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CLINICAL TRIALS AND TREATMENT UPDATES FOR AMYOTROPHIC LATERAL SCLEROSIS (ELA) BETWEEN 2020 AND 2025

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Abstract: Amyotrophic Lateral Sclerosis (ALS) is a progressive disease characterized by the degeneration of upper and lower motor neurons, which consequently leads to paresis of the skeletal and bulbar muscles and can ultimately affect all motor functions, as well as communication and breathing. Life expectancy is between 3 and 5 years after the onset of symptoms. Most patients die from respiratory failure or its complications. ALS is mainly a sporadic disease, however, around 5 to 10% of all cases have a history of autosomal dominant mutations caused by genes such as SOD1, FUS. Its etiology may be implicated in deregulated RNA metabolism, oxidative stress, impaired axonal transport and autophagy. The article aims to carry out a literature review on Amyotrophic Lateral Sclerosis, its etiology and pathophysiological mechanisms, and therapeutic treatments and clinical trials between 2020 and 2025. The scientific databases used were MDPI, *Scientific Electronic Library Online* (Scielo), *National Library of Medicine* (NIH), Medline. ALS can be recognized as a complex syndrome that often includes behavioral changes. Diagnosing ALS remains a significant challenge, with little change in the diagnostic approach over the last decade. Despite the increasing use of genetic testing, clinical history and examination are still the main methods of confirming an ALS diagnosis, and it takes between 10 and 16 months from the onset of symptoms to receiving a definitive diagnosis. ALS demonstrates diverse mechanisms in its pathology, such as the involvement of mitochondria from the onset of ALS, manifesting itself not only in the central nervous system (CNS), but also in muscle tissue, as well as oxidative stress that causes diverse lesions. To date, Edaravone and Riluzole, which is a glutamate antagonist, are the only two drugs approved for use in the treatment of ALS, despite their limited beneficial effects on the progression of the disease. Most

of the other drugs failed in phase III clinical trials, which were carried out with a larger number of ALS patients. However, there has been an increase in clinical trials and research over the last five years, despite ALS being a disease with a complex pathology, such as the use of human pluripotent stem cells, the CRISPR-9/Cas technique, drugs such as tamoxifen, among others. It is concluded that there are still many limitations in the development and selection of patients and pre-clinical and clinical studies, due to the low incidence and difficulty in making a diagnosis, as well as the presence of different presentations and mutations in its development. Therefore, there is still a need for more extensive research into drugs that can alter the natural history of ALS, prevent its progression and symptoms.

Keywords: Amyotrophic Lateral Sclerosis; Edaravone; Riluzole; Clinical Trials;

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is considered a multisystem neurodegenerative disease with heterogeneity at the clinical and genetic levels, altered function of upper motor neurons leads to spasticity and rapid deep reflexes and symptoms of lower motor neuron abnormalities include fasciculations, muscle atrophy and weakness, ALS has a reported incidence of between 0.6% and 3.8% per 100,000 people and prevalence is 4.1% to 8.4% per 100.000 people per year in Europe (LARREA *et al*., 2025), while in Brazil the prevalence is 65 people per 100,000 individuals (GONDIM *et al*., 2023)phenomenology, diagnosis, and management of the disorders of laughter and crying in ALS patients. Twelve members of the Brazilian Academy of Neurology - considered to be experts in the field - were recruited to answer 12 questions about the subject. After exchanging revisions, a first draft was prepared. A face-to-face meeting was held in Fortaleza, Brazil on 9.23.22 to discuss it. The revised version was subsequently emailed to all members of the ALS Scientific Department from the Brazilian Academy of Neurology and the final revised version submitted for publication. The prevalence of pseudobulbar affect/pathological laughter and crying (PBA/PLC. In this context, the progressive degeneration of upper and lower motor neurons in the motor cortex, brainstem and spinal cord in ALS causes spasticity and flaccid weakness of the limbs, associated with dysarthria and dysphagia, while between 50% and 65% of ALS patients may have a variety of cognitive impairments, thus reflecting the pathology in additional cortical regions (SMUKOWSKI *et al*.., 2022)

The clinical identification of ALS begins with the confirmation abnormalities the upper and lower motor neurons involving the brain, spinal regions and the peripheral neuromuscular system. Typical clinical presentations include bulbar onset ALS with speech and swallowing problems and limb onset ALS which initially manifests with weakness in the arms or legs, followed by progressive paralysis, in addition to respiratory failure, weight loss, cramps, fasciculations in the absence of muscle weakness, emotional lability and cognitive abnormalities. Consequently, several molecular and cellular pathways have been identified as causing ALS, however, treatments to halt or reverse the progression of the disease have yet to be found. Most clinical trials have focused on testing small molecules that affect cellular pathways common in ALS: targeting glutamatergic, apoptotic, inflammatory and oxidative stress mechanisms, in addition, clinical trials have emerged using stem cell transplantation and other biological products (AKÇIMEN *et al*.., 2023)

In this context, ALS could be considered one of the subtypes of motor neuron disease, it is characterized by the progressive deterioration of upper and lower motor neurons, causing muscle atrophy and paralysis and eventually death due to respiratory failure, however, several molecular pathogenic mechanisms are involved in motor neuron degeneration, including RNA metabolic defects, proteostasis imbalance, damaged axonal transport and oxidative stress. Under redox conditions, cells produce excessive ROS or free radicals, which are eliminated or neutralized by antioxidant systems. Excessive ROS production or defective antioxidant defense systems are associated with various diseases, especially neurodegenerative diseases (FELDMAN *et al.*., 2025)

As a result, it is understood that around 10% of ALS patients are familial ALS and, to date, more than 30 ALS-related genes have been identified in these cases. However, the remaining 90% of cases are clearly sporadic ALS. Pathogenic variants in superoxide dismutase 1 (SOD1), fused in sarcoma (FUS) and chromosome 9 locus 72 (C9ORF72), the most common genes associated with ALS. The treatments available for ALS show limited efficacy in slowing down the disease process. To date, four drugs have been approved by the FDA for ALS, including Riluzole approved in 1995, Edaravone approved in 2017, Relyvrio approved in 2022 and Tofersen approved in 2023 (LARREA *et al.*, 2025). This review will explore the pathology of ALS, delving into the mechanisms underlying the damage and associated heterogeneous factors, clinical and preclinical trials from 2020 to 2025, possible therapeutic targets and drugs.

METHODOLOGY

This article is a literature review, with several original articles, which were looked at in scientific databases such as MDPI, *Scientific Electronic Library Online* (Scielo), *National Library of Medicine* (NIH), Medline. The descriptors used in this research were: "Amyotrophic Lateral Sclerosis", "Therapy for ALS", "Edaravone", "Riluzol". The data was collected between 2020 and 2025, over the last 5 years. The inclusion criteria were free articles, the articles used were original as a literature review, randomized and double-blind studies, articles in Portuguese and English were used. While the exclusion criteria for this article were the exclusion of duplicate, incomplete, paid-for articles and articles that were not in English and Portuguese. A total of 68 articles were found, while 35 articles were used to develop this article.

RESULTS AND DISCUSSION

THERAPEUTIC STRATEGIES FOR THE TREATMENT OF AMYOTROPHIC LATERAL SCLEROSIS

ALS can be associated with an important mechanism correlated to the formation of reactive oxygen species such as the formation of peroxynitrite (ONOO-) which is harmful to the central nervous system (CNS), the consequence of the imbalance between the generation of reactive oxygen species (ROS), such as hydrogen peroxide (H2O2), superoxide anions (O2-) and hydroxyl radicals (OH-), and the ability of the antioxidant defense system to clean up or repair existing damage to proteins and/or DNA. Normally, SOD1 converts superoxide anion into H2O2, donates an electron to O2 to generate O2- at the Cu2+ catalytic site as a stronger oxidant and reacts with nitric oxide (NO) to form peroxynitrite (ONOO-), this is of importance pathophysiologically, as this mutation causes the death of

motor neurons, or directly aids in the exacerbation of the disease. In addition, mitochondrial dysfunction due to a high influx of calcium and high levels of glutamate may also be associated with these previously reported mechanisms, which would cause greater production of ONOO- (SMUKOWSKI *et al.*., 2022)

In a complementary way, the drug Edaravone, used for cerebrovascular accident (CVA), is a compound carrying a carbonyl group, which would convert into a hydroxyl group by tautomerization and eliminate radicals. edaravone is a free radical scavenger, which offers neuroprotection under oxidative stress. In this context, it is understood how oxidative stress plays a critical role in the pathogenesis of various neurodegenerative diseases, including ALS, Parkinson's disease (PD), Alzheimer's disease (AD) and Huntington's disease. Oxidative stress creates an imbalance in the cellular system, leading to the production of free radicals and peroxides such as ROS, as well as disrupted proteins, lipids and DNA. According to Cha and Kim(2022), Edaravone demonstrates neuroprotective effects against oxidative stress and anti-inflammatory properties against activated microglial cells, however, to date, there has been no oral dosage formulation of edaravone clinically, so it is used as intravenous therapy for the treatment of ALS.

According to Mahoney *et al.*,(2021), they suggested that Edaravone exerts neuroprotective effects by increasing neuronal density and reducing neuronal damage induced by kainate receptors involved in disease progression. In addition, treatment with Edaravone suppressed the downregulation of nuclear factor erythroid 2-related factor 2 (Nrf2), which is a transcription factor that regulates cellular defense against toxicity and heme-oxygenase 1 (HO-1) induced by kainate while decreasing the levels of NF-κB, pro-inflammatory cytokines and inflammatory proteins in the hippocampus. Treatment with edaravone reversed the downregulation of Nrf2 and nuclear translocation induced by Aβ. In addition to the above, there have also been several studies that have reported the neuroprotective properties of Edaravone, such as preventing the loss of hippocampal CA3 neurons in rats with traumatic brain injuries, decreasing oxidative stress and reducing programmed neuronal cell death. In addition, Edaravone also exerted protective effects on non-neuronal cells, such as decreasing the activation of astrocytes and glial (CHA; KIM, 2022).

In a different way, among other factors involved in the pathology of ALS, as previously mentioned, abnormal levels of glutamate can be seen, the main excitatory neurotransmitter in the brain, and therefore the α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) and N-methyl-D-aspartate (NMDA) receptors, two important ionotropic glutamate receptors, are mediators of glutamate excitotoxicity due to the low buffering calcium influx capacity of their subunits, such as the GluA2 subunit of the AMPA receptor. Therefore, high intracellular calcium influx stimulates phospholipases, proteases and endonucleases, causing devastation of energy metabolism and apoptotic or necrotic cell death. In addition, reduced expression of astrocytic excitatory amino acid transporters is crucial for the clearance of glutamate from the synaptic cleft to the astrocytes, and defects in glutamate transport have been associated with the pathogenesis of ALS (GOUTMAN *et al.*., 2022)

The drug Riluzole, a benzothiazole compound, is an inhibitor of glutamatergic neurotransmission and was the first disease-modifying therapy approved in ALS. Although treatment with Riluzole extends survival, patients will inevitably progress and experience complications associated with ALS, including dysarthria and dysphagia. It is therefore noted that Riluzole was approved by the *Food and Drug Administration* (FDA) in 1995 and sub-

sequently launched on the market under the trade name Rilutek®. This was the first drug approved by the FDA for the treatment of ALS, and its mechanism was shown to be increased extracellular glutamate uptake and inhibition of glutamate release from presynaptic terminals. In addition, riluzole also stabilizes the inactivated state of voltage-dependent sodium channels and responses mediated by the N-methyl-D-aspartic acid (NMDA) receptor (THAKORE *et al*.., 2022)

In this sense, it is understood that patients treated with Riluzole for 90% of the time had an average survival rate of 4 years, in contrast to people treated for less than 90% of the time who had a survival rate of 15 months, and it was found that this drug causes a delay in the onset of stage 4 ALS. According to Rokade *et al*, (2022) Riluzole is a drug that blocks sodium channels and acts as a neuroprotective drug. Its effect results from blocking sodium channels and preventing the excessive influx of calcium via NMDA receptors and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPAR), as discussed above, this drug also acts as an antiglutamatergic agent by reducing glutamate release, preventing glutamate receptor hypofunction and increasing glutamate uptake by activating glutamate transporters and then reducing excitotoxic glutamate release. A new multicenter, double-blind, placebo-controlled study is underway under identification NCT02118727 to determine whether combination therapy of memantine with riluzole can improve disease progression along with cognitive deficits.

The most widely used drugs for the treatment of neuropathic pain in ALS patients are gabapentin, pregabalin and tricyclic antidepressants. Although opioids are not recommended as first-line therapy, they can be used when pain is not controlled or in advanced stages in cases of increased pain or with symptoms related to respiratory failure, such as dyspnea and sleep disturbances (KWAK, 2022). Gabapentin is an analog of γ-aminobutyric acid (GABA), an antiepileptic drug and a modulator of the glutamatergic system. Due to its reduced effects on glutamate excitotoxicity, it has been found to be effective in ALS patients. Despite clinical studies of gabapentin and a randomized phase III clinical trial, no data was obtained showing any beneficial effect on symptoms and disease progression in ALS patients. While, according to Aizawa *et al*,(2022) there is a need to understand and carry out more clinical trials on the excitotoxicity of glutamate by AMPA receptors, topiramate, for example, is a drug that not only reduces membrane depolarization by AMPA and kainate receptors, but also has multiple effects, such as blocking voltage-dependent sodium channels and increasing GABA receptors.

Calcium channel blockers have also been found to be potent in the treatment of ALS, reducing the after-effects of glutamate excitotoxicity by bringing calcium into damaged neurons. Latif and Kang (2021) conducted a study which observed that L-Lysine exhibited neuroprotective effects with pro-inflammatory states in ALS disease, however, verapamil competitively inhibited L-Lysine uptake. Meanwhile, Zhang *et al*., (2019) found that verapamil administration rescued motor neuron survival and improved skeletal muscle denervation in mice, decreased SOD1 aggregation, suppressed glia activation and was considered neuroprotective. Thus, lamotrigine was also considered as a potential drug, as it causes inhibition of sodium and calcium channels and hinders the pre-synaptic release of glutamate. According to a double-blind, placebo-controlled, crossover study, no clinical effect of lamotrigine on ALS progression was detected (LOGAN *et al*., 2022). Retigabine or ezogabine is an anticonvulsant drug that activates a voltage-dependent potassium channel, potassium currents in motor neurons affected by ALS are decreased.

According to the study by Jiang *et al*,(2022) retigabine can be found to reduce hyperexcitability and extend motor neuron survival in motor neurons in ALS patients carrying SOD1 mutations, reduces excitability. A phase II randomized clinical trial of retigabine involving 65 ALS patients showed that retigabine decreased cortical and spinal motor neuron excitability in a dose-dependent manner, however, adverse effects were still present.

The vitamin B12 analog, methylcobalamin, has been reported to have neuroprotective properties in relation to glutamate-induced cytotoxicity. In a study conducted in the ALS mouse model, methylcobalamin was shown to improve motor symptoms at very high dose levels by increasing the amplitude of muscle action potentials (IKEDA; IWASAKI; KAJI, 2015). While another phase II/III clinical trial including 373 Japanese ALS patients within 3 years of diagnosed clinical onset found that ultra-high dose methylcobalamin at 25 mg or 50 mg was safe and tolerable, although it did not show significant efficacy (SUN *et al.*, 2021). Oki *et al*.,(2022) conducted a randomized study with a total of 130 ALS patients, in which they administered methylcobalamin or placebo, while 126 completed the double-blind stage, and observed that its administration was effective in reducing the functional decline of these patients in early stages of the disease, being safe to use during treatment of 16 weeks.

In addition, according to Akamtsu *et al*, (2016) reported that other drugs such as talampanel, a non-competitive AMPA receptor blocker with a short half-life, was not beneficial for ALS, while perampanel, a non-competitive AMPA receptor blocker with a longer half-life, did not show clinical benefit, it has voltage--dependent sodium channel modulation and potassium currents, however, it did not exert beneficial effects on lower motor neurons and exerted negative effects on other neurons in the CNS, especially at a dose of 8mg.

Among the mechanisms that can be used for therapeutic purposes in ALS, axonal degeneration is also a disorder that aids in the evolution of neurological decline, the most widely studied being Nogo A, an integral myelin protein, and its receptor Nogo 1 (NgR1), which is highly expressed in neurons and in the developing and adult CNS, which are expressed throughout the evolution of demyelinating lesions. The membrane protein Nogo-A is an inhibitor of neurite growth that was initially identified as a potent myelin-associated inhibitor of axonal growth and regeneration, high amounts of this protein have been detected in skeletal muscles of mice with ALS and SOD1 gene mutation, therefore, it is understood that Nogo-A causes retrograde axonal degeneration by destabilizing the neuromuscular junction in ALS. Therefore, the drug Ozanezumab, an anti-Nogo-A monoclonal antibody, was found to be well tolerated in single and repeated dose administration in a randomized clinical trial, the first in humans (NHEU; PETRATOS, 2024).

Ozanezumab is a monoclonal antibody targeting the N-terminus of Nogo A. It was first used in 2014 for a phase I study in ALS patients where the pharmacokinetic safety and functional effects of Ozanezumab were evaluated. According to Meininger *et al*, (2014) the trial was carried out as a randomized study, in which Ozanezumab was compared to placebo in a double-blind study, to which a single dose or two repeated doses were administered intravenously (IV) in 71 patients, the adverse effect reported was sinus tachycardia, despite the approval and realization of the II clinical trial, there was no change in the survival of the patients, being a target considered unreliable (POULIN-BRIÈRE; REZAEI; POZZI, 2021).

Dysregulation of membrane lipids leads to impaired neurotrophic functions and apoptosis of neurons in neurodegenerative diseases. Through studies, he observed that Olesoxime

is a small molecule compound derived from cholesterol that was synthesized and evaluated for the first time in 2007 as a potential drug candidate for the treatment of the neurodegenerative disease ALS. Because it is highly lipophilic and is able to cross the blood-brain barrier, although it has low aqueous solubility, it has been identified as allowing survival in cultured rat motor neurons deprived of neurotrophic factors (BDNF) (KOLIĆ *et al*., 2024), as well as in striatal and cortical neurons under various stress conditions. Although no significant benefits have been observed in patients, it is still being investigated for the treatment of various neurodegenerative diseases due to its broad neuroprotective effect on different types of neurons, can modulate neurotransmission, prevents mitochondrial cell death (BORDET *et al*., 2010), through the release of calcium, modulates oxidative stress and the production of reactive oxygen species (ROS). It can therefore be seen that lipids play an extremely important role in the CNS, as they are the main components of cell membranes, serve as a source of energy and participate in intercellular communication and the transmission of cellular signals (ALESSENKO; GUTNER; SHUPIK, 2023).

CLINICAL TRIALS AND PHARMACOLOGICAL INNOVATIONS

Neurodegenerative diseases are complex, multifactorial conditions that encompass a range of disorders, each characterized by unique pathological patterns, clinical manifestations and underlying causes. Various strategies have been developed to treat neurodegenerative diseases, including protein--based therapies, gene therapies and stem cell therapies. However, these current treatments can only alleviate symptoms, but do not provide a definitive cure for these conditions (PATHAK *et al*., 2022)

ALS is therefore a rapidly progressive disease with an average survival of 2 to 3 years. Although there has been some progress in non-pharmacological interventions, such as non-invasive ventilation and gastrostomy, and symptomatic pharmacological treatments in amyotrophic lateral sclerosis, trials over the last 25 years have largely failed to identify effective disease-modifying drugs. Riluzole, approved in 1995, is still currently considered the only globally licensed disease-modifying drug and prolongs survival by only 2 to 3 months on average. While Edaravone has been approved in some countries, including the United States (US), Canada, Japan and South Korea after a positive test in a highly selected population (WONG *et al*., 2021)

According to the aforementioned author, there are still limitations in the development of pre-clinical models and incomplete knowledge of the pathophysiology of ALS, which are still some of the factors that hinder translational success. This improved mechanistic insight, in turn, has led to the identification of many promising therapeutic targets that warrant not only further experimental studies, but also, in many cases, formal clinical trials. Riluzole is a small molecule that modulates voltage-dependent sodium (Na+) channels to mitigate motor neuron excitotoxicity. Edaravone is a small-molecule antioxidant, also used for stroke cases, while Relyvrio (AMX0035) relieves endoplasmic reticulum stress and mitochondrial dysfunction.

In addition, according to Cloud *et al.*,(2024), the main principle of Relyvrio is that it is a synergy between two main pharmacological components, which are sodium phenylbutyrate and ursodeoxycholtaurine. The mechanism of action is based on two properties, the first being sodium phenylbutyrate, which is an inhibitor of Pan-histone deacetylase. This will inhibit the gene activation process and prevent oxidative stress. On

the other hand, ursodeoxycholtaurine, which is a bile acid, has the function of improvising energy production by the mitochondria, activating them after they have been damaged by ROS. The clinical study of Relyvrio was conducted in a 24-week group study, with 37 adults with ALS disease who were randomized to receive Relyvrio or placebo, consequently demonstrating that the effect shows a slower rate of decline in muscular dystrophy. However, the debate is due to the small size of the clinical trials. However, it was recently withdrawn by Amylyx as it did not meet the primary endpoint of change on the ALS Functional Rating Scale-Revised (ALSFRS-R) in the 2024 Phase III PHOENIX clinical trial.

Inhibition of the serine and threonine kinase Rho kinase (ROCK) has been shown to neutralize neurodegenerative processes and promote neuronal regeneration in different animal models of neurodegenerative disease, thus resulting in cell growth, axonal regeneration and proteins important for axonal transport (OKI *et al.*, 2022). The inhibition of ROCK by Fasudil has been shown to modulate microglial phenotypes, neutralizing neuronal apoptosis and axonal degeneration and thus promoting axonal regeneration and microglia activation. The isoquinoline derivative Fasudil was shown to effectively inhibit ROCK and other kinases, significantly prolonged survival, improved motor function and induced a regenerative response at the neuromuscular junction accompanied by a modulation of microglial activity in a mouse test with ALS and SOD1 gene mutation. Adverse effects include allergic reactions, systolic arterial hypotension and renal dysfunction. Consequently, a phase IIa clinical trial testing the safety and efficacy of Fasudil in ALS patients began recruiting patients in February 2019 (KOCH *et al.*., 2020)

Among the new therapeutic options, carnitine is a clinically necessary nutrient that contributes to energy production and fatty acid metabolism, playing a key role in cellular energy production by transporting fatty acids to the mitochondria. In this context, bioavailability is higher in vegetarians than in meat-eaters, deficits in carnitine transporters occur as a result of genetic mutations or in combination with other diseases, such as liver or kidney disease (ALHASANIAH, 2023). Carnitines have been shown to be interesting factors in the treatment of ALS. Firstly, infusions of acetyl-L-carnitine and proprionyl-L-carnitine were able to increase plasma levels of adenosine and ATP in patients with peripheral arterial disease, improving markers of oxidative stress.

According to Schreiner *et al*,(2025) Clenbuterol is a beta agonist, which has several demonstrated mechanisms by which it could slow down the progression of ALS. These mechanisms include stimulation of BDNF release via the cyclic adenosine monophosphate pathway, which can be correlated with improved mitochondrial metabolism and reduced neuroinflammation and inhibition of microglial activation. Through an open trial, Li *et al*.,(2023) administered to 25 patients varying doses from 40 μg daily to 80 μg twice daily for 6 months, the analysis performed showed significant improvement in relation to vital force capacity, which is the amount of air exhaled during breathing, became measurably stronger in handgrip dynamometry and myometry measures in the treatment with Clenbuterol. This trial is limited by its small sample size and its lack of randomization, blinding or placebo control.

Meanwhile, tamoxifen is an oral estrogen receptor modulator and the most prescribed drug to prevent breast cancer recurrence, but patients show variable responses to tamoxifen (ALAM *et al.*, 2025). This drug can reduce oxidative stress markers in humans, and is

also capable of reducing neuroinflammatory markers such as interleukin-6 (IL-6), according to Bedlack *et al*, (2025) the first clinical trial tested 60 people with ALS using different doses such as 10 mg to 40 mg daily with survival and the progression of ALS over 2 years, but no other benefits were observed. The second randomized trial with 60 people administered tamoxifen from 40 mg to 80 mg daily for 38 weeks showed a 50% slower rate of decline in various muscle strength measurements.

Among genome editing methods, the CRISPR-9/Cas technique has been used especially for clinical trials where pluripotent stem cells are generated as fibroblasts from ALS patients that show mutations and are corrected by the CRISPR/Cas system9. Consequently, certain drugs such as Bosutinib, Ropinirole and Retigabine have been selected for ongoing clinical trials (DAI *et al*., 2024). While Gotkine *et al*,(2023) carried out a study with pluripotent human embryonic stem cells in transgenic mice and rats transforming them into astrocytes, they were shown to be normal, carrying out glutamate uptake, secreting various neurotrophic factors, promoting axon growth. The onset of the disease was delayed and motor performance improved.

FINAL CONSIDERATIONS

It is clear that ALS is a heterogeneous disease with different clinical phenotypes and molecular causes. Among the diverse factors that cause ALS, one can include stress, mitochondrial dysfunction, excitotoxicity due to increased glutamate, apoptosis, neuroinflammation, axonal degeneration, skeletal muscle deterioration and viral infections. Through 2020 to 2025 there has been an increase in development interest and many drugs have been tested in pre-clinical and clinical trials, but several of these trials have failed so far, due to the low incidence of affected individuals, limited funds, disharmony between clinical and pre--clinical results, the complexity of ALS. Although drugs such as Edaravone, which is a free radical scavenger, and improves oxidative damage in various neurodegenerative diseases and Riluzole prolong the lives of ALS patients, among other drugs that show attenuation of symptoms, however, evidence of generalizable effects is still limited, it has not yet been possible to develop a drug that causes prevention and reduction of ALS progression, due to the different receptors affected and heterogeneity. Nevertheless, the last decade has seen substantial progress in our understanding of the genetic and molecular pathobiology of ALS and related disorders.

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