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eISSN 2450-3118 · Open Access · Peer-reviewed

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BARANOWICZ, Michał, MAZURKIEWICZ, Weronika, BORECKA, Zuzanna, SOBCZAK, Agnieszka Marta, SZCZOT, Alicja, JAWOROWICZ, Anna, PIASECKA, Joanna, GOLEMBIEWSKI, Bartosz, MULSKI, Grzegorz and MANICKA, Martyna. Emerging Modern Therapeutic Options in Amyotrophic Lateral Sclerosis (ALS). *Quality in Sport*. 2026;68:74251. <https://doi.org/10.12775/QS.2026.68.74251>

ARTICLE TIMELINE

Received: 12.07.2026. Revised: 02.08.2026. Accepted: 02.08.2026. Published: 11.08.2026.

The journal has been awarded 20 points in the parametric evaluation by the Polish Ministry of Higher Education and Science (Annex to the announcement of 05.01.2024, No. 32553). Unique Journal Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).

Punkty Ministerialne z 2019 – aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych). © The Authors 2026.

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Emerging Modern Therapeutic Options in Amyotrophic Lateral Sclerosis (ALS)

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Abstract:

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by a rapidly progressive clinical course, ultimately leading to complete paralysis and a profound deterioration of physical and cognitive well-being. For decades, riluzole remained the sole approved therapeutic option. The pharmacological landscape has recently experienced significant revolution. While a definitive cure remains elusive, recent advancements have introduced novel, targeted agents into clinical practice, marking a critical milestone in ALS management. This review presents recent findings and emerging trends in ALS pharmacotherapy. Furthermore, it examines the complex pathophysiology of this multidimensional disease, highlighting the intrinsic biological challenges that complicate the development of universally effective, disease-modifying treatments.

Objective: This review examines currently approved and investigational therapeutic options for amyotrophic lateral sclerosis (ALS), a progressive neurodegenerative disorder. Through a systematic appraisal of the existing literature, we provide a comprehensive overview of contemporary treatment strategies, to delineate the current clinical possibilities and limitations in the management of ALS.

1. Introduction

Neurodegenerative disorders represent a major focus of clinical research worldwide. Among many of those frequently dramatically progressing diseases, amyotrophic lateral sclerosis (ALS) occupies a distinct position. The global prevalence of the ALS measures up to approximately 4.5/100.000 population and is more often diagnosed in men than women [1]. The clinical development of symptoms is often rapid and very dramatic for the patients, leading to complete paralysis with a median life expectancy of no longer than 2-5 years [2]. Despite the constant improvement of medical care standards, this prognosis has not radically changed over the last decades, indicating how difficult it is to fully understand the nature of the disease and effectively cure it.

In recent years, however, a growing understanding of the molecular and genetic mechanisms driving neurodegeneration has spurred the development of novel therapeutic strategies, and the treatment landscape for ALS is evolving rapidly.

This narrative review provides a comprehensive overview of currently approved and emerging therapeutic options for ALS, with a focus on recent advances and their potential to address current unmet clinical needs.

2. Methods

2.1. Study design

This study was conducted as a narrative review to provide an overview of emerging therapeutic options for ALS. A narrative approach was chosen to provide a broad, clinically oriented synthesis of recent advances, mechanisms of action, and treatment strategies relevant to current practice.

2.2. Search strategy

A literature search was performed to identify relevant studies on emerging treatments for ALS. The search was conducted in the following electronic databases: PubMed, Google Scholar

The search covered the period from 2000 to 2026. The following keywords or Medical Subject Headings (MeSH) terms were used: Amyotrophic lateral sclerosis, tofersen, edaravone, novel therapies in ALS. Boolean operators and database-specific filters were applied as appropriate. Additionally, the reference lists of selected articles were manually screened to identify further relevant publications.

2.3. Study selection

Studies were selected based on their relevance to the scope of this review. The inclusion criteria were:

- studies addressing emerging or novel treatments for amyotrophic lateral sclerosis
- clinical trials, observational studies, and relevant reviews
- studies published in English

The selection process was guided by clinical relevance, the recency of the evidence, and the contribution to understanding emerging therapeutic approaches.

2.4. Methodological considerations

This narrative review did not adhere to a formal systematic review protocol, nor did it include a quantitative meta-analysis. Nonetheless, efforts were made to present a balanced and comprehensive overview by including studies with different designs and critically assessing their clinical importance.

3. Results

3.1 Symptoms and Pathomechanisms of ALS

The symptoms of ALS are the result of the cellular death of upper motor neurons in the central nervous system. The clinical symptoms of ALS most commonly include progressive muscle weakness leading to complete paralysis. Cognitive functions may be affected in a subset of patients, leading to speech and cognitive impairments [3]. Notably, symptoms consistent with or identical to frontotemporal dementia are present in approximately 50% of cases, a finding that has substantially revised the earlier conceptualization of ALS as a purely neuromuscular disorder [4].

The clinical presentation of an ALS patient may deteriorate within a matter of months. The paralysis and loss of function of the muscles of the pharynx eventually lead to an elevated risk of aspiration and recurrent pneumonia [5]. Concurrent weakening of the respiratory muscles often leads to suffocation, which represents the primary cause of death in ALS [3,6]

Although these features are broadly characteristic of the disease, the diversity of its clinical manifestations and the number of genes implicated in its pathogenesis have led to a reconceptualization of ALS as a clinical spectrum rather than a discrete nosological entity [7]. Intracellular processes determine the clinical onset, which, due to many pathomechanisms, can lead to major differences in the onset of ALS among individuals. The two major clinical presentations are spinal onset, in which the first symptoms include muscle weakness in one limb, and bulbar onset, in which, at first, the muscles of the tongue and pharynx are affected [8].

Numerous genetic, environmental, and individual factors were identified as influencing the development of the disorder. Throughout extensive research, ALS was proven to be, in most cases, a heterogeneous and elusive disease [9]. Only approximately 10% a single gene mutation causes 15% of ALS cases; these types, however, hold the most promise in terms of effective

therapy development. The second group comprises 85%–90% of patients with the polygenic form [10]. To date, more than 40 genes have been implicated in the pathomechanism of ALS, and a significant number of additional causative genes likely remain unidentified [7,11]. The genetic architecture varies significantly across populations, with distinct, geographically specific mutation frequencies, inheritance patterns, and penetrance levels that challenge and undermine the traditional familial-sporadic classification approach [12].

In European populations, C9orf72 hexanucleotide repeat expansions account for approximately 33.7% of familial cases and 5.1% of sporadic cases, whereas in Asian populations, SOD1 is the predominant genetic factor, with C9orf72 accounting for a very small number of cases [12]. The four principal genes involved in the development of the disease - C9orf72, SOD1, FUS, and TARDBP are collectively liable for roughly 48% of familial and only 5% of sporadic cases in European populations [7].

Despite the considerable diversity of genetic factors, the cellular effects of their pathological expression or suppression led to similar pathological processes: impaired RNA metabolism, disrupted proteostasis and autophagy, cytoskeletal defects, impaired DNA repair processes, and mitochondrial dysfunction. The cumulative effect of these processes is motor neuron death, and, ultimately, the clinical syndrome of ALS [7,11].

3.2 Currently Approved ALS therapies

For more than two decades, riluzole remained the only drug approved by the FDA for the treatment of ALS. This landscape has recently changed with the approval of two additional agents — edaravone and tofersen — marking a significant expansion of the therapeutic armamentarium. Although the long-term efficacy and safety of these agents in real-world clinical settings require further evaluation, their approval represents a meaningful advance and a source of cautious optimism for the development of future treatments.

3.2.1 Riluzole

Riluzole, first approved by the FDA in 1995, was for many years the only drug to have been officially approved for the treatment of ALS [10]. Its mechanism of action includes blocking ion-gated channels, which decrease glutamate levels and thus reduce its excitotoxic potential. The motor neurons in ALS exhibit elevated late sodium current resulting from incomplete channel inactivation, which accounts for membrane overexcitability and subsequent cell death [13,14]. Riluzole's ability to stabilize the inactivated channel state reverses cellular

hyperexcitability without impairing normal action potential generation [14]. Its influence on both the central and peripheral nervous systems was measured in electrophysiological studies. A study conducted by Vucic et al. suggests that riluzole therapy partially normalizes cortical excitability by significantly increasing short-interval intracortical inhibition. Peripherally, the drug reduces axonal superexcitability and refractoriness, consistent with reductions in transient sodium conductances [15].

Although it offered a prospect of decelerating the progression of respiratory failure and, in some instances, enhancing motor functions, its efficacy was considerably below optimal standards. According to numerous clinical trials, riluzole was demonstrated to extend lifespan by a maximum of 2–3 months [5,16]. However, the validity of clinical research on riluzole is now questioned, as some large cohort studies seem to indicate that the drug might not significantly influence survival in ALS [17].

3.2.2. Edaravone

Edaravone is a free radical scavenger approved by the FDA for ALS treatment, currently available in both intravenous (approved in 2017) and oral formulation (approved in 2022) [18]. The precise mechanism of action is not fully defined, although edaravone's neuroprotective effects are presumed to result from its antioxidant properties, which eliminate free radicals [19]. Recent research suggests that edaravone may exert therapeutic effects far beyond simple antioxidant activity, including the mitigation of TDP-43 mislocalization through the SIRT1-XBP1 pathway and modulation of protein quality control systems [20,21].

Despite the promise of its biochemical effects, the available clinical data suggest that the benefits of edaravone therapy may be limited to specific patient subgroups. The agent was shown to modestly attenuate the decline in scores on the revised ALS Functional Rating Scale (ALSFRS-R) only in patients at an early disease stage with preserved respiratory function [22,23]. The dosage of edaravone in the ALS is 60 mg intravenously daily for 2 weeks, followed by a 14-day drug-free period, then repeated in 10-day cycles within 14-day periods. [24].

3.2.3. Tofersen

Approximately 1%–2% of all ALS cases are attributed to mutations in the SOD1 gene [25]. Approved by the FDA in 2023, tofersen, an antisense nucleotide, became the first targeted, causal ALS treatment, that targets the mRNA encoded by the SOD1 gene [26,27]. The SOD1

gene has been proven to play a pivotal role in many cases of familial ALS, although studies suggest that its role in the sporadic form should not be omitted [28].

Administered intrathecally at a dose of 100 mg, tofersen acts as an antisense oligonucleotide targeting specifically the SOD1 mRNA, resulting in reduced SOD1 protein synthesis and subsequent decrease in its pathological aggregation, manifesting itself in decreased SOD1 levels in cerebrospinal fluid, as well as decreased levels of plasma neurofilament light chain, a biomarker of neuronal damage in ALS [25,26,29]. The approval of tofersen has validated the concept of antisense oligonucleotide therapy. It has led to the ongoing development of similar therapies targeting other genetic forms of ALS, including C9orf72, FUS, and ATXN2 [12].

According to clinical data, the adverse effects associated with tofersen are, in the majority of cases, related to its mode of administration, which requires lumbar puncture. These include back pain, extremity pain, falls, and headaches, which are consistent with the procedure and its risks [26,30]. Nevertheless, there exists a risk of severe complications linked to tofersen itself, involving serious neurological conditions, which may occur in approximately 7%–9% of patients. Specifically, these adverse events include myelitis, radiculitis, papilledema with elevated intracranial pressure, and meningitis. Although these conditions are treatable and, in most cases, will not disrupt the process, in a subset of patients, therapy termination might be necessary [31].

3.3. Emerging and investigational therapies

As the preceding sections illustrate, a substantial proportion of patients with ALS remain without access to effective pharmacological treatment. The ongoing research effort holds considerable promise; the heterogeneous and polygenic nature of the disease, however, renders the development of broadly applicable therapies an inherently complex and multifaceted challenge.

3.3.1. Sodium phenylbutyrate-aurursodiol

Sodium phenylbutyrate-aurursodiol, also known as AMX0035 or Relyvrio, is an orally administered medication, that simultaneously reduces reticulocyte damage and mitigates mitochondrial dysfunction, thus slowing the processes leading to motor neuron death [32,33].

The CENTAUR trial, conducted in 2020, was a phase 2 randomized, double-blind, placebo-controlled study with 137 participants diagnosed with ALS who experienced symptom onset

within the previous 18 months [33]. Long-term results from the trial suggested that initiating sodium phenylbutyrate-taurursodiol prolonged tracheostomy and ventilation-free survival and delayed the need for hospitalization. A subsequent analysis showed a median survival benefit of 4.8 months with medication compared to the placebo group. [33]. Despite these encouraging phase 2 results, a subsequent phase 3 clinical trial, released in early 2024, showed that sodium phenylbutyrate-taurursodiol did not exceed the effects of placebo on participants' ALS functional scale after 48 weeks [34]. The medication also failed to elevate patient-reported quality of life, respiratory functions, or overall survival. These results forced the drug manufacturer to withdraw Relyvrio from the [34].

3.3.2. Stem cell therapy

Stem cells of various types have been investigated as potential therapeutic agents across a broad range of degenerative diseases, and their application in ALS has been the subject of increasing research interest.

Bone marrow-derived mesenchymal stem cells (MSCs) represent a particularly promising candidate, having demonstrated benefit in ALS through several biological mechanisms, including neuroregenerative and immunomodulatory effects, and correlating with improved scores on the ALSFRS-R [34]. Intrathecal administration of stem cells has additionally been associated with a prolonged duration of therapeutic effects [35,36]. In addition, a study by Zhang et al. showed that the administration of neural progenitor stem cells also delays symptom development and improves motor function among ALS patients [37]. Lastly, umbilical cord-derived stem cells have been shown to provide significant benefits for patients with ALS [38].

Despite these findings, at present, there are no stem cell-based therapies officially approved for the treatment of ALS. The topic requires further clinical trials and the development of appropriate application protocols and management, and remains a prospect in the field of ALS treatment.

3.3.3. Ultra-high dose Methylcobalamine

Methylcobalamin, an active form of the B12 vitamin and its potential use in the treatment of ALS, remained a topic of discussion due to its positive effects on the treatment of many neurological disorders [39]. After years of studies and trials, Japan approved methylcobalamin for the treatment of ALS in late 2024 [40,41]. Japan remains the only country to officially approve methylcobalamin for the disease.

Its efficiency is most likely linked to its critical role in converting homocysteine to methionine[42]. Elevated plasma homocysteine levels are a known risk factor for the development of vascular disease, but they also exert toxic effects on neurons [39,42] The main target of ultra-high-dose methylcobalamin (50mg i.m. 2x/week) is to slow disease progression, prolong overall survival, and slow the decline in quality of life for patients. These positive effects were proven in JETALS and Esai trials [41,43,44].

3.3.4 Ravilizumab

Ravilizumab, a complement C5 inhibitor, was tested in the CHAMPION-ALS trial to assess its potential to slow ALS progression [45]. The rationale for its use involved elevated complement units in the plasma of patients diagnosed with ALS, as well as the biochemical interactions of the C5 unit, which might lead to inflammatory processes in microglia [46]. However, ravilizumab did not outperform placebo in the trials and is therefore not recommended [45].

Further research targeting more specific pathways might be needed, while a recent preclinical study involving C5a-C5aR1 signaling axis antagonists, especially PMX205, demonstrated that this approach could yield beneficial outcomes in the treatment of ALS [46].

3.3.5. Arimoclomol

ORARIALS-01 was an international trial designed to inspect the potential efficiency and safety of arimoclomol, a heat-shock protein-70 (HSP70) co-inducer [47]. This compound is known to target misfolded proteins successfully; its potential usefulness in ALS has a strong theoretical basis, as misfolding and subsequent aggregation of various proteins are important factors in the pathophysiology of ALS [48,49]. Although the drug was neuroprotective in animal models and its potential therapeutic effects were strongly suggested in phase 2 trials, the large ORAL-01 trial did not demonstrate that arimoclomol was more effective or safer than placebo [47]. Arimoclomol was, however, recently officially approved by the FDA for the treatment of another serious disorder, type C of the Niemann Pick disease [50].

3.3.6. Memantine and Trazodone

Memantine and trazodone are known and proven to be effective in improving the cognitive functions of many patients suffering from various neurological diseases, such as Alzheimer's disease [51,52]. Hence, both drugs were tested in a multicenter MND SMART trial for their efficacy in ALS. The results of this phase 3 trial did not show an advantage of either agent over placebo [53].

3.3.7. CNM-Au8

The potential use of CNM-Au8, an orally applied suspension of catalytically active gold nanocrystals, was tested in the HEALEY-ALS trial. Although, in previously conducted RESCUE-ALS trial, the evidence suggested its presumed beneficial implications in slowing down the disease progression[54], the 24 weeks-long HEALEY-ALS trial published in 2024 did not show significant advantageous effect on disease progression over the placebo group [55]

3.3.8. Immunomodulatory drugs targeting the microglia

Numerous new substances produced promising results in the preclinical trials, including montelukast, azithromycin, belinostat, propranolol, ciprofloxacin, celecoxib, and a number of kinase inhibitors. These agents are being tested for their potential role in ALS treatment, due to their positive influence on the microglia, which plays an important role in disease pathophysiology and progression [56,57]. Studies focus on the possibility to activate the processes in the microglia which promote neuroprotection, as well as on limiting those molecular pathways in the microglia which promote neurodegeneration [56].

4. Discussion

Recent advancements in ALS treatment - both the accepted new drugs and various research attempts - prove that our knowledge about the disease has grown significantly. And although the disease remains morbid and devastating for patients, the official registration of edaravone and tofersen provide much needed hope in terms of finding effective cure. These innovations mark a significant change in the landscape of ALS treatment, previously dominated for many years by riluzole alone. Further research is required, as other drugs targeting different biochemical pathways may complement current therapies and significantly change the onset or the progression of symptoms and life expectancy among patients. As suggested in the text above, possibilities for future studies remains vast, and although a significant amount of substances are likely not to pass the clinical trials, it is crucial to persistently search for new options.

5. Summary

Although the recently approved treatments in the form of edaravone and tofersen have significantly extended the ability to help patients suffering from the ALS, the need for other agents that would improve the prognosis or the quality of life remains dire.

6. Disclosure

Authors' contribution

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All authors have read and agreed with the published version of the manuscript.

The research received no funding.

Institutional review board statement: not applicable

Informed consent statement: not applicable

Data availability statement: no data

The authors declare no conflict of interest

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