Efficacy of riluzole in the treatment of spinal cord injury: a systematic review of the literature

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OBJECTIVE Riluzole is a glutamatergic modulator that has recently shown potential for neuroprotection after spinal cord injury (SCI). While the effects of riluzole are extensively documented in animal models of SCI, there remains heterogeneity in findings. Moreover, there is a paucity of data on the pharmacology of riluzole and its effects in humans. For the present study, the authors systematically reviewed the literature to provide a comprehensive understanding of the effects of riluzole in SCI.

METHODS The PubMed database was queried from 1996 to September 2018 to identify animal studies and clinical trials involving riluzole administration for SCI. Once articles were identified, they were processed for year of publication, study design, subject type, injury model, number of subjects in experimental and control groups, dose, timing/route of administration, and outcomes.

RESULTS A total of 37 studies were included in this study. Three placebo-controlled clinical trials were included with a total of 73 patients with a mean age of 39.1 years (range 18–70 years). For the clinical trials included within this study, the American Spinal Injury Association Impairment Scale distributions for SCI were 42.6% grade A, 25% grade B, 26.6% grade C, and 6.2% grade D. Key findings from studies in humans included decreased nociception, improved motor function, and attenuated spastic reflexes. Twenty-six animal studies (24 in vivo, 1 in vitro, and 1 including both in vivo and in vitro) were included. A total of 520 animals/in vitro specimens were exposed to riluzole and 515 animals/in vitro specimens underwent other treatment for comparison. The average dose of riluzole for intraperitoneal, in vivo studies was 6.5 mg/kg (range 1–10 mg/kg). Key findings from animal studies included behavioral improvement, histopathological tissue sparing, and modified electrophysiology after SCI. Eight studies examined the pharmacology of riluzole in SCI. Key findings from pharmacological studies included riluzole dose-dependent effects on glutamate uptake and its modified bioavailability after SCI in both animal and clinical models.

CONCLUSIONS SCI has many negative sequelae requiring neuroprotective intervention. While still relatively new in its applications for SCI, both animal and human studies demonstrate riluzole to be a promising pharmacological intervention to attenuate the devastating effects of this condition.

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KEYWORDS riluzole; spinal cord injury; neuroprotection; excitotoxicity; review

SPINAL cord injury (SCI) remains a devastating problem, with traumatic SCI affecting 12,400 individuals annually and 250,000 living survivors reported to reside in the United States in July 2005.¹³ The prevalence of nontraumatic SCI is estimated to be 3–4 times greater than traumatic SCI.³⁶ A variety of complications, including genitourinary and respiratory complications, often occur after SCI with rehospitalization rates of up to 55% in the 1st year after SCI and around 37% for every year thereafter for 20 years.⁸ Moreover, while 58.1% of patients are

employed before injury, only 12.1% remained employed 1 year after injury. As a manifestation of both indirect and direct cost, patients sustaining an SCI at age 25 years can expect a lifetime cost of \$4.6 million for high tetraplegia and \$2.3 million for paraplegia.¹³ There remains a need to improve recovery after SCI, considering its high incidence and these associated complications.

The pathophysiology involved in SCI includes multiple mechanisms such as the shearing of axons,⁴⁵ followed by neural death due to ischemia,²⁸ production of inflamma-

ABBREVIATIONS AIS = American Spinal Injury Association Impairment Scale; ALS = amyotrophic lateral sclerosis; SCI = spinal cord injury.

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tory molecules,¹² and the rise of extracellular glutamate contributing to excitotoxicity.⁴³ Current acute management strategies of SCI include surgical decompression,¹⁹ maintenance of arterial pressure with fluids and vasoconstrictors,⁵² and methylprednisolone, an antiinflammatory corticosteroid that inhibits transmigration of neutrophils and macrophages into the spinal cord, thereby reducing peroxidation of lipids in the cell membrane.³ However, there remains a need for greater neuroprotective agents to promote long-term recovery after SCI.

Riluzole, a glutamatergic modulator used primarily in amyotrophic lateral sclerosis (ALS),²⁶ is currently being evaluated for use in SCI. Riluzole activates guanosine triphosphate-binding signal transduction proteins (G-proteins), resulting in inhibition of neurotransmitter release.¹⁴ Riluzole also indirectly inhibits phospholipase A2 (PLA2), preventing release of arachidonic acid, and directly inhibits protein kinase C (PKC).⁴² Recent studies have suggested that riluzole is neuroprotective in neurodegenerative and traumatic injuries through its blockade of sodium channel overactivation and modulation of glutamate uptake,⁴ as well as its stimulation of brain-derived neurotrophic factor expression.²⁹ The use and effects of riluzole specifically in SCI, however, remain relatively new.

In this article, we aim to provide an overview of riluzole's potential effectiveness in SCI and review current pharmacological, animal study, and clinical trial findings with this treatment.

Methods

A systematic review to analyze the use of riluzole in SCI was performed through PubMed with articles dating from 1996 to September 2018 (Fig. 1). The search term was "riluzole Spinal Cord Injury." This search yielded 99 results. Articles were included within this review if they presented primary human or animal data or investigated the pharmacology of riluzole in spinal cord injury. By this method, 37 experimental studies met the inclusion and exclusion criteria.

The extracted articles were then divided into 3 categories: 1) animal studies describing therapeutic benefit, 2) clinical studies describing outcomes, and 3) pharmacological studies. Two studies contributed findings to both pharmacology and therapeutic benefit in animals.^{39,58} Animal studies were evaluated for study design (in vivo vs in vitro); animal type; injury model; number of animals included in experimental and control groups; dose; timing and route of administration; and outcomes measured by behavior, histopathology, and electrophysiology. Clinical trials were reviewed for study design, number of patients in experimental and control groups, SCI level, American Spinal Injury Association Impairment Scale (AIS) grade, average age, timing and route of administration, dosage, adverse events, and outcomes measured by sensory and motor functional tests. Pharmacological studies were evaluated for study design, subject type, injury model, number of patients in experimental and control groups, timing and route of administration dosage, adverse effects and outcomes measured by electrophysiology, neurotransmitter uptake, receptor expression, and pharmacokinetics.

Results

Pharmacological Studies

Despite extensively published research on the pharmacology of riluzole, there are few studies reporting its effects on SCI. In this review, 8 studies on the pharmacological effect of riluzole in SCI were included. Pharmacological studies described the mechanisms of action and pharmacokinetics of riluzole in vivo, in vitro, and in human studies. The major findings included decreased riluzole bioavailability in the spinal cord after SCI,^{10,15} with 1 study suggesting the opposite;⁵⁸ blockage of sodium currents with riluzole after SCI;²⁵ and increase in glutamate uptake and expression,^{3,38,53} with 1 study suggesting no effect of riluzole on glutamate release after SCI.³⁵ A full description of the pharmacology articles within this study can be found in Table 1.

Animal Studies

Twenty-six animal studies describing the therapeutic effects of riluzole after SCI were included. There were 24 in vivo studies, 1 in vitro study, and 1 mixed study. A total of 520 animals/in vitro specimens were exposed to riluzole and 515 animals/in vitro specimens underwent other treatments for comparison. The average dose of riluzole used was 6.5 mg/kg in 7 in vivo studies in rats with predominantly intraperitoneal administration, with a few exceptions instead involving intrathecal and intracerebroventricular²⁴ or intravenous administration³³ and rabbits.^{31–33,39} For behavioral studies, locomotion was evaluated with the rotarod, grid walk, open field, and pellet-reaching tasks; strength was evaluated with the inclined plane test; and sensory function was evaluated with the hind paw withdrawal test. A plethora of behavioral studies demonstrated positive effects of riluzole on motor function including locomotion,^{21,27,34,38,48,58,57} strength,^{1,47,48} and stance and stride length.^{47,49} With regard to sensory function, behavioral studies have suggested that riluzole decreases nociception²⁴ and spastic reflexes,³⁰ which is both encouraging for reduction of neuropathic behaviors and concerning for decreased response to noxious stimuli. Histopathological experiments have shown that after SCI, riluzole increased rostrocaudal and epicenter tissue sparing with decreased lesion volume, increased axonal sparing, and increased serotonergic fibers.^{38,48,55} Other studies have shown an increase in glial cell and neuronal survival,^{6,34,44,58} decrease in reactive oxygen species,⁴⁹ increase in synaptophysin expression in the ventral horn,⁴⁷ decrease in capillary fragmentation,⁵⁰ decrease in pyknosis and hypoplasia of ventral motor neurons,⁴⁹ decrease in lymphocytes and granulocytes,⁷ increase in choline acetylcholine transferase staining in motor neurons,²¹ decrease in lactate dehydrogenase,²³ decrease in TUNEL staining apoptotic neurons,^{32,58,57} decrease in macrophages and microglia,⁵⁸ and decrease in lipid peroxidation and water content.¹ Electrophysiological experiments have suggested a decrease in muscle spasm,⁵ attenuation of altered reflex mechanisms,⁴⁷ and increase in amplitude of somatosensory evoked potentials.⁵⁸ Key findings within the animal data demonstrate spinal cord tissue sparing with cell survival after SCI,^{1,6,33,31–34,38,39,41,44,46,48,55,57,58} reduced inflam-

FIG. 1. Ninety-nine clinical studies regarding the use of riluzole in spinal cord injury were initially identified. Twenty-seven articles were removed for inadequate access to the full article. Seventy-two papers were fully reviewed. After applying inclusion and exclusion criteria, 37 articles were selected for review and analysis.

matory mediators and sequelae,^{7,49} improved locomotion,^{1,7,21,27,30,31–34,38,44,49,55} and decreased aberrant sensory responses.^{5,24} A full description of animal studies and the results from these investigations can be found in Table 2.

Human Clinical Studies

Three clinical studies were included in this systematic review. The average age of the patients was 39.1 years (range 18–70 years). In total, the percentage of patients included by AIS grade was 42.6% grade A, 25% grade B, 26.6% grade C, and 6.2% grade D. Most patients in the clinical studies included were severely impaired at baseline. The major findings from clinical studies included decreased pain,³⁷ increased motor functionality,²² and decreased spastic reflexes⁵⁴ after administration of riluzole for SCI. Specifically, with regard to motor function, Meshkini et al.³⁷ and Grossman et al.²² demonstrated statistically significant general motor improvement with riluzole at 6 and 3 months after acute SCI, respectively, while Theiss et al.⁵⁴ showed strong correlation of riluzole use with lower-limb volitional strength for patients with chronic, incomplete SCI. Of the 3 clinical studies included, only Meshkini et al.³⁷ evaluated reduction in pain after riluzole use, and only Theiss et al.⁵⁴ evaluated attenuation of spastic reflexes. Clinical studies consistently demonstrated incomplete recovery after SCI despite the use of riluzole as manifested by low motor^{10,37} and sensory³⁷ scores as well as debilitated voluntary contraction.⁵⁴ All patients in clinical studies were administered 50 mg of riluzole enterally. However, while Meshkini et al.³⁷ and Grossman et al.²² included a longitudinal dose of 50 mg BID (twice daily) for

8 and 4 weeks, respectively, Theiss et al.⁵⁴ only included a one-time dose of 50 mg before testing. Overall, riluzole showed promising results with a decrease in neuropathic pain and severity of SCI,³⁷ increase in motor function²² for cervical injury, and decrease in spasticity with preservation of normal voluntary movement.⁵⁴ However, these benefits were not without risk for complications, as 14%–70% of patients in the Grossman study had elevated liver enzymes and bilirubin levels, implying potentially hepatotoxic effects of riluzole in humans.²² A full description of clinical studies included within this analysis can be found in Table 3.

Discussion

This systematic review describes the potential use of riluzole for efficacy after SCI in humans and animals in improving functional and neurological outcomes after SCI, including positive neuroprotective results.¹⁸ Primary and secondary damage in SCI is mediated primarily by excitotoxicity¹⁶ and thus riluzole, a prominent antiglutamatergic agent,⁵⁶ has been a treatment of interest for SCI. Increased expression of glutamate transporters (EAAC1, GLST, and GLT-1) has been implicated in SCI with riluzole treatment increasing uptake activity of glutamate and attenuating any neuropathic pain sequelae from SCI.⁵³ Moreover, riluzole blocks persistent inward sodium currents and fast sodium spikes, which are particularly important in chronic SCI.²⁵ There is now a consensus that in neurodegenerative disorders, riluzole works predominantly through increasing glutamate uptake in astrocytes and presynaptic neurons,

TABLE 1. Pharmacology of riluzole in SCI

Authors & Year	Title	Study Design	Subject Type	Injury Model	Experimental Grp	Control Grp	Dose	Timing	Route	Adverse Effects	Main Findings
Dulin et al., 2013	The dual cyclooxygenase/5-lipoxygenase inhibitor riluzole attenuates p-glycoprotein-mediated drug resistance in the injured spinal cord	In vivo	Rat	Moderate contusion/compression injury at T10 w/ Infinite Horizon Spinal Impactor Device	Grp 1 (n = 7): SCI + riluzole; grp 2 (n = 8): SCI + riluzole + licoferone (total: 15)	Sham + riluzole (n = 7)	8 mg/kg	3 hrs postinjury & once daily for 3 days	IP	Tx-associated mortality of 30% in riluzole grp	1) PgP immunoreactivity & genetic expression ↑ in epicenter & distant rostrocaudal areas post-SCI; 2) riluzole bioavailability (spinal cord/plasma ratio) is significantly lower post-SCI; 3) knocking out PgP genetically & attenuating PgP expression w/ licoferone causes ↑ delivery of riluzole to spinal cord
Wu et al., 2013	Delayed post-injury administration of riluzole is neuroprotective in a preclinical rodent model of cervical spinal cord injury	In vivo	Rat	C7-T1 spinal cord compression extradurally w/ modified aneurysm clip	Grp 1 (n = 6): 8 mg/kg 1 hr postinjury, then 8 mg/kg BID for 7 days; grp 2 (n = 10): 6 mg/kg 1 hr postinjury, then 6 mg/kg BID for 7 days; grp 3 (n = 6): 4 mg/kg 1 hr postinjury, then 4 mg/kg BID for 7 days; grp 4 (n = 12) (p1): 8 mg/kg at 1 hr postinjury, then 6 mg/kg BID for 7 days; grp 5 (n = 12) (p3): 8 mg/kg at 3 hrs postinjury, then 6 mg/kg BID for 7 days (total: 46)	Grp 6 (n = 12): no injury + vehicle	8, 6, 4 mg/kg	1 or 3 hrs postinjury & BID for 7 days	IP	NA	Riluzole is substantially higher in spinal cord than plasma & half-life ↑ post-SCI
Chow et al., 2012	Pharmacology of riluzole in acute spinal cord injury	Phase 1 clinical trial	Human	Human	Grp 1 (n = 36): riluzole	Grp 2 (n = 36): control	50 mg	BID	PO & nasogastric	14–70% had elevated liver enzymes & bilirubin levels	Max concentration & systemic exposure of riluzole are lower in SCI pts than in ALS; riluzole has higher clearance & larger vol of distribution in SCI

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TABLE 1. Pharmacology of riluzole in SCI

Authors & Year	Title	Study Design	Subject Type	Injury Model	Experimental Grp	Control Grp	Dose	Timing	Route	Adverse Effects	Main Findings
Harvey et al., 2006	Persistent sodium currents and repetitive firing in motoneurons of the sacrocaudal spinal cord of adult rats	In vitro & in vivo	Rat	Acute SCI: transection at S2 in vivo; chronic SCI: transection at S2 at age 40–55 days	Grp 1 (n = 41): acute SCI in vivo; grp 2 (n = 24): chronic SCI in vivo; grp 3 (n = 9): in vitro (total: 74)		20 µM	Post-tissue harvesting	In vitro	NA	Riluzole blocks persistent inward currents of sodium in in vitro sacrocaudal spinal cord segments
McAdoo et al., 2005	The effect of glutamate receptor blockers on glutamate release following spinal cord injury. Lack of evidence for an ongoing feedback cascade of damage → glutamate release → damage → glutamate release → etc.	In vivo	Rat	Weight drop on MASCIS impactor (T10)	Grp 1 (n = 6): riluzole	Grp 2 (n = 6): control	2.0 mM	Continuous from preinjury to 4 hrs postinjury	Microdialysis fiber	NA	Riluzole does not affect glutamate release post-SCI
Sung et al., 2003	Altered expression and uptake activity of spinal glutamate transporters after nerve injury contribute to the pathogenesis of neuropathic pain in rats	In vivo	Rat	Chronic constriction nerve injury	Grp 1 (n = 6): CCI + 1 mg/kg riluzole pre-Tx; grp 2 (n = 6): CCI + 4 mg/kg riluzole pre-Tx; grp 3 (n = 6): CCI + 1 mg/kg post-Tx; grp 4 (n = 6): CCI + 4 mg/kg post-Tx (total: 24)	Grp 5 (n = 6): CCI + vehicle; grp 6 (n = 6): sham + 4 mg/kg post-Tx (total: 12)	1 or 4 mg/kg	Pre-Tx (grps 1 & 2): starts immediately postinjury; post-Tx (grps 3 & 4): starts 5 DPI; BID for 4 days for both grps	IP	NA	SCI induces significant expression of spinal glutamate transporters (EAC1, GLST, GLT-1) in ipsilesional spinal cord dorsal horn; riluzole significantly ↑ glutamate uptake in ipsilesional spinal cord dorsal horn; riluzole administered immediately postinjury or 5 DPI attenuates neuropathic behaviors including thermal hyperalgesia & mechanical allodynia

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TABLE 1. Pharmacology of riluzole in SCI

Authors & Year	Title	Study Design	Subject Type	Injury Model	Experimental Grp	Control Grp	Dose	Timing	Route	Adverse Effects	Main Findings
Azbill et al., 2000	Riluzole increases high-affinity glutamate uptake in rat spinal cord synaptosomes	In vitro & in vivo	Rat	None	Grp 1 (n = 6): riluzole	Grp 2 (n = 6): saline	8 mg/kg	2 × w/ 2 hrs btwn injection (euthanasia 2 hrs after last injection)	IP	NA	Riluzole ↑ glutamate uptake in spinal cord synaptosomes at 1 & 0.1 μM in vitro but not at higher doses; 0.1 μM riluzole causes 21% ↓ in Km & 31% ↑ in Vmax of glutamate
Mu et al., 2000 ³⁹	Riluzole improves measures of oxidative stress following traumatic spinal cord injury	In vivo	Rabbit	Contusion injury (impactor rod at T10)	Grp 1 (n = 9): riluzole; grp 2 (n = 9): riluzole + methylprednisolone (total: 18)	Grp 3 (n = 9): vehicle; grp 4 (n = 9): methylprednisolone (total: 18)	8 mg/kg	15 mins & 2 hrs post-injury	IP	NA	Riluzole ↑ glutamate & glucose uptake post-SCI

BID = twice daily; CCI = chronic constriction injury; DPI = days postinjury; grp = group; IP = intraperitoneal; MASCI = Multicenter Animal Spinal Cord Injury Study; max = maximum; NA = not available; PO = by mouth; pts = patients; p1 = rats treated with riluzole at 1 hour postinjury, p3 = rats treated with riluzole at 3 hours postinjury; Tx = treatment; ↑ = increase/increases/increased/increasing; ↓ = decrease/decreases/decreased/decreasing.
 Eight studies with 6 in vivo experiments, 3 in vitro experiments, and 1 human study.

TABLE 2. Impact of riluzole on SCI in vitro and in vivo animal experiments

Authors & Year	Title	Study Design	Subject Type	Injury Model	Experimental Grp	Control Grp	Dose	Timing	Route	Main Findings
Caglar et al., 2018	Effect of riluzole on spinal cord regeneration with hemisection method before injury	In vivo	Rat	Hemisection after T7–9 laminectomy	Grps 1–6 & 8 (n = 28): riluzole	Grp 7 (n = 4): vehicle	6 mg/kg	Grps 1 & 6: 12 hrs pre-SCI & BID post-SCI until 7 DPI; grps 2 & 5: 1 hr pre-SCI & BID post-SCI until 7 DPI; grps 3 & 4: BID post-SCI until 7 DPI; grp 8: BID for 5 days pre-SCI but not post-SCI	IP	Histopathology: early riluzole Tx causes lower histopathological spinal cord tissue damage & ↑ no. of surviving glial cells & neurons
Shimizu et al., 2018	Prophylactic riluzole attenuates oxidative stress damage in spinal cord distraction	In vivo	Rat	Bidirectional spinal distractor device	Grp 1 (n = 54): riluzole	Grp 2 (n = 54): vehicle	8 mg/kg initial dose, then 6 mg/kg	BID	IP	Histopathology: riluzole Tx ↓ reactive oxygen species formation & attenuates pyknosis & hypoplasia of ventral motor neurons post-SCI Behavior: riluzole Tx maintains normal gait post-SCI as measured by ↑ stance duration & ↓ stride length
Martins et al., 2018	Association of riluzole and dantrolene improves significant recovery after acute spinal cord injury in rats	In vivo	Rat	Extradural compression of dorsal surface of spinal cord using weight	Grp 1 (n = 5): laminectomy + SCI + riluzole + placebo (15 mins & 1 hr postlaminectomy); grp 2 (n = 6): laminectomy + SCI + riluzole + dantrolene (15 mins/1 hr postlaminectomy) (total: 11)	Grp 3 (n = 6): laminectomy + placebo; grp 4 (n = 6): laminectomy + SCI; grp 5 (n = 6): laminectomy + SCI + placebo + dantrolene (15 mins/1 hr postlaminectomy) (total: 18)	4 mg/kg	15 mins & 1 hr postlaminectomy	IP	Immunohistochemistry: when combined w/ dantrolene, riluzole significantly ↑ neuron survival in epicenter of injury & caudal regions as well Behavior: when combined w/ dantrolene, riluzole improves hindlimb performance on BBB scale; riluzole alone does not improve hindlimb performance
Can et al., 2017	Combined and individual use of pancaspase inhibitor Q-VD-OPH and NMDA receptor antagonist riluzole in experimental spinal cord injury	In vivo	Rat	Clip compression via T7–9 laminectomies	Grp 1 (n = 9): SCI + riluzole only; grp 2 (n = 9): SCI + both riluzole & Q-VD-OPH (total: 18)	Grp 3 (n = 9): SCI only; grp 4 (n = 9): SCI + vehicle; grp 5 (n = 9): SCI + Q-VD-OPH (pancaspase inhibitor) only (total: 27)	5 mg/kg	1 hr postinjury	IP	Histopathology: riluzole Tx significantly ↓ lymphocyte count & polymorphonuclear leukocytes/granulocytes post-SCI; riluzole Tx does not significantly attenuate no. of apoptotic cells post-SCI Behavior: riluzole significantly improves clinical motor score & inclined plane score post-SCI

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TABLE 2. Impact of riluzole on SCI in vitro and in vivo animal experiments

Authors & Year	Title	Study Design	Subject Type	Injury Model	Experimental Grp	Control Grp	Dose	Timing	Route	Main Findings
Gloviczki et al., 2017	Delayed spinal cord-brachial plexus reconnection after C7 ventral root avulsion: the effect of reinnervating motoneurons rescued by riluzole treatment	In vivo	Rat	C7 ventral root avulsion + C7 autologous nerve graft	Grp 1 (n = 5): avulsion + immediate reconnection + riluzole; grp 2 (n = 5): avulsion + 1-wk delay to reconnection + riluzole; grp 3 (n = 5): avulsion + 3-wk delay to reconnection + riluzole (total: 15)	Grp 4 (n = 5): avulsion + immediate reconnection; grp 5 (n = 5): avulsion + 1-wk delay to reconnection; grp 6 (n = 5): avulsion + 3-wk delay to reconnection (total: 15)	5 mg/kg	Daily for 1st wk & every 2nd day for 2nd wk	IP	Histopathology: riluzole Tx significantly improves motor neuron survival independent of timing of reconnection procedure relative to injury Behavior: riluzole significantly improves pellet reaching & dorsiflexion after reconnection after ventral root avulsion
Brocard et al., 2016	Cleavage of Na ⁺ channels by calpain increases persistent Na ⁺ current and promotes spasticity after spinal cord injury	In vivo	Rat	Spinal cord transection at T9	Grp 1 (n = 8): 8 mg/kg once; grp 2 (n = 8): 4 mg/kg BID for 2 wks; grp 3 (n = 7): 1 mg/kg BID for 2 wks (total: 23)	NA	8, 4, & 1 mg/kg	8 mg/kg once, 4 mg/kg BID for 2 wks, or 1 mg/kg BID for 2 wks	IP	Electrophysiology: as measured by EMG, riluzole Tx at moderate dose (8 or 4 mg/kg) significantly ↓ muscle spasm & augments muscle spasm reduction when voltage-gated sodium channels are spared post-SCI; riluzole does not attenuate monosynaptic reflexes associated w/ glutamatergic currents
Vasconcelos et al., 2016	Combining neuroprotective agents: effect of riluzole and magnesium in a rat model of thoracic spinal cord injury	In vivo	Rat	Thoracic spinal cord contusion w/ weight drop	Grp 1 (n = 4): riluzole; grp 2 (n = 5): riluzole + MgCl (total: 9)	Grp 3 (n = 5): saline; grp 4 (n = 5): MgCl (total: 10)	2.50 mg/kg	1 hr postinjury	IP	Histopathology: riluzole ↓ lesion vol, ↑ axonal preservation, & ↑ glutamatergic & serotonergic fiber sparing caudal but not rostral to epicenter of injury; riluzole does not significantly ↑ motor neuron survival Behavior: riluzole significantly improves locomotor score as measured on BBB scale; riluzole significantly ↑ distance traveled in activity box

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TABLE 2. Impact of riluzole on SCI in vitro and in vivo animal experiments

Authors & Year	Title	Study Design	Subject Type	Injury Model	Experimental Grp	Control Grp	Dose	Timing	Route	Main Findings
Satkun- drara- jah et al., 2016	Riluzole promotes motor and respiratory recovery associated with enhanced neuronal survival and function following high cervical spinal hemisection	In vivo	Rat	Complete lt hemisection from midline below C2 dorsal root	Grp 1 (n = 18): riluzole	Grp 2 (n = 17): vehicle	8 mg/kg	1 hr postinjury, then BID for 7 days	IP	Histopathology: riluzole Tx ↑ synaptophysin expression in caudal cervical ventral horn; riluzole Tx attenuates loss of NR2A subunit of NMDA receptor & GluR1 subunit of AMPA receptor; riluzole attenuates motor neuron loss as measured by ChAT positivity on ipsilesional & contralesional sides of injury Electrophysiology: riluzole Tx attenuates injury-mediated alteration in Hmax/Mmax ratio Behavior: riluzole Tx improves ipsilateral forelimb grip strength as early as 3 DPI & contralateral forelimb grip strength as early as 19 DPI; riluzole Tx ↑ stride length, swing speed, & forepaw width on catwalk test from 2 to 6 wks postinjury; riluzole Tx ↑ peak amplitude of inspiratory bursts of ipsilateral diaphragm 2 wks postinjury
Hachem et al., 2015	Evaluation of the effects of riluzole on adult spinal cord-derived neural stem/progenitor cells in vitro and in vivo	In vivo + in vitro	Rat	Rodent clip compression + injection of neural progenitor cells in proximal rostral & caudal regions to injury epicenter	Grp 1 (n = 4): riluzole	Grp 2 (n = 4): vehicle	8 mg/kg	Immediately post-transplant, 6 mg/kg BID for 3 days, then once daily for 10 days	IP	Histopathology In vitro: exposure to high doses of riluzole ↓ neural progenitor stem cell survival & membrane integrity; riluzole does not affect no. of living or proliferating neural progenitor stem cells after glutamate exposure. In vivo: riluzole does not affect survival or phenotype of cells in neural progenitor stem cell graft

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TABLE 2. Impact of riluzole on SCI in vitro and in vivo animal experiments

Authors & Year	Title	Study Design	Subject Type	Injury Model	Experimental Grp	Control Grp	Dose	Timing	Route	Main Findings
Hosier et al., 2015	A direct comparison of three clinically relevant treatments in a rat model of cervical spinal cord injury	In vivo	Rat	Lower cervical hemisection contusion at C7	Grp 1 (n = 10): riluzole	Grp 1 (n = 10): glibenclamide; grp 2 (n = 10): hypothermia; grp 3 (n = 10): vehicle (total: 30)	5 mg/kg	BID for 7 days	IP	Behavior: riluzole significantly improves locomotor score on mBBB scale 3 wks postinjury & accelerating rotarod 5 wks postinjury
Wu et al., 2014	Riluzole improves outcome following ischemia-reperfusion injury to the spinal cord by preventing delayed paraplegia	In vivo	Rat	High thoracic aortic balloon occlusion	Grp 1 (n = 7): riluzole	Grp 2 (n = 7): vehicle	8 mg/kg	4 hrs postinjury	IP	Histopathology: riluzole Tx ↑ neuron survival & ↓ no. of reactive astrocytes in laminae 7 & 9 but not 2; riluzole Tx ↓ macrophages & microglia in laminae 7, 8, & 9; riluzole Tx attenuates ischemia-related apoptosis as measured by TUNEL staining
Wu et al., 2013	Delayed post-injury administration of riluzole is neuroprotective in a preclinical rodent model of cervical spinal cord injury	In vivo	Rat	C7-T1 extradural spinal cord compression for 1 min w/ modified aneurysm clip	Grp 1 (n = 6): 8 mg/kg 1 hr postinjury, then 8 mg/kg BID for 7 days; grp 2 (n = 10): 6 mg/kg 1 hr postinjury, then 6 mg/kg BID for 7 days; grp 3 (n = 6): 4 mg/kg 1 hr postinjury, then 4 mg/kg BID for 7 days; grp 4 (p1) (n = 12): 8 mg/kg at 1 hr postinjury, then 6 mg/kg BID for 7 days; grp 5 (p3) (n = 12): 8 mg/kg at 3 hrs postinjury, then 6 mg/kg BID for 7 days (total: 46)	Grp 6 (n = 12): no injury + vehicle	8, 6, 4 mg/kg	1 or 3 hrs postinjury, then BID for 7 days	IP	Histopathology: early riluzole Tx ↑ tissue sparing caudal to injury epicenter & cytoskeletal integrity of axons while ↓ apoptosis; delayed riluzole Tx does not significantly reduce apoptosis; both early & delayed riluzole Tx improve axonal connections & reduce inflammation

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TABLE 2. Impact of riluzole on SCI in vitro and in vivo animal experiments

Authors & Year	Title	Study Design	Subject Type	Injury Model	Experimental Grp	Control Grp	Dose	Timing	Route	Main Findings
Sámano et al., 2012	A study of the potential neuroprotective effect of riluzole on locomotor networks of the neonatal rat spinal cord in vitro damaged by excitotoxicity	In vitro	Rat	Transient kainate (glutamate agonist) at 0.05–0.1 mM to produce excitotoxicity	Grp 1 (n = 3): riluzole alone for 3 hrs in vitro postkainate washout; grp 2 (n = 3): riluzole alone for 24 hrs in vitro postkainate wash out (total: 6)	Grp 3 (n = 6): sham; grp 4 (n = 3): 0.05 mM kainate alone (1 hr); grp 5 (n = 6): 0.01 mM kainate alone (1 hr) (total: 15)	5 µM	3 or 24 hrs postinjury	In vitro	Histopathology: continuous but not short duration of riluzole attenuates pyknosis in dorsal, central, & ventral horns of spinal cord; continuous duration of riluzole ↑ dorsal & central neuron survival w/ no significant effect on ventral neuron survival; short duration of riluzole had opposite effect Electrophysiology: riluzole does not significantly improve peak amplitude of polysynaptic response to dorsal root stimulation or reflex area
Simard et al., 2012	Comparative effects of glibenclamide and riluzole in a rat model of severe cervical spinal cord injury	In vivo	Rat	Unilat cervical impactor on dura mater near lt C8 nerve root	Grp 1 (n = 3): riluzole; grp 2 (n = 13): riluzole (total: 16)	Grp 3 (n = 3): vehicle; grp 4 (n = 13): glibenclamide; grp 5 (n = 15): vehicle (total: 31)	2.5 mg/kg	Grp 1: once postinjury; grp 2: 3 hrs postinjury, then BID for 7 days	Grp 1: IP; grp 2: os-motic pump injury	Histopathology: riluzole Tx ↓ capillary fragmentation in penumbra microvessels & ↑ NeuN+ neurons in ventral gray matter contralat to injury site; compared w/ glibenclamide, riluzole Tx had significantly larger lesion vol 6 wks post-SCI Behavior: compared w/ glibenclamide, riluzole-treated rats had significantly worse grip strength, performance on rotarod, & lower mBBB scores
Hama & Sagen, 2011	Antinociceptive effect of riluzole in rats with neuropathic spinal cord injury pain	In vivo	Rat	Compressive injury to mid-thoracic (T6/T7) spinal cord w/ microvascular clamp	Grp 1 (n = 18): ICV delivery post-SCI; grp 2 (n = 18): IT delivery post-SCI; grp 3 (n = 11): 8 mg/kg IP (total: 47)	Grp 4 (n = 10): ICV vehicle; grp 5 (n = 12): IT vehicle; grp 6 (n = 11): IP vehicle (total: 33)	IT/ICV: 5 µl; IP: 8 mg/kg	4 wks postinjury	IT, ICV, & IP	Behavior: IP riluzole Tx ↓ nociception in healthy controls & experimental animals undergoing SCI; ICV but not IT riluzole ↓ nociception post-SCI

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TABLE 2. Impact of riluzole on SCI in vitro and in vivo animal experiments

Authors & Year	Title	Study Design	Subject Type	Injury Model	Experimental Grp	Control Grp	Dose	Timing	Route	Main Findings
Pintér et al., 2010	Increased survival and reinnervation of cervical motoneurons by riluzole after avulsion of the C7 ventral root	In vivo	Rat	C7 ventral root avulsion + reimplantation	Grp 1 (n = 5): ventral root avulsion + reimplantation + riluzole; grp 2 (n = 5): ventral root avulsion + riluzole (total: 10)	Grp 3 (n = 5): ventral root avulsion; grp 4 (n = 5): ventral root avulsion + reimplantation; grp 5 (n = 5): ventral root avulsion + sural nerve graft implantation (total: 15)	4 mg/kg	Postop, daily for wk 1, then BID for wks 2 & 3	IP	Histopathology: riluzole ↑ motor neuron survival after ventral root avulsion & augments motor neuronal survival & axonal growth after reinnervation Behavior: riluzole augments functional recovery in forelimb after reinnervation in a time-delayed manner
Kitzman, 2009	Effectiveness of riluzole in suppressing spasticity in the spinal cord injured rat	In vivo cross-over	Rat	S2 spinal transection	Grp 1 (n = 10): riluzole 8 mg/kg; grp 2 (n = 9): saline 10 mg/kg (total: 19)	Grp 1 (n = 10): saline 8 mg/kg; grp 2 (n = 9): saline 10 mg/kg (total: 19)	8 or 10 mg/kg	Once daily for 3 DPI	IP	Histopathology: riluzole ↑ motor neuron survival after ventral root avulsion & augments motor neuronal survival & axonal growth after reinnervation Behavior: Tx w/ both 8 & 10 mg/kg riluzole ↓ response to noxious (pinch) & nonnoxious (light touch) stimuli, w/ 10 mg/kg also attenuating quick stretch reflex
Ates et al., 2007	Comparative neuroprotective effect of sodium channel blockers after experimental spinal cord injury	In vivo	Rat	Weight-drop trauma at T7–T10 (50 g/cm)	Grp 1 (n = 18): riluzole	Grp 1 (n = 18): sham; grp 2 (n = 18): vehicle; grp 3 (n = 18): mexiletine; grp 4 (n = 18): phenytoin (total: 72)	8 mg/kg	Single dose postinjury	IP	Histopathology: riluzole reduces spinal cord lesion area, lipid peroxidation, & spinal cord water content Behavior: riluzole improves motor function & inclined plane score
Nógrádi et al., 2007	Delayed riluzole treatment is able to rescue injured rat spinal motoneurons	In vivo	Rat	L4 ventral root avulsion + reimplantation dorsolaterally	Grp 1 (n = 5): injury + riluzole immediately; grp 2 (n = 5): injury + riluzole 5 DPI; grp 3 (n = 5): injury + riluzole 10 DPI; grp 4 (n = 5): injury + riluzole 14 DPI; grp 5 (n = 5): injury + riluzole 16 DPI (total: 25)	Grp 6 (n = 3): sham; grp 7 (n = 4): injury + no Tx (total: 7)	4 mg/kg	Immediately, 5, 10, 14, or 16 DPI 1st dose + daily 1 wk + BID for next 2 wks	IP	Histopathology: early (10 DPI & before) riluzole Tx ↑ motor neuron survival compared w/ delayed (14 DPI & after) riluzole Tx

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TABLE 2. Impact of riluzole on SCI in vitro and in vivo animal experiments

Authors & Year	Title	Study Design	Subject Type	Injury Model	Experimental Grp	Control Grp	Dose	Timing	Route	Main Findings
Springer et al., 1997	Rapid calpain I activation and cytoskeletal protein degradation following traumatic spinal cord injury: attenuation with riluzole pretreatment	In vivo	Rat	Contusion injury (Impactor probe at T10)	Grp 1 (n = 6): SCI + riluzole	Grp 2 (n = 6): vehicle	8 mg/kg	15 mins pre- & 2 hrs postinjury	IP	Histopathology: riluzole Tx significantly ↑ MAP2 levels, a marker of structural neuronal integrity
Schwartz & Fehlings, 2001	Evaluation of the neuroprotective effects of sodium channel blockers after spinal cord injury: improved behavioral and neuroanatomical recovery with riluzole	In vivo	Rat	Compressive SCI at C7-T1	Grp 1 (n = 15): riluzole	Grp 2 (n = 15): vehicle	5 mg/kg	15 mins postop	IP	Histopathology: riluzole attenuates gray matter loss rostrocaudal to ↑ injury epicenter; riluzole attenuates normalized epicenter cavity area; riluzole ↑ red nuclei neurons caudal to injury Behavior: riluzole significantly ↑ hindlimb function on BBB scale & strength on inclined plane scale
Mu et al., 2000 ³⁹	Riluzole and methylprednisolone combined treatment improves functional recovery in traumatic spinal cord injury	In vivo	Rat	NYU impactor	Grp 1 (n = 9): riluzole; grp 2 (n = 9): riluzole + methylprednisolone (total: 18)	Grp 3 (n = 9): vehicle	8 mg/kg	2 & 4 hrs postinjury	IP	Histopathology: riluzole w/ methylprednisolone & not alone causes significant tissue sparing at lesion epicenter Behavior: riluzole w/ methylprednisolone ↑ locomotor function in open field test
Lips et al., 2000	Neuroprotective effects of riluzole and ketamine during transient spinal cord ischemia in the rabbit	In vivo	Rabbit	Aortic occlusion w/ balloon catheter	Grp 1 (n = 15): injury + riluzole; grp 2 (n = 15): injury + riluzole + ketamine (total: 30)	Grp 3 (n = 15): injury + control	8 mg/kg	15 mins IV preinjury & BID IP for 3 DPI	IV & IP	Histopathology: riluzole Tx ↑ motor neurons in ventral horn Behavior: riluzole Tx reduces overall neurological deficits & paraplegia incidence, & improves Tarlov score

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TABLE 2. Impact of riluzole on SCI in vitro and in vivo animal experiments

Authors & Year	Title	Study Design	Subject Type	Injury Model	Experimental Grp	Control Grp	Dose	Timing	Route	Main Findings
Lang-Lazdunski et al., 2000 ³²	Ischemic spinal cord injury induced by aortic cross-clamping: prevention by riluzole	In vivo	Rabbit	Direct aortic arch + lt subclavian artery cross-clamping	Grp 1 (n = 15): injury + riluzole	Grp 2 (n = 15): no injury; grp 3 (n = 15): injury + control (total: 30)	4 mg/kg	30 mins preinjury & at onset of reperfusion	IV	Histopathology: riluzole Tx attenuates reduction of MAP2 levels in dorsal horn & intermediate zone, reduces apoptosis in gray matter & completely prevents apoptosis in ventral horns as measured by TUNEL staining, & reduces fragmenting of DNA Behavior: riluzole Tx ↑ neurological outcomes on MSDI as early as 24 hrs after reperfusion
Lang-Lazdunski et al., 2000 ³¹	Prevention of ischemic spinal cord injury: comparative effects of magnesium sulfate and riluzole	In vivo	Rabbit	Infraarenal aorta occlusion for 40 mins	Grp 1 (n = 17): riluzole before clamping; grp 2 (n = 17): MgSO ₄ + riluzole before clamping (total: 34)	Grp 3 (n = 17): vehicle; grp 4 (n = 15): MgSO ₄ before clamping (total: 32)	8 mg/kg	Before clamping	IV	Histopathology: riluzole Tx attenuates neuronal damage & preserves Map2 expression Behavior: riluzole Tx ↑ Tarlov score as early as 24 hrs after reperfusion
Mu et al., 2000 ³³	Riluzole improves measures of oxidative stress following traumatic spinal cord injury	In vivo	Rabbit	Contusion injury (impactor rod at T10)	Grp 1 (n = 9): riluzole; grp 2 (n = 9): riluzole + methylprednisolone (total: 18)	Grp 3 (n = 9): vehicle; grp 4 (n = 9): methylprednisolone (total: 18)	8 mg/kg	15 mins & 2 hrs postinjury	IP	Histopathology: riluzole Tx alone significantly ↑ mitochondrial function in synaptosomes; riluzole Tx alone does not significantly ↓ reactive oxygen species; riluzole Tx w/ methylprednisolone but not alone significantly reduces lipid peroxidation

BBB = Basso-Beattie-Bresnahan; EMG = electromyography; ICV = intracerebroventricular; IV = intravenous; mBBB = modified BBB; MSDI = motor sensory deficit index; NYU = New York University. Twenty-six studies with 24 in vivo studies, 1 in vitro study, and 1 combined study; 520 animals were in the riluzole treatment arm and 515 animals were in comparative control groups.

TABLE 3. Impact of riluzole on SCI in humans

Authors & Year	Title	Study Design	No. of Pts Receiving Riluzole	No. of Pts Receiving Placebo	SCI Level	AIS Grade	Average Age, yrs	Dose	Timing	Route	Adverse Effects	Main Findings
Meshkini et al., 2018	Riluzole can improve sensory and motor function in patients with acute spinal cord injury	Parallel grp, placebo controlled	30	30	NA	40% A; 30% B; 30% C	36.9	50 mg	BID for 8 wks	PO	NA	Pts on riluzole had ↓ pain on VAS system & significantly less severe SCI as determined by Frankel class 6 mos postop
Grossman et al., 2014	A prospective, multicenter, phase I matched-comparison grp trial of safety, pharmacokinetics, and preliminary efficacy of riluzole in patients with traumatic spinal cord injury	Parallel grp, placebo controlled	36	36	77.8% C4–8; 13.9% T1–6; 8.3% T7–12	52.8% A; 25% B; 22.2% C	40	50 mg	BID for 28 days	PO, nasogastric tube	14–70% had elevation of liver enzymes & bilirubin levels	Pts on riluzole w/ cervical SCI had significantly higher motor scores (ISNCSCI) than controls 90 days postop
Theiss et al., 2011	Riluzole decreases flexion withdrawal reflex but not voluntary ankle torque in human chronic spinal cord injury	w/in grp, placebo controlled	7	7 (same pts)	14.3% C1–4; 57.1% C4–8; 14.3% T1–6; 14.3% T7–12	35.7% C; 64.3% D	44	50 mg	Once	PO	None	Riluzole significantly ↑ threshold stimulation intensity & average sustained torque while ↓ peak amplitude of ankle dorsiflexion torque for flexion withdrawal response; riluzole does not significantly change mean peak torque during max voluntary contraction

ISNCSCI = International Standards for Neurological Classification of Spinal Cord Injury; VAS = visual analog scale. Three studies with corresponding baseline AIS grade distributions of 42.6% grade A, 25% grade B, 26.6% grade C, and 6.2% grade D.

blocking presynaptic release of glutamate, and blocking persistent sodium currents.¹¹ Of significance, in contrast to ALS where a high bioavailability (> 90%) is reported,⁹ riluzole in SCI in humans exhibited a lower maximum concentration and systemic exposure 0–12 hours after dosing.¹⁰ Even more importantly, in SCI, there is inflammation, which increases the spinal cord expression of PgP, a drug efflux transporter, which decreases the bioavailability of riluzole in the spinal cord compared to plasma, so anti-inflammatory medications such as COX or LOX-5 inhibitors decrease PgP expression and increase bioavailability of riluzole in the spinal cord.¹⁵ However, other studies have suggested that the half-life of riluzole increases with SCI and remains substantially higher in the spinal cord than in the plasma.⁵⁸ The effects of riluzole seem dose-dependent, with glutamatergic uptake activity of 0.1 and 1.0 μM riluzole in spinal cord synaptosomes that are not replicated at higher doses.² Careful dose management is likely required for effective treatment of riluzole in humans. Moreover, in one pharmacological study, there was a 30% treatment-associated mortality with riluzole,¹⁵ suggesting that despite therapeutic benefits, conservative administration of riluzole in SCI is required for most optimal results.

Within the animal studies, there were significant therapeutic benefits of riluzole manifested by increased tissue sparing,^{1,6,21,30,32,33,38,39,41,44,46–49,55,57,58} decreased neuropathy,^{5,24} improved motor function,^{1,7,21,27,32–34,38,44,47–49,55} and reduction of aberrant electrophysiology.^{5,47} Histological benefits of riluzole were often localized caudal to the injury epicenter.^{34,47,48,55,58} Specifically, riluzole decreased molecular markers of injury such as reactive oxygen species⁴⁹ and immune cells,^{7,58} while preserving markers of plasticity and structural integrity such as MAP2,^{32,51} synaptophysin, and subunits of the NMDA receptor and AMPA receptor.⁴⁷ This neuroprotective effect of riluzole was often augmented by other pharmacological agents, such as methylprednisolone^{38,39} and dantrolene.³⁴ Moreover, several studies demonstrated dose-dependent,⁵ time-dependent,^{41,46} and route-dependent²⁴ efficacy of riluzole in SCI, suggesting that dose, timing, and route are important factors to consider in clinical SCI. While studies demonstrate poor efficacy of riluzole in select experiments—behaviorally,³⁴ histologically,^{7,23,39,50,55} or via electrophysiological measurements^{46,50}—no study exclusively reported negative results. Rather, the efficacy of riluzole can be subtherapeutic or inferior to other neuroprotective agents contingent on a variety of aforementioned factors.

Many studies produced negative results, with riluzole having little effect on outcomes. For example, one study showed that riluzole alone without methylprednisolone does not improve locomotion or tissue sparing.³⁸ Likewise, another study showed that riluzole does not reduce apoptosis or increase motor function or strength after SCI.⁷ A similar study showed that riluzole does not affect survival or the phenotype of cells after a neural stem and progenitor cell graft.²³ Sámano et al.⁴⁶ suggested that there is no change in peak amplitude of polysynaptic response to dorsal root stimulation or reflex area in vivo, and no change in ventral motor neuron cell survival in vitro with riluzole. However, a variety of studies found the opposite with regard to ventral motor neuron cell survival.^{33,41,44} Mu et al.³⁹

suggested that riluzole does not reduce reactive oxygen species or lipid deoxidation, but the opposite was found by Shimizu et al.⁴⁹ and Ates et al.,¹ respectively. Given the discrepancy in outcomes between animal studies, riluzole may be neuroprotective in SCI on a selective basis. For example, studies have shown that with higher doses, riluzole had longer-lasting and more effective outcomes.^{5,23} However, also with high doses of riluzole, adverse outcomes such as death and respiratory distress have been reported.⁵⁸

Of encouragement, early clinical studies suggested that riluzole is efficacious in decreasing neuropathic pain,³⁷ increasing motor recovery,²² and decreasing aberrant reflexes.⁵⁴ However, given the relatively sparse number of patients ($n = 73$) and potential hepatotoxic effects of riluzole²² in SCI, there remains a need for more robust clinical data on safety and therapeutic benefit from the phase 2 and 3 clinical trials.¹⁸ This is especially true considering the wide range of adverse effects reported with riluzole use in ALS, including hypertension, peripheral edema, pancreatitis,¹⁷ neutropenia, renal disease, interstitial lung disease, and hepatotoxicity. The use of riluzole in SCI is documented far more extensively in animal models than in humans. Given this disparity in total subjects, animal studies have greater power, and the neuroprotective effects of riluzole after SCI in animals are well known. As more patients are enrolled in the ongoing phase 2 clinical trial, the effects of riluzole on motor, sensory, and neurological function will become better understood.¹⁸ Thus, the primary limitation of this review includes extrapolation of animal data to the clinical efficacy of riluzole. Moreover, the most common adverse effects of riluzole are described more extensively in ALS than in SCI. According to the National Spinal Cord Injury Center, life expectancy for patients with SCI remains significantly lower than for those without SCI, and this disparity has not been improving since the 1980s.⁴⁰ Given the astronomical inpatient and outpatient costs associated with SCI,²⁰ improving patient outcomes with neuroprotective agents can decrease cost and improve quality of life.

Conclusions

The neuroprotective effects of riluzole in SCI are promising, but the therapeutic benefit of riluzole in SCI must be appreciated in the appropriate clinical context. Success in animal models does not always translate to success in humans. While preliminary human studies suggest that riluzole may have a role in decreasing neuropathic pain and improving motor recovery for patients with SCI, there remains a need to substantiate these data with consistently reported clinical studies. However, other studies have demonstrated adverse effects, including pancreatitis, lung disease, and neutropenia, without conferring much clinical benefit. As the drug advances through the subsequent clinical trial stages, it will be important to titrate the dose and timing to maximize benefits in appropriately selected patients to minimize adverse or ineffective outcomes. Nevertheless, these efforts provide the opportunity to expand the existing, limited pharmacological treatment options to mitigate the devastating effects of SCI and to offer patients the possibility of medical options to improve long-term function and pain control.

References

1. Ates O, Cayli SR, Gurses I, Turkoz Y, Tarim O, Cakir CO, et al: Comparative neuroprotective effect of sodium channel blockers after experimental spinal cord injury. **J Clin Neurosci** 14:658–665, 2007
2. Azbill RD, Mu X, Springer JE: Riluzole increases high-affinity glutamate uptake in rat spinal cord synaptosomes. **Brain Res** 871:175–180, 2000
3. Bartholdi D, Schwab ME: Methylprednisolone inhibits early inflammatory processes but not ischemic cell death after experimental spinal cord lesion in the rat. **Brain Res** 672:177–186, 1995
4. Bellingham MC: A review of the neural mechanisms of action and clinical efficiency of riluzole in treating amyotrophic lateral sclerosis: what have we learned in the last decade? **CNS Neurosci Ther** 17:4–31, 2011
5. Brocard C, Plantier V, Boulenguez P, Liabeuf S, Bouhadfane M, Viallat-Lieutaud A, et al: Cleavage of Na⁺ channels by calpain increases persistent Na⁺ current and promotes spasticity after spinal cord injury. **Nat Med** 22:404–411, 2016
6. Caglar YS, Demirel A, Dogan I, Huseynov R, Eroglu U, Ozgural O, et al: Effect of riluzole on spinal cord regeneration with hemisection method before injury. **World Neurosurg** 114:e247–e253, 2018
7. Can H, Aydoseli A, Gömleksiz C, Göker B, Altunrende ME, Dolgun M, et al: Combined and individual use of pancaspase inhibitor Q-VD-OPh and NMDA receptor antagonist riluzole in experimental spinal cord injury. **Ulus Travma Acil Cerrahi Derg** 23:452–458, 2017
8. Cardenas DD, Hoffman JM, Kirshblum S, McKinley W: Etiology and incidence of rehospitalization after traumatic spinal cord injury: a multicenter analysis. **Arch Phys Med Rehabil** 85:1757–1763, 2004
9. Cheah BC, Vucic S, Krishnan AV, Kiernan MC: Riluzole, neuroprotection and amyotrophic lateral sclerosis. **Curr Med Chem** 17:1942–199, 2010
10. Chow DS, Teng Y, Toupes EG, Aarabi B, Harrop JS, Shaffrey CI, et al: Pharmacology of riluzole in acute spinal cord injury. **J Neurosurg Spine** 17 (1 Suppl):129–140, 2012
11. Cifra A, Mazzone GL, Nistri A: Riluzole: what it does to spinal and brainstem neurons and how it does it. **Neuroscientist** 19:137–144, 2013
12. David S, Kroner A: Repertoire of microglial and macrophage responses after spinal cord injury. **Nat Rev Neurosci** 12:388–399, 2011
13. DeVivo MJ, Chen Y, Mennemeyer ST, Deutsch A: Costs of care following spinal cord injury. **Top Spinal Cord Inj Rehabil** 16:1–9, 2011
14. Doble A: The pharmacology and mechanism of action of riluzole. **Neurology** 47 (6 Suppl 4):S233–S241, 1996
15. Dulin JN, Moore ML, Grill RJ: The dual cyclooxygenase/5-lipoxygenase inhibitor licofelone attenuates p-glycoprotein-mediated drug resistance in the injured spinal cord. **J Neurotrauma** 30:211–226, 2013
16. Dumont RJ, Okonkwo DO, Verma S, Hurlbert RJ, Boulos PT, Ellegala DB, et al: Acute spinal cord injury, part I: pathophysiological mechanisms. **Clin Neuropharmacol** 24:254–264, 2001
17. Falcão de Campos C, de Carvalho M: Riluzole-induced recurrent pancreatitis. **J Clin Neurosci** 45:153–154, 2017
18. Fehlings MG, Nakashima H, Nagoshi N, Chow DSL, Grossman RG, Kopjar B: Rationale, design and critical end points for the Riluzole in Acute Spinal Cord Injury Study (RISCIS): a randomized, double-blinded, placebo-controlled parallel multi-center trial. **Spinal Cord** 54:8–15, 2016
19. Fehlings MG, Wilson JR, Frankowski RF, Toupes EG, Aarabi B, Harrop JS, et al: Riluzole for the treatment of acute traumatic spinal cord injury: rationale for and design of the NACTN Phase I clinical trial. **J Neurosurg Spine** 17 (1 Suppl):151–156, 2012
20. French DD, Campbell RR, Sabharwal S, Nelson AL, Palacios PA, Gavin-Dreschnack D: Health care costs for patients with chronic spinal cord injury in the Veterans Health Administration. **J Spinal Cord Med** 30:477–481, 2007
21. Gloviczki B, Török DG, Márton G, Gál L, Bodzay T, Pintér S, et al: Delayed spinal cord-brachial plexus reconnection after C7 ventral root avulsion: the effect of reinnervating motoneurons rescued by riluzole treatment. **J Neurotrauma** 34:2364–2374, 2017
22. Grossman RG, Fehlings MG, Frankowski RF, Burau KD, Chow DS, Tator C, et al: A prospective, multicenter, phase I matched-comparison group trial of safety, pharmacokinetics, and preliminary efficacy of riluzole in patients with traumatic spinal cord injury. **J Neurotrauma** 31:239–255, 2014
23. Hachem LD, Mothe AJ, Tator CH: Evaluation of the effects of riluzole on adult spinal cord-derived neural stem/progenitor cells in vitro and in vivo. **Int J Dev Neurosci** 47 (Pt B):140–146, 2015
24. Hama A, Sagen J: Antinociceptive effect of riluzole in rats with neuropathic spinal cord injury pain. **J Neurotrauma** 28:127–134, 2011
25. Harvey PJ, Li Y, Li X, Bennett DJ: Persistent sodium currents and repetitive firing in motoneurons of the sacrocaudal spinal cord of adult rats. **J Neurophysiol** 96:1141–1157, 2006
26. Hinchcliffe M, Smith A: Riluzole: real-world evidence supports significant extension of median survival times in patients with amyotrophic lateral sclerosis. **Degener Neurol Neuromuscul Dis** 7:61–70, 2017
27. Hosier H, Peterson D, Tsybalyuk O, Keledjian K, Smith BR, Ivanova S, et al: A direct comparison of three clinically relevant treatments in a rat model of cervical spinal cord injury. **J Neurotrauma** 32:1633–1644, 2015
28. Kakulas BA: Neuropathology: the foundation for new treatments in spinal cord injury. **Spinal Cord** 42:549–563, 2004
29. Katoh-Semba R, Asano T, Ueda H, Morishita R, Takeuchi IK, Inaguma Y, et al: Riluzole enhances expression of brain-derived neurotrophic factor with consequent proliferation of granule precursor cells in the rat hippocampus. **FASEB J** 16:1328–1330, 2002
30. Kitzman PH: Effectiveness of riluzole in suppressing spasticity in the spinal cord injured rat. **Neurosci Lett** 455:150–153, 2009
31. Lang-Lazdunski L, Heurteaux C, Dupont H, Widmann C, Lazdunski M: Prevention of ischemic spinal cord injury: comparative effects of magnesium sulfate and riluzole. **J Vasc Surg** 32:179–189, 2000
32. Lang-Lazdunski L, Heurteaux C, Mignon A, Mantz J, Widmann C, Desmonts J, et al: Ischemic spinal cord injury induced by aortic cross-clamping: prevention by riluzole. **Eur J Cardiothorac Surg** 18:174–181, 2000
33. Lips J, de Haan P, Bodewits P, Vanicky I, Dzoljic M, Jacobs MJ, et al: Neuroprotective effects of riluzole and ketamine during transient spinal cord ischemia in the rabbit. **Anesthesiology** 93:1303–1311, 2000
34. Martins BC, Torres BBJ, de Oliveira KM, Lavor MS, Osório CM, Fukushima FB, et al: Association of riluzole and dantrolene improves significant recovery after acute spinal cord injury in rats. **Spine J** 18:532–539, 2018
35. McAdoo DJ, Hughes MG, Nie L, Shah B, Clifton C, Fullwood S, et al: The effect of glutamate receptor blockers on glutamate release following spinal cord injury. Lack of evidence for an ongoing feedback cascade of damage → glutamate release → damage → glutamate release → etc. **Brain Res** 1038:92–99, 2005
36. McDonald JW, Sadowsky C: Spinal-cord injury. **Lancet** 359:417–425, 2002
37. Meshkini A, Salehpour F, Aghazadeh J, Mirzaei F, Naseri

- Alavi SA: Riluzole can improve sensory and motor function in patients with acute spinal cord injury. **Asian J Neurosurg** **13**:656–659, 2018
38. Mu X, Azbill RD, Springer JE: Riluzole and methylprednisolone combined treatment improves functional recovery in traumatic spinal cord injury. **J Neurotrauma** **17**:773–780, 2000
 39. Mu X, Azbill RD, Springer JE: Riluzole improves measures of oxidative stress following traumatic spinal cord injury. **Brain Res** **870**:66–72, 2000
 40. National Spinal Cord Injury Statistical Center: Spinal cord injury facts and figures at a glance. **J Spinal Cord Med** **35**:197–198, 2012
 41. Nógrádi A, Szabó A, Pintér S, Vrbová G: Delayed riluzole treatment is able to rescue injured rat spinal motoneurons. **Neuroscience** **144**:431–438, 2007
 42. Noh KM, Hwang JY, Shin HC, Koh JY: A novel neuroprotective mechanism of riluzole: direct inhibition of protein kinase C. **Neurobiol Dis** **7**:375–383, 2000
 43. Park E, Velumian AA, Fehlings MG: The role of excitotoxicity in secondary mechanisms of spinal cord injury: a review with an emphasis on the implications for white matter degeneration. **J Neurotrauma** **21**:754–774, 2004
 44. Pintér S, Gloviczki B, Szabó A, Márton G, Nógrádi A: Increased survival and reinnervation of cervical motoneurons by riluzole after avulsion of the C7 ventral root. **J Neurotrauma** **27**:2273–2282, 2010
 45. Rowland JW, Hawryluk GW, Kwon B, Fehlings MG: Current status of acute spinal cord injury pathophysiology and emerging therapies: promise on the horizon. **Neurosurg Focus** **25**(5):E2, 2008
 46. Sámano C, Nasrabady SE, Nistri A: A study of the potential neuroprotective effect of riluzole on locomotor networks of the neonatal rat spinal cord in vitro damaged by excitotoxicity. **Neuroscience** **222**:356–365, 2012
 47. Satkunendrarajah K, Nassiri F, Karadimas SK, Lip A, Yao G, Fehlings MG: Riluzole promotes motor and respiratory recovery associated with enhanced neuronal survival and function following high cervical spinal hemisection. **Exp Neurol** **276**:59–71, 2016
 48. Schwartz G, Fehlings MG: Evaluation of the neuroprotective effects of sodium channel blockers after spinal cord injury: improved behavioral and neuroanatomical recovery with riluzole. **J Neurosurg** **94** (2 Suppl):245–256, 2001
 49. Shimizu EN, Seifert JL, Johnson KJ, Romero-Ortega MI: Prophylactic riluzole attenuates oxidative stress damage in spinal cord distraction. **J Neurotrauma** **35**:1319–1328, 2018
 50. Simard JM, Tsybalyuk O, Keledjian K, Ivanov A, Ivanova S, Gerzanich V: Comparative effects of glibenclamide and riluzole in a rat model of severe cervical spinal cord injury. **Exp Neurol** **233**:566–574, 2012
 51. Springer JE, Azbill RD, Kennedy SE, George J, Geddes JW: Rapid calpain I activation and cytoskeletal protein degradation following traumatic spinal cord injury: attenuation with riluzole pretreatment. **J Neurochem** **69**:1592–1600, 1997
 52. Stratman RC, Wiesner AM, Smith KM, Cook AM: Hemodynamic management after spinal cord injury. **Orthopedics** **31**:252–255, 2008
 53. Sung B, Lim G, Mao J: Altered expression and uptake activity of spinal glutamate transporters after nerve injury contribute to the pathogenesis of neuropathic pain in rats. **J Neurosci** **23**:2899–2910, 2003
 54. Theiss RD, Hornby TG, Rymer WZ, Schmit BD: Riluzole decreases flexion withdrawal reflex but not voluntary ankle torque in human chronic spinal cord injury. **J Neurophysiol** **105**:2781–2790, 2011
 55. Vasconcelos NL, Gomes ED, Oliveira EP, Silva CJ, Lima R, Sousa N, et al: Combining neuroprotective agents: effect of riluzole and magnesium in a rat model of thoracic spinal cord injury. **Spine J** **16**:1015–1024, 2016
 56. Wokke J: Riluzole. **Lancet** **348**:795–799, 1996
 57. Wu Y, Satkunendrarajah K, Fehlings MG: Riluzole improves outcome following ischemia-reperfusion injury to the spinal cord by preventing delayed paraplegia. **Neuroscience** **265**:302–312, 2014
 58. Wu Y, Satkunendrarajah K, Teng Y, Chow DS, Buttigieg J, Fehlings MG: Delayed post-injury administration of riluzole is neuroprotective in a preclinical rodent model of cervical spinal cord injury. **J Neurotrauma** **30**:441–452, 2013

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: all authors. Acquisition of data: Srinivas. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Pham. Statistical analysis: all authors. Administrative/technical/material support: Pham. Study supervision: Pham.

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