiple sclerosis; MSA, multiple system atrophy; NA, not applicable; PLS, primary lateral sclerosis; PSP, progressive supranuclear palsy; UMN, upper motor neuron; XSBMA, X-linked spinobulbar muscular atrophy.

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Downloaded from jamanetwork.com by Dominican Republic | Access Provided by JAMA, Rui Costa on 05/12/2026

Table 2. Commonly Used Tests in the Diagnosis of ALS

	Test	Indication	Typical finding
Tests used in the diagnosis of ALS	Genetic panels	Specific ALS genetic mutations	Identifiable genetic mutations in 70% of familial ALS and 5%-10% of sporadic ALS
	Nerve conduction studies	May alert to other causes, such as demyelinating neuropathies or polyneuropathies	Normal or reduced amplitudes or slight slowing
	Repetitive nerve stimulation	Rules out neuromuscular junction disorders	Normal or slight decrement
	Electromyography	Establishes lower motor neuron denervation and reinnervation; rules out myopathies	Shows evidence of active denervation and reinnervation; fasciculations
Tests used to exclude causes that might mimic or be misinterpreted as ALS	Complete blood cell count with differential, comprehensive metabolic panel with calcium and phosphate levels, and liver enzyme levels	Screen for systemic illness/malignancy	Normal in ALS
	Thyroid function tests, parathyroid hormone (if calcium level is elevated)	Myopathy	
	Erythrocyte sedimentation rate or high-sensitivity C-reactive protein	Infectious/inflammatory causes, including vasculitis	
	Antinuclear antibody and rheumatoid factor	Autoimmune disease, including vasculitis	
	Vitamin B_{12} level, syphilis, copper level	Myelopathy/subacute combined degeneration	
	Anti-GM1 antibody	Multifocal motor neuropathy	
	Serum protein electrophoresis with immunofixation	Paraproteinemia/hematology malignancy-related polyradiculoneuropathy	
	Acetylcholine receptor antibodies, MuSK antibodies, voltage-gated calcium channel	Neuromuscular junction disorders, such as myasthenia and myasthenic syndrome	
	Lyme disease, West Nile virus, HTLV-1/2, HIV	Polyradiculoneuropathy or myelopathy	
	Heavy metal panel, celiac testing, paraneoplastic panel	Neuropathy	
	Lumbar puncture/CSF	Infectious/inflammatory/malignant causes	
	Creatine phosphokinase	Myopathy	Normal or mildly to moderately elevated in ALS
	Brain MRI	Structural causes, including tumors, demyelination, stroke	Typically normal (or shows increased T2 hyperintensity in corticospinal tracts in up to 30% of patients)
	Spinal MRI or myelography	Myelopathy, including structural, demyelinating, metabolic, or spondylosis	Normal in ALS (or incidental abnormalities that are insufficient to explain symptoms)
	Muscle biopsy	Myopathies or other neuropathic causes	Fiber type grouping, which reflects denervation and reinnervation

Abbreviations: ALS, amyotrophic lateral sclerosis; CSF, cerebrospinal fluid; HTLV, human T-lymphotropic virus; MRI, magnetic resonance imaging; MuSK, muscle-specific kinase.

pseudobulbar affect, related to neurologic degeneration of bulbar UMNs.[14] Pseudobulbar affect is characterized by involuntary, sudden, and uncontrollable episodes of laughing or crying that are incongruent with the patient's underlying emotional state or the context. Approximately 15% to 30% of patients with ALS have subtle evidence of other neurologic features at diagnosis, such as parkinsonism with bradykinesia, rigidity, tremor, and postural instability; cerebellar degeneration with ataxia and dysmetria; minor sensory impairments with loss of proprioception or numbness; and autonomic dysfunction with urinary incontinence and erectile dysfunction (Table 1).[15,16] Among patients with ALS, 50% to 80% experience fatigue, weight loss, muscle cramps, joint or muscle pain, depression, and sleep disturbance.[17,18]

Diagnosis and Differential Diagnosis

ALS Diagnosis

Amyotrophic lateral sclerosis is diagnosed based on clinical criteria (Box). The key features are muscle weakness with mixed UMN and LMN characteristics that progressively involve other body regions and for which no alternative explanation exists. Laboratory tests, magnetic resonance imaging, electrodiagnostic testing, and other assessments are obtained based on specific symptoms, signs, and risk factors (**Table 2**). Typical laboratory testing to exclude other conditions includes a comprehensive metabolic panel, complete blood cell count with differential, thyroid function studies, creatine phosphokinase level, erythrocyte sedimentation rate or C-reactive protein level, antinuclear antibody and rheumatoid factor, vitamin B_{12} level, anti-GM1 antibody, and serum protein electrophoresis with immunofixation (Table 2). Additional testing is tailored to risks and exposures, such as human T-lymphotropic virus 1 and 2 antibody testing for patients exposed to regions where the viruses are endemic. For patients with bulbar symptoms, brain magnetic resonance imaging can exclude structural disease, such as tumors or multiple sclerosis. For patients with hand weakness, cervical spine magnetic resonance imaging can also exclude structural disease, such as cervical spondylitic myelopathy or central disc herniation. Patients typically have symptoms for approximately 10 to 16 months before the diagnosis of ALS.[19]

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.
Downloaded from jamanetwork.com by Dominican Republic | Access Provided by JAMA, Rui Costa on 05/12/2026

Table 3. Main Genetic Causes and Risk Variants of ALS

Gene, OMIM No.	Prevalence	Variant type	Inheritance pattern	Biologic implications
ATXN2, 601517	Risk variant found in 5% of sALS (compared with 2% of the general population)	PolyQ expansions	Autosomal dominant (risk)	Mediates TDP-43 mislocalization from nucleus and aggregation in cytoplasm
C9orf72, 614260	40% of fALS, 8% of sALS	Hexanucleotide repeat expansion mutations	Autosomal dominant (incomplete penetrance)	Generates abnormal RNA and unusual proteins (dipeptide repeat proteins) that cause cell dysfunction by unknown mechanism; also reduces normal gene functions that regulate internal cell homeostasis
FUS, 608030	1% of fALS	Missense variants	Autosomal dominant/recessive	Protein mislocalizes from nucleus, where its functions related to RNA splicing are lost; protein aggregates in cytoplasm and causes cell dysfunction by unknown mechanisms
SOD1, 147450	12%-20% of fALS; 1% of sALS	Missense variants	Autosomal dominant	Mutant SOD1 protein causes cell dysfunction by unknown mechanisms
TARDBP, 612069	1% of fALS	Missense variants	Autosomal dominant	TDP-43 mislocalizes from nucleus, where its usual functions related to RNA splicing are lost; protein aggregates in cytoplasm, where it disrupts functions
UNC13A, 606286	NA (variants in this gene modify disease course but are not associated with increased ALS risk)	SNP variant (modifier)	Susceptibility risk	Protein mediates neurotransmitter release at synapses; in ALS, it is downregulated as a consequence of TDP-43 abnormalities

Abbreviations: ALS, amyotrophic lateral sclerosis; fALS, familial ALS; NA, not applicable; OMIM, Online Mendelian Inheritance in Man; polyQ, polyglutamine; sALS, sporadic ALS; SNP, single-nucleotide polymorphism; *SOD1*, superoxide dismutase 1; TDP, TAR DNA-binding protein.

Diagnostic criteria include the revised El Escorial criteria,[20] the Awaji criteria,[21] Airlie House criteria,[22] and the Gold Coast criteria.[23] Consensus diagnostic criteria for primary lateral sclerosis, which is a pure UMN variant, were recently developed.[10] Strategies for communicating the diagnosis effectively to patients with ALS and their caregivers have been developed.[24,25]

Electrodiagnostic Testing

Patients with possible ALS typically undergo electrodiagnostic testing,[26,27] composed of electromyography and nerve conduction studies (Table 2). For patients with ALS, electromyography usually demonstrates active denervation (fibrillations, positive waves, and fasciculations) and chronic reinnervation (large, long voluntary motor unit potentials) in multiple regions of the neuraxis, including the cervical, thoracic, and lumbar regions. Nerve conduction study results for patients with ALS are generally normal, except for reduced motor response amplitudes in the affected muscle regions. Electrodiagnostic testing is useful to exclude other neurologic conditions or diseases, such as inclusion body myopathy; polyneuropathies caused by nutritional deficiencies, toxins, or paraproteinemia; myasthenia gravis; Guillain-Barré syndrome variants; and multifocal motor neuropathy with conduction block.

Differential Diagnosis

Depending on symptoms, the differential diagnosis of ALS includes neuromuscular diseases, such as Guillain-Barré syndrome variants, inclusion body myopathy, and myasthenia gravis, and other neurodegenerative disorders, such as progressive supranuclear palsy (Table 1).[28,29] Cervical myelopathy due to disc herniation, cervical spondylosis, or posterior longitudinal ligament ossification may cause spinal cord compression, resulting in UMN and LMN deficits in the arms, UMN deficits in the legs, and sensory involvement and bladder and bowel incontinence. Inclusion body myositis primarily causes LMN deficits, and myasthenia gravis should be considered in patients with bulbar weakness who have marked variability of symptoms throughout the day, as well as double vision (Table 1).

Biomarkers

No currently available biomarker is diagnostic of ALS. Neurofilament light protein is a nonspecific biomarker of neuroaxonal injury that is elevated in neurodegenerative disorders, such as Alzheimer disease, Parkinson disease, and ALS. For the diagnosis of ALS, neurofilament light protein levels in blood have a sensitivity of 71% and specificity of 86%, and in cerebrospinal fluid they have a sensitivity of 89% and specificity of 96%.[30] Serum and cerebrospinal fluid neurofilament light protein levels increase before symptom onset in individuals genetically predisposed to ALS, such as first-degree relatives of patients with *SOD1* gene variants.[31] Higher levels of neurofilament light protein have been thought but not proven to correlate with more severe disease, increased rates of progression, and reduced survival.[30]

Genetic Causes of ALS

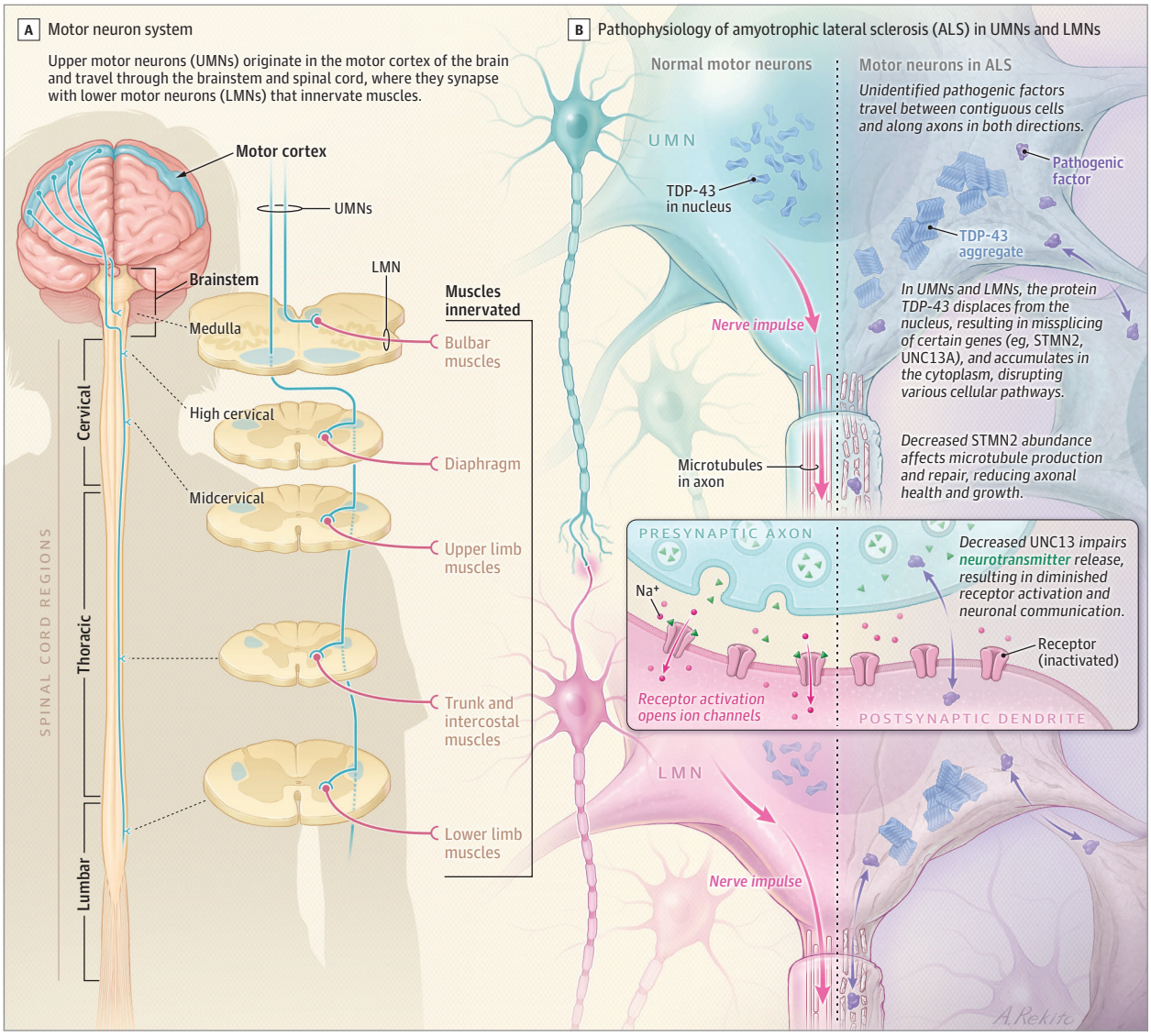
Fifteen percent of patients with ALS have a family history of ALS (ie, fALS),[32] and 85% of patients have sALS. Seventy percent of people with fALS have a single pathogenic genetic variant causing ALS, nearly all of which are autosomal dominant (**Table 3**). Approximately 5% to 10% of patients initially considered to have sALS are reclassified as having fALS after genetic testing.[33] Although patients with fALS typically present at a younger age (45-55 years) than individuals with sALS (55-65 years), presenting symptoms are similar with fALS and sALS.

Genetic Variants Associated With ALS

Hexanucleotide repeat expansions in the chromosome 9 open reading frame 72 (*C9orf72*) gene are the most common pathogenic genetic variant associated with ALS in European populations and account for approximately 40% of fALS and approximately 8% of

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.
Downloaded from jamanetwork.com by Dominican Republic | Access Provided by JAMA, Rui Costa on 05/12/2026

Figure. Amyotrophic Lateral Sclerosis Pathophysiology



TDP-43 indicates TAR DNA-binding protein 43.

sALS.[34] Pathogenic gene variants in the superoxide dismutase 1 (*SOD1*) gene are the second most common gene variant associated with ALS and occur in approximately 12% to 20% of fALS cases and 1% of sALS cases.[35] Pathogenic genetic variants in TAR DNA-binding protein (TDP), which encodes the RNA-binding protein TDP-43,[36] and fused in sarcoma (*FUS*)[37] are rare autosomal-dominant variants that cause fALS (1%). More than 60 genes have been associated with fALS, they are rare, and most are autosomal-dominant missense variants.[32]

Genetic Testing Guidelines

The Genetic Testing and Counseling Guidelines Expert Panel recommends genetic counseling and gene panel testing for all patients with a diagnosis of ALS.[38] Patients may undergo testing with commercially available multigene panels, including whole-exome or whole-genome sequencing. Identification of a genetic variant associated with ALS can affect the choice of therapy. For example, patients with *SOD1* pathogenic gene variants may be treated with tofersen, but it is not currently believed that patients without the *SOD1* gene variant will respond to tofersen. In addition, genetic testing may identify carriers at risk among first-degree relatives of patients with pathogenic gene variants and may elucidate the pathophysiology of ALS.

Pathophysiology

The multiple genetic variants associated with ALS suggest that multiple molecular pathways are involved in the pathophysiology of ALS.[39,40] However, the primary neuropathologic finding in 97% of patients with ALS is nuclear mislocalization and cytoplasmic aggregation of the protein TDP-43 in motor neurons and glial cells of the brain and spinal cord (**Figure**).[41,42] The remaining 3% of patients have aggregation of the proteins SOD1 and FUS. In ALS, TDP-43 translocates from its predominant nuclear location, accumulates and aggregates in the cytoplasm, and undergoes posttranslational

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.
Downloaded from jamanetwork.com by Dominican Republic | Access Provided by JAMA, Rui Costa on 05/12/2026

Table 4. Disease-Modifying Therapies for ALS

Drug	Indication	Mechanism of action	Dosing and route of administration	Efficacy	Most common adverse effects
Riluzole	All patients with ALS (sporadic and genetic forms)	Targets the excitotoxic effects of glutamate on motor neurons by inhibiting voltage-gated sodium channels on presynaptic glutamatergic neurons, thus reducing glutamate release	50 mg twice a day Oral tablets Oral suspension Oral film	Prolongs survival (defined as time to tracheostomy or death) by 60-90 d (60 d in a study of 959 patients who were followed up for at least 13 mo and 90 d in a study of 155 patients who were followed up for at least 12 mo) compared with placebo	Malaise, nausea, or asthenia (10%-20%) Hepatic injury (10%-19%) Dizziness, vomiting, abdominal pain or diarrhea (1%-10%)
Edaravone	All patients with ALS (sporadic and genetic forms)	Free radical scavenger that reduces oxidative stress on motor neurons by neutralizing reactive oxygen species	Dose: 60-mg intravenous infusion or 105 mg by oral liquid daily Initial cycle: dose daily for 14 d, followed by a 14-d drug-free period Subsequent cycles: dose 10 d of a 14-d period followed by 14 14-d drug-free periods	Reduction in the decline in ALS Functional Rating Scale-Revised score (≈2.5 points during 24 wk compared with placebo) in patients with early-stage ALS (disease duration ≤2 y, forced vital capacity ≥80%)	Bruising (15%) Hypersensitivity reaction (15%) Gait disturbance (10%-13%) Headache (10%)
Tofersen	*SOD1* mutant fALS	Antisense oligonucleotide targeting *SOD1* messenger RNA to decrease production of mutant toxic and wild-type SOD1 protein	100 mg intrathecally every 14 d for 3 doses and then every 28 d	Reduction in the decline in ALS Functional Rating Scale-Revised score in early initiation (−6.0 points during 52 wk) compared with delayed initiation (−9.5 points during 52 wk for patients initiated after 28 wk of placebo) in patients with *SOD1* mutation-associated ALS	Procedural pain or headache (40%) Malaise (17%) CSF inflammation, including pleocytosis, elevated protein level, aseptic meningitis, myelitis, or radiculitis (5%-8%) Increased intracranial pressure and papilledema (<5%)

Abbreviations: ALS, amyotrophic lateral sclerosis; CSF, cerebrospinal fluid; fALS, familial ALS; *SOD1*, superoxide dismutase 1.

modifications, including ubiquitination, phosphorylation, and acetylation. However, the specific role of TDP-43 and the mechanisms by which ALS spreads are unknown.

Clinical Care and Treatment

Disease-Modifying Therapies

Two disease-modifying medications for ALS (sALS and fALS) have received US Food and Drug Administration (FDA) approval: riluzole in 1995 and edaravone in 2017 (**Table 4**). There is currently no biomarker or other objective measure to evaluate responsiveness to riluzole or edaravone. Additionally, no published evidence about the efficacy or safety of combining riluzole and edaravone is currently available.

Riluzole, which can be administered orally or via feeding tube, reduces presynaptic glutamate release by inhibiting voltage-gated sodium channels, thereby limiting excitotoxicity, the overactivation of glutamate receptors on motor neurons, which may increase neuronal death. The American Academy of Neurology recommends administration of riluzole 50 mg twice daily to slow progression of ALS.[43] A 1994 clinical trial of 155 patients randomized to riluzole 50 mg twice daily (n = 77) or placebo (n = 78) and followed for at least 13 months reported that riluzole significantly improved the primary outcome of survival (defined as time to tracheostomy or death) compared with placebo in the subgroup of patients with bulbar onset.[44] Another study randomized participants with ALS to riluzole, dosed at 50 mg daily (n = 237), 100 mg daily (n = 236), or 200 mg daily (n = 244), or to placebo (n = 242) and followed up participants for at least 12 months.[45] The groups with riluzole at 100 and 200 mg had significantly improved tracheostomy-free survival, with 57% and 58% of patients alive at 18 months, respectively (*P* = .05-.08 and *P* = .06-.08), compared with 50% for placebo. The 50-mg daily dose was not statistically different from placebo, with 55% survival at 18 months (*P* = .2-.3), and the 200-mg daily dose was not statistically different from the 100-mg daily dose. A meta-analysis of 15 nonrandomized, noncontrolled, population observational studies in which median survival data were recorded found that in 8 of the 15 studies that met criteria, riluzole was associated with improved survival of approximately 6 to 10 months.[46]

Edaravone reduces hydroxyl, peroxyl, and peroxynitrite free radicals, thereby reducing effects of oxidative stress on motor neurons. Although edaravone was FDA approved in the United States in 2017, it was not approved for use in Europe or the United Kingdom.[47] A phase 3 clinical trial in Japan of 137 patients aged 20 to 75 years with early-stage ALS (disease duration ≤2 years; forced vital capacity ≥80%) reported that the rate of functional decline, defined by the ALS Functional Rating Scale–Revised (ALSFRS-R), at 24 weeks was lower with intravenous edaravone vs placebo (mean [SE] decrease of −5.01 [0.64] points in the edaravone group vs −7.50 [0.66] points in the placebo group), with a least squares mean difference between groups of 2.49 (SE, 0.76; 95% CI, 0.99-3.98; *P* = .0013) in favor of edaravone.[48] Serious adverse events were reported in 11 of 69 patients (16%) randomized to edaravone and 16 of 67 patients (24%) randomized to placebo. In an open-label, multicenter clinical trial comparing edaravone oral suspension with intravenous edaravone for 48 weeks in 185 patients with ALS, the oral suspension was well tolerated, with no significant safety concerns, compared with existing intravenous edaravone safety data. Pharmacokinetic studies demonstrated that oral edaravone (105 mg) was equivalent to intravenous edaravone (60 mg).[49,50] In these

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.
Downloaded from jamanetwork.com by Dominican Republic | Access Provided by JAMA, Rui Costa on 05/12/2026

open-label comparisons, the oral formulation was not recompared with placebo. However, 2 European studies of edaravone or the equivalent compound (called FAB122) had negative results. In a German, multicenter, propensity score–matched, observational study of 232 patients during a median of 14 months, there was no significant difference in disease progression measured in the ALSFRS-R slope (−0.91 [95% CI, −0.69 to −1.07] vs −0.85 [95% CI, −0.66 to −0.99]; *P* = .37).[51] In a separate placebo-controlled, double-blind, randomized, phase 3 clinical trial of 201 patients randomized in a 2:1 ratio to receive oral FAB122 or placebo during 48 weeks, FAB122 did not significantly slow the rate of functional decline measured by change from baseline in the ALSFRS-R score at 48 weeks.[52] However, quantitative results and statistical testing for this clinical trial have not been published.[52]

Tofersen is an intrathecally administered antisense oligonucleotide that binds and degrades *SOD1* messenger RNA, thereby reducing both normal and toxic versions of SOD1 protein. Tofersen is FDA approved for use only in patients with ALS who have *SOD1* pathogenic gene variants. In a meta-analysis of 12 studies (2 randomized clinical trials, 5 cohort studies, 1 case series, and 4 case reports) that included 195 patients with ALS and *SOD1* gene variants, tofersen was associated with a significantly lower rate of decline in ALSFRS-R scores from baseline (standardized mean difference = 0.44; 95% CI, 0.05-0.83; *P* = .03) and a significant reduction in the decline of predicted slow vital capacity (standardized mean difference = 0.53; 95% CI, 0.16-0.90; *P* = .005).[53] A trial of patients with ALS due to *SOD1* pathogenic gene variants reported that the primary outcome of disease progression, defined as change from baseline to week 28 in the ALSFRS-R, did not differ significantly in patients randomized to tofersen (n = 72) vs placebo (n = 36) (−6.98 vs −8.14 points; difference, 1.2 points; 95% CI, −3.2 to 5.5; *P* = .97).[54] However, in this trial, tofersen reduced SOD1 levels in cerebrospinal fluid by 29% and neurofilament light protein in plasma by 60% compared with increases of 16% and 20%, respectively, in the placebo group. After completion of the initial 28-week trial, 95 patients enrolled in an open-label treatment extension, of whom 63 had received tofersen (early-start cohort) and 32 had received placebo (delayed-start cohort). At 52-week follow-up, patients initially treated with tofersen had a decreased rate of decline in the ALSFRS-R score compared with those initially treated with placebo (ALSFRS-R score, −6.0 vs −9.5 points; difference, 3.5 points; 95% CI, 0.4-6.7). Follow-up data at 148 weeks for 46 participants who completed the open-label extension (early-start group, 34; placebo/delayed-start group, 12) showed that earlier initiation of tofersen compared with later initiation was associated with numerically less decline in multiple functional, respiratory, and quality-of-life measures than expected but was not powered to detect statistical significance.[55] For example, ALSFRS-R score declined 9.9 points in the early-start group and 13.5 points in the delayed-start group, and the expected decline based on natural history is 22 to 34 points. In addition, improvements in strength and function from baseline were observed in approximately 21% to 27% of early-start participants and 10% to 17% of patients in the late-start group at 148 weeks, which is unheard-of in ALS associated with pathogenic *SOD1* variants.

Multidisciplinary Teams for ALS Care

Patients with ALS progressively develop multiple functional limitations, such as difficulty communicating because of dysarthria, difficulty dressing or eating, and difficulty with walking and mobility. These impairments develop and progress at various rates and may be treated with both nonpharmacologic and pharmacologic methods. Amyotrophic lateral sclerosis multispecialty care teams, which typically include neurologists, nurse coordinators, physical therapists, occupational therapists, respiratory therapists, speech therapists, dietitians, and social workers with expertise in ALS, can provide longitudinal care individualized for each patient (**Table 5**).[43,56,57] In a systematic review and meta-analysis of 6 studies (3 prospective cohort studies, 2 cross-sectional studies, and 1 retrospective cohort study) that included 2179 patients with ALS, compared with treatment with general neurologic care, treatment with an ALS multidisciplinary team was associated with improved survival (4-7 months; mean difference, 4 months; 95% CI, 61-222; *P* < .001).[58] Amyotrophic lateral sclerosis teams often work closely with pulmonologists, who evaluate and manage respiratory muscle weakness that leads to progressive hypoventilation,[59] and with palliative care clinicians, who assist with symptom management, psychological effects of ALS (eg, anxiety and depression), advanced care planning and goals of care, end-of-life issues, and family/care partner distress.[58] Caregiving for patients with ALS may have negative effects on caregivers, as well as on patients with ALS. A meta-analysis of 25 observational studies reported that patient behavioral impairments, such as apathy and disinhibition, decline in physical function, and feelings of depression in caregivers, were factors related to caregiver burden.[60] ALSUntangled (https://www.alsuntangled.com/) is a public, web-based, free program that evaluates alternative therapies and anecdotal and off-label uses that lack evidence.

Symptom Management

Weakness of the bulbar muscles, which are distinct from the respiratory muscles, causes dysarthria and dysphagia and affects approximately 30% of people with ALS at diagnosis and 70% of patients in the disease course. Treatments for dysarthria include speech therapy to assist with articulation and use of assistive communication devices, such as mouse-controlled or eye gaze–controlled speech-generating devices that have recorded the patient's original voice. To maintain body weight, patients with ALS who have dysphagia should undertake diet modifications, such as making food softer and thicker to make swallowing food easier and using high-calorie oral supplementation, such as replacement shakes and nutrition drinks. American Academy of Neurology guidelines suggest considering percutaneous endoscopic gastrostomy tube placement in patients with ALS and severe dysphagia to stabilize weight and prolong survival. Gastrostomy tube placement should be considered before the onset of respiratory compromise, typically while forced vital capacity remains greater than 50% and before severe malnutrition develops. This approach may reduce risks of gastrostomy tube placement, such as death due to respiratory arrest and technical difficulties in placing the tube.[43]

Sialorrhea occurs in up to 50% of patients and can be treated with anticholinergic medications, such as glycopyrrolate tablets, scopolamine patch, or sublingual atropine drops.[61] However, high-quality studies have not demonstrated the efficacy of these treatments in patients with ALS. Selecting treatment for sialorrhea is typically based on local availability of medications, and for patients who have difficulty swallowing tablets, sublingual drops of 1% atropine may be administered. Adverse effects of anticholinergic

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.
Downloaded from jamanetwork.com by Dominican Republic | Access Provided by JAMA, Rui Costa on 05/12/2026

Table 5. Symptomatic Treatments and Support for Patients With ALS

Symptom/physical examination finding	Frequency	First-line medications and dosing	Common medication adverse effects (frequency when available)	Additional intervention and comments
Loss of mobility Impairment of activities of daily living Limb weakness	The initial presenting symptom in 60%-80% of patients with ALS	NA	NA	Physical therapy and occupational therapy evaluations Home safety evaluation DME, such as ankle/foot braces, walkers, wheelchairs/power chairs, hospital beds, toileting equipment, lifts
Spasticity Muscle cramps	Spasticity or muscle cramping (≈80% of patients with ALS); less than half require treatment because of functional impairments	Baclofen: initiate 5 mg 3 times a day, with gradual titration every 3 d based on clinical response (maximum total dose of 80 mg/d) Tizanidine: initiate 2 mg every 6-8 h (maximum 3 doses per 24 h), with gradual titration of 2-4 mg per dose every 1-4 d based on clinical response (maximum total dose of 36 mg/d) Gabapentin: initiate 100-300 mg 3 times a day and titrate to clinical response (maximum total dose of 3600 mg/d) Mexiletine: 150 mg twice a day	Baclofen: drowsiness (10%-60%), dizziness (5%-15%), weakness (5%-15%) Tizanidine: dry mouth (49%), somnolence and sedation (48%), asthenia (41%), dizziness (16%) Gabapentin: somnolence (21%), dizziness (28%), ataxia (13%) Mexiletine: GI effects (40%), tremor (12%), lightheadedness (10%), palpitations (4%)	Onabotulinum toxin injections to spastic muscles every 3 mo Physical therapy and occupational therapy evaluations Stretching and range-of-motion exercises
Sialorrhea	Affects ≈50% of patients with ALS	Atropine 1% ophthalmic solution: 1-2 drops sublingually administered 1-4 times a day Glycopyrrolate: 1 mg 3 times a day Amitriptyline: initiate 10-25 mg once a day; gradual titration up to 75 mg daily Scopolamine patch: 1.5-mg patch every 72 h	Atropine 1% ophthalmic solution: dry mouth, blurred vision, tachycardia, constipation Glycopyrrolate: dry mouth (40%), vomiting (40%), constipation (35%), flushing (30%), nasal congestion (30%) Amitriptyline: dry mouth, drowsiness, constipation, and blurred vision Scopolamine patch: dry mouth (29%), dizziness (12%), somnolence (8%), visual impairment (5%), pupil dilation (4%)	Onabotulinum toxin injections to the salivary glands every 3 mo Salivary gland radiation DME: suction, cough assist
Pseudobulbar affect (emotional lability)	Pseudobulbar affect during disease course (up to 50% of patients with ALS), more commonly observed in the bulbar ALS phenotype, often not disabling	Dextromethorphan quinidine: 20-mg/10-mg capsule, 1 capsule daily for 7 d and then increase to 1 capsule twice a day Amitriptyline: initiate 10-25 mg once a day; gradual titration up to 75 mg daily	Dextromethorphan quinidine: dizziness, nausea, somnolence (24% of patients discontinued treatment because of adverse effects) Amitriptyline: dry mouth, drowsiness, constipation, and blurred vision (frequency data not well documented)	
Depression/anxiety	Affects ≈30%-45% of patients with ALS, often not disabling	SSRIs Escitalopram (5-20 mg/d) Sertraline (50-200 mg/d) Citalopram (10-40 mg/d) Fluoxetine (20-80 mg/d) SNRI Venlafaxine (37.5-225 mg/d)	SSRIs GI effects Sexual dysfunction Headache SNRI Agitation Insomnia Hypertension	Counseling Support and advocacy groups Social worker evaluation Palliative care and hospice support
Dysarthria (impaired speech)	Affects ≈70% of patients throughout the disease course			Speech therapy evaluation Augmentative communication devices Voice banking
Dysphagia (impaired swallowing) or nutritional support	Affects ≈70% of patients throughout the disease course			Speech therapy evaluation Dietitian evaluation Dietary modifications Percutaneous endoscopic gastrostomy tube placement

(continued)

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.
Downloaded from jamanetwork.com by Dominican Republic | Access Provided by JAMA, Rui Costa on 05/12/2026

Table 5. Symptomatic Treatments and Support for Patients With ALS (continued)

Symptom/physical examination finding	Frequency	First-line medications and dosing	Common medication adverse effects (frequency when available)	Additional intervention and comments
Neuromuscular respiratory weakness (dysfunction of both inspiratory and expiratory muscles)	Emerges in nearly all patients as the disease progresses and is the main cause of death	Pulmonologist and respiratory therapy evaluation DME: suction, cough assist, noninvasive ventilation Tracheostomy		Usually becomes important to address as forced vital capacity decreases to 50%
Cognitive impairment	Cognitive impairment in ≈10%-15% of patients with ALS; deficits primarily observed in executive function and language, indicative of frontotemporal dementia, usually mild	SSRIs and SNRI for treatment of disinhibition related to cognitive impairment (dosing and adverse effects above)		Cognitive rehabilitation, environmental and behavioral interventions, counseling, support, and advocacy groups

Abbreviations: ALS, amyotrophic lateral sclerosis; DME, durable medical equipment; GI, gastrointestinal; NA, not applicable; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

therapies include excessive dry mouth and sedation. Botulinum toxin injections in the bilateral parotid glands and submandibular glands block acetylcholine release at the parasympathetic nerve terminals within salivary glands and provide symptomatic relief for up to 4 months. Alternatively, low-dose radiation to salivary glands destroys acinar cells, reducing saliva production, and can be considered in patients with ALS and refractory sialorrhea.[61]

Suction devices with soft-tip catheters inserted into the mouth can remove excessive oral and pharyngeal secretions and may be used at home. Cough-assist machines can mobilize chest secretions that cannot be cleared by a weak cough. Respiratory function should be measured at each 3-month visit with spirometry, including supine and standing forced vital capacity measurements, maximum inspiratory and expiratory pressures, and cough peak flows, to identify optimal timing of initiating respiratory equipment. Noninvasive ventilation, a mechanical ventilatory support method provided through a face mask or nasal mask, is recommended by practice guidelines to treat respiratory insufficiency in ALS to lengthen survival (up to 7 months). Guidelines also suggest noninvasive ventilation to enhance quality of life, but the evidence is mixed. Noninvasive ventilation is recommended for individuals when hypoventilation develops, defined as forced vital capacity less than 80% with symptoms, forced vital capacity less than 50% regardless of symptoms, or maximal inspiratory pressure less than 60 cm H_2O, indicating inspiratory muscle weakness.[43,57,59,62]

For patients with pseudobulbar affect, a combination of dextromethorphan and quinidine is recommended.[63] A double-blind, placebo-controlled study of 326 patients with ALS or multiple sclerosis with clinically significant pseudobulbar affect (baseline score ≥13 on the Center for Neurologic Study–Lability Scale) randomized patients to dextromethorphan 30 mg/quinidine 10 mg twice daily, dextromethorphan 20 mg/quinidine 10 mg twice daily, or placebo for 12 weeks. Patients in the 2 dextromethorphan/quinidine groups had significantly fewer pseudobulbar affect episodes per day than those in the placebo group (−47% [P < .001] and −49% [P < .001], respectively).[64] Dizziness, somnolence, and nausea led to treatment discontinuation in approximately 24% of patients in both groups. Low-dose amitriptyline (10-25 mg orally in the evening) may also improve pseudobulbar affect, but to date, randomized clinical trials are not available.[43,57]

Spasticity, resistance to passive movement that is more notable at high-velocity passive movement, occurs in approximately 80% of patients with ALS. However, only patients with spasticity that limits functioning should be treated.[43,57] To date, there are no large randomized clinical trials evaluating spasticity treatments in patients with ALS. GABAergic medications such as baclofen and benzodiazepines enhance inhibitory neurotransmission at the spinal cord level and are often first-line treatments for spasticity because they are oral treatments and have a more favorable adverse-effect profile than dantrolene, which decreases skeletal muscle contractility by blocking release of calcium from the sarcoplasmic reticulum. Second-line therapies for spasticity associated with ALS include injection of botulinum toxin into spastic muscles, which inhibits release of acetylcholine from nerve terminals and results in reduced muscle activity, and intrathecal baclofen pumps.[43,57] Medication doses for spasticity should be adjusted to minimize adverse effects, such as lethargy and weakness. Physical therapy for spasticity includes stretching and range-of-motion exercises and can be performed at home. Sodium-channel blockers, such as mexiletine, can treat muscle cramping (painful, involuntary, sudden contractions of skeletal muscles).[65] In a randomized clinical trial of 20 patients with ALS, compared with placebo, mexiletine 50 mg twice daily reduced cramp frequency by approximately 1.8 cramps per day and cramp severity by 15 units on a 100-unit scale during a mean follow-up of 6 weeks.[66] Durable medical equipment, such as walkers and wheelchairs, and home adaptations, including bathroom adaptations, support loss of limb strength that limits activities of daily living.[43,57,67]

Cognitive impairment evaluation, typically with the Edinburgh Cognitive and Behavioral ALS Screen or the ALS Cognitive Behavioral Screen, should be performed at diagnosis and thereafter if signs of cognitive impairment develop. Clinicians should ask patients about symptoms of depression, anxiety, and sleep disturbance at each 3-month visit.[58]

Goals of Care and Advanced Care Planning

Goals of treatment and advanced care planning should be assessed throughout the course of ALS because treatment goals may change.[24,68] For most patients with ALS, decline in daily function and respiratory weakness develops during 3 to 5 years. Most patients choose to die at home with the support of community-based resources, such as hospice, although some may elect tracheostomy with long-term ventilation.[69] Medical aid in dying, the practice by which terminally ill, mentally competent adult patients with a life

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.
Downloaded from jamanetwork.com by Dominican Republic | Access Provided by JAMA, Rui Costa on 05/12/2026

expectancy of fewer than 6 months self-administer prescription medications intended to hasten their death, may be elected by some patients with ALS in states where the procedure is legal.[70] Patients with ALS who are interested in pursuing medical aid in dying face a unique challenge of self-administering life-ending medications because muscle weakness and dysphagia may make them unable to do so.[71]

Prognosis

Patients with ALS typically die from hypercapnic respiratory failure due to progressive muscle weakness of the diaphragm and other respiratory muscles. Approximately 10% of patients survive for more than 10 years, and the reasons for this longer survival are unknown. Bulbar symptoms, respiratory compromise, and dementia are associated with poorer survival.[72] In approximately 1% of patients, respiratory failure is the first symptom.[73] Rarely, patients with ALS have symptom stabilization (<1%), and some may experience symptom improvement or reversals.[74,75] Tracheostomy and mechanical ventilation improve survival by supporting respiratory function and prolonging life but do not slow progression or reverse motor deficits associated with ALS.[69]

Current and Future Therapy Development

Ongoing clinical trials are testing treatments that include antisense oligonucleotides, short, chemically altered, 15- to 20-nucleotide sequences that modulate RNA from specific genes (so-called personalized medicine),[76-78] are delivered intrathecally, and are taken up by motor neurons. Prophylactic tofersen in asymptomatic individuals with pathogenic variants in the *SOD1* gene is being evaluated in randomized clinical trials. Trials of antisense oligonucleotides modulating *FUS*,[79] *CAPN2*,[80] *STMN2*,[81] and *UNC13A*[82,83] are ongoing. Adeno-associated viruses, which have motor neuron tropism, can deliver genes or gene-modifying agents for infusion into cerebrospinal fluid and are undergoing early phase 1 testing for ALS. Stem cell therapies that deliver specific neurotropic factors, such as glial cell line–derived neurotrophic factor,[84] or multiple neurotropic factors, such as glial cell line–derived neurotrophic factor, brain-derived neurotrophic factor, and vascular endothelial growth factor, are in development.[85] New brain-computer interface technologies that implant electrodes into the brain to transmit electroencephalographic activity to computers, with algorithms that translate electroencephalographic activity into words, are being developed to assist patients with ALS in communication, which can improve quality of life.[86]

Limitations

This review has limitations. First, some aspects of ALS diagnosis and treatment were not discussed. Second, the quality of included articles was not assessed. Third, articles in non-English languages were not reviewed. Fourth, some relevant articles may not have been included.

Conclusions

Amyotrophic lateral sclerosis is a progressive and fatal neurodegenerative disorder of UMNs and LMNs. No curative therapies exist for ALS. Two oral medications, riluzole and edaravone, have been approved by the FDA and modestly decrease disease progression in sALS (by 2-4 months). Tofersen, an intrathecally administered gene-based therapy, is also FDA approved and slows disease progression in patients with *SOD1* pathogenic gene variants.

ARTICLE INFORMATION

Accepted for Publication: April 7, 2026.

Published Online: May 11, 2026. doi:10.1001/jama.2026.6385

Conflict of Interest Disclosures: Dr Ravits reported grants from FightMND, Target ALS, and the National Institute of Neurological Disorders and Stroke (NINDS)/National Institutes of Health (NIH) to the University of California, San Diego (UCSD); serving as site principal investigator for amyotrophic lateral sclerosis (ALS) clinical trials for Biogen, Ionis, Novartis, Lilly, Denali Therapeutics, Alexion Pharmaceuticals, and Orion Pharma, with payments to UCSD; consulting fees from NINDS/NIH, Novavax, Zydus, Libra, Insmed, Iris, Maze, Guidepoint Global, Goldman Sachs & Co, and Boxer Capital; honoraria from Virginia Mason Medical Center; webinar fees from PeerView; support for attending meetings from the International MND Society, Western ALS Consortium, ALS Network, and Packard Foundation; holding patents for methods for modulating *C9orf72* expression and antisense expression; having a provisional patent for targeting ELAV-like RNA-binding protein 3 cryptic exon 4A by antisense oligonucleotide; serving on a medical advisory board for Transposon Therapeutics; serving on a medical oversight board for the California Institute of Regenerative Medicine; participating in an ALS white paper for ALSA and NIH; and receiving inhibitor compound and biomarker measurements for experiments in ALS mice from Biogen. Dr Ferrey reported payments to the regents of UCSD for clinical trials for Sanofi, Biogen, Transposon Therapeutics Inc, Novartis, Denali Therapeutics Inc, AL-S Pharma, Ionis Pharmaceuticals, Target ALS, AZTherapies, Mass General Brigham and NIH, Alnylam, and Alexion Pharmaceuticals; and grants from Mitsubishi Tanabe Pharma America and CSL Behring outside the submitted work. Dr Gundogdu reported grants from Ionis Pharmaceuticals outside the submitted work. Dr Qayoumi reported payments to UCSD for clinical trials from Sanofi, Biogen, Transposon Therapeutics Inc, Novartis, Denali Therapeutics Inc, AL-S Pharma, Ionis Pharmaceuticals, and Target ALS outside the submitted work; meeting reimbursement from the Western ALS Consortium (nonprofit organization) and ALS Network (nonprofit foundation); and support from the ALS Network (California nonprofit foundation) and ALS Association (for support of ALS clinical care programs), paid to UCSD. Dr Zale reported grants from FightMND, Target ALS, and the National Institute of Neurological Disorders and Stroke/NIH; participating in clinical trials for Biogen Pharmaceuticals, Ionis Pharmaceuticals, Novartis, Lilly, Denali Pharmaceuticals, Alexion Pharmaceuticals, and Orion Pharmaceuticals outside the submitted work; and support from the ALS Association for ALS clinical care at UCSD. No other disclosures were reported.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Kristin Walter, MD, at kristin.walter@jamanetwork.org.

REFERENCES

1. Morgan KH, Havranek K, Horn C, Lee ML, Thomas S. You look at life through a different lens: a phenomenological study of living with amyotrophic lateral sclerosis. *Neurodegener Dis Manag*. 2026;16(1):13-23. doi:10.1080/17582024.2025.2546761

2. Berry JD, Blanchard M, Bonar K, et al. Epidemiology and economic burden of amyotrophic lateral sclerosis in the United States: a literature review. *Amyotroph Lateral Scler Frontotemporal Degener*. 2023;24(5-6):436-448. doi:10.1080/21678421.2023.2165947

3. Oh YS, Jung R, Yon DK, et al. The burden of motor neuron diseases in the United States, 1990-2021: a systematic analysis of the Global Burden of Disease study 2021. *Muscle Nerve*. 2025;72(5):1130-1142. doi:10.1002/mus.70023

4. Li TM, Alberman E, Swash M. Comparison of sporadic and familial disease amongst 580 cases of motor neuron disease. *J Neurol Neurosurg Psychiatry*. 1988;51(6):778-784. doi:10.1136/jnnp.51.6.778

5. Ingre C, Roos PM, Piehl F, Kamel F, Fang F. Risk factors for amyotrophic lateral sclerosis. *Clin Epidemiol*. 2015;7:181-193. doi:10.2147/CLEP.S37505

6. McKay KA, Smith KA, Smertinaite L, Fang F, Ingre C, Taube F. Military service and related risk

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Downloaded from jamanetwork.com by Dominican Republic | Access Provided by JAMA, Rui Costa on 05/12/2026

factors for amyotrophic lateral sclerosis. *Acta Neurol Scand*. 2021;143(1):39-50. doi:10.1111/ane.13345

7. Ravits JM, La Spada AR. ALS motor phenotype heterogeneity, focality, and spread: deconstructing motor neuron degeneration. *Neurology*. 2009;73(10):805-811. doi:10.1212/WNL.0b013e3181b6bbbd

8. Swinnen B, Robberecht W. The phenotypic variability of amyotrophic lateral sclerosis. *Nat Rev Neurol*. 2014;10(11):661-670. doi:10.1038/nrneurol.2014.184

9. Meyer T, Boentert M, Großkreutz J, et al. Motor phenotypes of amyotrophic lateral sclerosis—a three-determinant anatomical classification based on the region of onset, propagation of motor symptoms, and the degree of upper and lower motor neuron dysfunction. *Neurol Res Pract*. 2025;7(1):27. doi:10.1186/s42466-025-00389-w

10. Turner MR, Barohn RJ, Corcia P, et al; Delegates of the 2nd International PLS Conference. Primary lateral sclerosis: consensus diagnostic criteria. *J Neurol Neurosurg Psychiatry*. 2020;91(4):373-377. doi:10.1136/jnnp-2019-322541

11. Grossman M, Seeley WW, Boxer AL, et al. Frontotemporal lobar degeneration. *Nat Rev Dis Primers*. 2023;9(1):40. doi:10.1038/s41572-023-00447-0

12. Lomen-Hoerth C, Anderson T, Miller B. The overlap of amyotrophic lateral sclerosis and frontotemporal dementia. *Neurology*. 2002;59(7):1077-1079. doi:10.1212/WNL.59.7.1077

13. Lomen-Hoerth C, Murphy J, Langmore S, Kramer JH, Olney RK, Miller B. Are amyotrophic lateral sclerosis patients cognitively normal? *Neurology*. 2003;60(7):1094-1097. doi:10.1212/01.WNL.0000055861.95202.8D

14. Nabizadeh F, Nikfarjam M, Azami M, Sharifkazemi H, Sodeifian F. Pseudobulbar affect in neurodegenerative diseases: a systematic review and meta-analysis. *J Clin Neurosci*. 2022;100:100-107. doi:10.1016/j.jocn.2022.04.009

15. Tahedl M, Tan EL, Kleinerova J, et al. Progressive cerebrocerebellar uncoupling in sporadic and genetic forms of amyotrophic lateral sclerosis. *Neurology*. 2024;103(2):e209623. doi:10.1212/WNL.0000000000209623

16. Bombaci A, Lupica A, Pozzi FE, Remoli G, Manera U, Di Stefano V. Sensory neuropathy in amyotrophic lateral sclerosis: a systematic review. *J Neurol*. 2023;270(12):5677-5691. doi:10.1007/s00415-023-11954-1

17. Bjelica B, Bartels MB, Hesebeck-Brinckmann J, Petri S. Non-motor symptoms in patients with amyotrophic lateral sclerosis: current state and future directions. *J Neurol*. 2024;271(7):3953-3977. doi:10.1007/s00415-024-12455-5

18. Fang T, Jozsa F, Al-Chalabi A. Nonmotor symptoms in amyotrophic lateral sclerosis: a systematic review. *Int Rev Neurobiol*. 2017;134:1409-1441. doi:10.1016/bs.irn.2017.04.009

19. Richards D, Morren JA, Pioro EP. Time to diagnosis and factors affecting diagnostic delay in amyotrophic lateral sclerosis. *J Neurol Sci*. 2020;417:117054. doi:10.1016/j.jns.2020.117054

20. Brooks BR, Miller RG, Swash M, Munsat TL; World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2000;1(5):293-299. doi:10.1080/146608200300079536

21. de Carvalho M, Dengler R, Eisen A, et al. The Awaji criteria for diagnosis of ALS. *Muscle Nerve*. 2011;44(3):456-457. doi:10.1002/mus.22175

22. van den Berg LH, Sorenson E, Gronseth G, et al; Airlie House ALS Clinical Trials Guidelines Group. Revised Airlie House consensus guidelines for design and implementation of ALS clinical trials. *Neurology*. 2019;92(14):e1610-e1623. doi:10.1212/WNL.0000000000007242

23. Shefner JM, Al-Chalabi A, Baker MR, et al. A proposal for new diagnostic criteria for ALS. *Clin Neurophysiol*. 2020;131(8):1975-1978. doi:10.1016/j.clinph.2020.04.005

24. Edwards WF, Malik S, Peters J, Chippendale I, Ravits J. Delivering bad news in amyotrophic lateral sclerosis: proposal of specific technique ALS ALLOW. *Neurol Clin Pract*. 2021;11(6):521-526. doi:10.1212/CPJ.0000000000000957

25. O'Connell C, Kavanaugh MS, Cummings C, Genge A. How to break the news in amyotrophic lateral sclerosis/motor neuron disease: practical guidelines from experts. *Amyotroph Lateral Scler Frontotemporal Degener*. 2025;26(1-2):5-14. doi:10.1080/21678421.2024.2397517

26. de Carvalho M, Dengler R, Eisen A, et al. Electrodiagnostic criteria for diagnosis of ALS. *Clin Neurophysiol*. 2008;119(3):497-503. doi:10.1016/j.clinph.2007.09.143

27. de Carvalho M, Swash M. Lower motor neuron dysfunction in ALS. *Clin Neurophysiol*. 2016;127(7):2670-2681. doi:10.1016/j.clinph.2016.03.024

28. Kwan J, Vullaganti M. Amyotrophic lateral sclerosis mimics. *Muscle Nerve*. 2022;66(3):240-252. doi:10.1002/mus.27567

29. de Carvalho M, Swash M. Diagnosis and differential diagnosis of MND/ALS: IFCN handbook chapter. *Clin Neurophysiol Pract*. 2023;9:27-38. doi:10.1016/j.cnp.2023.12.003

30. Obara K, Ito D, Nilsson C, et al. Diagnostic and prognostic value of blood and cerebrospinal fluid biomarkers in amyotrophic lateral sclerosis: a systematic review and meta-analysis. *Eur J Neurol*. 2025;32(10):e70382. doi:10.1111/ene.70382

31. Benatar M, Wuu J, Andersen PM, Lombardi V, Malaspina A. Neurofilament light: a candidate biomarker of presymptomatic amyotrophic lateral sclerosis and phenoconversion. *Ann Neurol*. 2018;84(1):130-139. doi:10.1002/ana.25276

32. Nijs M, Van Damme P. The genetics of amyotrophic lateral sclerosis. *Curr Opin Neurol*. 2024;37(5):560-569. doi:10.1097/WCO.0000000000001294

33. Van Daele SH, Moisse M, van Vugt JJFA, et al. Genetic variability in sporadic amyotrophic lateral sclerosis. *Brain*. 2023;146(9):3760-3769. doi:10.1093/brain/awad120

34. Mizielinska S, Hautbergue GM, Gendron TF, et al. Amyotrophic lateral sclerosis caused by hexanucleotide repeat expansions in *C9orf72*: from genetics to therapeutics. *Lancet Neurol*. 2025;24(3):261-274. doi:10.1016/S1474-4422(25)00026-2

35. Benatar M, Robertson J, Andersen PM. Amyotrophic lateral sclerosis caused by *SOD1* variants: from genetic discovery to disease prevention. *Lancet Neurol*. 2025;24(1):77-86. doi:10.1016/S1474-4422(24)00479-4

36. Balendra R, Sreedharan J, Hallegger M, et al. Amyotrophic lateral sclerosis caused by *TARDBP* mutations: from genetics to TDP-43 proteinopathy. *Lancet Neurol*. 2025;24(5):456-470. doi:10.1016/S1474-4422(25)00109-7

37. Moens TG, Da Cruz S, Neumann M, Shelkovnikova TA, Shneider NA, Van Den Bosch L. Amyotrophic lateral sclerosis caused by *FUS* mutations: advances with broad implications. *Lancet Neurol*. 2025;24(2):166-178. doi:10.1016/S1474-4422(24)00517-9

38. Roggenbuck J, Eubank BHF, Wright J, Harms MB, Kolb SJ; ALS Genetic Testing and Counseling Guidelines Expert Panel. Evidence-based consensus guidelines for ALS genetic testing and counseling. *Ann Clin Transl Neurol*. 2023;10(11):2074-2091. doi:10.1002/acn3.51895

39. Akçimen F, Lopez ER, Landers JE, et al. Amyotrophic lateral sclerosis: translating genetic discoveries into therapies. *Nat Rev Genet*. 2023;24(9):642-658. doi:10.1038/s41576-023-00592-y

40. Zhou W, Xu R. Current insights in the molecular genetic pathogenesis of amyotrophic lateral sclerosis. *Front Neurosci*. 2023;17:1189470. doi:10.3389/fnins.2023.1189470

41. Kawakami I, Arai T, Hasegawa M. The basis of clinicopathological heterogeneity in TDP-43 proteinopathy. *Acta Neuropathol*. 2019;138(5):751-770. doi:10.1007/s00401-019-02077-x

42. Taylor JP, Brown RH Jr, Cleveland DW. Decoding ALS: from genes to mechanism. *Nature*. 2016;539(7628):197-206. doi:10.1038/nature20413

43. Miller RG, Jackson CE, Kasarskis EJ, et al; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter update: the care of the patient with amyotrophic lateral sclerosis: drug, nutritional, and respiratory therapies (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2009;73(15):1218-1226. doi:10.1212/WNL.0b013e3181bc0141

44. Bensimon G, Lacomblez L, Meininger V; ALS/Riluzole Study Group. A controlled trial of riluzole in amyotrophic lateral sclerosis. *N Engl J Med*. 1994;330(9):585-591. doi:10.1056/NEJM199403033300901

45. Fang T, Al Khleifat A, Meurgey JH, et al. Stage at which riluzole treatment prolongs survival in patients with amyotrophic lateral sclerosis: a retrospective analysis of data from a dose-ranging study. *Lancet Neurol*. 2018;17(5):416-422. doi:10.1016/S1474-4422(18)30054-1

46. Andrews JA, Jackson CE, Heiman-Patterson TD, Bettica P, Brooks BR, Pioro EP. Real-world evidence of riluzole effectiveness in treating amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degener*. 2020;21(7-8):509-518. doi:10.1080/21678421.2020.1771734

47. Hardiman O, van den Berg LH. Edaravone: a new treatment for ALS on the horizon? *Lancet Neurol*. 2017;16(7):490-491. doi:10.1016/S1474-4422(17)30163-1

48. Abe K, Aoki M, Tsuji S, et al; Writing Group; Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*. 2017;16(7):505-512. doi:10.1016/S1474-4422(17)30115-1

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Downloaded from jamanetwork.com by Dominican Republic | Access Provided by JAMA, Rui Costa on 05/12/2026

49. Rothstein J, Genge A, De Silva S, et al. Efficacy and safety of once daily dosing vs approved on/off dosing of edaravone oral suspension up to 48 weeks in patients with amyotrophic lateral sclerosis (study MT-1186-A02). *Muscle Nerve*. 2025;72(3):433-442. doi:10.1002/mus.28448

50. Genge A, Pattee GL, Sobue G, et al. Safety extension study of edaravone oral suspension in patients with amyotrophic lateral sclerosis for up to an additional 96 weeks of treatment. *Muscle Nerve*. 2025;72(3):450-454. doi:10.1002/mus.28451

51. Witzel S, Maier A, Steinbach R, et al; German Motor Neuron Disease Network (MND-NET). Safety and effectiveness of long-term intravenous administration of edaravone for treatment of patients with amyotrophic lateral sclerosis. *JAMA Neurol*. 2022;79(2):121-130. doi:10.1001/jamaneurol.2021.4893

52. Ferrer. Ferrer reports top-line results from phase III ADORE study in ALS. Accessed March 16, 2026. https://www.ferrer.com/en/results-study-ADORE-ALS

53. Hamad AA, Alkhawaldeh IM, Nashwan AJ, Meshref M, Imam Y. Tofersen for *SOD1* amyotrophic lateral sclerosis: a systematic review and meta-analysis. *Neurol Sci*. 2025;46(5):1977-1985. doi:10.1007/s10072-025-07994-2

54. Miller TM, Cudkowicz ME, Genge A, et al; VALOR and OLE Working Group. Trial of antisense oligonucleotide tofersen for *SOD1* ALS. *N Engl J Med*. 2022;387(12):1099-1110. doi:10.1056/NEJMoa2204705

55. Miller TM, Cudkowicz ME, Shaw PJ, et al; VALOR and OLE Working Group. Long-term tofersen in *SOD1* amyotrophic lateral sclerosis. *JAMA Neurol*. 2026;83(2):115-125. doi:10.1001/jamaneurol.2025.4946

56. de Almeida FEO, do Carmo Santana AK, de Carvalho FO. Multidisciplinary care in amyotrophic lateral sclerosis: a systematic review and meta-analysis. *Neurol Sci*. 2021;42(3):911-923. doi:10.1007/s10072-020-05011-2

57. Van Damme P, Al-Chalabi A, Andersen PM, et al. European Academy of Neurology (EAN) guideline on the management of amyotrophic lateral sclerosis in collaboration with European Reference Network for Neuromuscular Diseases (ERN EURO-NMD). *Eur J Neurol*. 2024;31(6):e16264. doi:10.1111/ene.16264

58. Shoesmith C. Palliative care principles in ALS. *Handb Clin Neurol*. 2023;191:139-155. doi:10.1016/B978-0-12-824535-4.00007-0

59. Ackrivo J. Pulmonary care for ALS: progress, gaps, and paths forward. *Muscle Nerve*. 2023;67(5):341-353. doi:10.1002/mus.27779

60. de Wit J, Bakker LA, van Groenestijn AC, et al. Caregiver burden in amyotrophic lateral sclerosis: a systematic review. *Palliat Med*. 2018;32(1):231-245. doi:10.1177/0269216317709965

61. James E, Ellis C, Brassington R, Sathasivam S, Young CA. Treatment for sialorrhea (excessive saliva) in people with motor neuron disease/amyotrophic lateral sclerosis. *Cochrane Database Syst Rev*. 2022;5(5):CD006981. doi:10.1002/14651858.CD006981.pub3

62. Cunha-Correia CD, Gama MDP, Fontana PN, et al. Noninvasive mechanical ventilation assistance in amyotrophic lateral sclerosis: a systematic review. *Sao Paulo Med J*. 2023;142(1):e2022470. doi:10.1590/1516-3180.2022.0470.r1.100423

63. Smith R, Pioro E, Myers K, et al. Enhanced bulbar function in amyotrophic lateral sclerosis: the Nuedexta treatment trial. *Neurotherapeutics*. 2017;14(3):762-772. doi:10.1007/s13311-016-0508-5

64. Pioro EP, Brooks BR, Cummings J, et al; Safety, Tolerability, and Efficacy Results Trial of AVP-923 in PBA Investigators. Dextromethorphan plus ultra low-dose quinidine reduces pseudobulbar affect. *Ann Neurol*. 2010;68(5):693-702. doi:10.1002/ana.22093

65. Weiss MD, Macklin EA, Simmons Z, et al; Mexiletine ALS Study Group. A randomized trial of mexiletine in ALS: safety and effects on muscle cramps and progression. *Neurology*. 2016;86(16):1474-1481. doi:10.1212/WNL.0000000000002507

66. Oskarsson B, Moore D, Mozaffar T, et al. Mexiletine for muscle cramps in amyotrophic lateral sclerosis: a randomized, double-blind crossover trial. *Muscle Nerve*. Published online March 6, 2018. doi:10.1002/mus.26117

67. Hrastelj J, Robertson NP. Improving survival in amyotrophic lateral sclerosis: future treatments in a modern service. *J Neurol*. 2015;262(7):1791-1793. doi:10.1007/s00415-015-7811-7

68. Mazzola MA, Russell JA. Neurology ethics at the end of life. *Handb Clin Neurol*. 2023;191:235-257. doi:10.1016/B978-0-12-824535-4.00012-4

69. Spataro R, Bono V, Marchese S, La Bella V. Tracheostomy mechanical ventilation in patients with amyotrophic lateral sclerosis: clinical features and survival analysis. *J Neurol Sci*. 2012;323(1-2):66-70. doi:10.1016/j.jns.2012.08.011

70. Abrahao A, Downar J, Pinto H, et al. Physician-assisted death: a Canada-wide survey of ALS health care providers. *Neurology*. 2016;87(11):1152-1160. doi:10.1212/WNL.0000000000002786

71. Shavelson L, Pope TM, Battin MP, Ouellette A, Kluger B. Neurologic diseases and medical aid in dying: aid-in-dying laws create an underclass of patients based on disability. *Am J Bioeth*. 2023;23(9):5-15. doi:10.1080/15265161.2022.2105422

72. Pupillo E, Messina P, Logroscino G, Beghi E; SLALOM Group. Long-term survival in amyotrophic lateral sclerosis: a population-based study. *Ann Neurol*. 2014;75(2):287-297. doi:10.1002/ana.24096

73. Pinto S, Gromicho M, Oliveira Santos MO, Swash M, De Carvalho M. Respiratory onset in amyotrophic lateral sclerosis: clinical features and spreading pattern. *Amyotroph Lateral Scler Frontotemporal Degener*. 2023;24(1-2):40-44. doi:10.1080/21678421.2022.2067777

74. Bedlack RS, Vaughan T, Wicks P, et al. How common are ALS plateaus and reversals? *Neurology*. 2016;86(9):808-812. doi:10.1212/WNL.0000000000002251

75. Harrison D, Mehta P, van Es MA, et al; Pooled Resource Open-Access ALS Clinical Trials Consortium. "ALS reversals": demographics, disease characteristics, treatments, and co-morbidities. *Amyotroph Lateral Scler Frontotemporal Degener*. 2018;19(7-8):495-499. doi:10.1080/21678421.2018.1457059

76. Bennett CF. Therapeutic antisense oligonucleotides are coming of age. *Annu Rev Med*. 2019;70:307-321. doi:10.1146/annurev-med-041217-010829

77. Lauffer MC, van Roon-Mom W, Aartsma-Rus A; N = 1 Collaborative. Possibilities and limitations of antisense oligonucleotide therapies for the treatment of monogenic disorders. *Commun Med (Lond)*. 2024;4(1):6. doi:10.1038/s43856-023-00419-1

78. Boros BD, Schoch KM, Kreple CJ, Miller TM. Antisense oligonucleotides for the study and treatment of ALS. *Neurotherapeutics*. 2022;19(4):1145-1158. doi:10.1007/s13311-022-01247-2

79. Shneider NA, Harms MB, Korobeynikov VA, et al. Antisense oligonucleotide jacifusen for FUS-ALS: an investigator-initiated, multicentre, open-label case series. *Lancet*. 2025;405(10494):2075-2086. doi:10.1016/S0140-6736(25)00513-6

80. Yamashita T, Hideyama T, Hachiga K, et al. A role for calpain-dependent cleavage of TDP-43 in amyotrophic lateral sclerosis pathology. *Nat Commun*. 2012;3(1):1307. doi:10.1038/ncomms2303

81. Baughn MW, Melamed Z, López-Erauskin J, et al. Mechanism of *STMN2* cryptic splice-polyadenylation and its correction for TDP-43 proteinopathies. *Science*. 2023;379(6637):1140-1149. doi:10.1126/science.abq5622

82. Ma XR, Prudencio M, Koike Y, et al. TDP-43 represses cryptic exon inclusion in the FTD-ALS gene *UNC13A*. *Nature*. 2022;603(7899):124-130. doi:10.1038/s41586-022-04424-7

83. Brown AL, Wilkins OG, Keuss MJ, et al; NYGC ALS Consortium. TDP-43 loss and ALS-risk SNPs drive mis-splicing and depletion of *UNC13A*. *Nature*. 2022;603(7899):131-137. doi:10.1038/s41586-022-04436-3

84. Baloh RH, Johnson JP, Avalos P, et al. Transplantation of human neural progenitor cells secreting GDNF into the spinal cord of patients with ALS: a phase 1/2a trial. *Nat Med*. 2022;28(9):1813-1822. doi:10.1038/s41591-022-01956-3

85. Mazzini L, De Marchi F, Buzanska L, et al. Current status and new avenues of stem cell–based preclinical and therapeutic approaches in amyotrophic lateral sclerosis. *Expert Opin Biol Ther*. 2024;24(9):933-954. doi:10.1080/14712598.2024.2392307

86. Vansteensel MJ, Klein E, van Thiel G, et al. Towards clinical application of implantable brain-computer interfaces for people with late-stage ALS: medical and ethical considerations. *J Neurol*. 2023;270(3):1323-1336. doi:10.1007/s00415-022-11464-6

© 2026 American Medical Association. All rights reserved, including those for text and data mining, AI training, and similar technologies.

Downloaded from jamanetwork.com by Dominican Republic | Access Provided by JAMA, Rui Costa on 05/12/2026