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# The Impact of Riluzole on Neurobehavioral Outcomes in Preclinical Models of Traumatic and Nontraumatic Spinal Cord Injury: Results From a Systematic Review of the Literature

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## Abstract

**Study Design:** Systematic review.

**Objective:** To evaluate the impact of riluzole on neurobehavioral outcomes in preclinical models of nontraumatic and traumatic spinal cord injury (SCI).

**Methods:** An extensive search of the literature was conducted in Medline, EMBASE, and Medline in Process. Studies were included if they evaluated the impact of riluzole on neurobehavioral outcomes in preclinical models of nontraumatic and traumatic SCI. Extensive data were extracted from relevant studies, including sample characteristics, injury model, outcomes assessed, timing of evaluation, and main results. The SYRCLE checklist was used to assess various sources of bias.

**Results:** The search yielded a total of 3180 unique citations. A total of 16 studies were deemed relevant and were summarized in this review. Sample sizes ranged from 14 to 90, and injury models included traumatic SCI (n = 9), degenerative cervical myelopathy (n = 2), and spinal cord-ischemia (n = 5). The most commonly assessed outcome measures were BBB (Basso, Beattie, Besnahan) locomotor score and von Frey filament testing. In general, rats treated with riluzole exhibited significantly higher BBB locomotor scores than controls. Furthermore, riluzole significantly increased withdrawal thresholds to innocuous stimuli and tail flick latency following application of radiant heat stimuli. Finally, rats treated with riluzole achieved superior results on many components of gait assessment.

**Conclusion:** In preclinical models of traumatic and nontraumatic SCI, riluzole significantly improves locomotor scores, gait function, and neuropathic pain. This review provides the background information necessary to interpret the results of clinical trials on the impact of riluzole in traumatic and nontraumatic SCI.

## Keywords

riluzole, spinal cord injury, review, degenerative cervical myelopathy, locomotor scores, neuropathic pain

## Introduction

Nontraumatic and traumatic injuries to the spinal cord initiate a cascade of pathophysiological changes that may impair normal motor, sensory, and autonomic functions and cause irreversible tissue damage.[1,2] Surgical intervention is recommended as the preferred treatment strategy for patients with moderate to severe degenerative cervical myelopathy (DCM) as it can halt neurologic decline and significantly improve functional impairment, disability, and quality of life.[3,4] Furthermore, early

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surgical management of traumatic spinal cord injury (SCI) is increasingly prioritized due to emerging evidence that patients decompressed and stabilized within 24 hours of injury exhibit superior outcomes.[5,6]

There is also an opportunity to explore adjuvant treatments for the management of traumatic and nontraumatic SCI, including pharmacological strategies. Compression of the spinal cord alters its micro- and macro-vasculature, results in ischemia, and disturbs ionic homeostasis through the activation of voltage-gated sodium channels.[7] An influx of sodium results in cellular swelling, edema, and an increase in the activity of the sodium-calcium exchanger on the neuronal cell membrane.[8] Calcium entry pre-synaptically triggers the release of glutamate, which causes excitotoxicity and neuronal death. A neuroprotective drug such as riluzole may be effective at halting this cascade and preserving the structural integrity of the spinal cord.

Riluzole has neuroprotective, anti-ischemic, and anti-epileptic properties as well as several proposed mechanisms of action.[9] Specifically, it is a sodium channel blocker, a regulator of glutamate release, an antagonist at both NMDA and non-NMDA receptors, and an inhibitor of GABA reuptake.[10-12] Randomized controlled trials have demonstrated that riluzole increases survival, decreases the necessity for tracheostomy, and attenuates muscle deterioration in patients with amyotrophic lateral sclerosis.[13,14] Riluzole has also demonstrated promising results in other neurological conditions, including Huntington's disease, cerebellar ataxia, and cervical SCI.[15-18] Furthermore, in vitro studies have indicated that riluzole significantly improves axonal conduction, prevents cellular necrosis and apoptosis, and enhances nerve fiber regeneration.[19] Given its mechanism of action and the cellular changes that follow compression of the spinal cord, there may be a role for riluzole as an adjuvant therapy in the management of DCM and SCI.

This systematic review aims to evaluate the impact of riluzole on neurobehavioral outcomes in preclinical models of nontraumatic and traumatic SCI. This review serves as an initial step in evaluating the suitability of riluzole for the management of DCM and SCI.

## Methods

### Eligibility Criteria

Table 1 provides a detailed summary of the inclusion and exclusion criteria for this review.

**Table 1.** Inclusion and Exclusion Criteria.

| | Inclusion | Exclusion |
|---|---|---|
| Population | *Any Animal Model including*<br>• Rats<br>• Rabbits<br>• Mice<br>• Primates | • Humans |
| Injury models | • Traumatic spinal cord injury<br>• Degenerative cervical myelopathy<br>• Spinal cord ischemia | • Non-spinal pathologies<br>• Root evulsion injuries<br>• Peripheral nerve injuries (eg, sciatic nerve)<br>• Traumatic brain injury<br>• Epilepsy<br>• Parkinson's disease<br>• Amyotrophic lateral sclerosis |
| Intervention | • Riluzole delivered intraperitoneally, intrathecally, intravenously, and/or intracerebroventricularly | Not applicable |
| Comparison | • Control, vehicle injection | • Non-drug treatments (eg, hypothermia)<br>• Methylprednisolone<br>• Phenytoin<br>• Mexiletine<br>• Glibenclamide<br>• Other drug preparations |
| Outcomes | *Neurobehavioral assessment*<br>• BBB locomotor score<br>• Inclined board test<br>• von Frey filament test<br>• Beam balance<br>• Gait assessment<br>• Grip strength | Autonomic function or physiological parameters<br>• Bladder function<br>• Heart rate<br>• Rectal temperature<br>• Ptosis<br>In vitro assessment<br>• Oxidative damage<br>• Axonal or neuronal preservation<br>• Microglial activation<br>• Blood flow |

### Population and Injury Model

This review targeted studies on animal models (eg, rats, mice, rabbits, primates) of traumatic and nontraumatic SCI. Studies were excluded if they consisted of humans or if the animal model mimicked root avulsion or peripheral nerve injuries, traumatic brain injury, epilepsy, Parkinson's disease, or amyotrophic lateral sclerosis.

### Intervention and Comparison

The intervention of interest was riluzole, injected intravenously, intraperitoneally, intrathecally, or intracerebroventricularly. There were no limitations on the dosing, timing of administration, or duration of treatment. Studies were only included if they had a control group (eg, vehicle injection) and

specifically evaluated outcomes with respect to this group. Studies were excluded if they only compared the efficacy of riluzole to other treatments (eg, hypothermia) or drug regimens (eg, methylprednisolone, phenytoin, glibenclamide, mexiletine).

### Outcomes

This review primarily focused on neurobehavioral outcomes such as the Basso, Beattie, Besnahan (BBB) locomotor score, the inclined board test, the von Frey filament test, beam balance, gait assessment, and grip strength. Studies were excluded if they only discussed autonomic function or physiological parameters (eg, bladder function, heart rate, blood pressure) or if they evaluated in vitro changes (eg, oxidative damage, microglial activation, axonal loss) following riluzole administration.

### Information Sources

A systematic search was conducted of MEDLINE, MEDLINE In-Process, and EMBASE to identify relevant studies. The search was completed on November 13, 2017.

### Search Strategy

A search strategy was constructed with the assistance of a librarian at the Toronto Western Hospital. The strategy was originally prepared in MEDLINE and then appropriately modified for EMBASE. The terms used to search both databases are provided in Appendix A, available online. Only studies involving animal models of spinal pathologies and in English were considered for inclusion, with no other limits applied.

### Study Selection

Duplicates, conference proceedings, editorials, and reviews were first excluded in Endnote. The remaining abstracts were reviewed independently by 2 of the authors and sorted based on predefined inclusion criteria (MZ and LT). In some cases, full text investigation was required to clarify whether the study was relevant. Discussion was used to resolve disagreement between reviewers.

### Data Extraction and Synthesis

The following data were extracted from each article: author, year and location of investigation; sample characteristics, including sample size, type and weight of animals, and level of injury; injury model; intervention, including dose and route of drug administration; outcomes evaluated and timing of assessment; and statistical methods. Main study conclusions were also extracted if they highlighted the impact of riluzole on neurobehavioral outcomes compared to controls.

**Table 2.** Systematic Review Center for Laboratory Animal Experimentation (SYRCLE) Tool[a].

| Questions | Type of Bias Addressed |
|---|---|
| Was the allocation sequence adequately generated and applied? | Selection bias |
| Were the groups similar at baseline or was there adjustment for confounders in the analysis? | Selection bias |
| Was the allocation adequately concealed? | Selection bias |
| Were the animals randomly housed during the experiment? | Performance bias |
| Were the caregivers and/or investigators blinded from which intervention each animal received during the experiment? | Performance bias |
| Were animals selected at random for outcome assessment? | Detection bias |
| Was the outcome assessor blinded? | Detection bias |
| Were incomplete outcome data adequately addressed? | Attrition bias |
| Are reports of the study free of selective outcome reporting? | Reporting bias |
| Was the study apparently free of other problems that could results in high risk of bias? | Other |

[a] Derived from Hooijmans et al.[20]

### Assessment of Risk of Bias and Study Quality

The risk of bias of each study was evaluated using the SYRCLE tool (Systematic Review Center for Laboratory Animal Experimentation).[20] This checklist, presented in Table 2, was adopted from the Cochrane Collaboration risk of bias tool and modified to encompass certain biases that are relevant to animal experiments. It consists of 10 domains related to 6 types of bias: selection, performance, detection, attrition, reporting, and other biases.[20] Signaling questions provided by Hooijmans et al were used to assist in judging whether the experiment had a low, moderate, or high risk of bias for each entry.[20] The authors of this study also recommended not to compute a summary score as that would involve assigning weights to each domain.

### Reporting

This review was formatted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[21]

## Results

### Study Selection

The search yielded a total of 3180 unique citations. Using Endnote, 1799 articles were excluded because they were either not in English (n = 196) or were conference proceedings, editorials, literature reviews, or commentaries (n = 1603). After review of the remaining titles and abstracts, 1340 studies did not meet the inclusion criteria. Following full text investigation, an additional 25 studies were excluded; reasons for

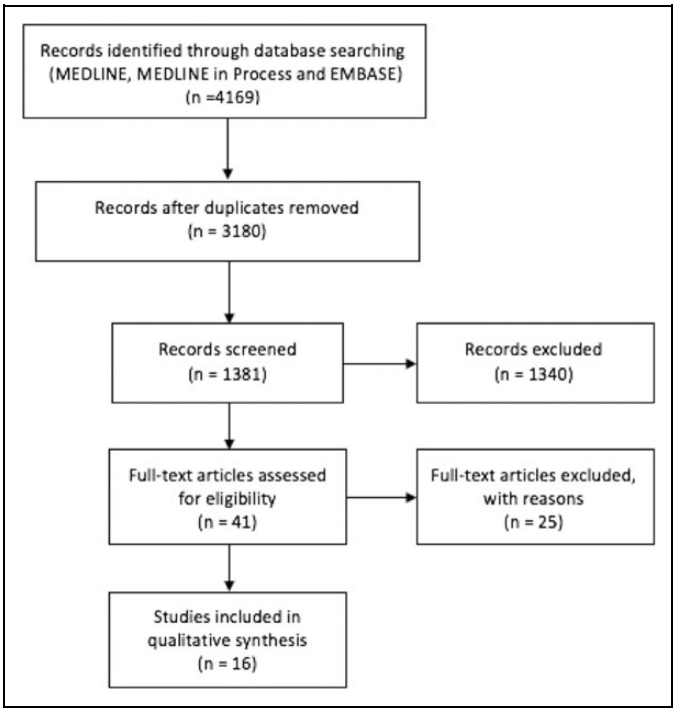



**Figure 1.** Overview of Study Selection.

exclusion are provided in Appendix B. A total of 16 studies were considered relevant following this review process (Figure 1).

## Study Characteristics

Sixteen studies evaluated the impact of riluzole on neurobehavioral outcomes in either rat (n = 14)[9,10,12,19,22-31] or rabbit (n = 2)[11,32] models of spinal cord pathology. Injury models included acute SCI via weight dropping, micro-scissors, or vascular clips (n = 9)[9,12,19,22,24,27-30]; DCM through progressive compression of the cord (n = 2)[26,33]; and spinal cord ischemia via occlusion of the aorta (n = 5).[10,11,25,31,32] Of the models of acute SCI, 4 were at the thoracic level, 3 were cervical, 2 were cervicothoracic (C7-T1), and 1 was sacral. The most commonly assessed outcome measures were BBB locomotor score (n = 7) and gait analysis (n = 4). Table 3 summarizes the tools used to evaluate outcomes. Table 4 provides an overview of the included studies.

## Risk of Bias

The SYRCLE tool evaluated risk of bias across studies. In the majority of studies, allocation sequence was adequately generated, applied (n = 16), and concealed (n = 15). Fifteen studies randomly selected animals for outcome assessment. Investigators were blinded from the intervention in 6 studies and outcome assessors were blinded in 11 studies. Animals were randomly housed during the experiment in only 6 studies and incomplete outcome data was only addressed in 3 studies. Finally, it was unclear whether outcomes were selectively reported in any of the studies (Appendix C).

## What Is the Impact of Riluzole on Neurobehavioral Outcomes?

The main results are summarized in Table 5.

*Basso, Beattie, Besnahan Locomotor Score.* Six studies evaluated the impact of riluzole on BBB locomotor scores in rats with SCI.[12,19,22,27,29,30] In a study by Hosier et al, rats treated with riluzole exhibited significantly higher BBB scores than controls in both the ipsilateral and contralateral limbs at 6 weeks following injury.[22] Vasconcelos et al also demonstrated improved BBB scores in a riluzole group at 1 and 2 weeks postinjury, but not at 3 or 4 weeks.[30] Furthermore, only rats in the riluzole group were able to achieve plantar weight support at 3 weeks. In a third study, rats treated with 8 mg/kg riluzole intraperitoneally at 1 and 3 hours after injury exhibited significant improvements in BBB score compared to controls at 2 to 6 weeks following injury.[19] However, only rats administered with riluzole 1 hour after injury demonstrated significant improvement on the BBB subscores. In contrast, 3 studies indicated no association between BBB score and riluzole administration in preclinical models of SCI.[12,27,29]

A single study by Wu et al examined BBB score and subscores in rats treated with riluzole 4 hours after occlusion of the aorta.[31] Based on their results, riluzole preserved function at 1 and 5 days following ischemia. Furthermore, rats treated with riluzole had significantly higher stepping and coordination subscores than controls.

*Von Frey Filament.* Four studies assessed sensitivity to innocuous mechanical stimulation using von Frey filament testing.[12,19,26,33] In a study by Haman and Sagen, riluzole administered intraperitoneally significantly increased withdrawal thresholds at 60, 90, and 120 minutes posttreatment.[12] Furthermore, intracerebroventricular injection of riluzole increased withdrawal thresholds in a dose-dependent manner.[12] In contrast, lower doses of intraperitoneal riluzole (0.8 or 2.5 mg/kg) or riluzole administered intrathecally did not affect the response to mechanical stimuli. A second study by Moon et al also demonstrated increased withdrawal thresholds in both paws in rats treated intraperitoneally with riluzole.[26] Furthermore, a combination of decompression surgery and riluzole was superior at attenuating mechanical allodynia as compared to decompression alone.[33] Finally a study by Wu et al failed to identify significant differences in response to mechanical stimuli between rats injected with riluzole and controls.[19]

*Tail Flick.* Three studies assessed thermal hyperalgesia using the tail flick test.[12,26,33] Intraperitoneal injection of riluzole significantly increased tail flick latency compared with controls.[12,26] Furthermore, rats receiving a combination of surgical decompression and riluzole had significantly reduced thermal

**Table 3.** An Overview of the Tools Used to Evaluate Outcomes.

| Scales | Summary of Tool |
|---|---|
| Basso, Beattie, Besnahan Locomotor score[12,19,22,27,29–31] | Assesses hindpaw movement and weight bearing, coordination of the hindlimb with the forelimbs, and placement of trunk and tail. Scores range from 0 to 21, where 0 is a complete lack of hindlimb movement and 21 is normal function. |
| Angle Board Test/Inclined plane[9,22,29] | Maximum angle at which an animal can support its weight on an inclined plane (up- and/or down-angled) for 5 seconds; measured from 0° to 90°. |
| von Frey filament test[12,19,26] | Assesses sensitivity to innocuous mechanical stimulation. A von Frey filament is applied to the skin of the hindpaw or forepaw and a withdrawal reaction is observed. If no reaction is elicited, then a higher force filament is used. The smallest filament that elicits a response is considered the threshold stimulus. |
| Tail flick test[12,26] | Assesses thermal hyperalgesia. A circle of light is applied to the dorsal tail. The tail flick withdrawal latency is the time between application of the radiant heat stimulus and withdrawal of the tail from the light. |
| Beam Balance[22] | 0, falls off; 1, hangs on; 2, stands on beam but one or two legs slip off; 3, stands on beam; 4, walks on beam. |
| Accelerating rotarod[22] | Accelerating rod, starting at 4 rpm and increasing at a rate of 2 rpm every 5 seconds to a maximum of 45 rpm. |
| Gait analysis[19,26,28,33] | Swing phase duration, swing speed, paw intensity, paw print width, paw print length, stride length, stance phase, 4-limb support, print positions, forepaw initial contact. |
| Grip strength[28] | Animals are allowed to grasp a bar. They are then pulled away parallel to the degree they grasped at until they release the bar. Grip force is measured. |
| Tarlov scale[10,11,32] | 0, no movement; 1, slight movement; 2, sits with assistance; 3, sits alone; 4, weak hop; 5, normal hop ***OR*** 0, paraplegic with no lower extremity function; 1, poor lower extremity function, weak antigravity movement only; 2, some lower extremity motor function with good antigravity strength but inability to draw legs under body or hop; 3, ability to draw legs under body and hop but not normally; 4, normal motor function. |
| Paw placement test[28] | Forelimb activity during exploration in a cylinder. The number of times the animals places its ipsilateral or contralateral forelimb or both is recorded. |
| Swimming test[30] | Animal swimming velocity is recorded in a circular pool over a duration of 2 minutes. |
| Activity box test[30] | Assesses motor behavior by calculating total distance traveled in 5 minutes. |
| Gridwalk analysis[19] | Assesses sensory-motor coordination of the limbs. Requires accurate paw placement and substantial motor control to cross a meter-long runaway of round metal bars. Spaced unevenly to avoid habituation. Number of footfalls are recorded. |
| Response to non-noxious tactile stimulation[22] | 0, dead; 1, alive, but no response; 2, weak response (moves head); 3, strong response (moves head, neck and forelimbs). |
| Response to quick stretch and pinch stimuli[24] | 0, minimal ($\leq$45° flexion) response to stimulus; 1, 50° to 90° flexion; 2, >90° to 180° flexion; 3, >180° to 225° flexion; 4, >225° to 360° flexion; 5, significant coiling of the tail and/or activation of the flexors, extensors and abductors lasting >2 seconds. |
| Response to light touch[22] | 0, no response; 1, minimal flexion of the tail away from the stimulus; 2, pronounced flexing of the tail away from the stimulus. |
| Motor function score, modified from Gale et al[9] | The animals were observed in an open field for at least 1 minute; 0, no movement of the hindlimbs; 1, barely perceptible movement of hindlimbs; 2, brisk movements at most hindlimb joints in one or both limbs but no coordination or weight support; 3, alternative stepping and propulsive movements of hindlimbs but no weight support; 4, can support weight on hindlimbs; 5, walks with only mild deficit; 6, normal walking. |
| Motor scores[22,25] | 0, no movement of hindlimbs, no weight bearing; 1, barely perceptible movements of hindlimbs, no weight bearing; 2, frequent and/or vigorous movement of hindlimbs but no weight support; 3, alternative stepping and propulsive movements of hindlimbs, some intermittent weight bearing; 4, can support weight and walk with deficit apparent; 5, normal walking. |
| Motor sensory deficit index (MSDI)[25] | Walking with lower extremities: 0, normal; 1, toes flat under body when walking but ataxia is present; 2, knuckle walking; 3, movements in lower extremities but unable to knuckle walk; 4, no movement, drags lower extremities. Pain sensation: 0, normal, withdrawal to toe pinch; 1, squeals to toe pinch but does not withdraw; 2, no reaction to toe pinch. MSDI is a summation of walking with lower extremities and pain sensation. |

allodynia compared with decompression alone.[33] There were, however, no significant changes in latencies between controls and rats receiving intrathecal or intracerebroventricular riluzole.[12]

*Tarlov Score.* Three studies evaluated the impact of riluzole on Tarlov scores.[10,11,32] Based on their results, rats receiving riluzole exhibited significantly improved Tarlov scores compared with controls. Furthermore, the incidence of complete paraplegia, defined as a Tarlov score of 0, was significantly lower in rats treated with riluzole.[11] In contrast, the incidence of paraparesis, defined as a Tarlov score of 1, 2, or 3, was not significantly different between riluzole and control groups.[11] Furthermore, results from the study by Lang-Lazdunski et al

**Table 4.** Summary of Included Studies.

| Author (Year), Location | Sample Features | Outcomes Assessed | Injury Model | Intervention | Time of Assessment |
|---|---|---|---|---|---|
| Ates et al (2007), Turkey[9] | N = 90<br>Adult male Wistar albino rats<br>Weight: 200-250 g<br>Level: T7-10 | • Motor function score modified from Gale et al<br>• Rivlin and Tator's angle board test | *Traumatic SCI*<br>5 g weight dropped using a guide tube at an impact of 50 g/cm to the dorsal surface of the spinal cord | • Sham, operated by laminectomy (n = 18)<br>• Vehicle i.p. (n = 18)<br>• Riluzole, 8 mg/kg once i.p. (n = 18)<br>• Mexiletine, 80 mg/kg once i.p. (n = 18)<br>• Phenytoin, 200 mg/kg once i.p. (n = 18) | Weekly for 6 weeks after injury |
| Hama and Sagen (2011), United States of America[12] | N = NA<br>Male Sprague Daley rats<br>Weight: 125-150 g<br>Level: T6-7 | • von Frey filament test<br>• Tail flick<br>• BBB locomotor score | *Traumatic SCI*<br>Microvascular clip clamped vertically around the spinal cord for 1 minute | • von Frey filament test: riluzole, 0.8, 2.5, or 8mg/kg i.p.; 0.3, 1, 10, or 30 μg i.c.v.; 10 or 30 μg i.t.; or vehicle<br>• Tail flick: riluzole, 8 mg/kg i.p.; 100 μg i.c.v.; 100 μg i.t.; or vehicle<br>• BBB test: riluzole, 8 mg/kg i.p. or vehicle | von Frey filament test and tail flick: Every 30 minutes for 120 minutes post-injection<br>BBB test: 2 hours post-injection |
| Hosier et al (2015), United States[22] | N = 35<br>Long-Evan rats<br>Weight: 200-225 g<br>Level: C8 | • Response to non-noxious tactile stimulation<br>• Motor scores<br>• BBB locomotor score<br>• Inclined plane<br>• Beam balance<br>• Accelerating rotarod | *Traumatic SCI*<br>Unilateral impact to the spinal cord via a 10 g weight released from a height of 25 mm using a guide tube | • Controls, no treatment (n = 10)<br>• Riluzole, 5mg/kg i.p. twice daily for 1 week (n = 10)<br>• Hypothermia (n = 8)<br>• Glibenclamide, 10 μg/kg loading dose 4 hours after trauma plus a continuous subcutaneous delivery of 400 ng/h for 1 week (n = 7) | 1 and 3 days and weekly for 6 weeks after injury |
| Karadimas et al (2015), Canada[33] | N = 34<br>Female Sprague-Dawley rats<br>Level: C6 | • Gait analysis<br>• von Frey filament<br>• Tail flick<br>• Handgrip strength | *CSM*<br>Progressively increased pressure on the cervical spinal cord by an implanted aromatic polyether | • Sham (n = 7)<br>• Vehicle (n = 7)<br>• Riluzole, 8 mg/kg i.p. daily starting 4 weeks after implantation of aromatic polyether and ending 2 weeks following decompression (n = 6)<br>• Surgical decompression (n = 7)<br>• Surgical decompression and riluzole (n = 7) | 1, 6, and 12 weeks after surgery |
| Kitzman (2009), United States[24] | N = 19<br>Female Sprague-Dawley rats<br>Weight: 200-250 g<br>Level: S2 | • Response to pinch, light touch, and stretch | *SCI*<br>Complete transection of the lower sacral spinal cord | • Vehicle<br>• Riluzole, 8 mg/kg i.p. once daily for 3 days<br>• Riluzole, 10 mg/kg i.p. once daily for 3 days | 1, 3, 6, and 12 hours post-injection on day 3 |

*(continued)*

**Table 4.** (continued)

| Author (Year), Location | Sample Features | Outcomes Assessed | Injury Model | Intervention | Time of Assessment |
|---|---|---|---|---|---|
| Lang-Lazdunski et al (2000), France[25] | N = 68<br>Male Sprague-Dawley rats<br>Weight: 350-400 g | • Modified Le May et al scoring system<br>• Motor sensory deficit index | *Spinal cord ischemia*<br>Cross-clamping of the aortic arch and left subclavian artery for 14 mins using micro-vessel clips | • Sham-operated (n = 15)<br>• Vehicle (n = 15)<br>• Riluzole, 4 mg/kg i.v. 30 minutes before clamping and at the onset of reperfusion (n = 15) | 6 and 24 hours and daily up to 96 hours after reperfusion |
| Lang-Lazdunski et al (2000), France[32] | N = 73<br>Female New Zealand white rabbits<br>Weight: 350-450 g | • Modified Tarlov scale | *Spinal cord ischemia*<br>Aortic occlusion with vascular clamps below the renal arteries and above the aortic bifurcation for 40 minutes | • Sham-operated (n = 5)<br>• Vehicle (n = 17)<br>• Riluzole, 8 mg/kg i.v. 30 minutes before clamping (n = 17)<br>• $MgSO_4$, 100 mg/kg i.v. 30 minutes before clamping (n = 17)<br>• Riluzole, 8 mg/kg and $MgSO_4$, 100 mg/kg i.v. 30 minutes before clamping (n = 17) | 3, 6, and 24 hours and daily |
| Lang-Lazdunski et al (1999), France[10] | N = 43<br>Female New Zealand white albino rats<br>Weight: 350-450 g | • Tarlov scale | *Spinal cord ischemia*<br>Cross-clamping of the aorta with micro-clamps for 40 minutes | • Sham-operated (n = 3)<br>• Vehicle (n = 10)<br>• Riluzole, 8 mg/kg i.v. 30 minutes before occlusion (n = 10)<br>• Riluzole, 4mg/kg i.v. 30 minutes before occlusion and at the onset of reperfusion (n = 10)<br>• Riluzole, 8mg/kg i.v. at the onset of reperfusion (n = 10) | 24, 48, and 120 hours after ischemia |
| Lips et al (2000), The Netherlands[11] | N = 60<br>New Zealand white rabbits<br>Mean weight: 340 ± 30 g | • Tarlov scale | *Spinal cord ischemia*<br>Aortic occlusion via a 5-French double-lumen wedge pressure balloon catheter for 29 minutes | • Control, i.v. injection of solvent 15 minutes before occlusion and i.p. twice daily for 3 days after occlusion (n = 15)<br>• Riluzole, 8 mg/kg i.v. 15 minutes before occlusion and i.p. twice daily for 3 days after occlusion (n = 15)<br>• Ketamine, 10 mg/kg i.v. after initial solvent injection and 1.5 mg/kg/min i.v. for 30 minutes, 10 minutes after reperfusion. Solvent was also given i.p. twice daily for 3 days after occlusion (n = 15)<br>• Riluzole and ketamine, riluzole 8 mg/kg i.v. 15 minutes before | 24, 48, and 72 hours after ischemia |

*(continued)*

**Table 4.** (continued)

| Author (Year), Location | Sample Features | Outcomes Assessed | Injury Model | Intervention | Time of Assessment |
|---|---|---|---|---|---|
| | | | | occlusion followed by ketamine 1.5 mg/kg/min for 30 minutes, 10 minutes after reperfusion. Riluzole was also given i.p. twice daily for 3 days (n = 15) | |
| Moon et al (2014), Canada[26] | N = 41<br>Female Sprague-Dawley rats<br>Weight: 300-400 g<br>Level: C2-T2 | • von Frey filament<br>• Tail flick<br>• Gait analysis | *CSM*<br>Chronic compression device: screw initially advanced 0.2 mm through rod and then 0.4 mm weekly for up to 3 weeks | • Sham, no compression (n = 6)<br>• Vehicle (n = 18)<br>• Riluzole, 8 mg/kg i.p. daily for 8 weeks initiated 1 week after surgery (n = 17) | Weekly for 8 weeks |
| Mu et al (2000), United States[27] | N = 36<br>Adult female Long-Evans rats<br>Weight: 225-250 g<br>Level: T10 | • BBB locomotor score | *Traumatic SCI*<br>Impactor rod dropped from a height of 12.5 mm onto the spinal cord | • Vehicle (n = 9)<br>• Riluzole, 8 mg/kg i.p. 2 and 4 hours after injury and once daily for 1 week (n = 9)<br>• MP, 30 mg/kg i.v. at 2 and 4 hours after injury (n = 9)<br>• Riluzole and MP (n = 9) | Weekly for 6 weeks |
| Satkunendrarajah et al (2016), Canada[28] | N = 40<br>Male Wistar rats<br>Weight: 300-325 g<br>Level: C2 | • Forelimb grip strength<br>• Paw placement test<br>• Gait analysis | *Cervical hemisection*<br>Left side hemisection from midline to lateral spinal cord with microscissors | • Vehicle, i.p. 1 hour post-injury and twice daily for 1 week (n = 17)<br>• Riluzole, 8 mg/kg i.p. 1 hour post-injury and 6 mg/kg i.p. every 12 hours thereafter for 1 week (n = 18)<br>• Sham, C2 laminectomy without hemisection (n = 5) | At defined intervals over a 6 week period |
| Schwartz and Fehlings (2001), Canada[29] | N = 60<br>Adult female rats<br>Weight: 225-280 g<br>Level: C7-T1 | • BBB expanded locomotor score<br>• Inclined plane | *Traumatic SCI*<br>Extradural compression of spinal cord for 1 minute between blades of a modified aneurysm clip (closing force of 53 g) | • Vehicle (n = 14)<br>• Riluzole, 5 mg/kg i.p. 15 minutes after injury (n = 13)<br>• Phenytoin, 30 mg/kg i.p. 15 minutes after injury (n = 13)<br>• CNS5546A, 15 mg/kg i.p. 15 minutes after injury (n = 14) | Weekly for 6 weeks |
| Vasconcelos et al (2016), Portugal[30] | N = 19<br>Female Wistar Han rats<br>Weight: 210-260 g<br>Level: T8 | • BBB locomotor score<br>• Activity box test<br>• Swimming test | *Traumatic SCI*<br>10-g weight rod dropped from a 20-cm height on the spinal cord | Treatment consisted of 5 injections<br>• Vehicle, saline (n = 5)<br>• Riluzole, 2.5mg/kg i.p. 1 hour post-trauma and then every 12 hours (n = 4) | 3 days post-injury and weekly for 4 weeks<br>Days 29, 31 |

*(continued)*

**Table 4.** (continued)

| Author (Year), Location | Sample Features | Outcomes Assessed | Injury Model | Intervention | Time of Assessment |
|---|---|---|---|---|---|
| | | | | • $MgCl_2$, 24.18 mg/kg 1 hour post-trauma and then every 12 hours (n = 5)<br>• Combined treatment of riluzole and $MgCl_2$ 1 hour post-trauma and then every 12 hours | |
| Wu et al (2013), Canada[19] | N = 50<br>Female Wistar rats<br>250-300 g<br>Level: C7-T1 | • BBB locomotor score<br>• BBB subscores<br>• Gridwalk analysis<br>• von Frey filament testing | *Traumatic SCI*<br>Extradural compression of spinal cord for 1 minute between the blades of a modified aneurysm clip (closing force of 35 g) | • Vehicle (n = 12)<br>• Riluzole, 8 mg/kg i.p. 1 hour (n = 12) or 3 hours (n = 12) post-injury followed by 6 mg/kg i.p. every 12 hours for 1 week | 1 to 6 weeks post-injury |
| Wu et al (2014), Canada[31] | N = 14<br>Female Sprague-Dawley rats<br>Weight: 350-430 g | • BBB locomotor score<br>• BBB subscores | *Spinal cord ischemia*<br>Inflation of a balloon catheter in the aorta with the tip at the left subclavian artery (6 minutes). The balloon was then deflated and blood reinfused slowly (60 seconds) | • Control (n = 7)<br>• Riluzole, 8 mg/kg i.p. 4 hours after occlusion (n = 7) | 4 hours, 1 and 5 days post-injury |

Abbreviations: SCI, spinal cord injury; CSM, cervical spondylotic myelopathy; NA, not available; i.p., intraperitoneally; i.v., intravenously; i.c., intracerebroventricularly; i.t., intrathecally; BBB, Basso, Beattie, Besnahan

**Table 5.** Statistical Analysis and Main Conclusions of Included Studies

| Author (Year) | Statistical Analysis | Main Conclusions |
|---|---|---|
| Ates et al (2007)[9] | • Kruskal-Wallis test<br>• Bonferroni Mann-Whitney test | • Rats treated with riluzole exhibited greater improvements in motor function and angle board scores compared to controls over the 6-week period ($P < .05$). |
| Hama and Sagen (2011)[12] | • Two-way ANOVA with repeated measures<br>• Newman-Keuls for post hoc comparisons | • On von Frey filament testing, riluzole (8 mg/kg i.p.) significantly increased withdrawal thresholds at 60 ($P < .05$ vs baseline), 90 and 120 ($P < .05$ vs baseline and vehicle) minutes post-injection.<br>• Lower doses of riluzole (0.8 or 2.5 mg/kg i.p.) did not affect withdrawal thresholds.<br>• No significant changes in withdrawal threshold were observed following i.t. riluzole or vehicle injection.<br>• Riluzole (1, 10, 30 μg i.c.v.) significantly increased withdrawal thresholds in a dose-dependent manner ($P < .05$ vs baseline and vehicle at 30 minutes).<br>• Riluzole (8 mg/kg i.p.) significantly increased tail flick latency at 30 to 120 minutes post-injection ($P < .05$ vs baseline and vehicle).<br>• No significant changes in latencies were observed following i.t. or i.c.v. injection of riluzole or vehicle ($P > .05$).<br>• BBB locomotor scores for rats receiving riluzole or vehicle were not significantly different than scores 4 weeks after SCI ($P > .05$). |
| Hosier et al (2015)[22] | • Kruskal-Wallis test with Dunn's post hoc comparison<br>• One-way ANOVA with Fisher's post hoc comparisons | • There were no significant differences in arousal scores and motor scores between the control and riluzole groups ($P > .05$, day 7 after trauma).<br>• Ipsilateral and contralateral modified BBB scores were significantly higher in rats receiving riluzole than controls ($P < .05$, week 6 after trauma).<br>• Time on accelerating rotarod was significantly longer in rats receiving riluzole than controls ($P < .05$, week 6 after trauma).<br>• There were no significant differences in inclined plane angle and beam balance scores between the control and riluzole groups ($P > .05$, week 6 after trauma). |
| Karadimas et al (2015)[33] | • One-way ANOVA with Tukey post hoc | • A combination of surgical decompression and riluzole administration resulted in longer forelimb stride length, higher regularity index and shorter forepaw initial contact than decompression alone ($P < .05$, 1 week after surgery).<br>• Forelimb stance phase, percentage 4-limb support and print positions did not differ between decompression only and decompression plus riluzole groups ($P > .05$, 1 week after surgery).<br>• A combination of surgical decompression and riluzole administration resulted in a shorter stance phase, longer stride length, stronger handgrip and decreased print positions than decompression alone ($P < .05$, 12 weeks after surgery).<br>• On von Frey filament testing, a combination of surgical decompression and riluzole significantly increased withdrawal thresholds in the hindpaw compared to decompression only ($P < .05$, 12 weeks after surgery).<br>• Rats receiving a combination of surgical decompression and riluzole had significantly increased tail withdrawal latency compared to rats treated with only decompression at 12 weeks ($P < .05$). |
| Kitzman (2009)[24] | • Kruskal-Wallis test<br>• Dunn's multiple comparison tests | • Rats receiving riluzole 8mg/kg had a significantly decreased response to light touch (1 hour but not 3, 6, and 12 hours post-injection) and pinch (1 and 3 hours but not 6 and 12 hours post-injection) compared to controls ($P < .05$).<br>• Rats receiving riluzole 10 mg/kg had a significantly decreased response to light touch, stretch and pinch compared to controls at 1 and 3 hours but not 6 and 12 hours post-injection ($P < .05$). |
| Lang-Lazdunski et al (2000)[25] | • Kruskal-Wallis test<br>• Mann-Whitney *U* tests | • MSDI scores were significantly better in the riluzole group than in the control group at 24 ($P = .0001$), 48 ($P = .0002$), and 96 hours ($P = .009$) after reperfusion |
| Lang-Lazdunski et al (2000)[32] | • Kruskal-Wallis tests<br>• Mann-Whitney *U* tests | • Modified Tarlov scores were significantly better in the riluzole and the riluzole with $MgSO_4$ groups than in the $MgSO_4$ only and control groups ($P < .01$). |

*(continued)*

**Table 5.** (continued)

| Author (Year) | Statistical Analysis | Main Conclusions |
|---|---|---|
| Lang-Lazdunski et al (1999)[10] | • Mann-Whitney *U* tests | • Tarlov scores were significantly better in the riluzole group than in the control group, regardless of dose and timing of administration ($P < .001$, 24 hours after ischemia).<br>• Rats receiving riluzole 4 mg/kg i.v. 30 minutes before ischemia and at the onset of reperfusion achieved significantly better Tarlov scores than rats treated with riluzole 8 mg/kg i.v. only at the onset of reperfusion ($P = .00444$, 24 hours after ischemia).<br>• Tarlov scores did not significantly differ between rats treated with riluzole 8 mg/kg i.v. 30 minutes before ischemia and those receiving riluzole 4 mg/kg i.v. 30 minutes before ischemia as well as at the onset of reperfusion ($P = .2004$, 24 hours after ischemia). |
| Lips et al (2000)[11] | • Fishers exact test | • Rats receiving riluzole exhibited a significant decrease in the incidence of complete paraplegia (48 and 72 hours) and improved Tarlov scores compared with controls ($P < .05$).<br>• Incidence of paraparesis was not significantly different between riluzole and control groups at any time point assessed ($P > .05$). |
| Moon et al (2014)[26] | • One- or 2-way ANOVA with Bonferroni correction<br>• *t* Tests | • On von Frey filament testing, riluzole significantly increased withdrawal thresholds in both the forepaw (2, 6, 7, and 8 weeks) and hindpaw (3 to 8 weeks) compared to the control group ($P < .05$).<br>• Riluzole significantly increased tail withdrawal latency compared to the control group at 8 weeks ($P < .05$).<br>• Rats in the riluzole group had significantly shorter forelimb and hindlimb swing phases, greater forepaw and hindpaw intensity, and faster hindlimb swing speed than the control group at 8 weeks ($P < .05$). |
| Mu et al (2000)[27] | • Two-way ANOVA<br>• Fishers test | • There were no significant differences in BBB open field locomotor scores between the riluzole and control group at any assessment point ($P > .05$).<br>• Rats receiving a combined administration of riluzole and MP exhibited higher BBB open field locomotor scores than controls at 4, 5, and 6 weeks ($P < .05$). |
| Satkunendrarajah et al (2016)[28] | • One- or 2-way ANOVA with Bonferroni correction<br>• *t* Test | • Rats in the riluzole group had significantly increased ipsilateral forelimb grip strength (3 to 43 days post-surgery) and contralateral forelimb grip strength (23 to 43 days post-surgery) compared to the control group ($P < .01$).<br>• Rats in the riluzole group had significantly faster swing speeds and longer ipsilateral stride lengths compared to the control group at 2 ($P < .005$, $P < .001$) and 4 weeks ($P < .05$, $P < .008$) post-surgery but not at 6 weeks.<br>• Rats in the riluzole group had significantly increased ipsilateral forepaw print width during stance phase and longer ipsilateral forepaw print length (2, 4, and 6 weeks post-injury) compared to the control group ($P < .05$). Print length and width of the contralateral forepaw were not significantly different between groups.<br>• Rats in the riluzole group had a significantly higher percentage of ipsilateral paw placements (2, 4, and 6 weeks post-injury) than the control group. |
| Schwartz and Fehlings (2001)[29] | • Two-factor ANOVA<br>• Student-Newman-Keuls multiple range test<br>• Fishers test | • Rats treated with riluzole exhibited higher inclined plane scores than controls at 1, 2, 3, 4, and 6 weeks following injury ($P < .05$).<br>• There were no significant differences in BBB locomotor scores between the riluzole and the control group at any assessment point ($P > .05$). |
| Vasconcelos et al (2016)[30] | • One-way or 2-way ANOVA with post-hoc Bonferroni test | • Rats treated with riluzole achieved significantly higher BBB sores than controls at 1 and 2 weeks post-injury ($P < .05$) but not at 3 and 4 weeks post-injury. There were no differences in BBB scores between the control group and the combined riluzole and $MgSO_4$ group.<br>• Rats treated with riluzole traveled a significantly longer distance than controls at 29 days post-injury ($P < .05$). There were no differences in distance traveled between the control group and the combined riluzole and $MgSO_4$ group.<br>• There were no significant differences in swimming velocities between the riluzole and control groups. |
| Wu et al (2013)[19] | | • Rats treated with riluzole (8 mg/kg 1 and 3 hours after injury) achieved significantly higher BBB scores than controls at 2 to 6 weeks after injury ($P < .05$). |

*(continued)*

**Table 5.** (continued)

| Author (Year) | Statistical Analysis | Main Conclusions |
|---|---|---|
| | • One-way or 2-way ANOVA with repeated measures with post hoc Bonferroni test | • Rats treated with riluzole (8 mg/kg at 1 but not 3 hours after injury) achieved significantly higher BBB subscores than controls ($P < .01$).<br>• Rats treated with riluzole (8 mg/kg at 1 but not 3 hours after injury) demonstrated a significantly reduced number of footfalls at 3 to 6 weeks post-injury than controls ($P < .05$).<br>• There were no significant differences in withdrawal threshold between riluzole and control groups. |
| Wu et al (2014)[31] | • Two-way ANOVA with repeated measures and post hoc Bonferroni test | • Rats treated with riluzole achieved significantly higher BBB scores (1 and 5 days post-ischemia) and coordination and stepping subscores (4 hours, 1 and 5 days post-ischemia) than controls ($P < .001$). |

Abbreviations: SCI, spinal cord injury; i.p., intraperitoneally; i.v., intravenously; i.c.v., intracerebroventricularly; i.t., intrathecally; BBB, Basso, Beattie, Besnahan; MSDI, Motor Sensory Deficit Index; ANOVA, analysis of variance.

indicated that riluzole given before ischemia is more effective than riluzole injected at the onset of reperfusion.[10]

*Gait Analysis and Grip Strength.* Gait analysis was performed in 4 studies.[19,26,28,33] Compared with controls, riluzole resulted in significantly shorter limb swing phases; greater paw pressure; longer ipsilateral stride length, print width during stance phase and print length; reduced number of footfalls; and a higher percentage of ipsilateral paw placements.[19,26,28] Print length and width of the contralateral forepaw, however, did not significantly differ between riluzole and control groups.[28] In a study by Karadimas et al, a combination of surgical decompression and riluzole resulted in longer forelimb stride length, higher regularity index, shorter forepaw initial contact, shorter stance phase, stronger hand grip, and decreased print positions than decompression alone.[33] Finally, ipsilateral and contralateral grip strength were significantly higher in rats treated with riluzole than controls.[28]

*Inclined Plane Scores.* Three studies assessed the association between riluzole and inclined plane scores.[9,22,29] In a study by Schwartz and Fehlings, rats treated with riluzole exhibited higher inclined plane scores than controls at 1 to 4 and 6 weeks following injury.[29] This positive finding was confirmed by Ates et al.[9] In contrast, the study by Hosier et al did not detect significant differences in inclined plane scores between the control and riluzole groups in a model of unilateral cervical SCI.[22]

*Other Measures.* Based on single studies, rats receiving riluzole exhibited significantly longer time on accelerating rotarod, improved motor sensory deficit index, and a longer distance traveled on an activity test than controls.[22,25,30] Furthermore, a study by Kitzman demonstrated that rats receiving 10 mg/kg of riluzole had a significantly decreased response to light touch, stretch, and pinch compared with controls at 1 and 3 hours, but not at 6 and 12 hours, post injection.[24] In contrast, single studies identified no association between treatment with riluzole and beam balance scores or swimming velocities.[22,30]

## Discussion

This systematic review aims to evaluate the association between riluzole and neurobehavioral outcomes in preclinical models of traumatic and nontraumatic SCI. Based on the results, riluzole has a significant impact on locomotor scores, gait parameters, and measures of hyperalgesia and mechanical allodynia.

The most common outcome assessment tool used across studies was the BBB locomotor score, which was originally designed to evaluate midline thoracic injuries.[22] Other tests were also conducted to assess upper extremity function in isolation as well as coordination of the forelimbs and hindlimbs; these included grip strength, accelerating rotarod, and beam balance.[22,28] As summarized by this review, riluzole significantly improved motor recovery, locomotion, and functional outcomes in a variety of animal models of traumatic and nontraumatic SCI. Potential explanations for these results include (1) sparing of serotonergic and glutamatergic fibers involved in maintaining posture, initiating locomotion, and/or modulating neuronal circuits and (2) increased neuron counts in the red, reticular, and vestibular nuclei.[29,30] In contrast, a study by Vasconcelos et al reported that riluzole did not affect swimming velocities; this is likely because swimming does not require body weight support due to buoyancy.[30] Furthermore, some studies indicated that riluzole does not have an impact on BBB locomotor score, upper extremity function, or coordination.[12,22,27,29] Timing and duration of riluzole administration may also be a relevant consideration; specifically, rapid and prolonged treatment enables immediate and continued blockage of glutamatergic excitotoxicity and improved neurobehavioral outcomes.[11,19]

This review also indicated that riluzole may attenuate neuropathic pain and suppress spasticity. Injury to the spinal cord

results in hyperalgesia and mechanical allodynia below the level of injury while increasing spontaneous activity at the dorsal horn.[12,26] These findings were confirmed by increased withdrawal thresholds to innocuous stimuli and an increase in tail flick latency following application of a radiant heat stimuli.[12,26] Moreover, there was a significant decrease in response to noxious and non-noxious stimuli, including stretch, pinch, and light touch.[24] Riluzole affects these outcomes by modulating glutamatergic excitotoxicity in the dorsal horn.[26] Furthermore, an increase in spontaneous activity may be due to a decrease in inhibitory GABAergic interneurons at the dorsal horn as well as a reduction of descending inhibition from the bulbospinal serotonergic and adrenergic neurons.[12] Longer term changes may also occur, including increased gene transcription of voltage gated sodium channels, causing abnormal physiological responses to peripheral stimulation. Finally, the administration dose may be an important consideration as lower doses of riluzole (eg, 0.8 or 2.5 mg/kg) do not improve sensitivity to innocuous mechanical stimuli.[12] The dose response gradient observed on intracerebroventricular injection of riluzole signifies that the brain (in addition to the peripheral nerves) may also be a key site of riluzole's actions; specifically, it is hypothesized that the ventral posterolateral nucleus of the thalamus may be an important target.[12]

Riluzole may also significantly improve gait parameters. In a study by Karadimas et al, surgical decompression was associated with increased blood flow and reperfusion of the spinal cord parenchyma.[33] Reperfusion of the gray matter resulted in chronic and persistent neuronal oxidative damage as well as increased expression of DNA damage repair processes.[33] This study also demonstrated that riluzole can attenuate ischemia reperfusion injury associated with decompression surgery, decrease oxidative damage, and protect against destruction of the mitochondrial membrane. Furthermore, a combination of surgical decompression and riluzole can significantly improve forelimb function and nearly restore a smooth and rhythmic gait pattern.[33] In addition to restoration of motor function, improvement in gait parameters may also reflect a reduction in sensitivity to mechanical stimulation. In a study by Moon et al, rats treated with riluzole had significantly longer contact between the paw and the glass plate.[26]

This review provides the background information necessary to interpret the results of clinical trials on the impact of riluzole in traumatic and nontraumatic SCI. Improvements in tissue damage and neurobehavioral outcomes may significantly affect quality of life in these patients.

### *Strengths and Limitations*

This systematic review reflects the first to evaluate the impact of riluzole on neurobehavioral outcomes in preclinical models of traumatic and nontraumatic SCI. Strengths of this review include the following: (1) the search strategy was extensive, (2) 2 reviewers independently evaluated the articles for eligibility, (3) the evidence was assessed using the SYRCLE tool, and (4) the review was formatted using the PRISMA guidelines. Limitations of this review include the following: (1) studies were excluded if they were not in English and (2) it was challenging to assess certain domains of the SYRCLE tool.

## Conclusion

In preclinical models of traumatic and nontraumatic SCI, riluzole significantly improves locomotor scores, gait function, and measures of neuropathic pain. This review provides the background information necessary to interpret the results of clinical trials on the impact of riluzole in traumatic and nontraumatic SCI.

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### Supplemental Material

Supplemental material for this article is available online.

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