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Editorial Commentary

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# Amyotrophic Lateral Sclerosis: Therapeutic Progress in Neurology Practice

**Anita K. Mehta[1*] and Jin Jun Luo[2*]**

[1]*Department of Neurology, Summit Health New Providence, New Jersey, USA*

[2]*Department of Neurology, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania, USA*

***Correspondence to:**
Dr. Anita K. Mehta
Department of Neurology, Summit Health New Providence, New Jersey, USA
**E-mail**: anitakhannamehta@gmail.com

Dr. Jin Jun Luo
Department of Neurology, Lewis Katz School of Medicine at Temple University, Philadelphia, Pennsylvania, USA
**E-mail**: jin.jun.luo@temple.edu

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## Editorial

The FDA recently approved a new drug Relyvrio™ (a coformulation of sodium phenylbutyrate and taurursodiol; previously known as AMX0035) for the treatment of amyotrophic lateral sclerosis (ALS). This is the third FDA-approved medication in treating patients with ALS after riluzole (Rilutek) in 1995 and edaravone (Radicava) in 2017 (Table 1) from more than 80 randomized controlled clinical trials for ALS therapies.

ALS is a rapidly progressive and fatal neurodegenerative disorder affecting motor neurons in the cerebral cortex, brain stem and spinal cord. The estimated incidence and prevalence of ALS in the USA is 1.5 - 1.7 [1] and 5.5 - 9.9 [2], respectively, per 100,000 population. Patients with ALS have a 50% mortality within 30 months of symptom onset [3]. Approximately 25,000 patients with ALS are living in the USA [2]. The vast majority of patients will die from respiratory failure within 2 - 5 years of disease onset. Approximately 10% of patients with ALS are familial [4]. The etiology remains incompletely understood but is thought to be due to a combination of genetic predisposition, environmental exposures, and aging-related dysfunction [5]. Currently there is no cure for ALS. Cares for patients with ALS are costly. The estimated annual expenses per patient are $69,475 and the national economic burden $279 - 472 million [6].

The first milestone in ALS treatment was set up in 1995 when the FDA approved riluzole as the first drug for ALS (Table 1). Riluzole is a benzothiazole drug with glutamate antagonist property. It inhibits neurotoxic effects of excitoamino acid by blocking excessive release of glutamate from motor neurons [7]. A meta-analysis of randomized controlled trials showed that riluzole delays the time of needed ventilator dependence or tracheostomy and prolongs survival in ALS patients by 2 - 3 months, and increases the possibility of survival for an additional year by about 9% [4]. The recommended dose is 50 mg orally every 12 hours. Riluzole should be taken at least one hour before or two hours after a meal to avoid a decrease in bioavailability. Common side effects include nausea, asthenia, and hepatic impairment. Elevated level of alanine transaminase may occur within 3 months of initiation of riluzole but return to below twice the upper range after 2 - 6 months of continuation of the treatment [7]. A more recent study showed that early initiating riluzole therapy prolongs surviving time in patients with ALS because an one-year delay in beginning with riluzole may lower median survival by 1.9 months and a two-year delay by a median of 4.9 months [8], highlighting the importance of the timing of treatment: namely the earlier the initiation of riluzole, the better the outcome with the therapy. The cost of riluzole is approximately $12,000 annually (Table 1) [7].

Twenty-two years later, the FDA approved the second drug, edaravone (Radicava), in May 2017 for the treatment of ALS (Table 1) [3], aiming to slowing down the progression of ALS. The pivotal Phase 3 study (MCI186-19 or Study

19) demonstrated that edaravone slowed the loss of physical function by 33% compared to placebo after 24 weeks. Study 19 was conducted in 137 people with ALS who met criteria identified in a post-hoc analysis of the previously conducted Phase 3 MCI186-16 study [5, 9]. The exact mechanism of action is unknown but is believed that the antioxidant properties are beneficial in against the oxidative stress which kills motor neurons in ALS patients [10]. It is administered either via intravenous infusion or orally. The oral formulation of edaravone (Radicava ORS®) has an identical biologic effect and dosing schedule to its intravenous formulation, which was approved by the FDA on May 12, 2022 [11]. The initial treatment cycle consists of daily dose of 60 mg for 14 days followed by a 14-day drug-free period; followed by daily dose of 60 mg in 10 out of the first 14 days of each successive 4-week cycle [3]. The cost of edaravone is approximately $144,000 - $171,000 annually while the Institute for Clinical and Economic Review's health benefit price benchmark (ICER's HBPB) values it only $1,400 - $3,200 annually (Table 1) [5, 7].

However, a recent multi-centered cohort study failed to show a therapeutic benefit of edaravone when compared patients received edaravone plus riluzole versus riluzole alone [12]. This study also negated the previous conclusion from patients with mild ALS of no more than 2 years of the disease [12]. Although edaravone has been approved for ALS treatment in Japan and the USA, it is not approved by European Medical Agency for use in the European Union. In AAN practice guidelines, which were reaffirmed in 2020, did not discuss the use of edaravone.

Another milestone was set up on September 29, 2022 (Table 1) when the FDA approved $AMX_{0035}$, after completion of a phase 2 clinical trial (Centaur NCT03127514), for the treatment of adult patients with ALS. This trial enrolled 137 ALS patients and comprised 2 segments: a 6-month randomized, double-blind, placebo-controlled segment and an open-label, long-term follow-up segment. The new drug is named relyvrio in the USA and albrioza in Canada.

Relyvrio is a combination of two compounds, taurours-deoycholic acid (TURSO) and sodium phenylbutyrate (PB), which was designed to slow ALS progression. The exact mechanism of action is not understood but is believed that the TURSO and PB synergistically prevent neuronal death by blocking stress signals between the mitochondria and endoplasmic reticulum [5]. Relyvrio is administered orally or given via a feeding tube [5, 13, 14] with a combined powdered oral formulation sachet of 3 grams PB and 1 gram of TURSO. Treatment starts once a day for three weeks, and then up to twice daily thereafter [5, 13, 14]. The most common side effects are diarrhea, nausea, abdominal pain, and upper respiratory infection [5]. Relyvrio is estimated to cost $158,000 - $169,000 annually while the ICER's HBPB scores it worth $9,100 - $30,600/year (Table 1) [5, 15].

The initial analysis of the trial showed that relyvrio slowed 25% functional decline than placebo as measured using the ALSFRS-R score over a period of 24 weeks; [13] while a later analysis on long-term survival showed a 6.5-month longer median survival than placebo [14]. Results combined from the trial showed that relyvrio may have both functional and survival benefits in ALS [14]. However, concerns on issues of the trial including the randomization, blindness, participants drop-outs, and effectiveness need to be clarified [16], for which an ongoing phase 3 PHOENIX study (NCT05021536) has initiated to enroll patients with definite ALS diagnosis within 18 months of symptom onset and differs from CENTAUR [17]. The results will expect in 2024.

To date, three drugs have been approved by the FDA for ALS treatment (Table 1). Although many clinical trials failed, the perseverance in searching for therapies continues. There are 26 clinical trials are currently ongoing [18]. Of them, an

**Table 1:** FDA approved drugs for ALS [5, 7, 15].

| | Riluzole | Edaravone | Relyvrio |
|---|---|---|---|
| Approved time | 1995 | 2017 | 2022 |
| Action | Block glutamatergic neurotransmission in the CNS | Antioxidant for free radicals | Block stress signals between the mitochondria and endoplasmic reticulum |
| Prolong survival | Yes, ~2-3 months | No | Yes, 6.5 months |
| Slow functional decline | No | Yes (33%) | Yes (25%) |
| Administration | Oral or feeding tube | IV, oral or feeding tube | Oral or feeding tube |
| Dosing | • 50 mg, twice per day<br>• Taken at least 1 hour before or 2 hours after a meal | • Initial: 60 mg daily for 14 days<br>• Followed by 14-day drug-free.<br>• Then, followed by 60 mg daily for 10 days out of the first 14 days of each successive 4-week cycle | • Sachet of 3-gram PB and 1 gram TURSO<br>• Initial: 1 sachet daily for 3 weeks<br>• Followed by 1 sachet twice daily |
| Side effects | Nausea, asthenia, hepatic impairment | Headache, itching, dry skin, chest pain or tightness, difficult breathing | Bitter taste, diarrhea, nausea, abdominal pain, upper respiratory infection |
| Annual cost | $12,000 | $144,000 - $171,000 | $158,000 - $169,000 |
| *ICER's HBPB (annually) | NA | $1,400 - $3,200 | $9,100 - $30,600 |

*: ICER's HBPB: The Institute for Clinical and Economic Review's health benefit price benchmark is the top price range at which a health system can reward innovation and better health for patients without doing more harm than good.

CNS: central nervous system; IV: intravenous; PB: sodium phenylbutyrate; TURSO: taursoursdeoycholic acid.

agent made of antisense oligonucleotides, named as tofersen, may be promising. Tofersen reduces superoxide dismutase 1 (SOD1) activity by targeting the mRNA of SOD1 via lowering the levels of mRNA and SOD1 enzymes. An open-label extension of Biogen's phase 3 VALOR trial showed that tofersen slowed down ALS neurodegeneration process with statistically significant benefits in the early-start group of ALS patients [19]. Namely, tofersen slowed function decline including measuring respiratory vital capacity and muscle strength, and reduced the contents of SOD1 in CSF and neurofilament light chain, a biomarker of neurodegeneration, in plasma [19]. However, those effects await validation.

Although ALS is incurable, there are treatments that can prolong meaningful quality of life. Thanks to the work from numerous scientists, healthcare providers, and pharmaceutical companies for their endless efforts in research, innovating, inventing and implementing novel therapies for treating patients with ALS. We hope that effective therapies will emerge in the future benefiting our patients with ALS, their families, caregivers, and communities.

## References


1. Mehta P, Raymond J, Punjani R, Larson T, Han M, et al. 2022. Incidence of amyotrophic lateral sclerosis in the United States, 2014–2016. *Amyotroph Lateral Scler Frontotemporal Degener* 23(5-6): 378-382. https://doi.org/10.1080/21678421.2021.2023190
2. Mehta P, Raymond J, Punjani R, Han M, Larson T, et al. 2023. Prevalence of amyotrophic lateral sclerosis in the United States using established and novel methodologies, 2017. *Amyotroph Lateral Scler Frontotemporal Degener* 24(1-2): 108-116. https://doi.org/10.1080/21678421.2022.2059380
3. Jackson C, Heiman-Patterson T, Kittrell P, Baranovsky T, McAnanama G, et al. 2019. Radicava (edaravone) for amyotrophic lateral sclerosis: US experience at 1 year after launch. *Amyotroph Lateral Scler Frontotemporal Degener* 20(7-8): 605-610. https://doi.org/10.1080/21678421.2019.1645858
4. Hinchcliffe M, Smith A. 2017. Riluzole: real-world evidence supports significant extension of median survival times in patients with amyotrophic lateral sclerosis. *Degener Neurol Neuromuscul Dis* 7: 61-70. https://doi.org/10.2147/DNND.S135748
5. ICER. AMX0035 and Oral Edaravone for Amyotrophic Lateral Sclerosis. [https://icer.org/wp-content/uploads/2022/02/ICER-ALS-Final-Report-09152022.pdf] Accessed on February 15, 2023
6. Gladman M, Zinman L. 2015. The economic impact of amyotrophic lateral sclerosis: a systematic review *Expert Rev Pharmacoecon Outcomes Res* 15(3): 439-50. https://doi.org/10.1586/14737167.2015.1039941
7. Jaiswal MK. 2019. Riluzole and edaravone: a tale of two amyotrophic lateral sclerosis drugs. *Med Res Rev* 39: 733-748. https://doi.org/10.1002/med.21528
8. Thakore NJ, Lapin BR, Mitsumoto H. 2022. Early initiation of riluzole may improve absolute survival in amyotrophic lateral sclerosis. *Muscle Nerve* 66(6): 702-708. https://doi.org/10.1002/mus.27724
9. Brooks BR, Heiman-Patterson T, Wiedau-Pazos M, Liu S, Zhang J, et al. 2022. Edaravone efficacy in amyotrophic lateral sclerosis with reduced forced vital capacity: Post-hoc analysis of Study 19 (MCI186-19)[clinical trial NCT01492686]. *Plos one* 17: e0258614. https://doi.org/10.1371/journal.pone.0258614
10. Cruz MP. 2018. Edaravone (Radicava): a novel neuroprotective agent for the treatment of amyotrophic lateral sclerosis. *P T* 43(1): 25-28.
11. CISION MTPA. Mitsubishi Tanabe Pharma America Announces FDA Acceptance of New Drug Application (NDA) for Oral Edaravone Formulation for the Treatment of ALS. https://www.prnewswire.com/ news-releases/mitsubishi-tanabe-pharma-america-announces-fda-acceptance-of-new-drug-application-nda-for-oral-edaravone-formulation-for-the-treatment-of-als-301459460.html Accessed February 15, 2023.
12. Witzel S, Maier A, Steinbach R, Grosskreutz J, Koch JC, et al. 2022. Safety and effectiveness of long-term intravenous administration of edaravone for treatment of patients with amyotrophic lateral sclerosis. *JAMA Neurol* 79(2): 121-130. https://doi.org/10.1001/jamaneurol.2021.4893
13. Paganoni S, Macklin EA, Hendrix S, Berry JD, Elliott MA, et al. 2020. Trial of sodium phenylbutyrate–taurursodiol for amyotrophic lateral sclerosis. *N Engl J Med* 383(10): 919-930. https://doi.org/10.1056/NEJMoa1916945
14. Paganoni S, Hendrix S, Dickson SP, Knowlton N, Macklin EA, et al. 2021. Long-term survival of participants in the CENTAUR trial of sodium phenylbutyrate-taurursodiol in amyotrophic lateral sclerosis. *Muscle nerve* 63(1): 31-39. https://doi.org/10.1002/mus.27091
15. Amylyx Sets ALS Drug Price at $158,000 per Year, Opening New Debate on Cost. [https://www.biopharmadive.com/news/amylyx-als-drug-price-relyvrio/633084/] [Accessed February 15, 2023]
16. FDA. Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee Meeting Announcement. [https://www.fda.gov/advisory-committees/peripheral-and-central-nervous-system-drugs-advisory-committee/updated-meeting-time-and-open-public-hearing-time-march-30-2022-meeting-peripheral-and-central#event-information] [Accessed February 15, 2023]
17. Amylyx Pharmaceuticals Announces Participants Dosed in the Global Phase 3 PHOENIX Study of AMX0035 in ALS.[https://www.businesswire.com/news/home/20211104005663/en/Amylyx-Pharmaceuticals-Announces-Participants-Dosed-in-the-Global-Phase-3-PHOENIX-Study-of-AMX0035-in-ALS] Accessed on February 15, 2023
18. CDC. ACTIVE – ALS Research Notification for Clinical Trials and Studies. National Amyotrophic Lateral Sclerosis (ALS) Registry. [https://www.cdc.gov/als/ALSResearchNotificationClinicalTrials-Studies_Active.html] Accessed on February 15, 2023
19. Biogen. New 12-month Tofersen Data Presented at ENCALS Meeting Show Clinically Meaningful Benefit in People with SOD1-ALS. [https://investors.biogen.com/news-releases/news-release-details/new-12-month-tofersen-data-presented-encals-meeting-show] Accessed on February 15, 2023