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MINI REVIEW

Riluzole and edaravone: A tale of two amyotrophic lateral sclerosis drugs

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Abstract

Over the past decades, a multitude of experimental drugs have been shown to delay disease progression in preclinical animal models of amyotrophic lateral sclerosis (ALS) but failed to show efficacy in human clinical trials or are still waiting for approval under Phase I–III trials. Riluzole, a glutamatergic neurotransmission inhibitor, is the only drug approved by the USA Food and Drug Administration for ALS treatment with modest benefits on survival. Recently, an antioxidant drug, edaravone, developed by Mitsubishi Tanabe Pharma was found to be effective in halting ALS progression during early stages. The newly approved drug edaravone is a force multiplier for ALS treatment. This short report provides an overview of the two drugs that have been approved for ALS treatment and highlights an update on the timeline of drug development, how clinical trials were done, the outcome of these trials, primary endpoint, mechanism of actions, dosing information, administration, side effects, and storage procedures. Moreover, we also discussed the pressing issues and challenges of ALS clinical trials and drug developments as well as future outlook.

KEYWORDS
Amyotrophic lateral sclerosis (ALS), clinical trials, drug development, edaravone, riluzole

"ALS is like a lit candle: it melts your nerves and leaves your body a pile of wax. You cannot support yourself standing. You cannot sit up straight. By the end, if you are still alive, your soul, perfectly awake, is imprisoned inside a limp husk. Like something from a science fiction movie, the man frozen inside his own flesh."

—Mitch Albom, Tuesdays with Morrie: An Old Man, a Young Man, and Life's Greatest Lesson[1]

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS functioning rating scale–revised; FDA, Food and Drug Administration; FVC, forced vital capacity; RCTs, randomised controlled trials.

1 | INTRODUCTION

These are the inspiring words of Mitch Albom, the American writer, about Morrie Schwartz, a professor of sociology at Brandeis University and a previous teacher of Albom diagnosed with amyotrophic lateral sclerosis (ALS) and passed away with this terminal disease. In his memoir, a witty and moving account of Morrie fight with ALS.

He questions what keeps myriad of nerve cells from joining together in a state of "cellular disorder" that can cause ALS and imparting wisdom about the happening of life and death. Although the answer to this question remains a complex multifactorial enigma, the past few years have seen a surge in clinical studies and drug trials exploring the intimate link between cell death, ALS, and possible drug interventions. In this context, the newly approved ALS drug edaravone is a fresh wind of hope for patients with ALS.[2,3]

ALS is a progressive and fatal neurodegenerative disease causing extensive loss of motor neurons (MNs) and glial cells in the brain stem and spinal cord,[4–7] with an average life expectancy of 2 to 5 years.[8,9] Because the description of ALS dates back to 1824 by Charles Bell and links between the ALS symptoms and the pathophysiology was first described by Jean-Martin Charcot in 1869, ALS became a *cause célèbre* in the USA when famous baseball legend Lou Gehrig's died in 1941 by the ALS.[10,11] More recently, British celebrity astrophysicist Stephen William Hawking, possibly one of the most famous patient with ALS to date, died on March 14, 2018.[12] The description of the physicians' art, "the medicine with eight components" (Skt. *cikitsāyām aṣṭāṅgāyāṃ*), is first originated in the Sanskrit epic the *Mahābhārata*, ca 4th century BCE.[13] Although, the history of clinical trials goes back to the biblical descriptions in the Old Testament, dates back to 605 BC, recorded in the "Book of Daniel" and King Nebuchadnezzar II an ingenious military leader conducts first experimentation resembling clinical trial during his rule in Babylon[14]; the first ALS clinical trial conducted very recently lead to riluzole approval by the Food and Drug Administration (FDA) in 1995.[15] In 1998, the El Escorial criteria were developed as the standard for classifying people with ALS in clinical research,[16] and subsequently, in 1999, the revised ALS Functional Rating Scale (AFRS-R) was published and became a gold standard for conducting ALS clinical trials.[17]

2 | TIMELINE OF DRUG DEVELOPMENT

There has been no curative drug discovered for ALS in its 160 years of recorded history despite more than 200 ALS clinical trials having been conducted by more than 60 academic institutions and companies worldwide. In the early 1990s, riluzole was the only drug that was FDA approved for clinical use.[18] Over the past decades, a multitude of experimental pharmaceutical therapies was shown to delay disease progression in transgenic ALS animal models but failed to show efficacy in clinical trials or are still in Phase I–III trials. After several decades, another drug, named edaravone, developed by Mitsubishi Tanabe Pharma, was approved by the FDA (edaravone was approved by FDA on May 5th, 2017) after it was shown to be effective in halting ALS progression during early disease stages.[3] Edaravone is currently approved for use in Japan and the USA. The timeline of ALS drug development is described in Figure 1.

3 | CLINICAL TRIALS

The efficacy of riluzole was established in two randomised controlled trials (RCTs).[18,19] Patients enrolled in these trials had been affected with ALS for less than 5 years and possessed a baseline forced vital capacity (FVC) ≥60%. In the first trial, 155 patients with ALS, recruited from France and Belgium, were followed up for at least 13 months after treatment with either 100 mg/day of riluzole or placebo[20] (Figure 2A). In the second trial, 959 patients with ALS recruited from both North America and Europe were followed up for at least 12 and 18 months, respectively, after treatment with either 50, 100, or 200 mg/day of riluzole or placebo (Figure 2A). The patients

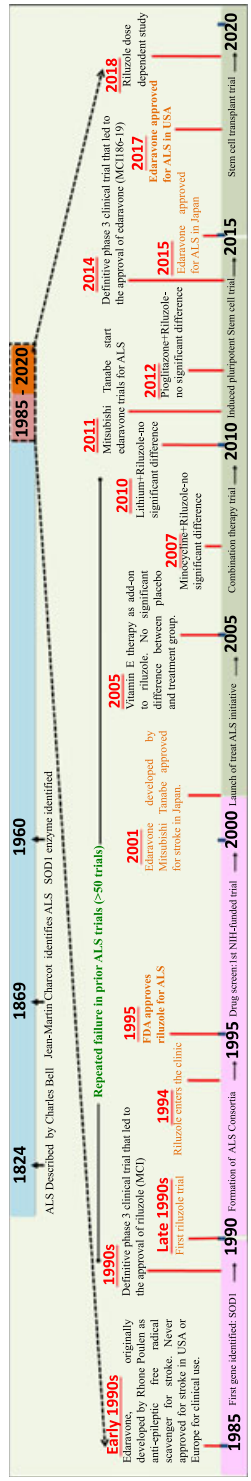


FIGURE 1 Brief history of ALS clinical trials and time line of riluzole and edaravone drug development. Time line of riluzole and edaravone clinical trials and drug development since the description of the ALS date back to 1824 by Charles Bell. ALS, amyotrophic lateral sclerosis [Color figure can be viewed at wileyonlinelibrary.com]

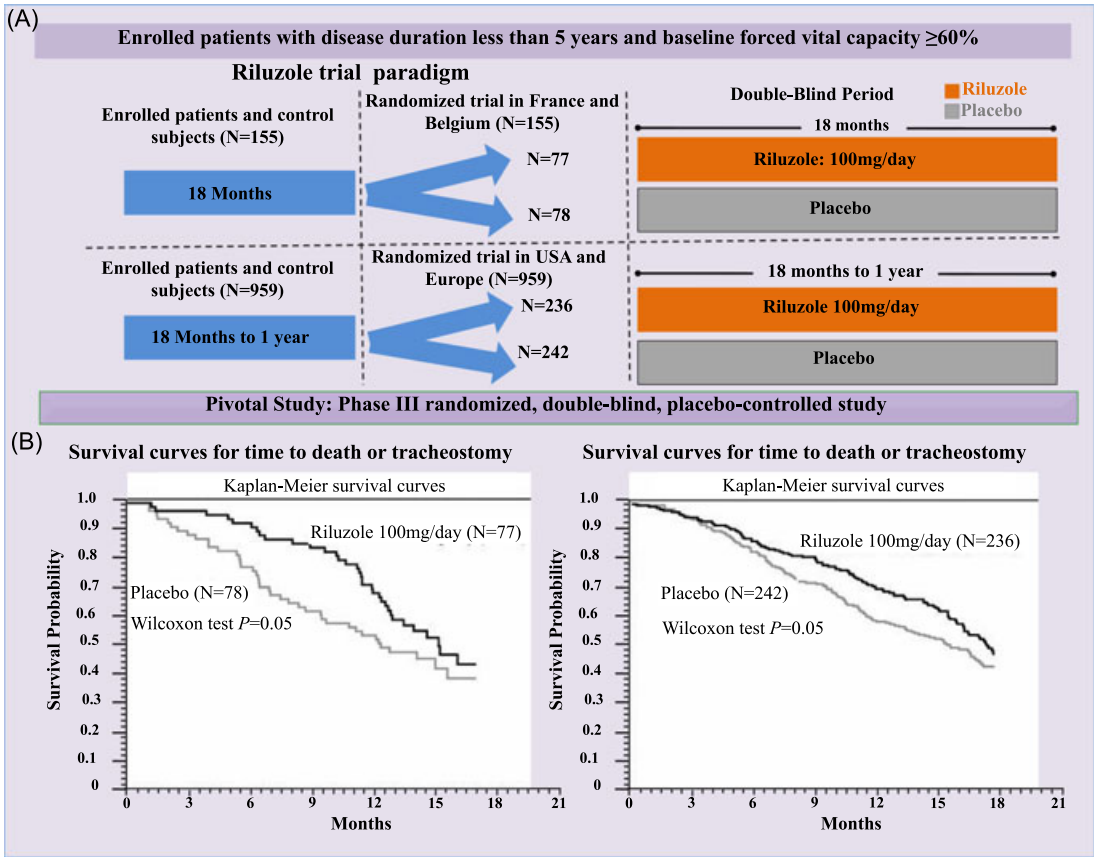


FIGURE 2 Riluzole clinical trials design and survival curve of patients for time to death or tracheostomy. A, Early open label small nonrandomized trials showed decrease in progression. In first randomized controlled trial (RCT), 155 patients participated; 77 patients randomized to receive riluzole compared with 78 patients on placebo. Later on, due to the concern that the number of bulbar onset patients was small but accounted for the most improved patients, in yet another large RCT, 959 patients were randomized for a dose-ranging study of 50, 100, and 200 mg riluzole. A total of 236 patients were treated with 100 mg riluzole compared with 242 placebo patients. At the end of the RCT, 134 were alive in the riluzole group compared with 122 in the placebo group. Riluzole demonstrated statistical significance on the primary endpoint. Better survival was seen across all drug doses, with a survival rate of 56.8% for 100 mg riluzole-treated patients compared with 50.4% for placebo patients. Cumulative data of pooled RCT for the 100 mg riluzole showed 14.8 months survival for the treated group compared with 11.8 months for the placebo group, an approximately 3.0-month difference, indicating 10% absolute increase in the survival probability. B, Survival curves for time to death or tracheostomy for double-blind, placebo-controlled RCT, performed in France and Belgium with explicit or possible ALS disease (left, data modified from.[20] The vertical axis denotes the number of individuals alive without tracheostomy at various times after treatment start (horizontal axis) and the difference was found to be significant by the Wilcoxon test ($P = 0.05$). Survival curves for time to death or tracheostomy for double-blind, placebo-controlled RCT, performed in seven countries in both Europe and North America with ALS followed for 14 to 18 months (right). 100 mg riluzole showed an early increase in survival in patients and found to be significant by the Wilcoxon test ($P = 0.05$). There was no statistically significant difference in mortality at the end of the riluzole RCT study. ALS, amyotrophic lateral sclerosis [Color figure can be viewed at wileyonlinelibrary.com]

who received 100 mg/day riluzole showed an increase in survival compared with the patients who received the placebo. In the first trial, the median survival time was 17.7 months in the riluzole group versus 14.9 months in the placebo group, whereas in the second trial, the median survival time was16.5 months in the riluzole group versus 13.5 months in the placebo group.[18,19] Among the patients in whom treatment failed during the trials (tracheostomy or death), there was a difference in median survival between the treatment group in the first trial compared with the treatment group in the second trial, approximately 60 days versus approximately 90 days, respectively. There was no statistically significant difference in mortality at the end of the trials. Patients treated with 50 mg/day of riluzole did not show a statistically significant difference compared with the placebo group, and the results of 200 mg/day were essentially identical to 100 mg/day. A systematic review and analysis of four RCTs of 1477 patients showed an increase in median survival from 11.8 to 14.8 months in the riluzole group (approximately 3 months) compared with the placebo group (Figure 2B).[8] A recent analysis of trial data of 959 patient with ALS revealed that riluzole prolongs survival in the last stage of ALS (stage 4) and most of the benefits

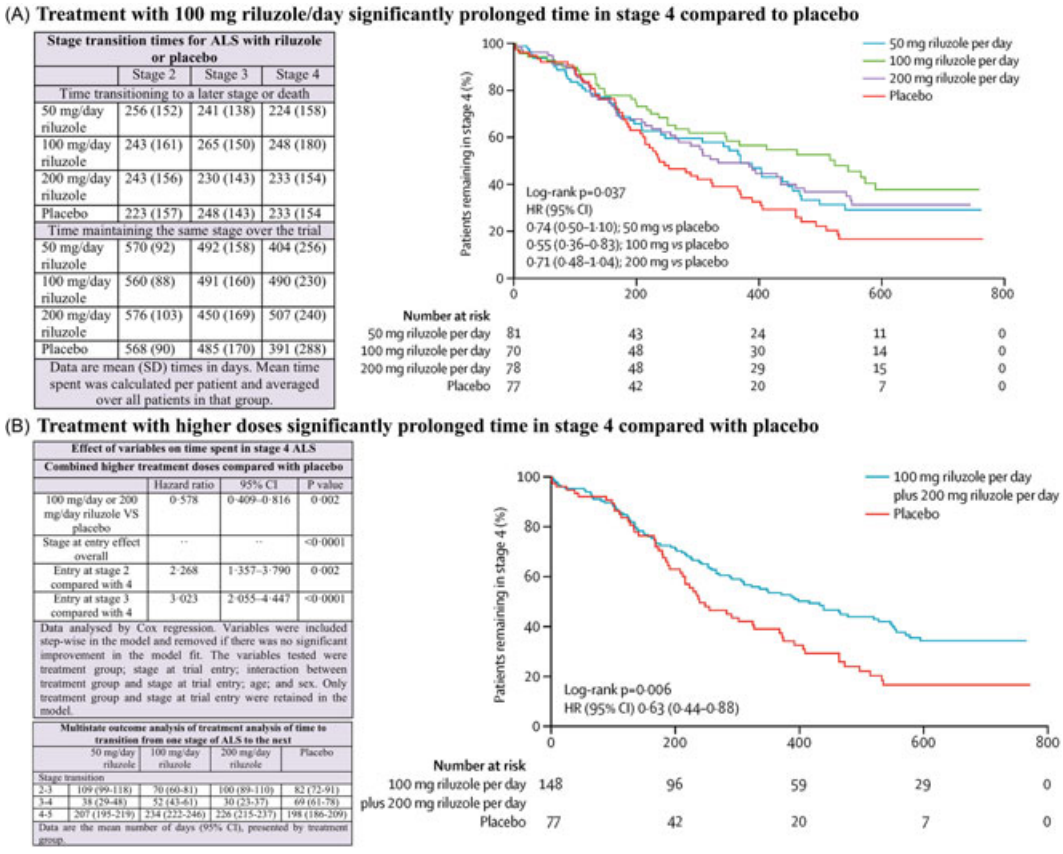


FIGURE 3 Patients with ALS progressing from each stage of ALS with riluzole or placebo. A, Dose-ranging trial study of 959 participants to determine stage at which riluzole treatment prolongs survival in patients with ALS. Recent analysis data showed that riluzole prolongs survival in the last stage of ALS (stage 4) rather than by slowing the entire disease course and needs further confirmation through prospective study. B, Time spent in stage 4 was longer for patients not transitioning who were on 100 mg/day riluzole medication compared with placebo group (long-rank $P = 0.037$). (Data taken and modified from.[21] Riluzole treatment with all doses did not prolong time in stage 2 ($P = 0.827$) and stage 3 ($P = 0.882$) compared with placebo group. ALS, amyotrophic lateral sclerosis; HR, hazard ratio [Color figure can be viewed at wileyonlinelibrary.com]

occur during this stage. Moreover, there is no difference in time from trial stages 2 or 3 to the next stages or death between the riluzole and the placebo treatment groups ($P = 0{\cdot}83$ for stage 2 and 0·88 for stage 3; Figure 3).[21]

For edaravone, so far, only one Phase II open-label trial and two Phase III placebo-control RCTs have been conducted. In all three trials, the primary outcome evaluated was motor function of patients. Open-label RCTs suggested that edaravone is safe and effective in ALS. It reduced 3-nitrotyrosine levels, a marker of oxidative stress.[22] A Phase III confirmatory study (MCI 186-16: NCT00415519) conducted at 29 RCTs sites in Japan recruited 246 eligible patients, and 206 patients were participated in trial after preobservation period. Changes in ALSFRS-R mean scores were −5.70 ($P = 0.85$) in the edaravone-treated groups compared with −6.35 ($P = 0.84$] for the placebo group, showing no statistically significant differences between the groups ($P = 0.411$) (Figure 4).[23,24] Nevertheless, post-hoc analysis suggested that edaravone was efficacious in a restricted subgroup (patients with milder symptoms and shorter duration of illness).[23] The definitive Phase III double-blind, parallel two-arm, placebo-control trial conducted in Japan led to the approval of edaravone (MCI186-19: NCT01492686).[3,25–27] Eligibility was restricted to patients with a relatively short disease duration and preserved FVC. The patients met the following four criteria: a) functionality retained most activities of daily living (scores of ≥ 2 points or better on revised ALSFRS-R), b) normal respiratory function (% FVC ≥ 80%), c) definite or probable ALS based on El Escorial revised criteria, and d) disease duration ≤2 years. The trial enrolled 69 and 68 patients for edaravone (60 mg, IV infusion) and placebo, respectively. The decline in ALSFRS-R scores from baseline was significantly less in the edaravone-treated patients as compared with placebo, showing greater functional ability (Figure 4).[3,23,26,27] For details see Tables 1,2.

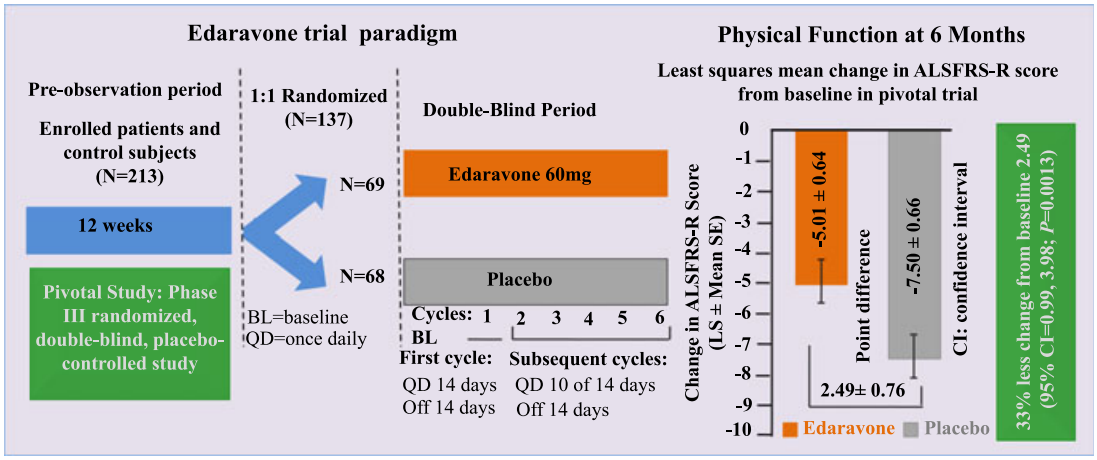
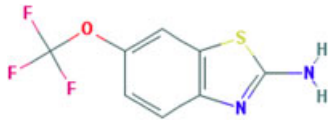
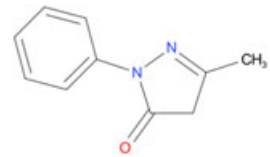


FIGURE 4 Overview of edaravone randomized clinical trials design. Edaravone clinical trials design and least square mean changes in ALSFRS-R more than 6 months time-period. In all three trials, edaravone administered intravenously every day for the first consecutive 2 weeks, followed by an edaravone-free time period for the next 2 weeks (the first cycle). Edaravone was then administered on 10 of 14 days followed by a 2 weeks drug-free period (second cycles). Phase III double-blind, parallel two-arm, placebo-control confirmatory trial for subgroup patients of ALS conducted over 24 weeks. A total of 137 patients were randomized and trial enrolled 69 and 68 patients for edaravone and placebo, respectively. The changes in ALSFRS-R were −5.01 ± 0.64 and −7.50 ± 0.66 (mean SE). RCTs data demonstrated that patients with ALS treated with edaravone for 6 months showed significant reduction in the rate of decline in physical function by approximately 33% (2.49 ± 0.76 ALSFRS-R points; $P = 0.0013$) compared with placebo. ALS, amyotrophic lateral sclerosis; ALSFRS-R, revised ALS functional rating scales [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 A brief summary of riluzole and edaravone: two FDA approved ALS drugs

	Riluzole: an old drug approved for ALS	Edaravone: a new drug approved for ALS
Drug name	Riluzole (Rilutek®)	Edaravone (Radicava®, Radicut)
Molecular formula	C8H5F3N2OS	C10H10N2O
Molecular weight	234.199 g/mol	174.203 g/mol
Structure:		
Chemical name	2-Amino-6-(trifluoromethoxy) benzothiazole	1-Phenyl-3-methyl-5-pyrazolone
Company developed	Sanofi-Aventis (Rhone Poulenc)	Mitsubishi Tanabe
Approval status	Licensed globally	Licensed in Japan and USA
Type	Small molecule	Small molecule
Pharmacokinetics	Well-absorbed (~90%) with oral bioavailability 60% with the percent coefficients of variation (CV) = 30%). Linear kinetics over a dose range of 25 to 100 mg/12 h. A high fat meal decreases absorption, reducing area under the plasma concentration-time curve (AUC) by 20% and peak blood levels 45%. The mean elimination half-life is 12 h (CV = 35%) after repeated doses. With multiple-dose, it accrue in plasma by~2-fold and steady-state is reached in < 5 d. Riluzole is 96% bound to plasma proteins, mainly to albumin and lipoproteins over the clinical concentration range.	Edaravone had a half-time of 0.15–0.17 h (h, α phase), 0.81–1.45 h (β phase), and 4.50–5.16 h (γ phase). Edaravone is thought to be metabolized by the liver. When edaravone was administered at 1.0 mg/kg to a healthy adult, 83.17% was excreted as glucuronated in the urine. No dosing adjustment is needed with mild-to-moderate hepatic impairment and renal impairment is not expected to significantly affect the exposure to the drug. Inhibitors of cytochrome P450 1A2 (CYP1A2) enzymes, UDP-Glucuronosyltransferases, or major drug transporters do not significantly affect the pharmacokinetic profile.
Dose form	Oral tablet. The recommended dose for riluzole is 50 mg every 12 h.	Intravenous infusion (IV). Recommended IV infusion of 60 mg/day for 14 d, followed by a 14-d drug-free period (cycle 1) and then daily dosing for 10 d out of 14-d periods, followed by 14-d drug-free periods (cycles 2-6).
Dose frequency	Daily.	10 d per month.
How supplied	Supplied as a capsule-shaped, white, film-coated tablet for oral administration containing 50 mg of riluzole in bottles of 60 tablets. Each tablet is engraved with "RPR 202" on one side. NDC 0075-7700-60.	Injection is supplied as a 30 mg/100 ml clear, colorless, sterile solution in single-dose polypropylene bags, each overwrapped with polyvinyl alcohol containing an oxygen absorber and oxygen indicator, reflecting appropriate oxygen levels. NDC 70510-2171-1: 30 mg/100 ml (0.3 mg/mL) single-dose bag. NDC 70510-2171-2: 2 bags per carton.

(Continues)

TABLE 1 (Continued)

	Riluzole: an old drug approved for ALS	Edaravone: a new drug approved for ALS
Drug ingredients	*Active*: riluzole. *Inactive*: core-anhydrous dibasic calcium phosphate, microcrystalline cellulose, anhydrous colloidal silica, magnesium stearate, croscarmellose sodium. Film coating: hypromellose, polyethylene glycol 6000, titanium dioxide.	*Active*: edaravone *Inactive*: L-cysteine hydrochloride hydrate, sodium bisulfite, sodium chloride, phosphoric acid and sodium hydroxide (NaOH).
Cost (monthly)	~$1000	~$3000 (Japan); 12 000 (USA); 2200 (other country)
Physical properties	White to slightly yellow powder highly soluble in dimethyl formamide, dimethyl sulfoxide and methanol, freely soluble in dichloromethane, sparingly soluble in 0.1 N hydrochloric acid and very slightly soluble in water and in 0.1 N NaOH. Melting point 119°C.	White crystalline powder with a melting point of 129.7°C. Freely soluble in acetic acid, methanol, or ethanol and slightly soluble in water or diethyl ether.
Dose at home	Yes	No
Cellular and molecular targets	Anti-excitotoxic. Riluzole is glutamate antagonist and used as an anticonvulsant. The precise mechanism is unknown. Pharmacological properties may be related to its effect: 1) an inhibitory effect on glutamate release, 2) inactivation of voltage-dependent sodium channels, and 3) ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors.	Antioxidant. Edaravone is thought to be a free radical/ reactive oxygen species (ROS) scavenger, and it reportedly eliminates lipid peroxides and hydroxyl radicals. The mechanism in ALS is uncertain. The drug presumably works to mitigate oxidative injury in neurons, principally motor neurons and neighboring glia at risk for degeneration in ALS. Drug company officially indicates that the mechanism is unknown.
Primary endpoint	Time to tracheostomy or death was longer for patients randomized to riluzole compared to placebo.	Monitoring the change in revised ALS functional rating scales (ALSFRS-R) score from baseline to six months.
Effects on patients	The drug clinically acts to increase the survival of patients. Median survival time was 17.7 mo vs 14.9 mo in first trial and 16.5 mo vs 13.5 mo in second trial for riluzole and placebo, respectively.	The drug clinically acts to slow disease progression as measured by ALSFRS-R to evaluate motor function of patients.
Side effects	Commonly observed adverse events: dose related nausea, asthenia, gastrointestinal problems, and elevated liver enzyme levels.	Urine glucose. Level of glucose in the blood exceeds the ability of the kidneys to absorb it.

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS functioning rating scale–revised; AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; FDA, Food and Drug Administration.

4 | MECHANISM OF ACTIONS

Oxidative stress, reactive oxygen species (ROS), and glutamate excitotoxicity are considered to be the main contributing factors in ALS.[22,28,29] A careful assessment of riluzole and edaravone reveals startling differences and few similarities in their mechanism of action (Figure 5).

Riluzole belongs to the benzothiazole class, a glutamate antagonist, and it appears to block the excessive release of glutamate from MNs.[30,31] Unrestrained secretion of glutamate at synaptic junction overstimulates the MNs receiving the signals, which leads to abnormally high levels of calcium in MNs soma and glial cells.

TABLE 2 Glossary

Term	Aim	Definition
1:1 Randomized	Reduce bias when testing a new treatment.	Participants were randomised to receive either drug or placebo, with half (50%) of patients on each arm of the trial. This is most common design for randomised trials is the parallel group, two-arm, superiority trial with 1:1 allocation ratio.
Placebo	Placebo treatment designed to have no real effect to delineate effects from treatment that do not depend on the treatment itself.	Nondrug compound, visually alike to trial drug and given to the patient in the exact same way as the trial drug.
Double-blind	Eliminate the power of suggestion and equalizes the placebo effect.	Patient and the doctor do not know whether the drug being given to the patient is the placebo or the trial drugs.
Primary endpoint	Primary endpoints outcomes answer the primary (most important) question being asked by a trial.	Primary question or measurement that the investigators are interested in while doing the trials.
Phase 0	Pharmacodynamics and pharmacokinetics in humans	Phase 0 trials are optional first-in-human trials. Single subtherapeutic doses of the drug are given to a small number of subjects (10-15) to collect pilot data on the drugs impact on body (pharmacodynamics) and pharmacokinetics (what the body does to the drugs).
Phase I clinical trial	Screening for safety	Screening for safety in a small group of patients. First-in-man trials within a small group of people (20-80) to evaluate safety, determine safe dosage ranges, and begin to identify side effects.
Phase II clinical trial	Establishing the efficacy of the drug, optimal dose usually against a placebo	Establishing the efficacy of the drug, optimal dose (by mouth, by injection, etc), usually against a placebo in a larger group of patients (100-300) to determine efficacy and to further evaluate its safety.
Phase III clinical trial	Final confirmation of safety and efficacy	Final confirmation of safety and efficacy in comparison to other commonly used drug treatment with large groups of subjects (1000-3000) to confirm its efficacy, evaluate its effectiveness and monitor side effects.
Phase IV clinical trial	Safety studies during sales	Post marketing studies provide additional information, such as treatment's risks, benefits, and optimal use.

High levels of intracellular calcium $[Ca^{2+}]i$ lead to peroxidation of membrane lipids, damage to RNA and DNA, and disruption of mitochondria, resulting in cell death. ROS, produced after the damage of mitochondria, leads to the formation of superoxide anion ($O^{\bullet-}_2$) and hydrogen peroxide (H_2O_2).[32] Reactions between $O^{\bullet-}_2$ and nitric oxide (NO) lead to the formation of peroxynitrite anion ($ONOO^-$), which causes nitration of protein tyrosine residues. H_2O_2 decomposes into hydroxyl radicals ($^{\bullet}OH$), and both $ONOO^-$ and $^{\bullet}OH$ are highly reactive and react with lipids, proteins, and DNA. Riluzole may contribute to excitotoxic cell death by a) inhibiting glutamate presynaptic release (activation of glutamate reuptake), b) inactivating voltage-dependent sodium channels (reducing hyperexcitability), c) slowing potassium channel inactivation, d)

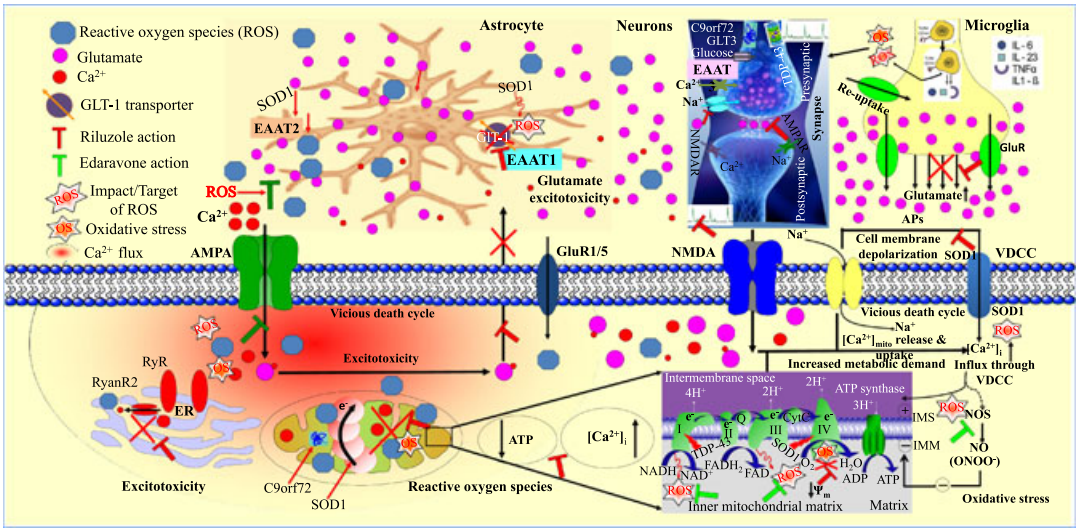


FIGURE 5 Riluzole and edaravone mechanism of actions. Molecular and cellular mechanism of therapeutic intervention and benefit afforded by riluzole ranging from anti-glutaminergic modulation of excitotoxic pathways, modulating low Ca^{2+} buffering capacity of motor neurons, mitochondrial membrane potential ($\Delta\Psi m$), metabolism and function, effects on persistent sodium currents, depolarization of voltage dependent calcium channels and potentiation of calcium-dependent potassium currents whereas edaravone interventions asserts their benefits through redox mechanism and amelioration of reactive oxygen species (ROS). Depending on the disease stage riluzole might affect different therapeutic pathways at different stage and patients for example changes in excitotoxicity pathways might be an early transient effect, with other molecular and therapeutic pathways becoming more involved at later stage. Moreover, mitochondrial malfunction in MNs inhibits complex IV of the electron transport chain, which leads to ROS generation reversed by blocking ROS production by riluzole in MNs or by inhibition of Ca^{2+} efflux at synapse sites. Similarly, edaravone is a potent radical scavenger and removes oxygen radicals, including nitric oxide and peroxynitrite anion. Edaravone trap hydroxyl radical and quench active oxygen, suggesting its neuroprotective property against excitotoxicity and oxidative stress [Color figure can be viewed at wileyonlinelibrary.com]

inhibiting protein kinase C, and e) interfering with intracellular events that follow transmitter binding at excitatory amino acid receptors.

The exact cellular and molecular targets of edaravone are unknown. Edaravone acts as a ROS scavenger[33] and inhibits peroxyl radical ($LOO^{\bullet}$)-induced peroxidation systems.[34] One of the most interesting findings suggests that edaravone scavenges H_2O_2 and protects cells against oxidative stress via upregulation of Peroxiredoxin-2, downregulation of protein disulfide isomerase A3, and inhibition of apoptosis.[35] The reaction between edaravone and $ONOO^-$ is approximately 30-fold greater than uric acid (physiological scavenger for $ONOO^-$). Edaravone traps $^{\bullet}OH$ and inhibits OH^--dependent lipid peroxidation or tyrosine nitration induced by $ONOO^-$. Under physiological states, 50% of edaravone is present as an anion form, and electrons released from edaravone anion exert radical scavenging. Afterward, edaravone radicals are generated, react readily with oxygen atoms, and form a peroxyl radical ($LOO^{\bullet}$) of edaravone, and eventually 2-oxo-3-(phenylhydrazone)-butanoic acid.[34]

5 | DOSING, ADMINISTRATION, SIDE EFFECTS, AND STORAGE

The recommended dose for riluzole is 50 mg/12 hours, which should be taken at least an hour before or two hours after a meal to avoid a food-related decrease in bioavailability. Nausea, asthenia, and elevated liver

enzyme levels are some of the dose-related side effects of riluzole. Increased alanine transaminase usually appears within 3 months after the start of riluzole medication but returns to below twice the upper normal range after 2 to 6 months while treatment is continued. Riluzole can be stored in the dark at RT 15°C to 30°C.

The recommended dose of edaravone is 60 mg (IV; 60 minutes), which is administered in two consecutive 30 mg/100 ml IV infusions at a rate approximately 1 mg/min or 3.33 ml/min.

During the initial treatment cycle, edaravone should be administered daily for 14 days followed by a 14-day drug-free period. For all subsequent cycles, the drug should be dosed daily for 10 days out of 14-day periods, followed by a 14-day drug free period. Edaravone can be stored in the dark at 25°C.

6 | ISSUES AND CHALLENGES OF CLINICAL TRIALS AND DRUG DEVELOPMENT FOR ALS

Conducting ALS RCTs is difficult, in part because doctors are concerned that clinical trials will increase their workload, whereas patients worry that RCTs will cost them time and money. The fundamental issues and challenges of developing new drugs, hindering major development in ALS treatment, are summarized in Box 1.

BOX 1

1. Inadequate and problem-related rodent study models
2. Problems related to preclinical experimental designs
3. Genetic complexity of ALS disease needs extensive study of all the genetic models
4. Due to genotypic features discrepancies in recognizing the ALS subtypes
5. Problems in understanding individual models and formulating focused clinical trials
6. Diverse phenotypes with same ALS mutation
7. Diverse phenotypes due to mutations in the same ALS gene
8. Heterogeneity among patients—one does not fit all
9. Pharmacokinetic differences between rodent preclinical trials and human
10. Issues with RCTs faulty designs and methodological issues
11. Lack of distinction between null versus negative effect
12. Lack of focus on clinical significance instead of just statistical significance
13. Insensitive biomarkers
14. Diagnostic delays

7 | SUGGESTIONS TO IMPROVE ALS CLINICAL TRIALS

We suggest measures and strategy that should reduce the number of false positives in preclinical studies and thereby prevent unwarranted clinical trials and improve RCTs in human patients. The possible measures for better RCTs and improvement of ALS clinical drug trials/development are summarized in Box 2.

BOX 2

1. Developing newer and better ALS model to understand disease better and identifying new causal genes.
2. Considering limitations of preclinical models for designing animal experiments and interpreting preclinical data in the context of ALS RCTs.
3. To overcome the inconsistent inheritances of well-characterized ALS genes, key genes should be monitored over many generations in preclinical trials, as not all ALS-causing genes are inherited onto next generations.
4. Performing thorough evaluation of physiochemical traits of preclinical animal models.
5. Using suitable numbers of preclinical animals littermates, littermate controls, and number of experiments for better experimental data.[36,37]
6. Symptoms should be systematically and periodically reported to study changes in the disease occurrence pattern.
7. Considering strict gender balance in test and control groups, seprating it in different groups, blinding in treatment assignment and using randomization and concealment of allocation in preclinical studies.[38–42]
8. Using guidelines for preclinical studies vis-avis standard RCTS, for example Animals in Research: Reporting *In Vivo* Experiments guideline.[43]
9. Use of correct experimental designs, statistical models and statistical measures.
10. Determining drug accessibility to target tissue/region, right time of treatment, better dose and dose response-curve as well as pharmacokinetics and toxicological studies.[44–47]
11. Distinction should be done between null versus negative drug effects.
12. Adapting innovative study designs and careful enrollment of patients to cut cost and increase RCT robustness.[48,49]
13. Classifying phenotypic variations among patients and stratification of patients in different groups for RCT.
14. Time-span of RCT duration is longer whenever possible and feasible.[48]
15. Evaluating multiple doses over different time-spans to evaluate the correct drug dose.[50,51]
16. Proper and detailed documentation of trials and drug treatment protocols.
17. Genome-wide association study should be supplemented with next generation sequencing.
18. Incorporating mathematical modeling and system and computational biology to discover gene-gene and gene-environment interaction.
19. Developing new models for drug screenings for example organotypic culture, organoid, induced pluripotent stem cells.[52,53]
20. Novel treatment: developing new target and testing of multidrug therapy, stem cells grafting, growth factor therapy, antisense therapies, mitochondrial replacement therapy.[54–58]

8 | DISCUSSION AND OUTLOOK

"The function of the controlled clinical trial is not the "discovery" of a new drug or therapy. Discoveries are made in the animal laboratory, by chance observation, or at the bedside by an acute clinician. The function of the formal controlled clinical trial is to separate the relative handful of discoveries which prove to be true advances in therapy from a legion of false leads and unverifiable clinical impressions, and to delineate in a scientific way the extent of and the limitations which attend the effectiveness of drugs."

(Taken from affidavit of William Thomas Beaver, M.D. in the case of Pharmaceutical Manufacturers Association v. Robert H. Finch and Herbert Ley, Civil Action No. 3797, United States District Court for the District of Delaware)

-William Thomas Beaver

Dr. William Thomas Beaver is credited with drafting the initial regulations defining "adequate and controlled" clinical studies. Over the time, clinical trials have evolved into a standardized procedure, focusing on scientific assessment of efficacy and guarding the patient safety. As the discipline of drug development is enriched by novel therapies and technologies, there will always be a continuing need to balance medical progress and patient safety. As the scientific advances continue to occur, there will be new ethical and regulatory challenges requiring dynamic updates in the ethical and legal framework of clinical trials.

Conducting ALS clinical trials is difficult for three reasons: a) clinicians and patients both are hesitant to joining clinical trials, due to the concerned that these trials will increase their workload; b) many patients and their family are reluctant because of the fear that trial will cost them time and money; and c) some patients concern that they will become "guinea pigs" at the mercy of scientists. Recent data suggest that only 10% of people with the ALS sign up for trial and people in trials are younger and more likely were men and took longer to diagnose than people with ALS overall.[59,60] More than 50 RCTs of ALS-modifying drugs have failed to show positive results due to three main reasons: a) Faulty clinical trial rationale and preclinical study results; b) pharmacological intervention issues, and c) problems associated with clinical trial design and methodology.

Premature death occurs quite frequently during ALS trials; therefore utilizing survival, as a primary outcome measure is a good practice but with caveats that it required big number of patients with ALS with an extended follow-up time. The clinicians may incorporate a combined survival/functional analysis as exploratory endpoints in an ALS drug trial which may provide enhanced power. Early prediction of ALS and individualized prognosis of patients are the best ways to help patients. In this context, a recent report in Journal Lancet concludes that classification of patients into very short, short, intermediate, long, or very long to reach an overall outcome (end of life or respiratory events) after symptom and onset helps the stratification of patients in RCTs and assists clinicians in obtaining an estimate of life expectancy for every patient with ALS in a personalized way, and thereby achieving ambitious precision ALS goals.[61]

9 | FORESIGHT FOR CLINICIANS BEYOND DRUGS TREATMENTS

More than 60 years ago, Karl Jaspers asserted that when patients want to know the truth of their condition, they just want assurance.[62] Famous ALS expert Forbes Norris used to convey ALS diagnoses and prognoses to his patients with some uncertainty "I think you have ALS, but I might be wrong" with intention to provide some hope to ALS patients.[63] A recent survey by rare disease Europe (EURODIS—a non-governmental patient-driven alliance of patient organizations representing 30 million people affected by rare diseases throughout Europe) concluded that the most important factor determining satisfactory participation of clinical trials is a "quality relationship with researchers" emphasizing the importance of "the human side of doctor-patient relations." I would like to end on a more positive note by quoting medical anthropologist and Prof. Adriana Petryna:

"I believe that it is the task of social science to produce nuanced and people-centered forms of knowledge, correcting asymmetries of information and helping to promote, to the best of our ability, informed consent, human protection, and safety in medical and research settings."
—Adriana Petryna, When Experiments Travel: Clinical Trials and the Global Search for Human Subjects.[64]

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CONFLICTS OF INTEREST

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The views expressed in this study are those of the author and do not reflect the official policy or position of the Georg-August University or Icahn School of Medicine at Mount Sinai.

AUTHOR CONTRIBUTIONS

M K Jaiswal conceived of, drafted, edited, and approved the manuscript for publication. All aspects of this study have been solely carried out by M K Jaiswal.

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