Amyotrophic Lateral Sclerosis (ALS): Overview and Emerging Treatment Strategies

A Resource for Clinicians

Background

- ALS is a progressive neurodegenerative condition that leads to muscle dysfunction caused by loss of motor neurons.
- Research continues to identify promising targets for therapies, and >25 genes have been identified in connection with ALS.
- ALS is optimally managed by a multidisciplinary care team. Following the first FDA-approved therapy in 1995, treatment options continue to emerge, including more targeted therapies in select populations.
- Information in this document highlights key points from an MDA mini-webinar with a neurologist with extensive experience managing ALS. **View the companion mini-webinar here.**

Overview[1-4]

Description

- Progressive neurodegenerative condition that results in muscle weakness, disability, and death.
- Loss of motor neurons causes muscle dysfunction.

Epidemiology

- Estimated prevalence: 7.7-9.9 cases per 100,000 people in the the United States (~28,000 cases)
- Most common among whites, males, and persons aged 60–69 years
- ~10% of cases have known genetic causes (familial ALS)

Onset

- Onset can occur at any age
- Symptoms most commonly develop between 51-66 years of age

Prognosis

- Most people die within 3-5 years of diagnosis
- ~30% survive for >5 years
- 10-20% survive for >10 years
- Survival beyond 20 years is rare, but possible

1. Mehta P. *Amyotroph Lateral Scler Front Degener*. 2023;24(1-2):108-116. doi: 10.1080/21678421.2022.2059380 2. Longinetti E. *Curr Opin Neurol*. 2019;32(5):771-776. doi:10.1097/WCO.0000000000000730. 3. Byrne S. *J Neurol Neurosurg Psychiatry*. 2011;82(6):623-627. doi:10.1136/jnnp.2010.224501 4. National Institute of Neurological Disorders and Stroke. ALS. www.ninds.nih.gov/health-information/disorders/amyotrophic-lateral-sclerosis-als. Accessed June 14, 2023.

TDP-43: An Emerging Mechanism of Disease in ALS[1-3]

The mRNA binding protein TDP-43 is depleted in 97% of ALS cases

- In healthy neurons, TDP-43 prevents “cryptic” exons from splicing into mRNA
- In TDP-43 depleted neurons, cryptic exons are spliced into mRNAs of different genes
- Cryptic exons can lead to truncated proteins, loss of gene expression, and impaired function

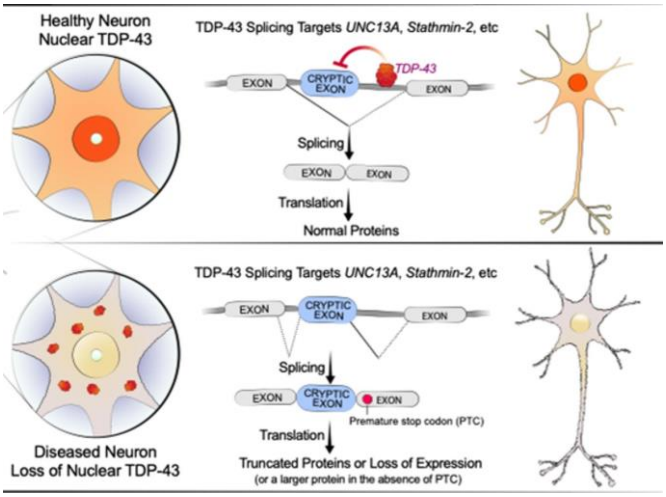

Figure from Halim D. 2022. Open Access (CC- 4.0)

1. Akiyama T. *Clin Transl Med*. 2022; 12:e818. doi:10.1002/ctm2.818. 2. Halim, D. *Transl Neurodegener*. 2022; 11, 12. doi.org/10.1186/s40035-021-00268-9.

Developed with the expertise of Senda Ajroud-Driss, MD, Northwestern University Feinberg School of Medicine, Chicago
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Clinical Features[1-2]

Primary abnormalities

- May manifest in bulbar, cervical, thoracic, or lumbosacral segments and as upper or lower motor neuron (UMN or LMN) symptoms
  - UMN symptoms: hyperreflexia, spasticity, impaired dexterity, Babinski/Hoffman reflexes, muscle weakness
  - LMN symptoms: hyporeflexia/areflexia, flaccidity, muscle atrophy, fasciculations, muscle weakness
- Asymmetric limb weakness (without pain) is the most common presentation (80%)

Respiratory conditions

- Progressive respiratory dysfunction
  - Most common cause of death in ALS
- Dyspnea
- Dysphagia
  - Risk of aspiration
  - Pneumonia

Other

- Pseudobulbar affect
- Sialorrhea
- Frontotemporal dementia and/or cognitive impairment

1. Boulis N,. Molecular And Cellular Therapies For Motor Neuron Diseases. London: Elsevier, Academic Press. 2017. 2. Kiernan MC, Vucic S, Talbot K. *Nat Rev Neurol*. 2021;17(2):104-118. doi: 10.1038/s41582-020-00434-z..

Though genetic testing is not required for diagnosis of ALS, sponsored genetic testing is available, and results can help define clinical trial opportunities.

Diagnosis: Newer Criteria May Speed Early Identification

El Escorial (1994, 2000), Awaji (2008)

Suspected → Possible → Probable → Definite ALS

- Lack of sensitivity: Patients remain in possible/probable category despite progressing disease
- Poor interrater reliability: Complex and prone to error
- Potential misinterpretation: Patients may interpret diagnosis as their risk of having ALS

Gold Coast[1] (2019)

"ALS" vs "Not ALS"

- Data-supported increased sensitivity
- Diagnostic accuracy maintained despite ALS duration, functional status, site of onset
- Differentiates atypical phenotypes (e.g., PLS)

Vucic S. *Muscle Nerve*. 2021;64(5):532-537. doi: 10.1002/mus.27392.

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ALS: Overview and Emerging Treatment Strategies (cont.)

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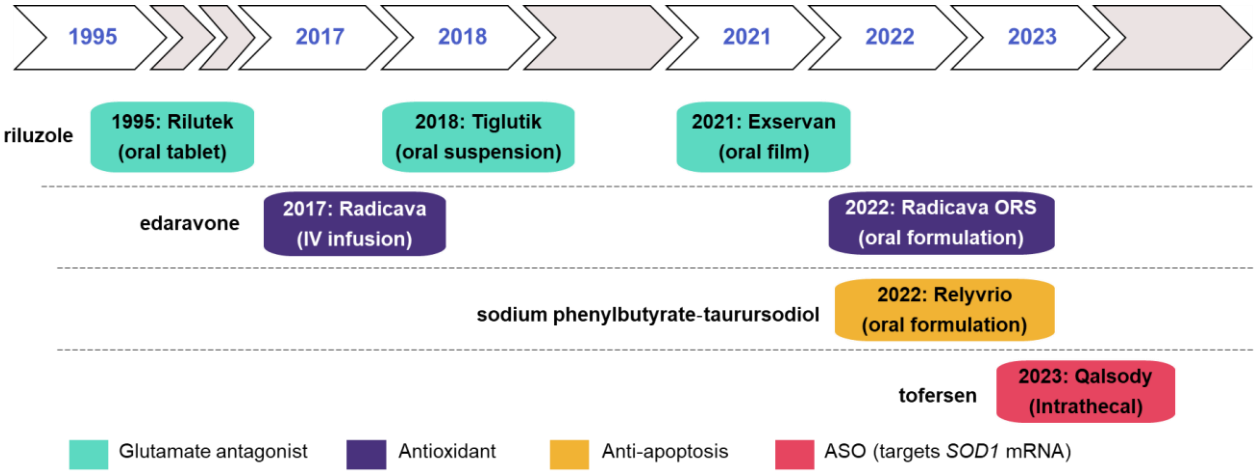
FDA-Approved Therapies for ALS

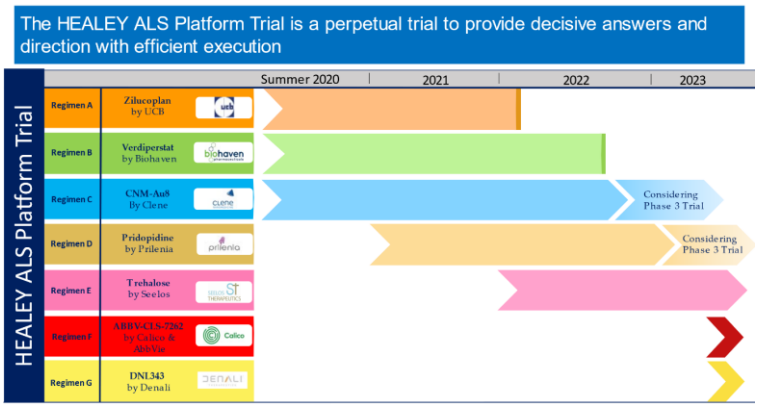


As ALS understanding has evolved, many therapies are being evaluated in ongoing studies. Visit **clinicaltrials.gov** for the most up-to-date information on enrolling trials and eligibility.

Trial Design in ALS: A Model to Evaluate Multiple Candidate Therapies[1]

Advantages of Platform Design[1]

- Faster/shorter timelines
- Efficient use of resources and execution
- Parallel evaluation of drug candidates
- Less reliance on placebo controls



- Visit the Healey ALS Platform Trial on ClinicalTrials.gov: https://www.clinicaltrials.gov/study/NCT04297683
- Watch a brief video about the platform trial approach: Something New Is Here.

Figure and resources courtesy of Mass General Hospital, Patient Navigator, Healey ALS Platform Trial

1. Park JJH.. *JAMA*. 2022;327(1):67–74. doi:10.1001/jama.2021.22507. 2. Mass General Brigham Hospital. YouTube channel. Healey ALS Platform Trial. Weekly Q&A. July 22, 2021. https://youtu.be/5WqXFADbvjM . Accessed June 2023. 3. ClinicalTrials.gov. Accessed Jun 2023.

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Resources and Additional Reading

Select Publications

- Miller, CE. ALS Management Guidelines. Neurology. 2009; 73 (15):1227-1233[1]
- Vucic S. Gold Coast diagnostic criteria: Implications for ALS diagnosis and clinical trial enrollment. *Muscle Nerve.* 2021;64(5):532-537[1]
- Kiernan MC. Improving clinical trial outcomes in ALS. *Nat Rev Neurol.* 2021;17(2):104-118
- Mehta PR. The era of cryptic exons: implications for ALS-FTD. *Mol Neurodegener.* 2023;18(1):16.

Sponsored (no-charge) Genetic Testing Programs[1,2]

- **Invitae ALS Identified**
  - Includes C9orf72 and ALS panel

- **PreventionGenetics ALS Testing Program**
  - Includes analysis of ATXN2, as well as C9orf72 and ALS panel

Clinical Trial Resources[3-6]

- ATLAS study
- HEALEY platform trial
- MDA Clinical Trial Updates & Trial Finder
- National ALS Registry

1. INVITAE. www.invitae.com/en/sponsored-testing/als-identified. 2. Prevention Genetics. www.preventiongenetics.com/sponsoredTesting/Ionis_ALS. 3. ATLAS Study webpage. www.alsatlasstudy.com/en-us/home/for-healthcare-professionals.html . Accessed June 2023. 4. HEALEY ALS Platform Trial webpage. www.massgeneral.org/neurology/als/research/first-platform-trial-treatments 5. MDA webpage. www.mda.org/clinical-trial-updates. Accessed June 2023. 6. CDC National ALS Registry. www.cdc.gov/als/Default.html. Accessed June 2023.