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Update on ALS Treatment

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Abstract

Purpose of Review While amyotrophic lateral sclerosis (ALS) remains a progressive fatal diagnosis, there have been numerous advances in the last several years, both in disease-modifying and symptomatic treatment. This review aims to provide a comprehensive and updated review of the literature of current treatment options for ALS.
Recent Findings We will discuss the proposed mechanisms of action, evidence for efficacy, and safety profiles for the four current Food and Drug Administration (FDA)–approved disease-modifying treatments: riluzole, edaravone, AMX0035 (combination of sodium phenylbutyrate and taurursodiol) and tofersen. Additionally, we will review several therapies that are under active investigation for the more common genetic forms of ALS. Finally, we will discuss options for symptomatic treatment, including a review of Nuedexta (combination of dextromethorphan hydrobromide and quinidine sulfate) approved for pseudobulbar affect, but recent evidence is suggesting that it also improves bulbar function.
Summary There are four FDA-approved disease-modifying treatments for ALS, which likely confer a modest benefit in survival with good safety profile and tolerability, through different mechanisms of action. More post-marketing and population studies will be needed to assess the overall efficacy of each medication and potential combinations of each.

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive disease characterized by combined upper motor neuron and lower motor neuron degeneration. Approximately 70–75% of cases are limb-onset, which is typically characterized by initial asymmetric weakness in either one arm or leg, while 25–30% of cases are bulbar onset, with initial symptoms of dysarthria and dysphagia. ALS is known for its progressive nature, with

weakness eventually involving diaphragmatic muscles, causing respiratory failure. The mean survival of ALS patients is estimated 2–5 years. However, there is significant heterogeneity in both initial presentation and speed of progression among ALS patients [1].

ALS remains a clinical diagnosis, with laboratory and imaging primarily used to exclude other diagnoses. The El Escorial criteria, revised in 2015, is the more commonly used diagnostic framework, particularly in selection of patients for research and clinical trials. Electrodiagnostic testing is also useful for evaluating the lower motor neurons, and under the El Escorial criteria, can be used supportively. Finally, there is increasing use of biomarkers, particularly serum and cerebrospinal neurofilament light chain and phosphorylated neurofilament heavy chain levels [2, 3].

While ALS is fatal, there are still many therapeutic options available for patients. Treatment for ALS can be broadly separated into two categories: disease-modifying and symptomatic. In terms of disease modifying, there has been several advances in the last several years, with three new medications receiving FDA approval since 2017. There are also numerous trials for therapeutic interventions in sporadic and hereditary ALS.

In addition to disease-modifying treatment, it is important to concurrently emphasize symptomatic treatment, for common issues including spasticity, cramps, difficulty with secretions, depression or anxiety, sleep disturbance, and emotional lability. ALS patients benefit significantly from a multidisciplinary approach given the numerous symptoms they experience through their course [1, 4].

Riluzole

In 1995, riluzole became the first drug approved by the Food and Drug Administration for the treatment of ALS. The exact mechanism of riluzole is unknown, but overall, it is thought to exert neuroprotective effects through inhibiting presynaptic glutamate release, stabilizing inactivated state of voltage-gated sodium channels and thereby reducing neuron hyperexcitability [1–3].

To date, there have been four randomized controlled trials on riluzole [5]. The first landmark trial for riluzole was done in 1994, with 155 patients total, and the treated group ($n = 77$) receiving 100 mg/day of riluzole [6]. A second trial was done in 1996 with a larger cohort of patients (959 total, with 717 in the treated group), receiving dose range of 50, 100 and 200 mg/day [7]. A third trial in 2002 again used a fixed dose of 100 mg/day and focused on the safety and efficacy of riluzole in patients with more advanced disease [8]. In particular, the trial targeted the patients excluded in the first two trials; namely, patients either older than 75 years of age, with forced vital capacity less than 60%, or disease greater than 5 years in duration. Finally, the fourth trial was done in Japan with 195 patients, although the full data for tracheostomy-free survival was not available at time of publication [9].

The most recent Cochrane review, published in 2012, performed a meta-analysis of the 4 above clinical trials, with the study in Japan not included in the final analysis as the full data was not available [5]. When pooling results of the first 2 trials, the median survival difference was 2.3 months (15.5 vs 13.2). When combined with all 3 trials, the median survival difference was 3 months (14.8 vs 11.8), as well as a 9% gain in probability of surviving 1 year. With pooled data from the first 2 trials, the hazard ratio of tracheostomy-free survival was 0.80 (CI 0.64—0.99, $p = 0.042$). The hazard ratio of all three trials was 0.84 (0.698–0.997; $p = 0.046$). With inclusion of the

third trial, there was more significant heterogeneity of the results, as expected given the inclusion of patients with more advanced ALS. Despite this, there was still modest treatment benefit seen with pooled data from all three trial results, with overall estimated 2–3-month median survival benefit. In terms of secondary outcomes, there was no benefit in muscle strength based on manual strength testing, but with pooled data from the 3 studies, there was mild positive effect on limb function (mean difference – 3.94, 95% CI – 7.25 to – 0.64). There was also beneficial effect on bulbar function (mean difference – 2.06, 95% CI – 3.86 to – 0.27) [5].

Following the initial trial, however, there have been numerous population studies that suggest the survival benefit of riluzole may be longer than the purported 2–3 months seen in RCTs. The limitation of RCTs include not fully accounting for patients who survived beyond the limited 18–21-month follow-up period. Another potential limitation of the initial trial in 1994 was the mean duration of disease prior to initiation of riluzole was roughly 2 years; in the 1996 trial, the mean duration of disease before treatment was 1.8 years. Given this, it was hypothesized that patients who are started on riluzole earlier (as seen more commonly in clinical practice) may have longer survival benefit. A review in 2020 looked at available prospective and retrospective studies to better understand "real world evidence" of riluzole [10]. Of the 14 included studies, 8 studies found the median survival benefit as long as 6–19 months. Three studies found a survival benefit of 3–5.9 months, and the remaining four found no difference between treated and riluzole-free patients. Therefore, given evidence from these retrospective/prospective studies, it is estimated the median survival benefit of riluzole may, in fact, be closer to 6–19 months.

In terms of adverse effects, generally riluzole is well tolerated with few adverse reactions. An international study of 516 patients looked at long-term safety of riluzole and found no adverse event was related to the dose level or from patients switching from placebo to open-label enrollment [11]. The most commonly reported adverse effect is gastrointestinal upset (i.e. nausea); it is recommended for patients to take riluzole either 1 h before or 2 h after a meal. Riluzole was observed to cause elevated liver enzymes in the initial trials (10.6% vs 3.8% in treated vs placebo) [5]. Therefore, it is recommended to monitor liver function tests monthly for the first 3 months followed by 3-month intervals thereafter. Severe hepatic dysfunction may require treatment cessation. Other rare adverse events included neutropenia and hypersensitivity pneumonitis, both of which also likely require treatment cessation.

Edaravone

In 2017, edaravone in IV formulation became the second disease-modifying medication approved by the FDA for ALS. Edaravone is a free-radical scavenger, with proposed mechanism of action of reducing oxidative stress [12]. The IV and oral formulation have the same dosing schedule. They are given as a daily infusion or orally for 14 days, followed by 2 weeks without treatment.

Subsequent cycles involve daily edaravone for 10 days within a 2-week period, followed by another 2-week drug-free period.

The efficacy of edaravone has been evaluated by 3 main RCTs (MCI186-ALS16, MCI186-ALS18 and MCI186-ALS19, all conducted in Japan) as well as 2 extension studies [13–15]. The first study, MCI186-16, was conducted from 2006—2008 with 206 patients. 101 were randomized to IV edaravone, with 104 receiving placebo, over 24 weeks. The inclusion criteria included FVC of at least 70%, disease duration of 3 years, and ALSFRS-R score that changed by -1 to -4 during the pre-observation phase. These patients also had a Japanese ALS severity classification of 1 or 2 (see Table 1). The primary outcome was change in ALSFRS-R score. MCI186-16 did not find a statistically significant difference in change in ALS-FRS score (– 5.7 versus – 6.35; 0.65 difference using analysis of covariance, with $p = 0.411$) [13].

The initial hypothesis of why MCI186-16 had failed was due to the heterogeneity of ALS disease progression; therefore, a post hoc analysis of MCI186-16 was done[14]. This post hoc analysis found that a subgroup of patients did have a modest, but statistically significant, slowing of disease. This population, defined as definite/probable efficacy-expected population 2 years (dpEESP2y), had the following main differences compared to the first group: definite or probable ALS, FVC of at least 80% (rather than 70%), onset less than 2 years (rather than 3 years), and the specification of at least greater than 2 points on baseline ALSFRS-R score on all categories (not specified in the initial study). This analysis found a statistically significant difference, with a change of ALSFRS-R of 0.65 ($p = 0.4108$) in the full analysis group versus 3.01 ($p = 0.0270$) in the dpEESP2y group [14].

Given these findings, a subsequent RCT (MCI186-ALS19) was done between 2011 and 2014 to validate the findings seen in the post hoc analysis. 137 patients were chosen to match similar characteristics as the dpEESP2y subgroup (see Table 2). The primary outcome was ALSFRS-R as before. In the treated group, ALSFRS-R score change was – 5.01, compared to -7.50 in the placebo group. The least squares mean difference was 2.49 ($p = 0.0013$), showing a statistically significant difference of edaravone in this subset of patients. Overall, this study showed that edaravone slowed disease progression by approximately 33% after 24 weeks [16].

Table 1. Japanese ALS Severity Scale. The Japanese ALS Severity Scale used as part of the inclusion criteria for a number of randomized control trials for edaravone

1	Able to work or perform housework
2	Independent living but unable to work
3	Requiring assistance for eating, excretion or ambulation
4	Presence of respiratory insufficiency, difficulty in coughing out sputum or dysphagia
5	Using a tracheostomy tube, tube feeding or tracheostomy positive-pressure ventilation

Table 2. Main differences in inclusion criteria. Highlights differences in patient inclusion criteria between two randomized control trials for edaravone

Inclusion criteria	MCI186-16	MCI186-ALS19
Diagnosis	Definite, Probable or Probable with Laboratory Support	Definite or Probable
FVC	FVC > 70 percent	FVC > 80 percent
Onset of ALS	3 years	2 years
Baseline ALSFRS-R score	Not specified	> 2 in all 12 items

Finally, a RCT (MCI186-18) was performed in 2016 assessing the efficacy of edaravone in patients with more advanced disease. These patients were defined as Japan ALS severity classification grade 3, FVC greater than 60%, and disease duration of less than 3 years. This study had 25 patients and, similarly to MCI186-16, did not find a statistically significant difference in ALSFRS-R score (2.49, $p = 0.0013$) [17].

In summary, two of the three initial trials for IV edaravone were negative, based on change in ALSFRS-R score. There was also insufficient evidence for effect on survival in all three trials. Based on these, it was considered that a subset of patients may benefit from edaravone, particularly those with earlier and less advanced disease, as defined as FVC score greater than 80% and duration less than 2 years [13, 14, 16].

Given this limited evidence for efficacy, a cohort study was done between 2017 and 2020, using propensity score-matching. Ultimately, the analysis was done with 116 patients treated with edaravone and 116 score-matched patients receiving standard therapy. The primary outcome was ALSFRS-R score. The study found no difference in disease progression (– 0.91 points/month for treated patients versus – 0.85 patients for matched controls). There was also no survival benefit. The analysis, when using the subgroup as defined by the earlier MCI186-ALS19 trial, still found no significant differences in disease progression [18].

While the efficacy of edaravone is limited, it is overall safe and generally well-tolerated, despite initially only available as an IV formulation. In terms of the IV formulation, the three trials show similar rate of adverse events between treated and placebo groups. The most frequent adverse events for edaravone include injection-site contusion, gait disturbance and headache.

The SUNRISE study was a post-marketing surveillance study conducted in Japan to assess the safety of edaravone. 800 patients were included, with 12.1% reporting one adverse event. Hepatic dysfunction was the most frequently reported adverse event with up to 4.4%, which was not seen in the initial trials. Most patients had improvement or resolution of hepatic dysfunction with cessation of edaravone [19].

AMX0035

AMX0035 is the third ALS medication to receive FDA approval in September 2022. It is the combination of two medications. The first is sodium phenylbutyrate, which is a histone deacetylase inhibitor, is thought to reduce the stress response in the endoplasmic reticulum. The second is taurursodiol which is thought to maintain mitochondrial integrity and reduce cellular apoptosis. It is taken orally daily for 3 weeks, then twice daily thereafter [20].

The data for efficacy of AMX0035 is driven from CENTAUR, 24 weeks, phase 2, multicenter, randomized, and double-blind trial of 137 patients. They were randomized in a 2:1 ratio, so that 89 patients received AMX0035 and 48 were on placebo. The primary outcome was rate of decline in ALSFRS-R score through week 24. CENTAUR-OLE followed, with a total of 90 patients (56 patients from the treated arm and 34 from the placebo arm) receiving AMX0035 for up to 132 weeks.

In the CENTAUR trial, the authors utilized a modified intention to treat analysis, which showed a mean ALSFRS-R score of 29.06 versus 26.73 in the treated versus placebo group at week 24. The difference was 2.32 points. The change in ALSFRS-R score per month was – 1.24 versus – 1.66, giving a 0.42 point per month difference (95% CI 0.03–0.81). This translated to a slowing of disease by 25%.

In terms of survival, the interim intent to treat analysis in CENTAUR-OLE, showed that the median difference in survival between the patients originally randomized to active treatment versus the ones originally on placebo was 6.9 months with $p = 0.023$ [20]. Using rank-preserving structural failure time models and post hoc analyses adjusting for treatment crossover in CENTAUR, showed a significant longer survival of 10.6 months in the group originally on AMX0035 compared to the group originally on placebo [21, 22].

AMX0035 was overall safe; most common side effects include gastrointestinal upset (including diarrhea, abdominal pain, and nausea) as well as upper respiratory infection. It was also found to cause fluid retention. It was overall felt that AMX0035 is safe, but further, larger trials will be needed to assess the true efficacy in both slowing disease progression and survival. Currently, a phase 3 trial (PHOENIX) is underway, with estimated completion of November 2023 [23].

Combining therapies

Many patients ask about the utility of taking a combination of the current 3 FDA-approved medications. In the three RCTs of edaravone, roughly 84–91% of patients were on concomitant use of riluzole. In CENTAUR, 71% of patients were on concomitant, stable dose of riluzole, and 34% of patients were on concomitant use of edaravone. Based on this data, it is overall considered safe to be on all three or a combination of two medications, with the adverse events for each medication as outlined above.

No RCTs have been done comparing each of these medications against one another. Data is further limited regarding the exact degree to which a combination of these medications can extend survival. Overall, as each of these medications confer their neuro-protective effects through a different mechanism, it is hypothesized that a combining them would likely have an additive effect. Further population studies will be needed to assess to what extent survival benefits are seen, as well as balancing the cost-effectiveness and patients' quality of life.

Treatment for genetic forms ALS

ALS is mainly sporadic but 10% of the patients have genetic form of ALS with C9ORF72 and SOD1 being the most affected genes.

a. ***C9orf72***

C9orf72 is the most common mutation identified in both inherited and sporadic ALS, comprising roughly 40% of familial ALS cases and 5% of the sporadic. It is also the most common genetic cause of frontotemporal dementia, accounting for approximately 25%. The mutation is a repeat expansion of the hexanucleotide GGGGCC in the first intronic region. Unaffected people have an estimated repeat size of 2–24 units, while those with ALS can span several thousand repeat units. However, there are outliers, with reports of unaffected people with 32 units, and some ALS patients having as few as 24 units. Furthermore, the relationship between repeat expansion size and severity of disease is not well understood nor can be predicted [1, 2, 24].

There is no current FDA approved treatment for *C9orf72*. There are several ongoing phase 1–2 studies targeting *C9orf72* mutations and its downstream pathways, summarized in Table 3 [25–30].

b. **SOD1 mutation**

The SOD1 mutation, located on chromosome 21, is the second most common mutation in familial ALS. It comprises 12–20% of familial ALS and 2% of ALS cases overall. With over 200 mutations identified, A5V and H47R are some of the most identified SOD1 mutations. It is hypothesized that SOD1 mutations cause a toxic gain of function of the SOD1protein [1, 31].

Tofersen is an 2nd generation anti-sense oligonucleotide that induces RNA degradation of the SOD1 mRNA, thereby overall reducing the synthesis of SOD1 protein.

VALOR is a 28 week, phase 3, double-blind, randomized, placebo-controlled trial followed by an ongoing extension phase. Participants were randomly assigned in a 2:1 ratio to receive Tofersen (100 mg) administered through an intrathecal bolus injection or equivalent volume of placebo. 108 participants were enrolled in VALOR; 72 were assigned to receive tofersen and 36 to receive placebo. The trial was enriched for fast progressing mutations as 60 of the 108 participants made up the faster-progression subgroup in which

Table 3. Highlights all ongoing clinical trials for *C9orf72* mutations in ALS

NCT number	Drug and route of administration	Mechanism of action	Phase	Study design	Primary outcomes
NCT05163886	**LAM-002A** Oral 250 mg total daily dose	PIKfyve kinase inhibitor, resulting in activation of the transcription factor EB, ultimately stimulating production of lysosomes	Phase 2	12 patients, randomized 2:1, over 12 weeks, followed by 24 week OLE	Safety and occurrence of treatment-emergent adverse events, tolerability, levels of LAM-002A and metabolites in plasma and CSF
NCT04993755	**TPN-101** Oral 400 mg/day	Inhibits reverse transcriptase enzyme LINE-1	Phase 2a	40 patients randomized, over 24 weeks, followed by OLE	Safety and tolerability
NCT04931862	**WVE-004** Intrathecal	Anti-sense oligonucleotide to deplete mRNA transcription of V1 and V3 protein, s	Phase 1–2	35 patients divided into 4 groups receiving 4 different doses vs. placebo, over 24 weeks, followed by OLE	Safety (adverse events)
NCT05053035	**AL001** IV every 4 weeks	Monoclonal antibody that blocks sortillin receptor, ultimately increasing progranulin levels, which regulates cell growth and repair	Phase 2	Placebo controlled	Safety and tolerability, concentration of AL001 at specified times, maximum plasma AL001 concentration, area under the curve AL001 concentration, and change from baseline in serum and CSF proganulin
NCT03626012	**BIIB078**	Antisense oligonucleotide, binding mRNA for ataxin-2, causing degradation of ataxin-2 protein	Phase 1	106 patients, divided into 6 cohorts in the treated arm vs. matching placebo arm	Number of patients with adverse events and serious adverse events
NCT04220021	**Metformin** (500 mg dose to start, up to maximal oral dose of 2000 mg)	Decreases RAN protein levels	Phase 2	18 patients, single group assessment	Safety and tolerability, change in RAN protein levels

the primary analysis was performed. 88% of VALOR participants enrolled in the open label portion of the study. The primary efficacy endpoint was the change from baseline to week 28 in the ALSFRS-R total score in the faster-progression subgroup. Secondary endpoints included the change from baseline in the total concentration of SOD1 protein in CSF, the concentration of neurofilament light chains in plasma, the percentage of the predicted slow vital capacity and the handheld dynamometry megascores.

In the faster-progression subgroup, patients who received Tofersen had a 29% decrease in their SOD1 protein concentration in CSF and a 60% decrease in their mean plasma neurofilament concentration by week 28. Unfortunately, there was no significant change in ALSFRS-R between the two arms of the study. During the open label phase of the trial the reduction in SOD1 CSF concentration and plasma neurofilaments levels were sustained in the early start group and the late start group also showed similar reduction. By week 52, a 3.5 points difference in the ALSFRS-R was apparent between the early and the late start groups. A difference favoring the early start group was also appreciated in the percent predicted SVC and in the HHD megascores.

Overall, the drug was well tolerated with post LP headache present in both patients and placebo however severe adverse events including myelitis, aseptic meningitis, lumbar radiculopathy, increased intracranial pressure, and papilledema were noted in 7% of the patients and CSF pleocytosis and elevated protein concentrations were noted in patients receiving tofersen [32]. Tofersen just received accelerated FDA approval on April 25th, 2023, based on its effect on plasma neurofilament levels.

There is an ongoing clinical trial, ATLAS, that is studying the efficacy of tofersen in pre-symptomatic adults with known SOD1 mutations that have high penetrance and rapid progression, as well as elevated neurofilament levels. It is the first interventional trial studying the pre-symptomatic phase of ALS [33].

iii. **FUS mutation**

Fused in sarcoma (FUS) mutation accounts for 4% of familial ALS patients. FUS mutations are associated with an aggressive and early-onset form of ALS. FUS encodes an RNA-binding protein; the exact mechanism through which FUS mutations lead to motor neuronal degradation is still being studied. It is overall thought FUS mutations create a toxic gain of function, but some evidence from knock-in mouse models suggests there may also be loss of function [34, 35].

ION363 is an antisense oligonucleotide against the sixth intron of the FUS transcript, overall lowering FUS levels. It was hypothesized that ION363 could be an effective therapeutic intervention, given the data favoring FUS causes motor neuron degeneration more so through toxic gain of function. After demonstration of safety and efficacy of delayed motor neuron degradation in mice, Columbia University Medical Center and Ionis administered ION363 under compassionate use to one woman with FUS mutation. She received repeated ION363 intrathecal infusions without related adverse effects. While the patient ultimately passed away from ALS-related complications, her post-mortem analysis showed significant reduction of FUS protein levels [35].

Given these promising results and the demonstrated safety, there is an ongoing phase 3 clinical trial studying ION363 in up to 77 patients. Patients will be randomized in 2:1 ratio, and receive ION363 versus placebo for a period of 61 weeks, followed by an open label extension where they will receive ION363 for a period of 85 weeks [36].

iv. **Ataxin-2**

Ataxin-2 mutations are another repeat expansion in exon 1 associated with ALS. It was first linked to spinal cerebellar ataxia 2. However, intermediate repeat CAG expansion of Ataxin-2 increases the risk of ALS. Ataxin-2 mutations are overall associated with increasing the toxicity of TDP-43 aggregates [37, 38]. There is an ongoing phase 1–2 clinical trial studying BIIB105 in patients with ALS with or without Ataxin-2 mutations (Identifier: NCT04494256) [39].

Brief review of non-invasive ventilation

It is now widely accepted that noninvasive ventilation (NIV) extends survival in ALS patients and likely improves quality of life, although direct RCTs are limited as use of NIV has become standard of care. In 1995, Pinto et al. studied 20 ALS bulbar patients; 10 were treated with BiPAP and 10 with standard care at the time [40]. This study was not randomized and had small sample size but did demonstrate significant improvement in survival with NIV. In 1999, a study done by Kleopa et al. retrospectively studied NIV in ALS patients. 122 patients were offered NIV if FVC was below 50%. Group 1 used BiPAP greater than 4 h per day, group 2 used BiPAP less than 4 h, and group 3 refused. The study found that BiPAP extended survival in group 1 to 14.2 months, 7 months in group 2 and 4.6 months in group 3, all of which were statistically significant. Using BiPAP also slowed the decline of FVC [41]. Thirdly, in 2006, Bourke et al. published a pivotal RCT in which 41 patients were randomized to NIV ($n = 22$) versus standard care ($n = 19$). The study found that in patients with normal to moderate bulbar impairment, NIV improved median survival by up to 216 days. The treated group also reported stable quality of life throughout most of the follow-up period. In patients with severe bulbar impairment, there was no survival benefit, but some benefit in quality of life regarding sleep apnea symptoms [42].

More recent studies are exploring when NIV should be initiated in patients, as there are some variances in practice and guidelines. While AAN guidelines suggest starting NIV if FVC is less than 50%, EFNS suggests starting NIV if FVC is less than 80%. Furthermore, a retrospective study in 2018 examined 194 patients, 129 of whom were initiated on NIV when FVC was less than 80%, and 65 of whom were initiated on NIV when FVC was greater than 80% (very early group). The study found that mortality for the very early group was 35% versus 52.7 [43]. To this end, a review published by Dorst et al. in 2019 emphasized the importance of nocturnal polysomnography

and capnometry as a sensitive screen to encapsulate all ALS patients who may benefit from NIV, including those who are asymptomatic or with FVC greater than 80% [44].

Symptomatic treatment

To date, the disease-modifying treatments as discussed confer a modest benefit in survival. It is critical for clinicians to concurrently focus on symptomatic treatment to maximize patient quality of life. In the extremities, these include cramps, spasticity, pain, and dependent edema. Bulbar-related symptoms include sialorrhea, pseudobulbar affect and jaw spasticity, which can limit dental hygiene. Other common issues patients experience include depression, anxiety, sleep disturbances, and dementia.

Given this multitude of debilitating symptoms, ALS patients benefit most from a multidisciplinary approach. It is also important to address each patient's goals of care and their advance directives, preferably early in their diagnosis and to revisit these discussions as patients progress through their disease.

In terms of other symptomatic treatment, recommendations are generally provided by expert opinion and guidelines. For spasticity, common medications include tizanidine, baclofen, and range of motion exercises with physical therapy. For sialorrhea, atropine drops and transdermal scopolamine patches are most commonly used; other options include amitriptyline and botulinum injections to parotid or submandibular glands. For cramps, there is limited evidence, but some experts recommend quinidine. There was a randomized control trial with 32 participants that found use of mexiletine resulted in significant reduction in cramps with 300 mg per day; higher doses led to higher rates of discontinuation due to side effects [45]. Finally, nutrition is another important metric to monitor, particularly as the disease progresses to involve dysphagia, putting patients at risk for aspiration. Enteral feeding, most often through percutaneous endoscopic gastrostomy tube (PEG), is a safe way to ensure adequate caloric intake [4]. We will highlight one of the more recent advances in symptomatic treatment, which is dextromethorphan hydrobromide-quinidine sulfate, also known as Nuedexta, used to treat pseudobulbar affect (PBA).

Nuedexta

In 2011, Nuedexta was approved by the FDA for the treatment of PBA. As mentioned, Nuedexta is a combination of dextromethorphan hydrobromide 20 mg and quinidine sulfate 10 mg. Quinidine blocks the metabolism of dextromethorphan, increasing its serum concentration and bioavailability. While the exact mechanism of action of dextromethorphan as it relates to pseudobulbar affect is not known, it is thought to act as agonist for sigma-1 receptors, as well as an antagonist for N-methyl-D-aspartate [46].

There were three clinical trials evaluating Nudexta's efficacy for alleviating PBA [47–49]. Each study used the Center for Neurologic Study–Lability Scale (CNS–LS) as its primary outcome and found significant improvement in CNS-LS score with Nuedexta. A 12-week study with 326 patients found reductions in rate of PBA episodes were 49% for patients treated with dextromethorphan 20 mg/quinidine 10 mg and 46.9% for patients treated with dextromethorphan 30 mg/quinidine 10 mg. The second RCT with 150 patients studied PBA in patients with multiple sclerosis and defined "complete remission" as no inappropriate crying or laughing up to week 12 of treatment or placebo. 20.8% of treated patients achieved complete remission, whereas only 6.9% of patients in the placebo group did ($p = 0.028$). The third study with 140 patients found the combination of dextromethorphan/quinidine improved CNS-LS score by at least 13 points, compared to either medication alone [46].

Interestingly, after Nuedexta was approved for PBA, patients reported that it was also improving their speech and swallow function. To investigate this further, a RCT crossover trial was done with 60 patients. They first received Nuedexta or placebo for 28–30 days, followed by a 10–15-day washout period. The patients then switched to the other treatment arm and followed for a total of 70 days. The primary outcome was reduction in Center for Neurologic Study Bulbar Function Scale (CNS-BFS) score. With Nuedexta, the CNS-BFS score decreased from a mean of 59.3 in the placebo arm to 53.5 during the treatment arm ($p < 0.001$) [50].

Nuedexta is contraindicated in patients with certain arrhythmias, including atrioventricular bock and prolonged QT interval. It should not be used with other medications that contain quinidine or related structure. It is also contraindicated in patients using monoamine oxidase inhibitors (MAOI) or MAOI within the last 14 days, as there is risk for serotonin syndrome. It can also more rarely cause quinidine-induced thrombocytopenia and lupus-like syndrome [46].

Conclusion

While ALS remains a fatal disease, there have been promising advances in the last several years. Many clinical trials and potential drug targets are under active investigation. Genetic forms of ALS are not only a promising avenue for disease modifying treatment but may yield further insight into the pathogenesis behind sporadic cases. Finally, emphasizing wholistic, multi-disciplinary care remains a key factor in treating all ALS patients.

Compliance with Ethical Standards

Competing interests

Author Senda Ajroud-Driss has served on advisory boards for Biogen, Amylyx and Orphazyme in the past two years. Author Shubadra Priyadarshini has no relevant financial or non-financial interests to disclose.

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