REVIEW ARTICLE

# Pathophysiology of neurodegenerative diseases and available treatments: Amyotrophic lateral sclerosis

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## ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a neurogenerative disease. It affects the motor neurons, resulting in muscle weakness and causing the death of the patient. Multiple factors including genetics, environment, and age are involved in the etiopathogenesis of ALS. ALS is a highly complex and equally challenging disease that involves various pathogenesis linked with progressive motor neuron degeneration, it is difficult to have a single therapeutic target against the disease. To date, very few drugs have been Food and Drug Administration (FDA) approved, and many drugs are still under clinical trial, reducing the number of viable treatment options. Some drugs like riluzole, tafamidis, and edaravon are the only drugs given to ALS patients. As data suggest, these drugs exceed the lifespan of ALS patients by only a few months, but are unable to treat ALS permanently. In this review, the pathophysiology mechanism and the currently available drug treatments for the pathophysiology of ALS are discussed. All the data are collected from PubMed open sources

**Keywords:** ALS, Neurodegenerative diseases, Motor neurons, TDP-43, FUS, SOD-1, Pathophysiology.

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## INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a disease of motor neurons also called Lou Gehrig's disease. Amyotrophic means' no muscle nourishment', Lateral indicates the 'locations' of the affected motor neurons in the spinal cord, and sclerosis indicates 'scarring'.[1] In 1824, Charles Bell, a Scottish surgeon and neurologist known for the discovery of sensory neurons and motor neurons in the spinal cord first reported about ALS. Later in 1869, Jean-Martin Charcot, a French neurologist whose careful clinical observation and most relevant laboratory work in pathophysiology, established ALS as a separate disease. He described and diagnosed the first case of ALS to report a significant cause of neurological issues and a relationship between the symptoms and using the title amyotrophic lateral sclerosis.[2]

ALS is a neurodegenerative disorder. Neurodegenerative disorders affect the nerve cells in the brain or peripheral nervous system and give rise to loss of function and ultimately die over time. It affects voluntary muscles by attacking motor neurons. Over time, muscles weaken, muscle atrophy is observed in the partial or entire body, and the patient gets paralyzed.[3] The frequency of ALS cases in India is 4 in 100,000, according to the Foundation for Rare Diseases and Disorders.[4] ALS occurrence rate in the USA is 5.2 per 100,000 population[5] and worldwide 1.6 per 100,000 cases were observed.[6]

Various genes have been associated with the pathogenesis, including SOD1, FUS, TARDBP, VAPB, VCP and OPTN.[7] These genes are commonly found in all types of the pathophysiology of ALS. ALS is found in two forms sporadic as well as familial. Familial ALS involves these genes in the pathogenesis.[8] Apart from this, ALS is also caused by family history and lifestyle factors, including smoking,[9] and dietary factors such as alcohol.[10] There have also been found that occupations in which exposure to chemicals, electromagnetic fields, metals, and pesticides are more risk than others.[11] Some viruses, such as retroviruses, are also involved in causing motor neuron syndrome.[12] It also found that some antidiabetic drugs also cause ALS.[13]

According to drug development and disease treatment and decision making 'AdisInsight Springer database' (August 2022), there are 92 approved drug development programs.[14] Out of 92 programs, 52 programs are where disease treatment has at least one significant ALS trial updated from 12 months. And out of 52, 39 trials are focused on targeted drugs. 14 trials are related to marketed drugs and reformulate the existing drugs.

ALS is not a single disease but it has different pathophysiological forms that share common results of increasing motor neuron loss. Many papers have discussed the clinical overview as well as pathophysiology but are not solely focused and widely discussed on pathophysiology very few papers discuss the FDA-approved drug treatment of ALS. Hence, this review gives new insight and an overview of ALS and its pathophysiology.

We summarise here the pathophysiology involved in ALS, the respective genes involved, and their targeted drug treatment.

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**Table 1:** Pathophysiology involved in ALS, genes, and its drug approved by FDA. Here glutamate excitotoxicity depends on glutamate and no genes are involved in the pathogenicity. Until now axonal transport does not have any FDA-approved drug treatment available. Other pathophysiologies have genes involved as well as FDA approved drugs were found

| *Pathophysiology* | *Genes involved in pathogenesis* | *Possible drug treatment* | *FDA approved drugs* | *References* |
|---|---|---|---|---|
| Glutamate excitotoxicity | | Riluzole | Riluzole | 18 |
| Protein aggregation and RNA dysregulation | TDP-32, FUS, C9orf72 | Tafamidis | Tafamidis | 23 |
| Oxidative stress | SOD1 | Edaravone, Mastinib, EPI-589, Riluzole, anti-glutamatergic | Edaravone, anti-glutamatergic | 35 |
| Endoplasmic reticulum stress | C9orf72, VCP, OPTN, SOD1, FUS, TDP-43, TBK1 | Sodium phenylbutyrate–taurursodiol | Sodium phenylbutyrate–taurursodiol | 40 |
| Mitochondrial dysfunction | CHCHD10, VCP, TBK1, SOD1 | Sodium phenylbutyrate–taurursodiol, Dextromethorphan | Sodium phenylbutyrate–taurursodiol | 40 |
| Neuroinflammation | TBK1, OPTN, C9orf72, UBQLN2 | Masitinib, Fingolimod, NP001, Tocilizumab, Ibudilast (MN-166) | | 56 |
| Axonal transport | SOD1, OPTN, VAPB | - | - | - |

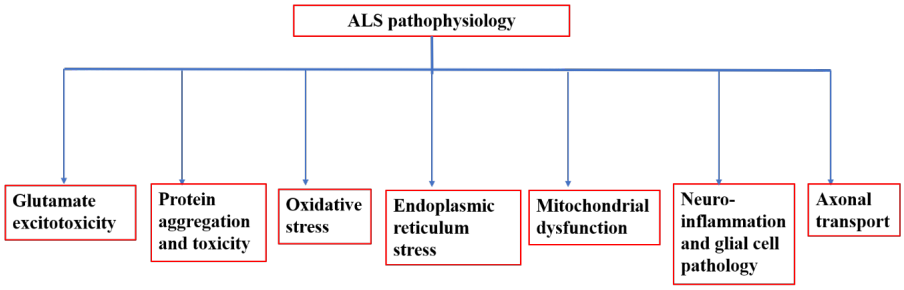


**Figure 1:** Types of pathophysiology in ALS

Detailed pathophysiology and their related drugs are given in Table 1.

## Pathophysiology of ALS and their Available Drug Treatment

In ALS, motor neurons get affected leading to various interacting pathophysiology. Such different types of pathophysiology cause heterogeneity in ALS hence treatment of ALS becomes challenging. Different types of cellular mechanisms take part in the pathogenesis of ALS. Detailed pathophysiology, the genes responsible for the respective pathophysiology, and its FDA-approved treatment are discussed.

In ALS, there are different types of pathophysiology seen mentioned in Figure 1. Glutamate excitotoxicity, protein aggregation, oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, neuroinflammation, and glial cell pathology, axonal transport can cause ALS type of neurodegenerative disease.

## Glutamate-mediated Excitotoxicity

In the mammalian nervous system, glutamate is the almost found neurotransmitter in the central nervous system. It is a nonessential amino acid metabolized through Kreb's cycle. Overexcitation of the glutamate receptor results in a higher amount of $Na^+$ and $Ca^+$ influx. This phenomenon causes neuronal injury and death of neurons.[15]

AMPA receptors (α-amino 3hydroxy 5methyl 4 isoxazole propionic acid) have four subunits GluA1 to GluA4. In the motor neurons of animals and humans, AMPA receptors is a glutamate-gated and present abundantly.[16] Calcium and sodium influx in postsynaptic neurons mediated by AMPA and NMDA receptors. In the wild-type rat, overactivation of AMPA receptors results in motor neuron degeneration and hindlimb paralysis.[17]

Riluzole, which inhibits glutamate excitotoxicity, has become the first FDA-approved drug being used for the treatment of ALS. It slows disease progression improving lifespan of about 6 to 7 months but does not affect disease symptoms.[18]

## Protein Aggregation and RNA Dysregulation

Proteins like OPTN, UBQLN2, and C9orf72 are found in cellular protein aggregation in ALS. Also, TDP-43, ATXN2, FUS, TAF15, hnRNPA1, EWSR1,hnRNPA2/B1, TIA1, and MATR3 have the RNA binding domains, nuclear localization signals, and glycine-rich region, except MATR3 doesn't have glycine-rich region, TIA1 doesn't have nuclear localization signal and ATXN2 do not have both glycine-rich region and nuclear localization signals. They also have some functional similarities, such as RNA metabolism. Due to stress, they form

stress granules in the cell. ALS is found in protein aggregation and pathogenesis after mutation.[19,20] The hallmark of ALS is protein aggregation. Protein misfolding causes protein aggregation, it is toxic to cells and alters motor neuron functions. These protein aggregates alter RNA splicing, capping, polyadenylation, and transport of target RNA.[20] TDP-43 and FUS impair mRNAs and miRNA metabolism, which results in a defective transcription and, eventually defect in protein formation and splicing, which leads to the development of neurogenerative diseases like ALS.[21]

TDP-43 knockdown in murine tissues is seen as an alternate splicing dysregulation in many mRNA transcripts.[22]

Tafamidis is the only anti-amyloidogenic approved drug that targets the misfolding and aggregation of protein.[23]

*Increase oxidative stress*

Oxidative stress causes an imbalance of free radicals or redox homeostasis in the body. It can lead to tissue and cellular damage. In Oxidative stress, free radicals are generated, including hydrogen peroxide ($H_2O_2$), nitric oxide (NO), Superoxide, peroxide, hydroxyl ion, and reactive free radicals[24] During the cellular defense in opposed to cytokine releases, bacterial infection reactive oxygen species (ROS) is generated inside the electron transport chain in mitochondria through oxidative phosphorylation.[25] SOD helps to clear ROS. Because of mutation, it forms cytoplasmic aggregation in the cytoplasm.[26] In many studies, SOD1 causes sporadic kind of ALS.[27]

Oxidative stress-mediated accumulation of ROS is also a critical factor linked to TDP-43 aggregation. Aggregates become insoluble and affect the nuclear activity in ALS.

Many studies show oxidative stress damages the motor neurons and leads to ALS.[28,29] In sporadic ALS patients, oxidative stress biomarkers were seen.[30] Antioxidant Glutathione protects cells from oxidative stress, after mutation and defective glutathione homeostasis, this antioxidant enzyme causes neurodegenerative diseases like ALS.[31] Due to oxidative stress, cellular and biochemical assay are detecting acetylated TDP-43 aggregates. These acetylated TDP-43 aggregates accumulated into insoluble, hyperphosphorylated TDP-43 form as they failed to bind RNA-binding protein.[32] Due to exposure to oxidative stress in the primary transformed cell line of TDP-43, found stress granules.[33] In sporadic ALS, one study shows an extracellular accumulation of glutamate due to oxidative stress it gives insight into motor neurons, astrocytes, and microglial exchange.[34]

In 2017, Edaravone was the first FDA-approved drug sold under the brand name Radicava for ALS it is a free radical scavenger and potent antioxidant and free radical scavenger.[35]

*Endoplasmic reticulum stress*

Newly synthesized proteins are properly folded and assembled in the endoplasmic lumen.[36] Due to the impairment of ER-associated degradation, mifolded or unfolded proteins transported from the ER lumen to the cytoplasm. This phenomenon is designated as ER stress. Recently, in many neurological disorders including Parkinson's, Alzheimer's, and ALS, ER stress has been observed.[37]

Mutated SOD1 aggregates as well as UPR markers get colocalized in the ER which can increase ER stress was noticed in ALS patients.[38] $SOD1^{mut}$ specifically interacted with Derlin1 is the ER component of ER-associated degradation (ERAD) machinery and induced ER stress through ERAD dysfunction.[39]

For endoplasmic stress and mitochondrial dysfunction, Sodium phenylbutyrate–taurursodiol is found in clinical trials to slow neuronal death and is also approved by the FDA.[40]

*Mitochondrial dysfunction*

Mitochondria plays a central role in metabolism and cell survival. They play an important role in ATP production, apoptosis, phospholipid biogenesis, and calcium homeostasis.[41] Because of this mitochondrion is an essential structure in neurons since neurons have high energy and metabolic requirements.[42] They are also essential for calcium buffering in neurons that regulate native calcium dynamics.[43] Neurons are long-lived cells therefore they are more tend to accumulative damage arises due to mitochondrial dysfunction. In multiple neurodegenerative diseases, models have seen mitochondrial dysfunction and fragmentation.

Mutations in various ALS-specific genes were seen in defective mitochondrial function in different mechanisms.[44] It is also seen that ALS-associated genes compromise mitochondrial function, a mouse model for C9orf72 is developed in which poly GR is articulated in the brain, and they found that poly GR level is reduced in 3 to 7 months compared to C9orf72 affected ALS and FTD patients. This poly GR expression is related to neuronal loss, synaptic dysfunction, and DNA damage. This increase in DNA damage is associated with mitochondrial dysfunction.[45] C9orf72 localized to the inner membrane of mitochondria and maintains protein homeostasis and cellular energy of mitochondria with the help of TIMMDC1. TIMMDC1 is a key factor of oxidative phosphorylation complex correct assembly. In C90rf72 mutant ALS patients, the function of mitochondrial complex I is impaired is seen.[46] TDP-43 has a role in mRNA/tRNA stabilization in mitochondria by regulating DNA transcript. Due to the mutation in TDP-43, this mitochondrial function gets compromised.[47]

Dextromethorphan is a drug that has done a successful clinical trial regarding mitochondrial dysfunction.[48]

• *Neuroinflammation and glial cell pathology*

Neuroinflammation is referred to as an inflammatory response within the spinal cord or the brain. This inflammatory response is mediated by the activation of astrocytes and microglial cells, T lymphocyte infiltration, and inflammatory cytokines excess production all are connected to neuronal loss.[49]

In both imaging and histological studies in CNS patients

and preclinical models, neuroinflammation is seen, as one of the hallmarks of ALS.[50] Microglial cells can acquire either a toxic M1 phenotype or a neuroprotective M2 phenotype.[51,52] In transgenic mice, mutant SOD1 microglia switch neuroprotective M2 to toxic M1 phenotype during the disease progression.[53] It was reported that microglial NLRP3 inflammasome activation is a potential contributor to neuroinflammation. Microglial ALS disease progression and amyloid-like aggregates were reduced by inhibition of NLRP3. It could be therapeutic to treat ALS.[54] NF-kB is a nuclear factor kappaβ protein found as a master regulator in the neuroinflammation of ALS it is upregulated in SOD1-G93A mouse and spinal cord of ALS patients.[55]

Masitinib (2017) (currently in phase III of clinical trial) is a selective tyrosine kinase inhibitor that mainly targets type III growth factor receptors.[56]

*Axonal transport*

Motor neurons' long axonal transport is required for cellular physiological functions such as organelles like mitochondria and protein, lipid, and RNA-like molecules.[57] Also, neurofilaments are the part of the axon that are linked to control processes such as axonal transport, maintenance of axon structure, and conduction of electric impulses.[58] Disorder neurofilaments network found in both sporadic and familial ALS.[59] Defects in axonal transport were reported in ALS-causing genes as well as other neurodegenerative diseases.[60] Microtubule motor protein Kinesin family member 5A (KIF5A) is found a causative agent for ALS.[61] Similar case was seen in ANAX11 is also found to disturb the axonal RNA transport and become a cause of ALS.[53] In the $SOD1^{G93A}$ mouse, P38MAPK is found in the axonal retrograde transport defect. After treatment with an inhibitor of P38MAPK, the axonal retrograde transport gets restored.[62] Axonal transporter inhibitor HDAC6, after knockdown or pharmacological intervention restored axonal transport defect in FUS-ALS cellular model.[63]

## DISCUSSION

Pathophysiology of ALS is not a single event as it contains many types of mechanisms and factors involved in contributing to neuronal death and neurodegeneration. Glutamate excitotoxicity is seen due to the over-activation of glutamate receptors and the imbalance of $Ca^+$ and $Na^+$ channels. In protein aggregation and RNA dysregulation, after mutation, many RNA binding proteins are involved in causing protein aggregation in the neuronal cells and subsequently cause ALS. Due to oxidative stress, free radicals are generated in the cell and these can cause cellular stress, resulting in ALS. Endoplasmic reticulum stress is generated due to ER-associated degradation. As well as mitochondrial dysfunction is generated due to an imbalance of calcium homeostasis. Neuroinflammation and glial cell pathology cause ALS due to neuronal loss due to the overproduction of inflammatory cytokines and T lymphocyte infiltration. Impairment in axonal transport also results in ALS. In many disease models, they found the cause of ALS is due to abnormal protein aggregation in motor neurons.

ALS comes into the category of 'Rare diseases and disorders', also found heterogeneous pathophysiology and lack of specific biomarkers make diseases more complicated. It is complicated due to its cause being not definite and the pathophysiology also overlaps symptoms of some diseases such as frontotemporal dementia as well as other neurodegenerative diseases. Though much research is going on the treatment of ALS still, there is no permanent treatment for such a rare neurodegenerative disease. In this review, we have discussed the pathophysiology of ALS and drugs of their respective pathophysiology.

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## PEER-REVIEWED CERTIFICATION

During the review of this manuscript, a double-blind peer-review policy has been followed. The author(s) of this manuscript received review comments from a minimum of two peer-reviewers. Author(s) submitted revised manuscript as per the comments of the assigned reviewers. On the basis of revision(s) done by the author(s) and compliance to the Reviewers' comments on the manuscript, Editor(s) has approved the revised manuscript for final publication.