Amyotrophic Lateral Sclerosis

There are both disease-modifying and symptom-reducing treatments available and emerging treatment possibilities.

By Zachary S. Gillis, BS and Michael S. Cartwright, MD, MS

Amyotrophic lateral sclerosis (ALS) is a progressive terminal neurodegenerative disease that causes weakness in the extremities and progresses to development of dysarthria, dysphagia, and dyspnea. There are myriad debilitating symptoms including pseudobulbar affect, sialorrhea, fatigue, spasticity, cramping, and weakness. On average, death occurs 2 to 5 years after symptom onset, typically secondary to a decline in swallowing and breathing. Symptoms are caused by loss of central and peripheral motor neurons. The exact pathophysiology of ALS is still an active area of study and the disease is complex; multiple theories have been proposed. There is no cure; however, disease-modifying treatments (DMTs) that slow disease progression are approved by the Food and Drug Administration (FDA) but unfortunately do not improve strength or function. A number of medications are also used, often without an FDA-approved indication for this use (ie, “off label”), to treat specific symptoms. A variety of potentially therapeutic medications are in clinical trials, some of which have demonstrated promising results. This article summarizes available medications to slow the disease progression and reduce symptom severity, and briefly discusses emerging treatment possibilities.

Pathophysiology

A promising theory for etiology and progression of the ALS disease process is that abnormal RNA processing leads to aggregation of proteins, including TAR DNA binding protein 43 (TDP43). Another theory with strong evidence proposes that abnormal increases in reactive oxygen species occur and subsequently injure cells. Other theories include excitotoxicity caused by excess glutamate, immune-mediated inflammatory responses, or mitochondrial dysfunction possibly related to superoxide dismutase 1 (SOD1) mutations. These theories are not mutually exclusive, and it is likely that multiple factors, perhaps both genetic and environmental, contribute.

Disease-Modifying Treatments

Approved Disease-Modifying Treatments

There are 2 FDA-approved medications shown to modify the disease course of ALS: riluzole, and edaravone (Table 1).

Riluzole. A glutamate inhibitor, riluzole has been shown to play a neuroprotective role, likely through decreased glutamate transmission and inhibition of toxic excess glutamate. Riluzole was approved after a randomized clinical trial demonstrated significantly higher 1-year survival rates with riluzole (74%) compared with placebo (58%). Additional studies confirmed the efficacy of riluzole in improving 1-year survival rates and established the optimal therapeutic dose as 100 mg daily in two 50-mg doses. The most common adverse effects are fatigue, dizziness, and gastrointestinal issues (eg, nausea, abdominal pain, or diarrhea). Reduction to a once-daily 50-mg dose may eliminate these symptoms. Riluzole can cause elevated liver enzymes, which typically normalize after riluzole discontinuation and, in very rare cases, can induce neutropenia.

Edaravone. Approved in 2017, edaravone is thought to ameliorate ALS progression via neuroprotective elimination of free radicals. In clinical trials, edaravone treatment resulted in significantly smaller declines on the revised ALS functional rating scale, and significant improvements in survival. Edaravone is only approved for adults who have had ALS for 2 years or less and still have 80% FVC and score of at least 2 on every ALSFRS item. Abbreviations: ALSFRS, amyotrophic lateral sclerosis functional rating scale; FVC, functional vital capacity; IV, intravenous.

---

**TABLE 1. APPROVED DISEASE MODIFYING TREATMENTS FOR AMYOTROPHIC LATERAL SCLEROSIS**

<table>
<thead>
<tr>
<th></th>
<th>Riluzole</th>
<th>Edaravone*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>50 mg orally twice daily</td>
<td>60 mg/day IV on 10 days/month</td>
</tr>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Glutamate inhibition</td>
<td>Free radical scavenger</td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Anaphylaxis, hepatotoxicity, neutropenia, interstitial lung disease, and pneumonia</td>
<td>Anaphylaxis, hypersensitivity, erythema multiforme, and intravenous administration complications</td>
</tr>
<tr>
<td><strong>Efficacy in clinical trials</strong></td>
<td>12-month survival was 74% with riluzole vs 58% with placebo</td>
<td>At 24 weeks decline on ALSFRS was 2.49 points less with edaravone vs placebo</td>
</tr>
</tbody>
</table>

*Insurance companies will typically approve reimbursement of edaravone only for adults who have had ALS for 2 years or less and still have 80% FVC and score of at least 2 on every ALSFRS item.
rating scale (ALSFRS-R) compared with placebo, although it should be noted that this benefit occurred specifically in participants who were in early stages of ALS, and edaravone efficacy may decrease as ALS progresses. Edaravone is administered intravenously with a standard dose of 60 mg delivered over 1 hour. Treatment begins with 14 days of daily infusion, followed by 14 days without treatment, and continues with 10 consecutive days of infusion each month (which may be split into 5 days, 2 days off, and then another 5 days). Side effects include bruising at the injection site, headache, and gait disturbances. Complications with intravenous delivery methods (eg, port-a-caths and central lines) may include thrombosis, bleeding, and infection. Most insurance companies in the US have a strict set of criteria for reimbursement of edaravone treatment that mimics the enrollment criteria for the clinical trial (Table 1).

**Investigational Disease-Modifying Treatments**

The many potentially disease-modifying treatments being investigated are summarized in Table 2.

<table>
<thead>
<tr>
<th>Category</th>
<th>Agent</th>
<th>Phase, status</th>
<th>NCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASO</td>
<td>Tofersen</td>
<td>3, recruiting</td>
<td>NCT02623699</td>
</tr>
<tr>
<td>Stem cells</td>
<td>NurOwn</td>
<td>3, active</td>
<td>NCT03280056</td>
</tr>
<tr>
<td>Skeletal muscle activators</td>
<td>Tirasemtiv</td>
<td>3, completed</td>
<td>NCT01486849</td>
</tr>
<tr>
<td></td>
<td>Reldesemtiv</td>
<td>2, completed</td>
<td>NCT03160898</td>
</tr>
<tr>
<td></td>
<td>Levosimendan</td>
<td>3, active</td>
<td>NCT03505021</td>
</tr>
<tr>
<td>Immune modulators</td>
<td>Tocilizumab</td>
<td>2, completed</td>
<td>NCT02469896</td>
</tr>
<tr>
<td></td>
<td>Masitinib</td>
<td>3, NYS</td>
<td>NCT03127267</td>
</tr>
<tr>
<td></td>
<td>Ravulizumab</td>
<td>3, NYS</td>
<td>NCT04248465</td>
</tr>
<tr>
<td></td>
<td>Ibudilast</td>
<td>2/3 recruiting</td>
<td>NCT02714036</td>
</tr>
<tr>
<td></td>
<td>Zilucoplan</td>
<td>2/3, NYS</td>
<td>NCT04297683</td>
</tr>
<tr>
<td></td>
<td>Verdiperstat</td>
<td>2/3, NYS</td>
<td>NCT04297683</td>
</tr>
<tr>
<td>Neuroprotective agents</td>
<td>Arimoclomol</td>
<td>2/3, completed</td>
<td>NCT00242442</td>
</tr>
<tr>
<td></td>
<td>Copper (metallocomplex)</td>
<td>3, active</td>
<td>NCT04297683</td>
</tr>
<tr>
<td></td>
<td>Deferiprone</td>
<td>2/3 recruiting</td>
<td>NCT03290696</td>
</tr>
<tr>
<td></td>
<td>Gold (microcrystalline)</td>
<td>2/3 recruiting</td>
<td>NCT04297683</td>
</tr>
<tr>
<td></td>
<td>Mecobalamin</td>
<td>2/3, recruiting</td>
<td>NCT03548311</td>
</tr>
<tr>
<td></td>
<td>TUDCA/sodium phenylbutyrate</td>
<td>3, recruiting</td>
<td>NCT03800524</td>
</tr>
<tr>
<td></td>
<td>TUDCA</td>
<td>2/3 recruiting</td>
<td>NCT03800524</td>
</tr>
</tbody>
</table>

Abbreviations: ASO, antisense oligonucleotide; NYS, not yet recruiting; TUDCA, taurosodeoxycholic acid.

**Genetic Modulation**

Modulation of genetic expression to promote neuronal growth and repair is an active area of investigation for potential treatments. The antisense oligonucleotide (ASO) tofersen, which reduces SOD1 levels by preventing translation of SOD1 mRNA, has demonstrated some success in clinical trials in participants with ALS who have SOD1 mutations. The use of ASOs has been extremely beneficial in spinal muscular atrophy (SMA), another type of inherited motor neuron disease.

**Skeletal Muscle Activators**

Muscle weakness is among the more debilitating symptoms of ALS and is an ideal treatment target. Skeletal muscle activators, which activate troponin and thereby indirectly increase the calcium sensitivity of muscle sarcomeres, are being investigated for that purpose. Recent clinical trials have examined 3 such therapies: tirasemtiv, reldesemtiv, and levosimendan. In a phase 3 trial, tirasemtiv improved slow vital capacity, but this was not statistically significant and improvement in disease progression as measured by ALSFRS-R did not improve. Similarly, both reldesemtiv and levosimendan failed to demonstrate significant efficacy in improving ALS symptoms in phase 2 trials. Despite these results, investigation of both reldesemtiv and levosimendan is continuing with phase 3 trials planned.

**Immune Modulators**

Because inflammatory processes promote neuronal death in ALS, immune-modulating drugs are a prominent focus of treatment development. Multiple immunomodulators with various mechanisms are currently in clinical trials, including tocilizumab, masitinib, ibudilast, and ravulizumab. Tocilizumab and masitinib have both demonstrated benefit in early trials, with tocilizumab normalizing inflammation in participants with sporadic ALS and masitinib reducing ALSFRS-R score deterioration. Ibudilast decreased brain atrophy in a phase 2 trial for treatment of multiple sclerosis, another neurodegenerative disease. The immunomodulators zilucoplan and verdiperstat will be part of the upcoming Healey platform trial. This innovative platform trial approach will assess multiple different potential therapies at once with a shared placebo group, which will decrease cost and trial time and increase the number of participants.
Neuroprotective Agents

Tauroursodeoxycholic acid (TUDCA) inhibits programmed cell death and significantly reduced ALSFRS-R score decline in a phase 2 clinical trial. Another phase 2 trial has been completed for TUDCA in combination with sodium phenylbutyrate, thought to function as a neuroprotective agent by regulating gene expression; results have not been published as this review is being written. Deferiprone is an iron-reducing agent that may have antioxidant properties that could slow ALS.

Mecobalamin, an active form of vitamin B12, seems to play a neuroprotective role by decreasing inflammatory homocysteine levels, and a phase 2/3 clinical trial provided evidence that high doses may reduce ALSFRS-R score decline. Arimoclomol, which activates heat shock proteins that act as chaperones to repair misfolded proteins, also reduced ALSFRS-R score deterioration in a recent phase 2 clinical trial. Metallocomplex copper and microcrystalline gold are thought to reduce oxidative species and improve mitochondrial function; both are being tested in the upcoming Healey platform trial.

Treatments for Symptoms of Amyotrophic Lateral Sclerosis

Table 3 summarizes treatments for symptoms of ALS.

Pseudobulbar Affect

Pseudobulbar affect is emotional lability caused by degeneration of the corticobulbar tracts in ALS, which presents as laughing, crying, or yawning that does not reflect a person’s actual mood or cognitive state. Successful treatment of pseudobulbar affect has been demonstrated with a combination of dextromethorphan and quinidine. An early formulation containing 30 mg of each dextromethorphan and quinidine, was associated with a decreased emotional lability score, improved quality-of-life and quality-of-relationships scores, and reduced number of laughing/crying episodes compared with either quinidine or dextromethorphan alone. Later studies showed reduced adverse effects with preserved therapeutic value with a lower quinidine dose. The standard dosage now is 20 mg of dextromethorphan and 10 mg of quinidine, taken twice daily.

Amitriptyline significantly decreases episodes of emotional lability. The therapeutic dose is approximately 60 mg daily, although that can be adjusted depending on individual patient response and side effects. In addition to amitriptyline, there is limited evidence that another antidepressant, the selective serotonin reuptake inhibitor (SSRI) fluvoxamine, may be effective in reducing pseudobulbar affect symptoms. In a small case series, 100 mg of fluvoxamine reduced emotional lability episodes from more than 30 to less than 5 per day.

Sialorrhea

Sialorrhea, excessive drooling, is a common complication of ALS that can be frustrating and embarrassing for patients. First-line treatments are anticholinergic drugs such as scopolamine, glycopyrrolate, atropine, hyoscyamine, and amitriptyline. Transdermal scopolamine patches have shown efficacy in treating ALS-related sialorrhea, reducing oral secretions in a randomized trial. Glycopyrrolate reduced Parkinson disease–related sialorrhea in a randomized trial when 1 mg was given orally 3 times daily. Although there is little evidence for the use of atropine or hyoscyamine to treat ALS-specific sialorrhea, these medications have been shown effective for the treatment of sialorrhea from other causes. The most common adverse effects associated with anticholinergic medications are dry mouth and gastrointestinal issues, and transdermal patches have been associated with adverse skin reactions in some patients. Amitriptyline, mentioned previously as a treatment for pseudobulbar affect, can also be used to treat sialorrhea owing to its anticholinergic side effects.

Anticholinergic drugs are not successful in treating all ALS-related sialorrhea. For individuals with refractory sialorrhea, botulinum injections into the salivary glands can be effective. Dysphagia is a significant adverse effect of botulinum toxin injected into the parotid gland, so patients given such injections should be monitored afterward. Botulinum toxin treatment may not be appropriate if dysphagia is already present and the patient wishes to avoid enteric feeding.

Although not necessarily related to sialorrhea, people with ALS can also experience a build-up of mucus secretions in their respiratory tract. N-acetylcysteine, a medication with mucolytic properties, may aid in clearing mucus; however, there are no controlled trials in ALS so evidence is lacking.

Spasticity

Spasticity is common in ALS and can negatively affect coordinated movement, making activities of daily living difficult or unmanageable. Baclofen and tizanidine are commonly used to treat spasticity, although there is limited evidence supporting either in alleviating ALS-specific spasticity symptoms. In a small controlled trial, baclofen had a moderate therapeutic effect for ALS-specific spasticity. Both baclofen and tizanidine have demonstrated efficacy for treating spasticity in other conditions. Baclofen and tizanidine have comparable efficacy; however, tizanidine is more likely to cause dry mouth as an adverse effect, whereas baclofen is more likely to cause weakness. Tizanidine has also been noted to increase liver enzyme levels in some, although this is typically asymptomatic and resolves with discontinuation. Baclofen can initially be given 1 to 3 times per day in 5-mg doses and increased to a typical maximum of 80 mg/day, although even higher doses may be used in cases unresponsive to lower doses. Baclofen can also be administered intrathecal, typically in the range of 90 to 900 mcg daily if oral medication therapy is ineffective, but this is not common in ALS. Tizanidine dosage begins at 2 mg daily and can be increased to a max of 24 mg per day.
In cases of refractory spasticity in which baclofen and tizanidine are ineffective, injections of botulinum toxin type A have a therapeutic effect. Botulinum toxin treatment can decrease spasticity and muscle tone for up to 90 days after injection with limited adverse effects. Dosage and injection site are dependent on the location of spasticity, and this treatment is not commonly used in ALS because it may increase weakness.

Limited evidence suggests cannabinoids may be an emerging therapy for spasticity. Although not currently FDA approved, nabiximols are oromucosal Δ9-tetrahydrocannabinol (THC).
and cannabidiol (CBD) sprays that have reduced motor neuron disease-related spasticity in a phase 2 randomized clinical trial.28 A phase 3 clinical trial for another potential cannabinoid therapy, a formulation of CBD oil, is currently recruiting.

Muscle Cramps and Pain

Pain and discomfort from muscle cramping is a common concern for those with ALS. In randomized controlled trials, mexiletine decreased the severity and frequency of muscle cramps in a dose-dependent manner. The optimal dose is 300 mg daily and dizziness, nausea, and tremors were observed at higher doses.29,30 Traditionally, such cramping pain has been treated with quinine sulfate, gabapentin, baclofen, tizanidine, and anticonvulsants, such as levetiracetam.31 Quinine sulfate has shown efficacy in reducing muscle cramp frequency and severity; however, the FDA limits the use of quinidine because of potentially severe adverse effects, including thrombocytopenia, hypersensitivities reactions, and QT prolongation.31 Some individuals with ALS find benefit from taking 2 to 3 ounces of tonic water once or twice per day, which includes small doses of quinine. Gabapentin has been successful in treating non-ALS-related muscle cramps, although controlled studies in participants with ALS have shown no benefit.32,33 Baclofen and tizanidine, which are used to treat ALS spasticity, may have some therapeutic benefits in cases of cramping pain, but this has not been well documented in controlled trials. Levetiracetam successfully reduced motor neuron disease–induced cramping in a randomised trial, although no controlled trials for ALS-related spasticity have been performed.34

Fatigue

Fatigue is a ubiquitous symptom of ALS, present in as many as 90% of people with ALS.35 Despite that high prevalence, few controlled trials have been conducted for the treatment of ALS-related fatigue. Some of the medications discussed (eg, riluzole, baclofen, nabiximols, and tizanidine) have fatigue as a possible side effect, so discontinuation of such treatments may be warranted depending on the severity of fatigue. Modafinil provided increased independence, less fatigue, and less sleepiness according to participant self-report in an open-label trial, although no controlled trials for ALS-related spasticity have been performed.34


Zachary S. Gillis, BS
Department of Neurology, Wake Forest School of Medicine
Winston-Salem, NC

Michael S. Cartwright, MD, MS
Department of Neurology, Wake Forest School of Medicine
Winston-Salem, NC

Disclosure
ZSG and MSC report no disclosures.