Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Riluzole

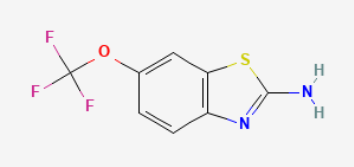
Evidence Summary

Riluzole is approved for the treatment of ALS. It may preserve cerebral glucose metabolism in Alzheimer's patients. Adverse effects include elevated liver enzymes and blood pressure.

Neuroprotective Benefit: Riluzole may preserve cerebral glucose metabolism in Alzheimer's patients based on a phase 2 study. However, a larger trial of troriluzole, a prodrug of riluzole, failed in Alzheimer's patients. Riluzole is a substrate of P-glycoprotein.

Aging and related health concerns: Riluzole increases survival in ALS patients, but it has also been associated with increased blood pressure in a small study. The evidence for peripheral neuropathy is mixed, with some studies suggesting potential harm.

Safety: Riluzole is generally well-tolerated in people with ALS and other neurological/psychiatric conditions, though some adverse effects have been reported including elevated serum alanine transferase, nausea, and high blood pressure.

Availability: Rx	**Dose**: The usual adult dose for ALS is 50 mg orally every 12 hours.	**Chemical formula:** $C_8H_5F_3N_2OS$ **MW**: 234.20  Source: PubChem
Half-life: elimination half-life is 12 hours	**BBB**: substrate of P-glycoprotein	
Clinical trials: The phase III trial in ALS enrolled 950 patients.	**Observational studies**: No observational studies exist for riluzole.	

What is it?

Riluzole (2-amino-6-trifluoromethoxy benzothiazole) is a neuroprotective agent used to treat ALS. Riluzole decreases presynaptic glutamate release (Martin et al., 1993), facilitates glutamate reuptake by astrocytes (Frizzo et al., 2004), acts as a sodium channel blocker, and increases oxidative metabolism with mitochondria-enhancing properties (Mu X et al., 2000).

Riluzole has been tested in Alzheimer's patients (Matthew et al., 2021). It has also been tested for Parkinson's and Huntington's disease, but failed in phase 3 clinical trials. Studies suggest riluzole also possesses anti-depressant and anxiolytic effects in patients with depression and anxiety (Salardini et al., 2016; Brennan BP et al., 2010; Mathew SG et al., 2008). A small clinical trial also reported that riluzole treatment improved some symptoms in people with schizophrenia (Farokhnia et al., 2014).

Neuroprotective Benefit: Riluzole may preserve cerebral glucose metabolism in Alzheimer's patients based on a phase 2 study. However, a larger trial of troriluzole, a prodrug of riluzole, failed in Alzheimer's patients. Riluzole is a substrate of P-glycoprotein.

Types of evidence:

- 2 phase III studies (one in acute spinal cord injury and one in degenerative cervical myelopathy)
- 1 double-blind randomized controlled trial in Alzheimer's patients
- 2 double-blind randomized controlled trials in secondary progressive multiple sclerosis
- 1 double-blind randomized controlled trial in spinocerebellar ataxia type 2
- 1 double-blind randomized clinical trial in Huntington's disease patients
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

No studies have tested whether riluzole prevents dementia or cognitive decline in people. One double-blind randomized controlled clinical trial in 63 Huntington's disease patients reported that while riluzole treatment (100 or 200 mg/day) reduced chorea (involuntary movement) after 8 weeks, no other effects were seen on motor, cognitive, behavioral, or functional components of the Unified Huntington's Disease Rating Scale (Huntington Study Group, 2003).

Human research to suggest benefits to patients with dementia:

In a phase 2 double-blind randomized controlled trial of 50 patients with probable Alzheimer's disease, riluzole treatment (50 mg twice daily) for 6 months resulted in significantly less decline in cerebral glucose metabolism (measured by FDG-PET) in prespecified regions of interest (e.g., posterior cingulate, precuneus, lateral temporal, right hippocampus, and frontal cortex) compared to the placebo group (Matthew et al., 2021). At baseline, the riluzole group showed a trend of more impaired cognitive function (ADAS-Cog) than placebo ($p=0.08$) and there was a greater proportion of APOE4 carriers in the riluzole group compared to placebo. Cerebral metabolic changes over 6 months of treatment was the study's main primary outcome measure. The difference in cerebral metabolic changes in the posterior cingulate (a hub network region) between riluzole and placebo ($p<0.0002$) survived Bonferroni correction for multiple comparisons.

Regional cerebral glucose metabolism was more preserved in the riluzole-treated group in comparison to placebo in several other prespecified brain regions including precuneus ($p<0.007$), lateral temporal ($p<0.014$), right hippocampus ($p<0.025$), and frontal cortex ($p<0.035$), and in a few exploratory subregions, orbitofrontal cortex ($p<0.008$) and posterior cingulate-precuneus subregion ($p<0.007$). Most of these subregions showed trend-level significance after correction for multiple comparisons. A few caveats to this study include the lack of amyloid characterization at baseline and the relatively small sample size.

It is worth noting that the phase 2/3 double-blind randomized controlled trial of troriluzole, a prodrug of riluzole, failed to show significant effects in the co-primary outcomes of ADAS-Cog11 and CDR-SB in 336 mild to moderate Alzheimer's patients after 48 weeks of treatment compared to placebo (Biohaven

press release, 1/18/2021). Troriluzole also failed to differentiate from placebo on the key secondary measure of hippocampal volume assessed by MRI.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Spinal cord injury: Spinal cord injury is associated with glutamatergic excitotoxicity, starting several minutes after injury and until 2 weeks post-injury (Park et al., 2004). In a phase 3 double-blind randomized controlled trial of 193 patients with acute spinal cord injury, riluzole treatment (100 mg twice daily for the first 24 hours followed by 50 mg twice daily, orally) for 13 days resulted in a numerically higher average gain of 1.76 in Upper Extremity Motor (UEM) score at 180 days (16.4 vs 14.7; 95% CI of gain, -2.54 to 6.06) and higher total motor scores (34.0 vs. 31.1; difference of 2.86; 95% CI of difference, -6.79 to 12.52) compared with placebo (Fehlings et al., 2023). However, these results did not reach statistical significance. The study had a planned enrollment of 351 patients, but it was halted in May 2020 and terminated in April 2021 due to the COVID-19 pandemic. The primary outcome (change in UEM) was not statistically significant, likely due to insufficient power. Preplanned secondary analyses also failed to reach statistical significance, but riluzole treatment showed numerical gains in functional recovery. For example, riluzole-treated patients had a gain of 33.9 Spinal Cord Independence Measure (SCIM) points at 180 days compared with a gain of 27.8 points in the placebo group (95% CI for change in SCIM, -2.5 to 14.5; p=0.082). The average gain was numerically higher in the riluzole group compared to placebo for neurological levels at 180 days (1.2 vs 0.4; 95% CI of difference, -0.5 to 2.0), SF36 mental (-3.0 vs -5.2; 95% CI of difference, -8.3 to 13.2) and physical component (-23.5 vs -25.5; 95% CI of difference, -2.3 to 6.2) score change at 180 days and EuroQol 5-Dimension (EQ5D) Health State change at 180 days (-14.9 vs. -17.4; 95% CI of difference, -8.25 to 13.2).

Degenerative cervical myelopathy is the most common form of non-traumatic spinal cord injury. It is characterized by acquired stenosis of the cervical spinal canal secondary to osteoarthritic degeneration or ligamentous aberrations of the spinal column, leading to chronic spinal cord compression and loss of functional ability (reviewed in Badhiwala et al., 2020). The standard of care therapy for degenerative cervical myelopathy is surgical decompression. In a phase 3 double-blind randomized controlled trial of 290 patients undergoing decompression surgery for degenerative cervical myelopathy, riluzole treatment (50 mg twice a day, orally) for 14 days before surgery and then for 28 days after surgery did not significantly affect the primary endpoint of change in modified Japanese Orthopedic Association (mJOA) score at 6-month follow-up: 2.45 points (95% CI, 2.08 to 2.82 points) versus 2.83 points (95% CI, 2.47 to 3.19)(p=0.14) (Fehlings et al., 2021). Patients in both riluzole and placebo groups showed improvement in all secondary outcome measures following surgical decompression; however, there

were no significant between-group differences for secondary endpoints. With regards to other endpoints, at 1 year, patients in the riluzole group (−2.28 points, 95% CI, −2.82 to −1.74) had a greater reduction in the neck pain numeric rating scale (NRS) score than did those in the placebo group (−1.52 points, 95% CI, −2.01 to −1.03; p=0.040). However, pain was not the primary endpoint in this trial and these analyses were exploratory.

Spinocerebellar ataxia type 2: Spinocerebellar ataxia type 2 (SCA2) is a condition characterized by progressive problems with movement, such as with coordination and balance. Over time, people with SCA2 may develop peripheral neuropathy, muscle wasting, and weakness in the limbs. In a double-blind randomized controlled trial of 45 people with SCA2, riluzole treatment (50 mg twice daily, orally) for 12 months did not significantly improve clinical outcomes (measured by the scale for the assessment and rating of ataxia [SARA] score)(Coarelli et al., 2022). The SARA score improvement of at least 1 point after 12 months, was observed in 7 patients (32%) in the riluzole group versus 9 patients (39%) in the placebo group. SARA score showed a median increase (i.e., worsening) of 0.5 points in the riluzole group versus 0.3 points in the placebo group (p=0.70). The composite cerebellar functional severity score (CCFS) worsened significantly in the riluzole group compared with the placebo group (0.055 vs 0.004; p=0.0050). There were no significant differences in upper or lower motor neuron improvement in the riluzole group compared with the placebo group. Riluzole treatment did not improve clinical or radiological outcomes in these patients.

Multiple sclerosis: Multiple sclerosis is a chronic disease of the central nervous system, involving an autoimmune attack of myelin in the brain, optic nerves, and spinal cord. In a phase 2b double-blind randomized controlled trial of 393 patients with secondary progressive multiple sclerosis, twice-daily oral treatment of amiloride (5 mg), fluoxetine (20 mg), riluzole (50 mg), or placebo for 96 weeks failed to show any differences in % brain volume change between active treatment and placebo (Chataway et al., 2020). Of 60 clinician-reported and patient-reported outcome comparisons against placebo, 5 were statistically significant, which is similar to what is expected due to random chance at the 5% significance level. Thus, these results suggests that riluzole (and amiloride and fluoxetine) do not exert neuroprotective benefits in this population.

Preclinical models of cognitive decline: Many studies have reported that riluzole improves cognitive functions in aged rats (Pereira et al., 2014; Pereira et al., 2017), numerous mouse models of Alzheimer's disease (Hunsberger et al., 2015; Mokhtari et al., 2017; Saba and Patel, 2022; Hascup et al., 2021; Okamoto et al., 2018), a mouse model of chemotherapy-induced cognitive decline (Usmani et al., 2023), and a rat model of brain injury (McIntosh et al., 1996). Some mechanisms of action observed in rodent

models included decreased glutamate release (Hunsberger et al., 2015; Hascup et al., 2021), increased vesicular glutamate transporter 1 levels (which packages glutamate into vesicles), increased glutamate transporter 1 levels (which removes glutamate from extracellular space), restored gene expression of NMDA receptor subunits (Okamoto et al., 2018), improved metabolic activity of glutamatergic neurons (Saba and Patel, 2022), reduced oxidative stress markers (Mokhtari et al., 2017), reduced neuroinflammation (Usmani et al., 2023), attenuated acetylcholinesterase activity (Mokhtari et al., 2017), decreased tau pathology (Hunsberger et al., 2015), increased clustering of dendritic spines (thought to enhance synaptic strength; Pereira et al., 2014), increased neurogenesis (Usmani et al., 2023), and increased levels of the brain-derived neurotrophic factor (BDNF) in the hippocampus (Katoh-Semba et al., 2002; Usmani et al., 2023), which was associated with increased proliferation of precursor cells (Katoh-Semba et al., 2002). In models of Alzheimer's disease, the effects of riluzole treatment on Aβ plaques are not consistent. In male APP/PS1 mice, riluzole treatment (12.5 mg/kg/day in drinking water) from 2 to 6 months of age did not lower Aβ plaque accumulation (Hascup et al., 2021). In a study in 5xFAD mice, riluzole treatment (13 mg/kg/day in drinking water) from 1 to 6 months of age significantly enhanced cognition and reduced Aβ42, Aβ40, Aβ oligomers levels, and Aβ plaque load in the brain (Okamoto et al., 2018).

In young and aged rats, many of the gene changes seen in Alzheimer's disease are reversed by riluzole treatment (Pereira et al., 2017). For example, riluzole treatment resulted in an increase in the glutamate transporter (EAAT2) expression in the hippocampus, which suggests that the efficient removal of glutamate may prevent excitotoxicity and underlie neuroprotection and improved cognitive functions. Animals treated with riluzole had 908 gene transcripts increased and 927 gene transcripts decreased. Notably, there is a large overlap of genes (435) that were changed with aging and were also altered by riluzole treatment. Many pathways reversed by riluzole treatment were related to synaptic transmission and plasticity. Examples of learning- and neuroplasticity-related gene products that decrease with aging that were reversed/increased by riluzole treatment include: glutamate NMDA receptor subunit NR2b (GRIN2b), voltage-gated sodium channel subunit (Scn2a1), calcium/calmodulin protein kinase II alpha (CAMK2A), microtubule-associated protein 1B (MAP1B), the synaptic scaffolding protein enriched in the postsynaptic density of excitatory synapses called SHANK3, and the matrix metalloproteinase 9 (MMP9). Several neuroprotective genes were also increased with riluzole treatment, including tropomyosin receptor kinase B (TrkB; NTRK2), which is a receptor for the neurotrophic factor BDNF.

Blood-brain-barrier penetrance: Riluzole is a substrate of P-glycoprotein, a transporter highly expressed at the blood-brain-barrier that regulates removal of various molecules from the brain, including cholesterol, lipids, peptides, and brain-active drugs (Milane et al., 2007). In ALS, P-glycoprotein

expression and activity are increased, resulting in resistance to drugs such as riluzole (Mohamed et al., 2017). In normal aging and in Alzheimer's disease, P-glycoprotein expression appears to be decreased (Chiu et al., 2015), suggesting that resistance to riluzole may be less pronounced; however, as long as P-glycoprotein is present, riluzole is actively pumped out of the brain.

***APOE4 interactions**:* Unknown.

Aging and related health concerns: Riluzole increases survival in ALS patients, but it has also been associated with increased blood pressure in a small study. The evidence for peripheral neuropathy is mixed, with some studies suggesting potential harm.

Types of evidence:

- 1 Cochrane meta-analysis of 4 randomized controlled trials in ALS patients
- 3 clinical studies, 2 in peripheral neuropathy and 1 in ALS
- Numerous laboratory studies

Lifespan: INCONCLUSIVE

No studies have examined the effects of riluzole on lifespan in healthy people. A meta-analysis of 4 randomized controlled trials totaling 1,477 patients with ALS reported that riluzole (100 mg/day) prolongs median survival by about 2 to 3 months (Miller et al., 2012). Also, in a mouse model of progressive motor neuronopathy (a hereditary autosomal recessive wasting disease which shares some symptoms of ALS), riluzole treatment (8 mg/kg, oral) started at 7-days-old increased lifespan while slowing the appearance of paralysis and improving motor performance at the early stage of the disease (Kennel et al., 2000). Seventy-five percent of the mice were dead at day 46 for the vehicle-treated group compared to 54 days for the riluzole-treated group.

Peripheral neuropathy: NO BENEFIT, POTENTIAL HARM

A study reported results from 2 double-blind randomized placebo-controlled crossover studies in people with peripheral neuropathic pain (Galer et al., 2000). Study 1 had 22 patients who received 100 mg/day of riluzole and Study 2 had 21 patients who received 200 mg/day of riluzole. No statistical difference was found for any outcome measure between riluzole and placebo for either study. If anything, in one of the trials (Study 1), pain intensity (on a 100 mm pain intensity analog scale) was more likely to increase than decrease with riluzole (mean treatment difference 8.7 mm; 95% CI, -19.5 to +2.1 mm). However in Study 2, very slight (non-significant) pain reduction was observed with riluzole compared with placebo

(mean treatment difference 1.4 mm; 95% CI, -5.1 to +8.0 mm). In both studies, the majority of subjects chose "no change" in pain on the category relief scale after placebo and riluzole treatment phases and no treatment preference was reported. These results suggest that riluzole is not effective in alleviating peripheral neuropathic pain.

In a phase 2b double-blind randomized controlled trial of 445 people with neuropathic pain associated with secondary progressive multiple sclerosis, riluzole (50 mg twice daily, orally), fluoxetine (20 mg twice daily, orally), amiloride (5 mg twice daily, orally) or placebo treatment (twice daily, orally) for 96 weeks did not result in any significant differences on ratings of neuropathic pain or pain overall (Foley et al., 2022). Compared to placebo, adjusted mean differences in pain intensity was 0.38 for amiloride (positive values favoring placebo, 95% CI, -0.30 to 1.07), 0.52 for fluoxetine (95% CI, -0.17 to 1.22,), and 0.40 for riluzole (95% CI, -0.30 to 1.10).

In a randomized controlled trial of 48 patients receiving chemotherapy (oxaliplatin), riluzole treatment (50 mg twice daily prior to the second oxaliplatin dose, continuing to the end of treatment and for 2-week post-completion of treatment) led to greater neuropathy, represented by a higher total neuropathy score-reduced (TNSr) at 4-week post-chemotherapy of 8.3 ± 2.7 compared with 4.6 ± 3.6 in the placebo group (p=0.032) (Trinh et al., 2021). The TNSr remained worse in the riluzole-treated group compared to placebo at 12-week post-chemotherapy with a score of 8.5 ± 2.5 in comparison with 6.5 ± 3.9 for the control group (p=0.09). Patients treated with riluzole also reported worse neurotoxicity and impact on quality of life (measured with FACT-GOG NTX score) of 37.4 ± 10.2 compared with 43.3 ± 7.4 in the placebo group at 4-week post-treatment (p=0.02). While the study was small and not conclusive, results may suggest that riluzole worsens neuropathy associated with oxaliplatin treatment.

Cardiovascular function: POTENTIAL HARM/MIXED
Although hypertension is not considered a frequent adverse effect of riluzole, a clinical study of 50 ALS patients (and 88 controls without ALS) reported that riluzole treatment (50 mg, twice daily) is associated with elevated blood pressure (Scelsa and Khan, 2000). Median systolic and diastolic blood pressures were both significantly higher in riluzole-treated ALS patients (140/86 mm Hg) compared to control patients without ALS (120/70 mm Hg). In ALS patients, systolic blood pressures (but not diastolic) were significantly higher in riluzole-treated (140 mm Hg) than those not on riluzole (126 mm Hg).

In contrast, a series of studies from a single group reported that riluzole exerts protective effects in models of myocardial infarction (Weiss and Saint, 2010), myocardial ischemia (Weiss et al., 2013), and ischemia and reperfusion injury (Weiss et al., 2010). For example, in a pig model of acute myocardial

infarction, riluzole was effective in reducing the number of ischemic ventricular tachycardia, ventricular fibrillation, and premature ventricular contractions (Weiss and Saint, 2010). Riluzole also decreased arrhythmias and myocardial damage in a pig model of myocardial ischemia (Weiss et al., 2013). Proposed mechanism of action for these protective benefits appears to be riluzole's ability to block cardiac persistent sodium current.

Safety: Riluzole is generally well-tolerated in people with ALS and other neurological/psychiatric conditions, though some adverse effects have been reported including elevated serum alanine transferase, nausea, and high blood pressure.

Types of evidence:

- 1 Cochrane meta-analysis of 4 randomized controlled trials in ALS patients
- 8 double-blind randomized clinical trials (1 in spinal cord injury, 1 in degenerative cervical myelopathy, 1 in Alzheimer's disease, 1 in Huntington's disease, 1 in multiple sclerosis, 1 in spinocerebellar ataxia type 2, 1 in major depressive disorder, and 1 in schizophrenia)
- 1 case study of an ALS patient

A Cochrane meta-analysis of 4 randomized controlled trials totaling 1,477 patients with ALS reported that riluzole (100 mg/day) is reasonably safe and likely prolongs median survival by about 2 to 3 months (Miller et al., 2012). However, more treated participants developed a threefold or greater elevation of serum alanine transferase (ALT; measure of liver injury) compared to controls in Lacomblez 1996, Bensimon 2002 and in the combined data (RR=2.62; 95% CI, 1.59-4.31). Nausea was more frequent in riluzole-treated subjects with RR of 1.5 (95% CI, 1.06-2.28). There was a trend toward more asthenia (physical weakness) among the treated participants in each trial, and this became statistically significant when the data from 3 trials were combined (RR=1.50; 95% CI, 1.07-2.12). Vomiting, diarrhea, anorexia and dizziness were more frequent in treated participants compared to controls, but differences did not reach statistical significance. Five riluzole-treated participants reported circumoral paresthesias (unusual or abnormal sensations around the mouth) in one of the trials (Lacomblez 1996) but this symptom was not reported by any controls (MD=7.71; 95% CI, 1.33-44.84).

A double-blind randomized controlled trial of 63 Huntington's disease patients reported that riluzole treatment (100 or 200 mg/day) for 8 weeks was associated with an elevation in ALT in a dose-dependent manner, though levels normalized within 12 days of drug discontinuation (Huntington Study Group, 2003). One serious adverse event was observed, which was a psychiatric hospitalization in a subject who

had received riluzole 200 mg/day, occurring only after riluzole had already been suspended because of other symptoms (fatigue, urinary incontinence, and diaphoresis) that had subsequently resolved. The proportion of subjects reporting adverse events was higher in those receiving riluzole. Of the seven subjects who were unable to complete the study, 2 were on placebo (fatigue, dizziness/ fatigue), 2 were on riluzole 100 mg/day (nausea, generalized weakness/ nausea), and 3 were on riluzole 200 mg/day (nausea/vertigo/ weight loss/anorexia, obsessive-compulsive behavior, abdominal pain/elevated ALT of 183 U/L).

In a phase 2 double-blind randomized controlled trial of 50 patients with probable Alzheimer's disease, riluzole treatment (50 mg twice daily) for 6 months did not result in statistical differences in adverse events compared to placebo (Matthew et al., 2021). Twenty-three of 26 patients (88.5%) in the riluzole group and 22 of 24 (91.7%) in the placebo group had at least one adverse event during the study. Serious adverse events occurred in 2 participants (7.7%) in the riluzole group and 1 participant (4.2%) in the placebo group. The most common side effects in the riluzole group consisted of abdominal discomfort (15.4% in riluzole, none in placebo); diarrhea (15.4% in riluzole, 8.3% in placebo); dizziness (15.4% in riluzole, 4.2% in placebo); urinary frequency (11.5% in riluzole and none in placebo), nausea (7.7% in riluzole, none in placebo), cough (19.23% in riluzole, 12.5% in placebo), and elevated liver enzymes (7.7% in riluzole and 4.2% in placebo). Among randomized participants, 4 of 26 (15.4%) in the riluzole group and 3 of 24 (12.5%) in the placebo group had an adverse event that led to discontinuation from the trial.

In a phase 3 double-blind randomized controlled trial of 193 patients with acute spinal cord injury, riluzole treatment (100 mg twice daily for the first 24 hours followed by 50 mg twice daily, orally) for 13 days did not result in withdrawal of study medication due to adverse events (Fehlings et al., 2023). In the riluzole group, there were 1722 adverse events in 96 participants and 110 serious adverse events in 51 participants with nine deaths. In the placebo group, there were 1786 adverse events in 97 participants with 52 serious adverse events in 132 participants and 10 deaths. Laboratory measures did not reveal any statistically significant differences in liver enzymes at 14 days between riluzole and placebo groups.

In a phase 3 double-blind randomized controlled trial of 290 patients undergoing decompression surgery for degenerative cervical myelopathy, riluzole treatment (50 mg twice a day, orally) for 14 days before surgery and then for 28 days after surgery resulted in adverse events including neck or arm or shoulder pain, arm paraesthesia, dysphagia, and worsening of myelopathy (Fehlings et al., 2021). There were 43 serious adverse events in 33 (22%) out of 147 patients in the riluzole group and 34 serious adverse

events in 29 (19%) out of 153 patients in the placebo group. The most frequent severe adverse events were osteoarthrosis (degeneration of the joint) of non-spinal joints, worsening of myelopathy, and wound complications.

In a phase 2b double-blind randomized controlled trial of 393 patients with secondary progressive multiple sclerosis, twice-daily oral treatment of amiloride (5 mg), fluoxetine (20 mg), riluzole (50 mg), or placebo for 96 weeks did not lead to emergent safety issues (Chataway et al., 2020). The incidence of serious adverse events was low and similar across treatment groups (9% of patients in the amiloride group, 6% in the fluoxetine group, 11% in the riluzole group, and 12% in the placebo group). Three patients died during the study, from causes judged unrelated to active treatment; one patient in the amiloride group died from metastatic lung cancer, one patient in the riluzole group died from ischemic heart disease and coronary artery thrombosis, and one patient in the fluoxetine group had a sudden death with multiple sclerosis and obesity listed as secondary causes.

In a double-blind randomized controlled trial of 45 people with SCA2, riluzole treatment (50 mg twice daily, orally) for 12 months did not result in any serious adverse events while 4 patients in the placebo group had a serious adverse event (hepatic enzyme increase, fracture of external malleolus, rectal bleeding, and depression)(Coarelli et al., 2022). The number of patients with adverse events was similar between riluzole (16; 73%) and placebo (19; 83%) groups. In the riluzole group, no patient exhibited clinically significant blood biomarker abnormalities. Liver enzymes did not increase with treatment except in one patient (ALT increased less than 2 times the normal value at month 2 of treatment followed by regression at month 3). In the placebo group, one patient had an ALT increase (5 times the normal value).

Other randomized clinical trials, one in major depressive order and the other in schizophrenia, reported no significant differences in adverse events between the riluzole and placebo groups (Salardini et al., 2016; Farokhnia et al., 2014). The trial in major depressive disorder included 60 patients who received citalopram with riluzole (50 mg, twice daily) or placebo, and this study reported no effects on blood tests including serum ALT levels (Salardini et al., 2016). Adverse events which occurred at equivalent rates in both riluzole and placebo groups included drowsiness, constipation, dizziness, abdominal pain, increased appetite, decreased appetite, nausea, headache, dry mouth, cough, and diarrhea.

In a case study, an ALS patient taking riluzole (50 mg twice daily) for one month was admitted to the hospital due to severe upper quadrant abdominal pain, nausea and fever (Cabras et al., 2020). Physical examination, blood tests and CT scan confirmed a severe, acute, hemorrhagic, necrotizing pancreatitis

with abdominal fluid collections, ileus, and bilateral pleural effusions, without any evidence of biliary obstruction. Riluzole treatment was immediately stopped, and therapy with crystalloids, tramadol, paracetamol, proton pump inhibitors and parenteral nutrition was started. Riluzole-induced pancreatitis is a rare adverse reaction (Falcao de Campos and Carvalho, 2017), but worth keeping in mind given it can be potentially life-threatening.

Drug interactions: Based on drugs.com, there are 4 major drug interactions and 23 moderate interactions. The 4 drugs that can cause major drug interactions with riluzole are leflunomide, lomitapide, mipomersen, and teriflunomide; all of these drugs may cause liver problems and therefore using these with riluzole may increase that risk. Riluzole may also interact with drugs that affect liver enzymes (e.g., caffeine, amitriptyline, omeprazole, rifampin, quinolone antibiotics).

Sources and dosing:

Riluzole is a prescription drug marketed as Rilutek® or Teglutik® and is available in tablet and liquid forms. The usual adult dose for ALS is 50 mg orally every 12 hours (Drugs.com). Riluzole is best taken at the same time of day and on an empty stomach.

Research underway:

Clinical trials are testing the effects of riluzole in ALS (NCT05508074), spinal cord injury (NCT02859792), atrial fibrillation (NCT05292209), oxaliplatin-induced peripheral neuropathy (NCT03722680), and cancer (NCT01303341; NCT04761614).

Search terms:
Pubmed, Google: Riluzole

- + cognitive, + memory, + ApoE, + meta-analysis, + clinical trial, + lifespan, + cardiovascular, + diabetes, + peripheral neuropathy, + blood-brain-barrier, + trigriluzole

Websites visited for riluzole:

- Clinicaltrials.gov
- Drugs.com
- WebMD.com
- DrugBank.com
- DrugAge (0)

- Geroprotectors (0)

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