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NAVIGATING THE COMPLEXITIES OF AMYOTROPHIC LATERAL SCLEROSIS: CURRENT PERSPECTIVES AND FUTURE DIRECTIONS

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Abstract:

The progressive neurodegenerative disease known as amyotrophic lateral sclerosis (ALS) is characterized by the death of motor neurons, which eventually results in atrophy, weakening, and paralysis of the muscles. A thorough summary of the state of knowledge regarding ALS is given in this review, which includes information on the disease's pathophysiology, epidemiology, etiology, clinical manifestations, diagnostic standards, and treatment options. Recent scientific developments—such as the identification of novel therapeutic approaches, biomarker development, and genetic discoveries—are highlighted. The study seeks to draw attention to the difficulties and potential paths forward for ALS clinical care and research.

Degeneration of motor neurons is the cause of the debilitating disease known as amyotrophic lateral sclerosis (ALS). For a variety of reasons, the development of disease-modifying medicines has proven difficult, as it does with all major neurodegenerative conditions. However, ALS is among the select few neurodegenerative illnesses for which treatment with disease-modifying agents is authorized. Over the past ten to fifteen years, significant advancements and discoveries have been achieved in the fields of genetics, pathology, imaging, biomarkers, ALS preclinical models, and clinical readouts. In the meantime, new treatment approaches are being used in high-unmet medical need areas, such as neurodegenerative diseases. Our understanding base has expanded as a result of these advancements, making it possible to identify targeted candidate therapeutics for ALS with a variety of modes of action. In this Review, we go over how this new understanding combined with fresh methods can facilitate efficient translation.

KEYWORDS: *amyotrophic lateral sclerosis; epidemiology; pathophysiology; diagnosis; Pharmacological therapies, Incidence and prevalence of ALS, clinical trials, supportive therapy.*

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INTRODUCTION:

Definition and overview of amyotrophic lateral sclerosis (ALS)

The neurological condition known as amyotrophic lateral sclerosis (ALS), originally called Lou Gehrig's disease, affects motor neurons, which are the nerve cells in the brain and spinal cord that regulate breathing and voluntary muscle movement. When motor neurons deteriorate and die, they cease communicating with the muscles, resulting in a weakening, twitching, and atrophy of the muscles. The brain eventually loses the capacity to start and regulate voluntary movements, including breathing, walking, talking, chewing, and other activities, in individuals with ALS. Since ALS is a progressive disease, worsening symptoms occur gradually. A number of ALS medications that could increase survival time, slow the rate of decline, or help with symptom management have received approval from the US Food and Drug Administration. [1]

Early signs and symptoms consist of:

- Twitches in the tongue, arm, leg, or shoulder muscles.
- Cramping in the muscles.
- Tense, rigid muscles (spasticity).
- Weakness in a muscle affecting the neck, arm, or leg.
- Nasal and slurred speech.
- Difficulty swallowing or chewing.

Muscle atrophy and weakness expand to other areas of your body as the condition worsens. Individuals who have ALS may experience issues with:

- swallowing and chewing food (dysphagia)
- salivation (sialorrhea)
- Using words or speaking (dysarthria)
- Dyspnea, or difficulty breathing
- Unintentional sobbing, laughing, or exhibiting other strong emotions (pseudobulbar symptoms)
- Constipation
- Keeping a healthy weight and consuming adequate nutrients

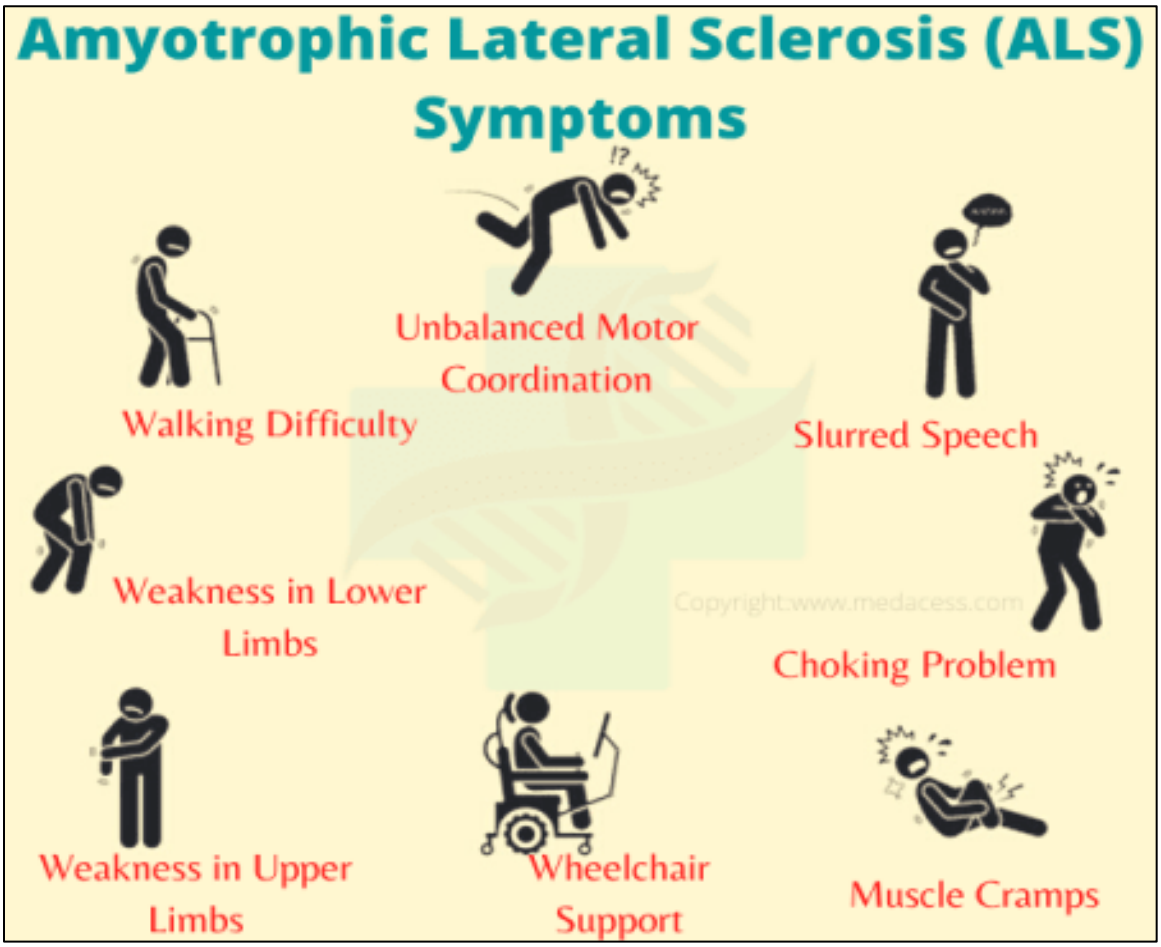

Figure 2: Symptoms of ALS [25]

People who have ALS will eventually lose the ability to breathe on their own, stand or walk, get in and out of bed independently, or use their hands and arms. They know their loss of function is progressive because they can still think, remember, and comprehend most of the time. The ALS patient and their loved ones may experience anxiety and depression as a result of this. Though less frequent, ALS patients may also have difficulty speaking or making decisions. FTD-ALS is a type of dementia that some people also experience.

The majority of ALS patients pass away from respiratory failure, also referred to as being unable to breathe on their own, three to five years after the disease initially manifests. But just 10% make it for a decade or more. [2-3]

EPIDEMIOLOGY:

A progressive neurodegenerative illness of the motor neurons known as amyotrophic lateral sclerosis (ALS) causes voluntary muscular weakening that worsens until respiratory failure kills the patient. In European communities, the annual incidence of ALS is two to three cases per 100,000 persons. Crude prevalences in Europe vary from 1.1/100,000 in the Faroe Islands to 8.2/100,000 in Yugoslavia. While significant progress has been made in our understanding of the genetic underpinnings of ALS, it has been more challenging to evaluate the role of environmental factors, and extensive research has not yet identified a reliable environmental risk factor. As of now, the only known risk factors for ALS are advanced age, male gender, and a family history of the disease.

Three years is typically the median survival time from the onset of symptoms until death. Poorer outcomes are frequently linked to older age and bulbar onset. Data on gender, diagnostic delay, and El Escorial criteria, however, are contradictory. It has been discovered that the rate at which symptoms progress is a separate prognostic factor. Nutritional status and respiratory function are associated to the prognosis of ALS, while psychosocial factors and decreased cognitive function are inversely correlated with the outcome of ALS. While it has been discovered that non-invasive positive pressure breathing (NIPPV) increases survival, the impact of enteral feeding on survival is yet unknown. These results have important ramifications for how future trials should be planned.

INCIDENCE AND PREVALENCE OF ALS

Table 1: Worldwide incidence and prevalence of amyotrophic lateral sclerosis. [4]

Countries	Incidence (10^5 persons/year)	Prevalence (10^5 persons/year)
Argentina	3.17	8.86
Canada	2.24	NA
Europe	2.08	5.4
USA	1.75	3.4
Japan	1.97	11.3
China	0.46	2.01
Uruguay	1.37	1.9
Costa Rica	0.97	NA
Brazil	0.4	0.9 to 1.5
Ecuador	0.2 to 0.6	NA

Demographic factors (age, gender, ethnicity)

➢ **Age**

- ALS is most prevalent among older age groups, with the highest rates observed in individuals aged 70-79 years. [5-6]
- The majority of ALS patients, over two-thirds, are diagnosed at 60 years of age or older. [7]

➢ **Gender**

- ALS is more commonly diagnosed in males compared to females, with a male-to-female ratio of approximately 1.7:1. [5-6]
- Women with ALS tend to have a significantly older age at symptom onset, diagnosis, and death compared to their male counterparts. [7]

➢ **Ethnicity**

- Individuals of white/Caucasian ethnicity have a higher prevalence of ALS compared to other racial groups; with a prevalence rate more than double that of Black individuals. [5]
- In the Midwest region of the United States, the majority of ALS patients are Caucasian. [7]

PATHOPHYSIOLOGY:

Degeneration of upper and lower motor neurons

Amyotrophic lateral sclerosis (ALS) is marked by the simultaneous degeneration of upper motor neurons (UMNs) in the motor cortex and lower motor neurons (LMNs) in the brainstem and spinal cord. This dual impairment distinguishes ALS from other motor neuron disorders. The connection between UMN and LMN degeneration in ALS is a subject of ongoing research. Three theories have been proposed: [10-12]

- The dying forward hypothesis suggests that ALS begins in the motor cortex, with overactive UMN leading to the degeneration of LMNs. [10]
- The dying back hypothesis proposes that ALS starts in the muscles or neuromuscular junction, with toxic substances traveling back to LMNs.
- The independent hypothesis posits that UMN and LMN degeneration occur independently and randomly, following anatomical boundaries.

Recent evidence indicates that UMN degeneration precedes and is related to LMN degeneration in a specific pattern. Studies have shown that UMN depletion occurs early in the disease course, supporting a possible cortical origin. Histologically, ALS is characterized by the loss of both UMN and LMN, accompanied by astrogliosis. In the LMN system, there is degeneration of anterior horn cells, anterior nerve roots, and brainstem motor nuclei. The motor cortex shows a loss of neurons, particularly Betz cells, with astrogliosis. Affected motor neurons exhibit characteristic changes such as Bunnia bodies and skein-like inclusions. [10-13]

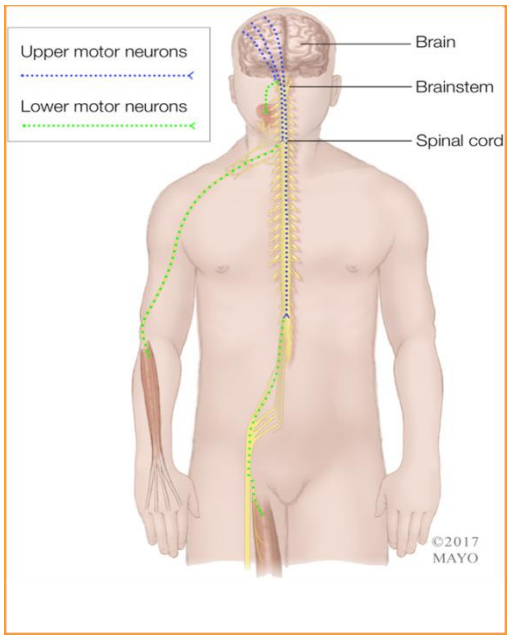

Figure 3: The primary motor system showing connections among upper motor neurons, lower motor neurons, and the muscle effector organ. [9]

Molecular mechanisms and genetic factors:

Molecular Mechanisms:

Reticulum Stress:

- Endoplasmic reticulum (ER) stress is a key mechanism in ALS.
- Mutations in genes associated with ER protein folding, processing, and sorting contribute to this stress.
- This leads to the accumulation of misfolded proteins and the activation of the unfolded protein response (UPR). [14]

Neuroinflammation:

- Neuroinflammation is another critical mechanism in ALS.
- The activation of microglia and astrocytes leads to the production of pro-inflammatory cytokines.
- These cytokines can exacerbate motor neuron degeneration.

RNA Metabolism:

- Abnormalities in RNA metabolism, including the aggregation of RNA-binding proteins, are implicated in ALS.
- Mutations in genes such as TARDBP and C9orf72 affect RNA processing and stability, contributing to disease pathogenesis. [15]

Protein Aggregation:

- The aggregation of proteins, particularly TDP-43, is a hallmark of ALS.
- This aggregation leads to the formation of cytoplasmic inclusions, which disrupt normal cellular function and contribute to motor neuron degeneration.

Mitochondrial Dysfunction:

- Mitochondrial dysfunction is another important mechanism in ALS.
- Impaired mitochondrial function can lead to reduced ATP production, increased oxidative stress, and ultimately, motor neuron degeneration. [16]

Genetic Factors:

a. Familial ALS:

- Approximately 10% of ALS cases are familial, meaning they are inherited.
- Mutations in genes such as SOD1, TARDBP, C9orf72, and VAPB are commonly associated with familial ALS.

b. Sporadic ALS:

- The majority of ALS cases (90%) are sporadic, meaning they are not inherited.
- The etiology of sporadic ALS is less well understood but is thought to involve a combination of genetic and environmental factors. [17]

c. Genetic Heterogeneity:

- ALS is genetically heterogeneous, with over 20 genes linked to the disease.
- The genetic mutations can affect various cellular processes, including protein stability, RNA metabolism, and mitochondrial function. [18]
- ALS is a complex disease with multiple molecular mechanisms and genetic factors contributing to its pathogenesis. Understanding these mechanisms and genetic factors is crucial for developing effective therapeutic strategies for ALS.

Mutations in genes like SOD1, C9orf72, TDP-43, etc.: [19-21]

Genetic Factors:

SOD1 Mutations:

- Mutations in the SOD1 (superoxide dismutase 1) gene are a common cause of familial ALS (fALS), accounting for about 2% of total ALS cases.
- Patients with SOD1 mutations exhibit distinct transcriptional signatures compared to those with C9orf72 mutations or sporadic ALS (sALS).

C9orf72 Mutations:

- Hexanucleotide repeat expansions in the C9orf72 gene are the most common genetic cause of both fALS and frontotemporal dementia (FTD).
- Patients with C9orf72 mutations show the presence of misfolded wild-type SOD1 inclusions in motor neurons.

TDP-43 and FUS Mutations:

- Mutations in the TARDBP (encoding TDP-43) and FUS genes are also found in a small percentage of fALS cases.
- Like C9orf72 mutations, patients with TARDBP or FUS mutations also exhibit misfolded wild-type SOD1 inclusions in motor neurons.

Genetic Heterogeneity:

- ALS is a genetically heterogeneous disease, with over 20 genes linked to the disease.
- The genetic mutations can affect various cellular processes, including protein stability, RNA metabolism, and mitochondrial function.

Molecular Mechanisms:

Protein Misfolding and Aggregation:

- Misfolding and aggregation of proteins, particularly SOD1, TDP-43, and FUS, are hallmarks of ALS pathology.
- These protein aggregates can disrupt normal cellular function and contribute to motor neuron degeneration.

Propagation of Misfolded SOD1:

Misfolded wild-type SOD1 can be induced by the presence of pathological TDP-43 or FUS, and can then propagate in a prion-like fashion to neighboring cells.

CLINICAL FEATURES:

Early symptoms:

ALS symptoms can manifest in various ways, including:

Muscle Weakness:

Weakness or fatigue in a limb, such as a hand, arm, leg, or foot, can make everyday activities like buttoning a shirt, holding a pen, or walking difficult.

Fasciculations:

Muscle twitching or rippling under the skin, often visible as small, localized muscle contractions, can occur in any muscle group but are most common in the arms, legs, and tongue.

Cramps:

Muscle cramps, especially in the legs, can be painful and disrupt daily activities.

Muscle Atrophy:

Muscle wasting or shrinkage can lead to a visible decrease in muscle mass.

Tingling or Numbness:

Abnormal sensations, such as tingling, numbness, or prickling, can occur in the hands or feet.

Muscle Stiffness:

Stiffness or rigidity in the muscles can make it difficult to move or perform everyday tasks.

Speech and Swallowing Issues:

Difficulty speaking, slurred speech, or a change in voice quality, as well as trouble swallowing (dysphagia) or choking on food or liquids, can occur.

Fatigue:

Feeling unusually tired or exhausted, even after resting, is a common symptom.

Weight Loss:

Unintentional weight loss, particularly in the early stages of the disease, is another symptom.

It is crucial to note that these symptoms can be similar to those of other conditions, and only a thorough medical evaluation can confirm an ALS diagnosis. If you or someone you know is experiencing these symptoms, consult a healthcare professional for proper evaluation and diagnosis.

Progression of symptoms:

Respiratory Involvement:

- Respiratory symptoms may manifest at any point in the disease course, but they typically worsen over time.
- In the early stages, respiratory symptoms may include shortness of breath, coughing, or difficulty swallowing food or liquids.
- As the disease progresses, respiratory failure becomes a significant concern, and patients may require ventilator support to breathe.

Bulbar Involvement:

- Bulbar symptoms can also appear at any stage of the disease, but they typically worsen over time.
- Early bulbar symptoms may include difficulties with speaking, swallowing, or breathing.
- As the disease progresses, bulbar symptoms can lead to a complete loss of speech, swallowing, and breathing, necessitating the use of feeding tubes and ventilators.

Limb Involvement:

- Limb symptoms can manifest at any stage of the disease, but they typically worsen over time.
- Early limb symptoms may include muscle weakness, twitching, or cramping.
- As the disease progresses, limb symptoms can lead to complete paralysis of all limbs, resulting in a loss of mobility and independence.
- Important Note: It's important to note that the progression of ALS can vary significantly from individual to individual, and the rate of progression can be influenced by various factors, such as the person's age, genetics, and overall health.

DIAGNOSIS:

Amyotrophic lateral sclerosis (ALS) can be challenging to diagnose in its early stages due to its similarity in symptoms with other diseases. To rule out other conditions or confirm an ALS diagnosis, the following tests may be conducted: [22-24]

Electrodiagnostic Tests

Electromyogram (EMG): This test involves inserting a needle into various muscles to record their electrical activity when contracting and at rest, helping to identify muscle or nerve problems.

Nerve Conduction Study: This test measures the ability of nerves to transmit impulses to muscles in different parts of the body, determining if there is nerve damage. EMG and nerve conduction studies are usually performed together.

Imaging Studies

Magnetic Resonance Imaging (MRI): This test uses radio waves and a strong magnetic field to produce detailed images of the brain and spinal cord, helping to identify spinal cord tumors, herniated disks, or other conditions that may be causing symptoms. In some cases, high-resolution MRI cameras may detect ALS-related changes.

Laboratory Tests

Blood and Urine Tests: Analyzing blood and urine samples in a laboratory can help rule out other possible causes of symptoms. Serum neurofilament light levels, measured from blood samples, are often elevated in people with ALS, making it a useful diagnostic tool.

Other Diagnostic Tests

Spinal Tap (Lumbar Puncture): This involves removing a sample of spinal fluid for laboratory testing, which can help identify alternative causes of symptoms. In people with ALS, the spinal fluid typically appears normal.

Muscle Biopsy: If a muscle disease is suspected, a muscle biopsy may be performed under local anesthesia to remove a small piece of muscle tissue for laboratory analysis.

Nerve Biopsy: If a nerve disease is suspected, a nerve biopsy may be performed under local anesthesia to remove a small piece of nerve tissue for laboratory analysis.

MANAGEMENT AND TREATMENT:

Multidisciplinary Care Approach for ALS

Multidisciplinary care has become the recommended approach for managing patients with ALS. This comprehensive model involves coordination between various healthcare professionals, including:

- Neurologists
- Respiratory therapists
- Nutritionists
- Speech therapists
- Physical/occupational therapists
- Palliative care specialists

Pharmacological therapies:

Pharmacological therapies for amyotrophic lateral sclerosis (ALS) include several medications that aim to slow disease progression and improve patient outcomes:

Riluzole

Approved Indication: Riluzole is the first FDA-approved drug for the treatment of ALS, also known as Lou Gehrig's disease.

Proposed Mechanism of Action: The exact mechanism is not fully understood, but riluzole is believed to inhibit glutamate release, inactivate voltage-dependent sodium channels, and interfere with intracellular events following transmitter binding at excitatory amino acid receptors.

Dosing: Typically taken orally, twice daily, on an empty stomach.

Adverse Effects: Common side effects include weakness, dizziness, dry mouth, numbness, difficulty falling asleep, and increased blood pressure. Serious adverse events include allergic reactions, liver problems, and breathing difficulties.

Clinical Efficacy: Riluzole has been shown to modestly extend survival by 2-3 months on average and may delay disease progression.

Edaravone

Approved Indication: Edaravone was approved by the FDA in 2017 for the treatment of ALS.
Proposed Mechanism of Action: Edaravone is believed to have antioxidant and neuroprotective effects, potentially slowing disease progression.
Dosing: Administered intravenously, typically for 10 days followed by a 14-day break, then repeated for up to 14 cycles.
Adverse Effects: Common side effects include headache, nausea, and anemia. Serious adverse events include allergic reactions and liver problems.
Clinical Efficacy: Clinical trials have shown edaravone can modestly slow the decline in physical function for some ALS patients.

AMX0035 and Relyvrio

Approved Indication: AMX0035 and Relyvrio were approved in 2022 for the treatment of ALS.
Proposed Mechanism of Action: AMX0035 targets mitochondrial dysfunction and endoplasmic reticulum stress, while Relyvrio combines sodium phenylbutyrate and taurursodiol to reduce oxidative stress and endoplasmic reticulum stress.
Dosing: Specific dosing information for these combination therapies is not detailed in the sources.
Adverse Effects: Information on specific adverse effects for these newer therapies is limited, but they are expected to have similar profiles to their individual components.
Clinical Efficacy: Clinical trials have demonstrated that AMX0035 and Relyvrio can modestly extend survival and slow the decline in physical function in ALS patients.

DEVELOPMENT AND FUTURE PERSPECTIVES:

Therapies Currently Being Tested

As various trials aiming for new drug validation are taking place at the moment, we attempt to highlight some of the latter, focusing on the different techniques and the targeted pathways [26-28]. In this review, ongoing trials are divided into four distinct groups:

1. development of small molecules
2. gene-specific therapies
3. monoclonal-antibody therapies
4. stem-cell therapies.

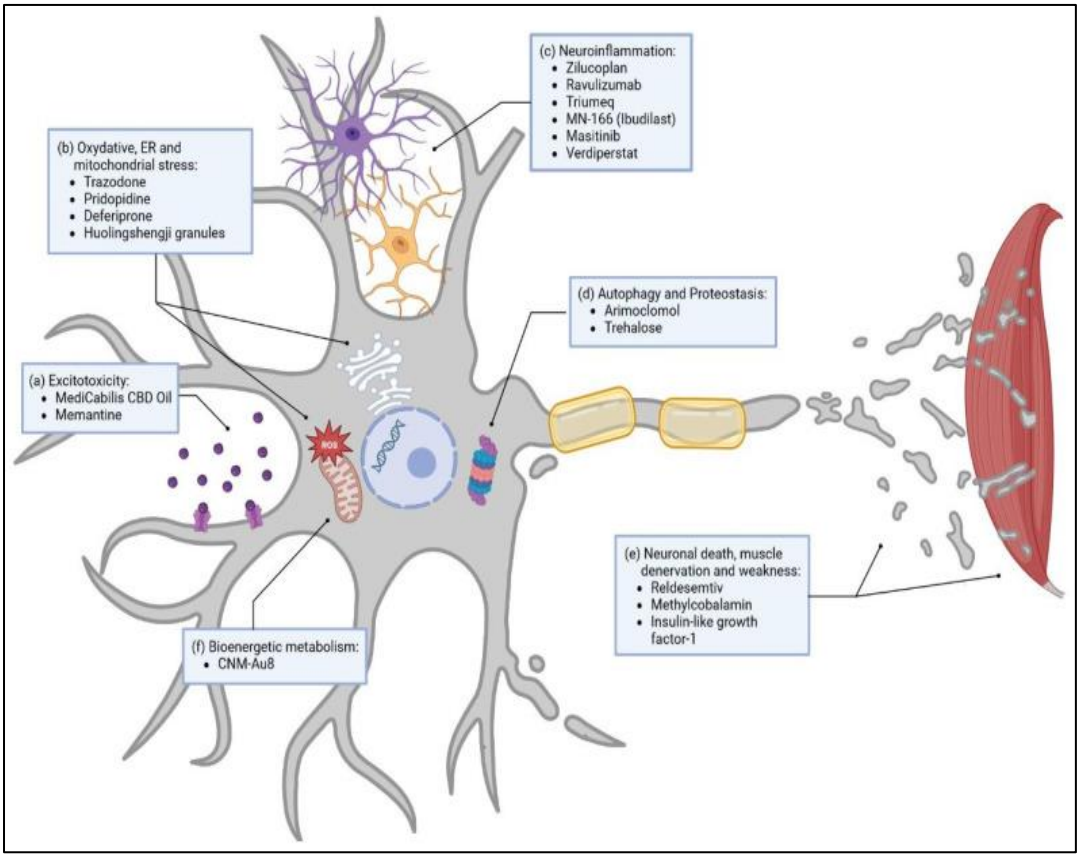

Figure 4: Small molecules in phase II/III and III clinical trials, grouped by mode of action: (a) Excitotoxicity, (b) Oxidative, ER, and mitochondrial stress, (c) Neuroinflammation, (d) Autophagy and Proteostasis, (e) Neuronal death, muscle denervation and weakness, and (f) Bioenergetic metabolism. ER: Endoplasmic reticulum.

Tiny Particles Small molecule development is the subject of several active investigations, many of which are undertaking clinical phase III trials [27-28]. In order to study medications that are closest to potential approval, we will mostly concentrate on compounds tested in phase II/III and phase III clinical studies in this section. Every one of these tiny compounds directly affects a number of dysregulated ALS-related pathways. These include neuronal death, muscular denervation and weakening, oxidative stress, inflammation, autophagy, and metabolism. Glutamate excitotoxicity is also one of them. We attempted to classify molecules based on the pathway to which they are most closely related in order to provide a concise summary (Figure 4).

Targeting excitotoxicity, particularly that of glutamate, is one of the key therapeutic mechanisms of riluzole. In addition, lowering excitotoxicity in ALS is the goal of additional phase III clinical trials (Fig.4). For instance, it has been demonstrated that cannabinoids reduce spasticity, which is why they are used to treat ALS symptoms [30]. MediCabilis CBD Oil was tested in a single-center phase III clinical trial in Australia with a small sample of participants to further assess a potential disease-modifying effect based on their protective effect on excitotoxicity and oxidative cell damage [31-32]. In addition, a phase II/III clinical experiment called the multiarm MND-SMART trial is testing memantine, a noncompetitive NMDA receptor antagonist used in the management of Alzheimer's disease, in an effort to lessen excitotoxicity [33].

One phase III trial is currently testing a fast skeletal muscle troponin activator, Reldesemtiv. This drug is a small molecule designed to slow the release of calcium during muscle contraction, improving muscle function and movement. In phase IIb, a benefit for Reldesemtiv could be demonstrated over time, when measuring the revised ALS functional rating scale (ALSFRS-R) and the slow vital capacity, especially at the study endpoint of 12 weeks. The authors postulate that the magnitude of the effect of Reldesemtiv could be even greater after a longer period of treatment [34]. However, this trial has been discontinued on 31 March 2023 due to futility, as no further evidence of positive effect had been observed on the primary and secondary endpoint after 24 weeks in patients treated with Reldesemtiv when compared to placebo-treated patients.

In a mouse model, methyl cobalamin, a type of vitamin B12, was found to lessen denervation and muscle weakness when administered at an extremely high dosage [36]. Similar beneficial outcomes in humans with a slower functional decline in people with early-stage ALS and a modest progression rate are shown by the clinical phase III trial's results [35].
To conclude the part on small molecules, there are many clinical trials currently ongoing, in phase II as well as I, and not detailed in here but nicely described in other recent reviews [26,27,28]]. There are high expectations from current trials of small molecules, particularly for phase II/III trials approaching several new molecules at the same time. Examples are the multiregimen HEALEY ALS Platform Trial (estimated completion date: April 2026) or the multiarm MND-SMART (estimated completion date: December 2026) trial.

Novel Therapeutic Approaches (Unaddressed or Poorly Addressed Yet)
We previously discussed the different clinical trials including molecules or techniques targeting certain ALS pathways. However, some ALS-dysregulated pathways are still unaddressed. In this section we will highlight different unaddressed mechanisms, amongst them post-translational modification (PTM), axonal transport, and others, discussing their potential benefit for future ALS treatment. These pathways are represented in green in (Fig.5)

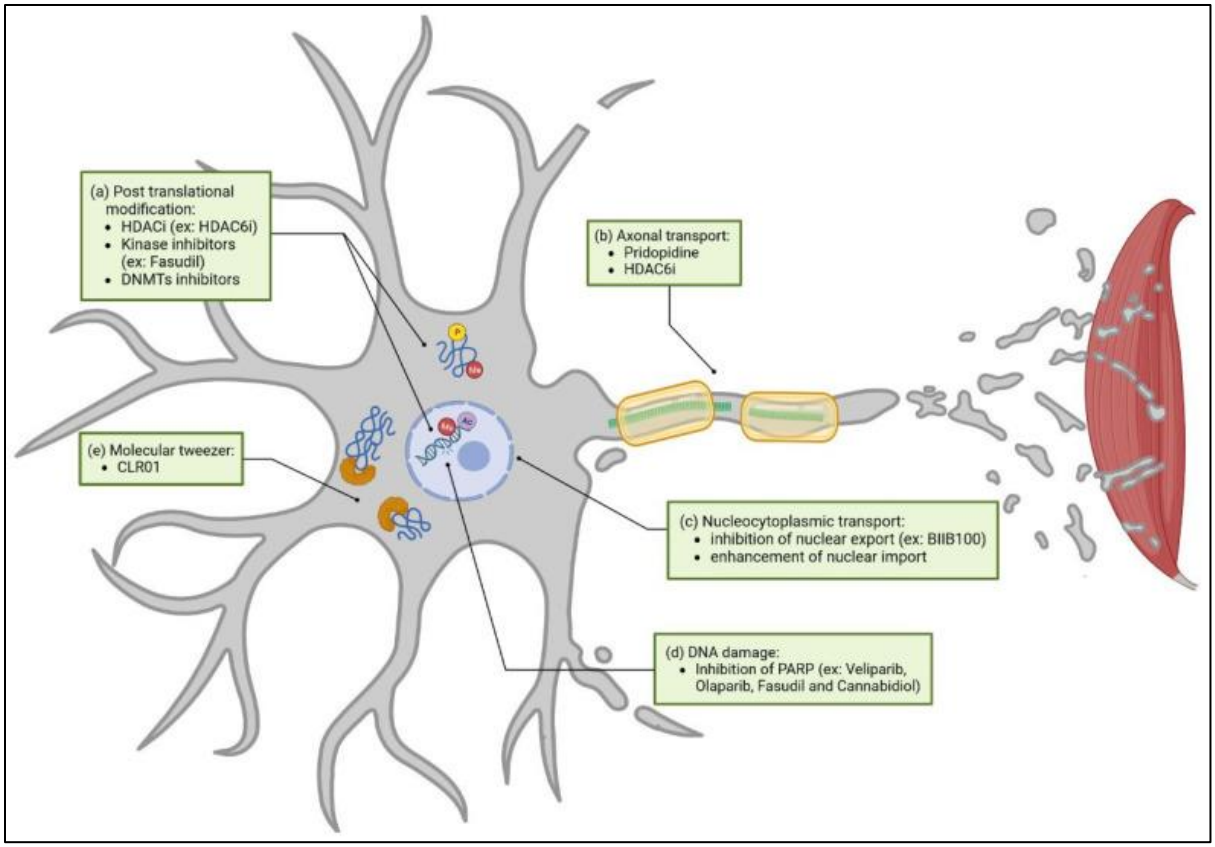

Figure 5: Future strategies and approaches: (a) Post-translational modification, (b) Axonal transport, (c) Nucleocytoplasmic transport, (d) DNA damage, and (e) Molecular tweezer. DNMTs: DNA methyltransferases; HDACi: histone deacetylase inhibitors; PARP: Poly ADP-ribose polymerase.

Post-Translational Modification

Post-translational modifications (PTMs) impact proteins involved in the neuropathology of ALS, including FUS, SOD1, and TDP-43. Changes in acetylation, methylation, or phosphorylation are known to influence not only protein function but also their subcellular locations, interaction with other proteins or RNA, liquid-liquid phase separation, stress granule formation, cell death, as well as other processes [37-43]. A few strategies to target post-translational modification can be cited (Figure 5)

Epigenetic mechanisms, such as DNA methylation and histone modifications, play a crucial role in regulating gene transcription and repairing DNA damage. Research has shown that histone modifications are disrupted in various models of amyotrophic lateral sclerosis (ALS), including changes in acetylation, methylation, and phosphorylation. To reverse these disease-related changes, many studies have focused on using histone deacetylase inhibitors (HDACi). For example, one HDAC6 inhibitor has been shown to restore axonal transport and metabolic functions in motor neurons derived from ALS patient stem cells. However, the delivery and tolerance of HDACi can be improved, as some have cytotoxic effects. Recently, the FDA approved a combination of sodium phenylbutyrate, an HDACi, and Taurursodiol, although the underlying mechanism is unclear. Other studies have reported promising results using kinase inhibitors to target protein and histone phosphorylation, improving TDP43 localization and aggregation. One kinase inhibitor, Fasudil, is currently being tested in a phase II clinical trial for ALS treatment and has shown promise in restoring phosphorylation levels of proteins associated with synaptic and neuroinflammatory functions in ALS mouse models. [44-60]

a. Axonal Transport

Efforts to address axonal transport in clinical trials are underway. For instance, Pridopidine, which has shown promise in enhancing axonal transport in a SOD1 mouse model, is currently being evaluated in a phase II/III trial. Additionally, HDAC6 inhibitors have been found to correct axonal transport defects in motor neurons derived from patients with FUS or TDP43 mutations. These inhibitors have also been shown to restore endoplasmic reticulum transport in FUS iPSC models and mitochondrial transport in both FUS and TDP43 iPSC models. Notably, these

studies have also revealed that HDAC6 inhibitors can rectify multiple other pathways disrupted in ALS, including metabolic and lipidomic functions, protein aggregation, and subcellular localization [61-64]. Given the interconnectedness of axonal transport with other disease mechanisms, restoring these pathways may have a broader positive impact on disease progression (Fig.5).

b. Nucleocytoplasmic Transport

Despite being a significantly disrupted process in ALS, nucleocytoplasmic transport has received limited attention in clinical trials. However, modulating this process by blocking nuclear export or boosting nuclear import could be a promising therapeutic approach to restore nucleocytoplasmic function in ALS (Figure 4c). To date, the only clinical trial focused on nucleocytoplasmic transport that we are aware of was conducted by Biogen, which involved testing BIIB100, an XPO1 inhibitor that blocks nuclear export. Unfortunately, the phase I trial was discontinued in June 2021, with no clear explanation provided [65-68].

c. DNA Damage

Although the connection between excessive DNA damage and ALS is becoming increasingly evident, clinical trials targeting this pathway are scarce. One potential therapeutic strategy is to modulate the activity of Poly ADP-ribose polymerase 1 (PARP1), a protein that is primarily activated in response to DNA damage. PARPs are a family of enzymes that utilize NAD+ to catalyse the sequential addition of ADP-ribose subunits to target proteins, resulting in the formation of poly (ADP-ribose) (PAR) polymers. Notably, elevated levels of PAR have been detected in the motor neurons of ALS spinal cords. Inhibiting PARP with Veliparib, an FDA-approved medication, has been shown to decrease TDP-43 aggregation in cultured cells and mitigate TDP-43-associated neuronal loss in rat spinal cord cultures. Similarly, Olaparib, another FDA-approved PARP inhibitor, has been found to reduce PAR levels and prevent TDP-43-induced cell death in cultured cells. Several other approved PARP inhibitors could be explored as potential therapeutic options for ALS. Furthermore, Fasudil and Cannabidiol (CBD) [69-72], which have been discussed previously, have been shown to downregulate PARP expression (Fig.5).

d. Molecular Tweezer

Most current strategies for inhibiting protein aggregation in ALS rely on monoclonal antibodies, as seen in the AL001 and AP-101 clinical trials. However, a promising alternative approach involves the use of small molecules called molecular tweezers, which can prevent toxic protein aggregation (Fig.5). These molecules have open cavities that can bind to other molecules, and they work by targeting the process of abnormal protein self-assembly rather than a specific protein. One such molecular tweezer, CLR01, has been shown to decrease SOD1 aggregation in vitro and in vivo, but unfortunately, it did not slow down motor symptoms in the SOD1 mouse model. However, CLR01 was effective in reducing Tau aggregation and improving muscle strength and behaviour in an Alzheimer's disease mouse model. While CLR01 has only been tested in the SOD1 model, its potential impact on other ALS models, such as FUS-ALS and C9orf72, remains to be explored [73-76].

CONCLUSION:

Despite the devastating and incurable nature of amyotrophic lateral sclerosis (ALS), significant advancements have been made in comprehending its complex pathophysiology and developing novel management strategies. Improvements in diagnostic criteria, including the incorporation of electrodiagnostic tests, have enabled earlier and more accurate identification of the condition. Pharmacological interventions such as riluzole, edaravone, AMX0035, and Relyvrio have demonstrated the ability to modestly slow disease progression, while a multidisciplinary care approach focused on symptom management, respiratory support, nutrition, and palliative care has been shown to enhance quality of life and extend survival. However, a cure for this relentless disease remains elusive. Ongoing research delving into the genetic and molecular underpinnings of ALS is crucial to identify new therapeutic targets and improve outcomes for patients. Continued efforts in both basic science and clinical care are essential to combat this devastating neurodegenerative condition.

As the global ALS population is projected to reach 380,000 by 2040, driven in part by aging demographics, the need for optimized treatments and innovative therapeutic approaches has become increasingly pressing. To address this, researchers should focus on enhancing drug delivery and administration, as well as exploring new target strategies. Personalized treatment plans can be achieved by combining genetic, molecular, and clinical stratification methods, which may improve treatment outcomes. Genetic testing for common ALS-causing genes is a crucial step towards tailored therapies, such as Tofersen. Early treatment initiation will likely be essential for future therapies, emphasizing the importance of early patient identification. To facilitate this, developing sensitive and specific biomarkers and offering genetic testing to at-risk family members may help identify pre-symptomatic carriers. Until a cure is found,

supportive care remains vital, and further research is needed to quantify its effects. The growing number of clinical trials and substances being tested offers hope for future breakthroughs in ALS treatment and potential cure.

CONFLICTS OF INTEREST:
The authors declare no conflict of interest.

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