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

Used to treat ALS and is in clinical trials for Alzheimer's and other neurological/psychiatric conditions; a few adverse effects have been reported including elevated liver enzymes and blood pressure.

Neuroprotective Benefit: Many preclinical studies have shown promise for neuroprotection but it is a substrate of P-glycoprotein. A clinical trial in Alzheimer's patients is ongoing.

Aging and related health concerns: Riluzole increases survival in ALS patients and in animal models, but it has also been associated with increased blood pressure in a small study.

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 and nausea.

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). It has also been tested for Parkinson's and Huntington's, but failed in phase 3 clinical trials. ADDF is currently funding a phase II clinical trial for Alzheimer's disease, led by Ana Pereira, MD, at Rockefeller/Mount Sinai (NCT01703117). Recent clinical 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: Many preclinical studies have shown promise for neuroprotection but it is a substrate of P-glycoprotein. A clinical trial in Alzheimer's patients is ongoing.

Types of evidence:

- 1 double-blind randomized clinical trial in Huntinton'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:

Unavailable. ADDF is currently funding a phase II trial led by Ana Pereira, MD, at Rockefeller/Mount Sinai to test the effects of riluzole on cognitive functions and a neuronal viability marker (N-acetylaspartate measured with MRS) in mild Alzheimer's disease patients (NCT01703117).

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

Many studies have reported that riluzole improves cognitive functions in aged rats (Pereira et al., 2014; Pereira et al., 2017), mouse models of Alzheimer's disease (Hunsberger et al., 2015; Mokhtari et al., 2017), 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), increased vesicular glutamate transporter 1levels (which packages glutamate into vesicles), increased glutamate transporter 1 levels (which removes glutamate from extracellular space), reduced oxidative stress markers (Mokhtari et al., 2017), 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), and increased levels of the brain-derived neurotrophic factor (BDNF) in the hippocampus, which was associated with increased proliferation of precursor cells (Katoh-Semba et al., 2002).

The most recent study in young and aged rats led by Ana Pereira reported that many of the gene changes seen in Alzheimer's disease are reversed by riluzole (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 excitotoxcity 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 and in animal models, but it has also been associated with increased blood pressure in a small study.

Types of evidence:

- 1 Cochrane meta-analysis of 4 randomized controlled trials in ALS patients
- 2 clinical studies, 1 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. 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.

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 and nausea.

Types of evidence:

- 1 Cochrane meta-analysis of 4 randomized controlled trials in ALS patients
- 3 double-blind randomized clinical trials, 1 in Huntington's disease, 1 in major depressive disorder, and 1 in schizophrenia

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).

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.

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: ADDF is funding a phase II trial led by Ana Pereira, MD, at Rockefeller/Mount Sinai to test the effects of riluzole (50 mg twice a day) in mild Alzheimer's disease patients (NCT01703117). Other clinical trials are testing the effects of riluzole in spinal cord injury (NCT01597518; Fehlings et al., 2016; NCT02859792), multiple sclerosis (NCT01910259), post-traumatic stress disorder (NCT02019940), and social anxiety disorder (NCT03017508).

Biohaven Pharmaceuticals will be collaborating with the Alzheimer's Disease Cooperative Study Group (ADCS) to test trigriluzole, a third-generation prodrug of riluzole, in Alzheimer's disease patients. Trigriluzole is in a phase II clinical trial for spinocerebrellar ataxia and is also scheduled to be tested for obsessive compulsive disorder (also phase II) starting at the end of 2017 (Biohaven pipeline). Compared to riluzole, trigriluzole appears to have improved bioavailability and lower overall drug burden to the liver due to mitigated first-pass liver metabolism and lower therapeutic concentrations (Trigriluzloe vs Riluzole comparison chart).

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
- Treato.com
- Drugs.com
- WebMD.com
- DrugAge (o)
- Geroprotectors (o)