Systematic Review/Meta-Analysis

A critical appraisal of clinical practice guidelines on pharmacological treatments for spinal cord injury

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Received 19 July 2022; revised 16 September 2022; accepted 20 September 2022

Abstract

BACKGROUND CONTEXT: Spinal cord injury brings devastating consequences and huge economic burden. Different authoritative organizations have developed different guidelines for pharmacological treatments of spinal cord injury, but there is a lack of a critical appraisal of them.

PURPOSE: To systematically review and appraise guidelines regarding their recommendations for pharmacological treatments for spinal cord injury.

STUDY DESIGN: Systematic review.

METHODS: We searched Medline, Embase, Cochrane, and Web of Science from January 2000 to January 2022 as well as guideline-specific databases (eg, Congress of Neurological Surgeons) and Google Scholar. We included the most updated guideline containing evidence-based recommendations or consensus-based recommendations developed by specific authoritative organizations if multiple versions were available. We appraised guidelines through the Appraisal of Guidelines for Research and Evaluation, 2nd edition instrument consisting of six domains (eg, applicability). With supporting evidence, recommendations were classified as: for, against, neither for nor against. We utilized an evidence assessment system to categorize the quality of supporting evidence as poor, fair, or good.

RESULTS: Eight guidelines developed from 2008 to 2020 were included, but all of them scored lowest in the domain of applicability among all six domains. Twelve pharmacological agents (eg, methylprednisolone) were studied. For methylprednisolone, three guidelines (3/8=37.5%) recommended for (one evidence-based and two consensus-based), three (3/8=37.5%) recommended against (all evidence-based), and two (2/8=25%) recommended neither for nor against. For monosialotetrahexosylganglioside (GM-1), one guideline (1/4=25%) recommended for (consensus-based), one (1/4=25%) recommended against (evidence-based), and two (2/4=50%) recommended neither for nor against. For other agents (eg, minocycline), most guidelines (3/5=60%) recommended neither for nor against, one (1/5=20%) recommended against naloxone (evidence-based) and nimodipine (evidence-based), and one (1/5=20%) recommended for neural growth factor (consensus-based). The quality of most of the supporting evidence was poor, and the rest was fair.

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CONCLUSIONS: There were inconsistencies among recommendations for methylprednisolone and GM-1. Evidence-based recommendations tended to recommend against, whereas consensus-based recommendations tended to recommend for.   © 2022 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Introduction

Spinal cord injury is an increasingly important global health challenge [1,2]. The Global Burden of Disease study showed that there were 0.91 (95% uncertainty interval [UI]: 0.71−1.16) million incident cases and 20.64 (95% UI: 18.93−23.61) million prevalent cases worldwide in 2019 [3]. In the United States, there were 0.11 (95% UI: 0.08 −0.15) million incident cases and 2.04 (95% UI: 1.87 −2.22) million prevalent cases in 2019 [3]. More importantly, spinal cord injury brings huge economic burdens through high health-care costs [1,4]. The average direct cost for the care of a patient is up to $1.1−4.8 million over his lifetime in the United States, as indicated by National Spinal Cord Injury Statistical Center [4].

Pharmacological treatments are commonly used [5]. A survey conducted by AO Spine for spine surgeons from Latin America, Europe, Asia-Pacific, North America, and the Middle East shows 52.9% of them use methylprednisolone to treat spinal cord injury [6]. In China, 50.4% of patients are treated with methylprednisolone [7].

Accesses to high-quality clinical practice guidelines can facilitate consistent, efficient, and evidence-based practices for health conditions [8]. However, clinicians may face the challenge to select a high-quality guideline to apply in clinical practices without knowing the quality of different guidelines [9]. Especially when different authoritative organizations issue inconsistent recommendations, it is more likely to result in confusion in clinical practice and bring concerns about the quality of the guidelines [10]. Besides, considering that research continues to add evidence, a critical appraisal of existing published guidelines is beneficial to suggest an agenda for future work in this area [11]. Some authoritative organizations have already published clinical practice guidelines addressing pharmacological treatments for spinal cord injury; however, to our knowledge, the quality of guidelines and the degree of consistency of the recommendations has not been formally assessed.

Gerber et al. [12] conducted a narrative review of guidelines for spinal cord injury rehabilitation in 2021, but not with a quality appraisal or specific targeting of pharmacological treatments. Liang et al. [13] performed a critical appraisal of Paralyzed Veterans of America (PVA) guidelines for spinal cord injury in 2021, but they did not systematically review and include all available guidelines developed by different authoritative organizations.

Therefore, it was our purpose to focus on the appraisal of guidelines on pharmacological treatments for spinal cord injury and summarize relevant recommendations with the quality of their supporting evidence.

Methods

Registration

The systematic review was conducted consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14] and was registered on PROSPERO (CRD42022302185).

Search strategy

Considering that guidelines published too early were of minimal relevance to current clinical practice, we limited our retrieval time range from January 2000 to January 2022, referring to one prior study published in the Annals of Internal Medicine [10]. We searched Medline, Embase, Cochrane, and Web of Science, using search strategies (Appendix 1) developed by an academic librarian. Some guideline-specific databases (National Institute for Health and Care Excellence, Congress of Neurological Surgeons, etc.) and Google Scholar were also searched (Appendix 2). Our results were limited to the English language.

Guideline selection

After duplicates were removed, three reviewers independently reviewed the literature by titles and abstracts to exclude literature that was either not relevant to spinal cord injury or not a guideline. We performed a pilot test by randomly selecting 5% from the remaining literature to increase consistency among three reviewers before the formal process of reviewing full-text articles [15]. Any discrepancies were discussed. If not solved, senior scientists were consulted.

Referring to the inclusion criteria in the prior study [10], literature was included according to the following criteria: (1) developed by national accredited committees, publicly funded agencies, or medical associations that provided recommendations on spinal cord injury; (2) included explicit methodological sections (eg, literature search, review of evidence, and methods of formulating recommendations) in text parts or supplementary materials; and (3) was the most updated guideline if multiple versions were available. For

criterion (2), we included guidelines containing evidence-based recommendations (based on the body of evidence with quality assessment) or consensus-based recommendations (based on a systematic/literature review where evidence was found to be limited or lacking) [16−18].

Quality assessment of guidelines

Three raters independently appraised the included guidelines using the Appraisal of Guidelines for Research and Evaluation, 2nd edition (AGREE II) instrument (Appendix 3, www.agreetrust.org). The AGREE II instrument comprises 23 items divided into six domains: domain 1: scope and purpose (concerning objectives, health questions, and target population of guidelines); domain 2: stakeholder involvement (concerning extent of participation of appropriate stakeholders in the development of guidelines); domain 3: rigor of development (concerning methods to gather evidence and formulate recommendations); domain 4: clarity of presentation (concerning languages, structures, and formats of guidelines); domain 5: applicability (concerning barriers, facilitative strategies, and resources implications of applying guidelines); and domain 6: editorial independence (concerning competing interests in the development of guidelines) [19].

Each item in AGREE II instrument is appraised by a seven-point scale: 1 implies a strong disagreement, and 7 means a strong agreement about the matching degree between the reporting of the item in the guidelines and all the criteria in the AGREE II instrument [19]. The score for each domain is calculated by (obtained score−minimum possible score) / (maximum possible score−minimum possible score) [19]. As defined by the AGREE II instrument, we set 50% as the minimal threshold for the score of each domain [8,19]. Guidelines with a majority of domains (5−6 domains) scoring above 50% were judged as "recommended." Guidelines with some domains (1−4 domains) scoring above 50% were judged as "recommended with modifications." Guidelines with all domains scoring below 50% were judged as "not recommended" [16].

Before the formal appraisal, we selected two guidelines as a pilot to increase consistency among three raters [15]. We calculated the median score and the interquartile range (IQR) for each domain. The interrater agreement was also calculated by the intraclass correlation coefficient with a corresponding 95% confidence interval (CI) with poor agreement when it was 0.01 to 0.20, fair agreement when 0.21 to 0.40, moderate agreement when 0.41 to 0.60, substantial agreement when 0.61 to 0.80, and very good agreement when 0.81 to 1.00 to measure the reliability of the results [10]. Differences in the item ratings of three points or fewer among raters were allowed [10]. Any discrepancies were discussed, and senior scientists were available when necessary. All calculations were conducted by Microsoft Excel 2016 and IBM SPSS Statistics 25.0.

Recommendations on pharmacological treatments

One reviewer extracted the recommendations on pharmacological treatments with their supporting evidence from the guidelines judged as "recommended" and "recommended with modifications," and two reviewers checked them [20]. Any discrepancies were solved through discussion. Each recommendation was classified as for, against, or neither for nor against (meaning there was no sufficient evidence to make a definitive recommendation) [8]. We considered that there were inconsistencies among recommendations on one certain pharmacological agent, when at least one guideline recommended for it and another recommended against it.

Quality of evidence for recommendations

Considering that the topic of one prior study published in The Spine Journal was close to ours [8], the evidence assessment system (Appendix 4) used by the prior study were utilized in our study to categorize the quality of the supporting evidence for each recommendation as poor, fair, or good.

Results

Selection of guidelines

After duplicates were removed, 12,017 articles were retrieved. After the reviewing of titles, abstracts, and full-text articles, eight guidelines were included (Figure). They were developed by PVA [21], American Association of Neurological Surgeons and Congress of Neurological Surgeons [22], Chinese Association of Spine and Spinal Cord Injury [23], National Institute for Health and Care Excellence [24], AO Spine [25], Congress of Neurological Surgeons [26], French Society of Anesthesia and Intensive Care Medicine [27], and World Federation of Neurosurgical Societies Spine Committee [28]. Two of them [23,28] were expert consensuses that made contributions in clinical practice [29]. A description of all the included guidelines was showed in Table 1.

Quality assessment of guidelines

The scores of the guidelines in each domain were as follows: scope and purpose (range: 51.9%−95.6%, median: 66.1%, IQR: 55.3%−76.8%), stakeholder involvement (range: 12.6%−88.5%, median: 52.9%, IQR: 34.1%−61.8%), rigor of development (range: 41.9%−83.8%, median: 66.5%, IQR: 57.1%−79.3%), clarity of presentation (range: 80.6%−92.6%, median: 87.0%, IQR: 84.7%−89.6%), applicability (range: 4.4%−59.3%, median: 13.2%, IQR:9.6%−24.8%), editorial independence (range: 27.8%−96.7%, median: 77.8%, IQR:45.9%−83.6%; Table 2). The intraclass correlation coefficients were from 0.714 (95% CI, 0.519−0.854) to 0.926 (95% CI, 0.859−0.965) which corresponding to substantial agreement to very good agreement for the interrater agreement. Four guidelines [21−23, 28] with 1−4 domains scoring
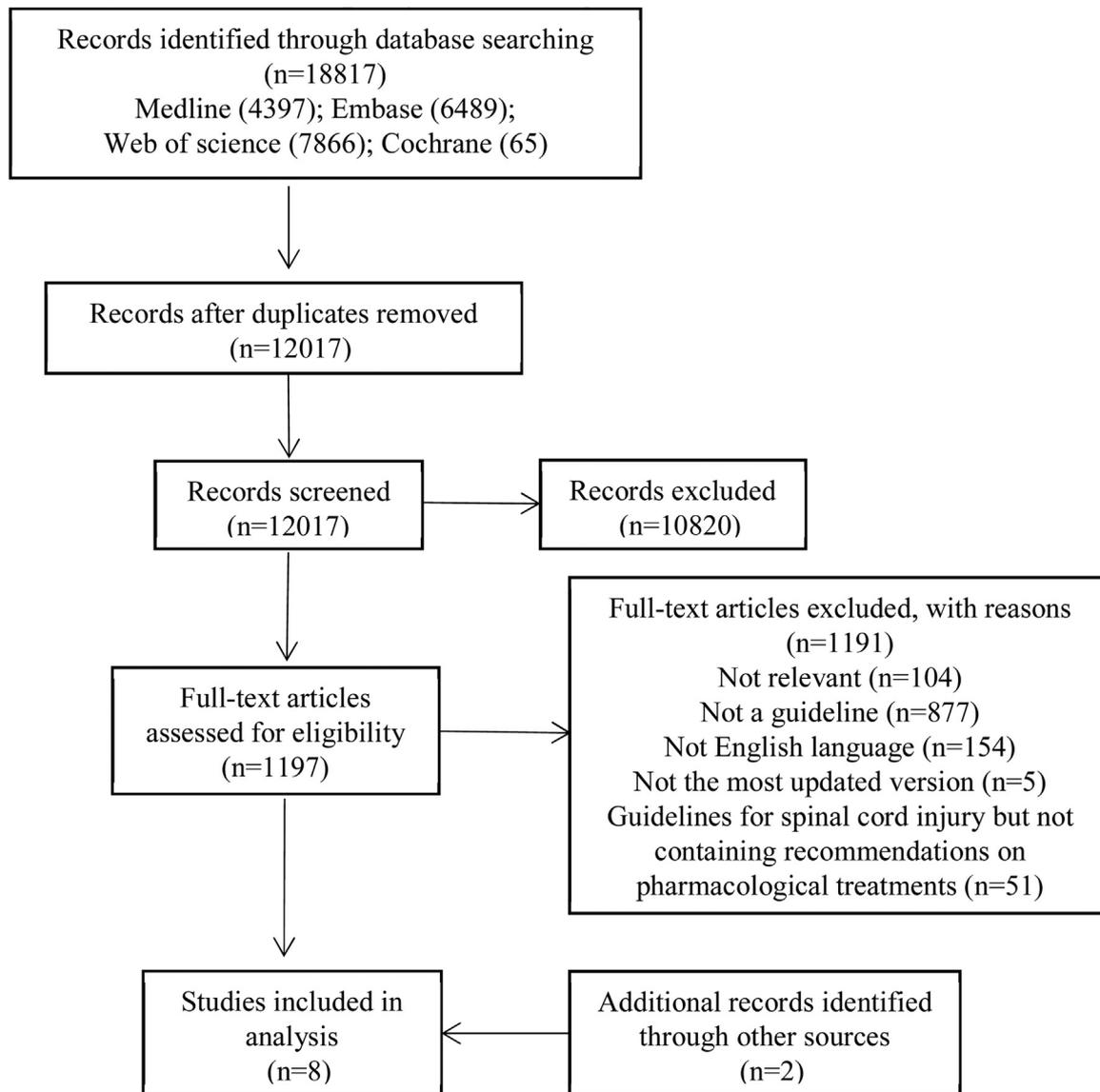
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┌─────────────────────────────────────────────┐
│   Records identified through database         │
│   searching                                   │
│   (n=18817)                                    │
│   Medline (4397); Embase (6489);               │
│   Web of science (7866); Cochrane (65)         │
└─────────────────────────────────────────────┘
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          ┌──────────────────────────────┐
          │  Records after duplicates      │
          │  removed                       │
          │  (n=12017)                     │
          └──────────────────────────────┘
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   ┌──────────────────────┐      ┌──────────────────────┐
   │  Records screened     │─────▶│  Records excluded      │
   │  (n=12017)            │      │  (n=10820)             │
   └──────────────────────┘      └──────────────────────┘

                                 ┌────────────────────────────────────┐
                                 │ Full-text articles excluded, with   │
                                 │ reasons                             │
                                 │ (n=1191)                            │
   ┌──────────────────────┐      │ Not relevant (n=104)                │
   │  Full-text articles   │─────▶│ Not a guideline (n=877)             │
   │  assessed for         │      │ Not English language (n=154)        │
   │  eligibility          │      │ Not the most updated version (n=5)  │
   │  (n=1197)             │      │ Guidelines for spinal cord injury   │
   └──────────────────────┘      │ but not containing recommendations  │
                                 │ on pharmacological treatments (n=51)│
                                 └────────────────────────────────────┘
                      │
                      ▼
   ┌──────────────────────┐      ┌──────────────────────┐
   │  Studies included in  │◀─────│  Additional records    │
   │  analysis             │      │  identified through    │
   │  (n=8)                │      │  other sources         │
   └──────────────────────┘      │  (n=2)                 │
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Figure. PRISMA flow chart showing the process in the systematic review.

more than 50% were judged as "recommended with modifications," and four guidelines [24−27] with 5−6 domains scoring more than 50% were judged as "recommended."

Pharmacological treatments

Twelve pharmacological agents (methylprednisolone, monosialotetrahexosylganglioside [GM-1], naloxone, tirilazad, nimodipine, gacyclidine, minocycline, erythropoietin, cethrin, riluzole, granulocyte colony-stimulating factor, and neural growth factor) were involved in the study. There were inconsistencies among the recommendations on methylprednisolone and GM-1 in different guidelines. A full description of all recommendations was showed in Appendix 5, and a summary was showed in Table 3. Considering that the evidence assessment system (Appendix 4) took randomized controlled trials (RCTs) as the main classification standard, all RCTs supporting recommendations on

methylprednisolone and GM-1 from different guidelines were listed in Table 4.

Methylprednisolone

Three guidelines [23,25,28] (3/8=37.5%) recommended for (one evidence-based [25] and two consensus-based [23,28]), three [22,24,27] (3/8=37.5%) recommended against (all evidence-based), and two [21,26] (2/8=25%) recommended neither for nor against. For guidelines recommending for, more specifically, they recommended for an intravenous high-dose of methylprednisolone within 8 hours after injury [23,25,28] for 24 hours [25,28] based on National Acute Spinal Cord Injury Study (NASCIS) II [32,33] or stopping as soon as possible [23], but not for patients 8 hours post-injury [23,25] or a 48-hour duration [25] based on NASCIS III [35,36]. The quality of the relevant evidence ranged from poor to fair.

Table 1

Characteristics of included guidelines

Guideline	Development Committee/ Agency/ Association	Method Used in Developing Process	Recommendation on Methylprednisolone	Type of Recommendations on Methylprednisolone	Recommendation on GM-1[*]	Type of Recommendations on GM-1
Early acute Management in Adults with Spinal Cord Injury: A Clinical Practice Guideline for Health-Care Professionals (PVA, 2008)	PVA[†]	Guidance from CMA[‡]	Neither for nor against		Neither for nor against	
Pharmacological Therapy for Acute Spinal Cord Injury (Hurlbert et al., 2013)	AANS/CNS[§]	Modification of the NASS[‖] criteria	Against	Evidence-based	Against	Evidence-based
An Expert Consensus on the Evaluation and Treatment of Acute Thoracolumbar Spine and Spinal Cord Injury in China (Zhang et al., 2013)	Chinese Association of Spine and Spinal Cord Injury	Delphi method	For	Consensus-based	For	Consensus-based
Spinal Injury: Assessment and Initial Management (NICE, 2016)	NICE[¶]	GRADE[♯] system	Against	Evidence-based		
A Clinical Practice Guideline for the Management of Patients with Acute Spinal Cord Injury: Recommendations on the Use of Methylprednisolone Sodium Succinate (Fehlings et al., 2017)	AO Spine	GRADE system	For	Evidence-based		
Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines on the Evaluation and Treatment of Patients with Thoracolumbar Spine Trauma: Pharmacological Treatment (Arnold et al., 2018)	CNS**	Modification of the NASS criteria	Neither for nor against		Neither for nor against	
French Recommendations for the Management of Patients with Spinal Cord Injury or at Risk of Spinal Cord Injury (Roquilly et al., 2020)	SFAR[††]	GRADE system	Against	Evidence-based		
Pharmacologic and Regenerative Cell Therapy for Spinal Cord Injury: WFNS Spine Committee Recommendations (Takami et al., 2020)	WFNS[‡‡] Spine Committee	Delphi method	For	Consensus-based		

The characteristics of all eight guidelines are outlined in Table 1. This includes their names, development committees/agencies/associations, methods used in developing process, recommendations on methylprednisolone and GM-1 with their types, respectively.

* GM-1, monosialotetrahexosylganglioside.
† PVA, Paralyzed Veterans of America.
‡ CMA, Canadian Medical Association.
§ AANS/CNS, American Association of Neurological Surgeons and Congress of Neurological Surgeons.
‖ NASS, North American Spine Society.
¶ NICE, National Institute for Health and Care Excellence.
♯ GRADE, Grading of Recommendations Assessment, Development and Evaluation.
** CNS, Congress of Neurological Surgeons.
†† SFAR, French Society of Anesthesia and Intensive Care Medicine.
‡‡ WFNS, World Federation of Neurosurgical Societies.

Table 2
Appraisals of guidelines through AGREE II* instrument

Guideline	Intraclass Correlation Coefficient (95% CI†)	Scope and Purpose (%)	Stakeholder Involvement (%)	Rigor of Development (%)	Clarity of Presentation (%)	Applicability (%)	Editorial Independence (%)	Overall Rating
Paralyzed Veterans of America (2008)	0.908(0.826~0.956)	59.8	54.1	73.8	85.7	15.3	27.8	4.4
American Association of Neurological Surgeons and Congress of Neurological Surgeons (2013)	0.888(0.792~0.947)	51.9	34.1	59.1	80.6	10.6	46.7	3.9
Chinese Association of Spine and Spinal Cord Injury (2013)	0.872(0.765~0.939)	53.3	34.1	41.9	81.5	11.1	77.8	3.7
National Institute for Health and Care Excellence (2016)	0.756(0.579~0.878)	88.9	88.5	81.8	87.0	59.3	77.8	5.8
AO Spine (2017)	0.714(0.519~0.854)	95.6	81.7	83.8	92.6	36.9	94.4	5.7
Congress of Neurological Surgeons (2018)	0.926(0.859~0.965)	72.4	55.2	78.5	91.7	4.4	80.0	4.8
French Society of Anesthesia and Intensive Care Medicine (2020)	0.894(0.802~0.950)	72.8	51.7	56.3	87.0	20.8	96.7	4.6
World Federation of Neurosurgical Societies Spine Committee (2020)	0.889(0.792~0.947)	55.9	12.6	57.4	88.9	6.5	43.3	3.7

The results of appraisals of all eight guidelines through the AGREE II instrument are outlined in Table 2. This includes six domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence, and overall rating with intraclass correlation coefficient companied with 95% CI.
* AGREE II, Appraisal of Guidelines for Research and Evaluation, 2nd edition.
† 95% CI, 95% confidence interval.

Monosialotetrahexosylganglioside

One guideline [23] (1/4=25%) recommended for GM-1 for patients 48 hours post-injury (consensus-based), one [22] (1/4=25%) recommended against (evidence-based), and two [21,26] (2/4=50%) recommended neither for nor against. The quality of the relevant evidence was poor.

Other pharmacological agents

One guideline [24] (1/5=20%) recommended against naloxone (evidence-based) and nimodipine (evidence-based), and one guideline [23] (1/5=20%) recommended for neural growth factor for patients 48 hours post-injury (consensus-based). Other guidelines [21,26,28] (3/5=60%) recommended neither for nor against. The quality of the relevant evidence ranged from poor to fair.

Discussion

Eight guidelines were included in the systematic review. All reached the minimum threshold in the domain 1 (scope and purpose) and domain 4 (clarity of presentation). Most reached the minimum threshold in the domain 3 (rigor of development), and more than half reached in the domain 2 (stakeholder involvement) and domain 6 (editorial independence). However, all guidelines scored lowest in domain 5 (applicability) through the AGREE II instrument, which implied that potential barriers (eg, insufficient skills of practitioners), facilitative strategies (eg, guideline online tools), and resource implications (eg, drug acquisition costs) of application of guideline recommendations were not well shown in the guidelines.

The recommendations on methylprednisolone among different guidelines were inconsistent. The results of neurological improvements of most RCTs on methylprednisolone were not statistically significant, and the only statistically significant one was a selected subgroup post-hoc analysis in NASCIS II [32,33] (Table 4). The controversy was that guidelines treated the only statistically significant evidence differently. Two guidelines [23,28] deemed that it was insufficient to prove efficacy of methylprednisolone, but still supported methylprednisolone as a treatment option for selected young patients. One guideline [25] recommended for methylprednisolone as a treatment option because it deemed that even minor recoveries might have a great influence on quality of life of patients, although the effect of methylprednisolone was considered to be minimal. Two guidelines [21,26] treated the only statistically significant evidence objectively and did not make definitive recommendations. Three guidelines [22,24,27] did not accept the only statistically significant evidence and recommended against methylprednisolone. The level of the evidence was degraded in one guideline [22] because it originated from a partial data set of NASCIS II [32,33] and constituted a retrospective analysis. The limitation in neurological scoring

Table 3

Recommendations with supporting evidence on pharmacological treatments for spinal cord injury from guidelines

Medications		PVA, 2008	Hadley et al., 2013	Zhang et al., 2013	NICE, 2016	Fehlings et al., 2017	Arnold et al., 2018	Roquilly et al., 2020	Takami et al., 2020
	Methylprednisolone	?	- -	+*	- -	+†	?	- -	+‡
Time (after injury)	<8 hours			+		+			+
	>8 hours			- -		- -			
Dose	High-dose§			+		+			+
Approach	Intravenous			+		+			+
	24-hour					+			+
Duration	48-hour					-			
	Stop as soon as possioble	+		+					
	GM-1	?	-	+‖			?		
	Naloxone	?			- -				
	Tirilazad	?							
	Nimodipine				-		?		
	Gacyclidine	?							
	Minocycline	?					?		?
	Erythropoietin	?					?		
	Cethrin						?		?
	Riluzole						?		?
	Granulocyte colony-stimulating factor						?		?
	Neural growth factor			+¶					
Guideline Recommendations		+	++	+++	?	-	- -	- - -	
		Recommended with poor evidence	Recommended with fair evidence	Recommended with good evidence	Recommended neither for nor against	Not recommended with poor evidence	Not recommended with fair evidence	Not recommended with good evidence	

Evidence supporting each recommendation: poor (no evidence or evidence from non-randomized trials only); fair (evidence from one high-quality study or multiple properly designed studies with limitations); good (evidence from two or more high-quality studies or consistent findings from a meta-analysis review).

* Recommended for as a treatment option, but not as a routine treatment or patients with absolute contraindications or relative contraindications (a history of gastrointestinal ulcer or bleeding, existing heart disease, and severe infection).

† Recommended for as a treatment option.

‡ Recommended for selected young patients.

§ Indicated a 30mg/kg bolus for 15 minutes followed by a 45-minute pause and then a 5.4mg/kg/h infusion for 23 hours based on the National Acute Spinal Cord Injury Study II.

‖ Recommended for as a treatment option for patients 48 hours post-injury.

¶ Recommended for as a treatment option for patients 48 hours post-injury.

Table 4

Randomized Controlled Trials (RCTs) supporting recommendations on methylprednisolone and GM-1 from relevant guidelines

Evidence	Description of Evidence	Result of Evidence
Methylprednisolone		
NASCIS* I (Bracken et al., 1984, 1985) [30,31]	1) High dose of methylprednisolone (1,000mg bolus and 250 mg every six hours thereafter for ten days) (n=165) 2) Standard dose of methylprednisolone (100mg bolus and 25 mg every six hours thereafter for ten days) (n=165)	Neurological improvement-Not statistically significant Complications-Statistically significant
NASCIS II (Bracken et al., 1990, 1992) [32,33]	1) Methylprednisolone (30 mg/kg bolus and 5.4 mg/kg/h for 23 hours) (n=162) 2) Naloxone (5.4 mg/kg bolus and 4.0 mg/kg/h for 23 hours) (n=154) 3) Placebo (n=171)	Neurological improvement-Not statistically significant (Post hoc analysis: Within 8 hours: Neurological improvement-Statistically significant)
Otani et al., 1994 [34]	1) Methylprednisolone at NASCIS II protocol (n=82) 2) Observational controls (n=76)	Neurological improvement-Not statistically significant
NASCIS III (Bracken et al., 1997, 1998) [35,36]	All patients received an intravenous bolus of methylprednisolone (30 mg/kg) before randomization. 1) 24 MP† (a methylprednisolone infusion of 5.4 mg/kg/h for 24 hours) (n=166) 2) 48 MP (a methylprednisolone infusion of 5.4 mg/kg/h for 48 hours) (n=167) 3) 48 tirilazad (a 2.5 mg/kg bolus infusion of tirilazad mesylate every 6 hours for 48 hours) (n=166)	Neurological improvement-Not statistically significant Complications-Statistically significant
Pointillart et al., 2000 [37]	1) Nimodipine (a dose of 0.15 mg/kg/h for 2h followed by 0.03 mg/kg/h for 7 days) (n=27) 2) Methylprednisolone (a dose of 30 mg/kg over 1h followed by 5.4 mg/kg/h for 23h) (n=27) 3) Nimodipine and methylprednisolone (same doses used in two above groups) (n=27) 4) No medical treatment (n=25)	Neurological improvement-Not statistically significant
Matsumoto et al., 2001 [38]	1) Methylprednisolone at NASCIS II protocol (n=23) 2) Placebo (n=23)	Complications-Statistically significant
GM-1‡		
Geisler et al., 1991 [39]	All patients received a 250 mg bolus of methylprednisolone followed by 125 mg/q6h for 72 hours before randomization. 1) GM-1 (100mg/d for 18 to 32 doses with the first dose taken within 72 hours of the injury) (n=17) 2) Placebo (n=20)	Neurological improvement-Statistically significant
Geisler et al., 2001 [40]	All patients received the NASCIS II dose regimen of methylprednisolone within 8 hours after injury. 1) High dose of GM-1 (a 600 mg loading dose followed by 200 mg/day for 56 days) (n=99) 2) Low dose of GM-1 (a 300 mg loading dose followed by 100 mg/day for 56 days) (n=331) 3) Placebo (n=330)	Neurological improvement-Not statistically significant

All RCTs supporting recommendations on methylprednisolone and GM-1 from relevant guidelines are outlined in Table 4. This includes their names, brief descriptions about them and types.

* NASCIS, National Acute Spinal Cord Injury Study

† MP, methylprednisolone

‡ GM-1, monosialotetrahexosylganglioside.

systems used by the evidence was also mentioned in another guideline [24].

The recommendations on GM-1 were inconsistent among different guidelines. The controversy derived from two RCTs with conflicting results [39,40] (Table 4). One guideline [23] recommended for GM-1 for patients 48 hours post-injury as a treatment option given the lack of adverse

effects, although there was insufficient evidence to prove its efficacy. Considering the controversial evidence, two guidelines [21,26] recommended neither for nor against, and one [22] recommended against. Naloxone, tirilazad, nimodipine, and gacyclidine were recommended against or neither for nor against because there was insufficient evidence to prove their efficacies. Minocycline, erythropoietin,

cethrin, riluzole, and granulocyte colony-stimulating factors were recommended neither for nor against due to insufficient evidence. Neural growth factor was recommended for patients 48 hours post-injury with no specific reason given [23].

When faced with inconsistent evidence, evidence-based recommendations tended to recommend against, whereas consensus-based recommendations tended to recommend for. One possible reason was that the processes of assessing evidence and formulating recommendations for evidence-based recommendations were based on standard criteria, which treated evidence more objectively and considered more comprehensively when recommendations were formulated [41−44]. Two guidelines [24,27] used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, which took many aspects into consideration when formulating recommendations, such as, the quality of evidence, the balance between desirable and undesirable effects, the values and preferences of stakeholders, and whether the intervention represents a wise use of resources [45−47]. One guideline [22] used a modification of the North American Spine Society (NASS) criteria [48], which degraded evidence where there were defects. This also explained why there were recommendations that were neither for nor against in two other guidelines [21,26]. Consensus-based recommendations in two expert consensuses [23,28] were formulated only by the Delphi method without assessing evidence strictly (Table 1). Another possible reason was that the development panels were almost composed by clinical experts but no other stakeholders in expert consensuses, so some statistically significant evidence for neurological improvements might be overemphasized [43,49,50]. Also, the fear of litigation and peer pressure could not be neglected [51].

In the future, there is a need to pay more attention to potential barriers, facilitative strategies, and resource implications of application of guideline recommendations when developing guidelines. Besides, there is a need for more high-quality evidence of methylprednisolone and GM-1 for the development of spinal cord injury guidelines, but this could be difficult and challenged along with the increasing cost of care and research. Additionally, it is expected that a rating panel could utilize the Appropriate Use Criteria (AUC) methodology to synthesize existing evidence, clinical practice experience, and expert judgment to determine the appropriateness of methylprednisolone and GM-1 in various clinical scenarios [52]. Also, some new pharmacological agents, such as, VX-210 [53], minocycline [54,55], riluzole [56], and granulocyte colony-stimulating factors [57], are expected to be involved in guidelines.

There were two strengths in the study. First, we searched guidelines for spinal cord injury in the previous twenty-two years systematically. Second, we appraised the quality of the included guidelines through the AGREE II instrument, summarized recommendations on pharmacological treatments, and unified the level of evidence by the evidence assessment system [8,58], which allowed readers to compare the quality of guidelines and acquire similarities and differences among recommendations with the level of their supporting evidence among different guidelines more intuitively.

This study also had some limitations. First, to some extent, the AGREE II instrument is a subjective evaluation tool, and the difference of raters' experience might cause bias to the evaluation results. However, the pilot test before the formal appraisal and the calculated intraclass correlation coefficient were utilized to increase the reliability of the evaluation results. Second, the exclusion of non-English literature might miss some available guidelines.

In conclusion, there were inconsistencies among the recommendations for methylprednisolone and GM-1. Evidence-based recommendations tended to recommend against, whereas consensus-based recommendations tended to recommend for.

Declarations of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.spinee.2022.09.009.

References

[1] GBD 2016 Traumatic Brain Injury and Spinal Cord Injury Collaborators. Global, regional, and national burden of traumatic brain injury and spinal cord injury, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18(1):56–87. https://doi.org/10.1016/s1474-4422(18)30415-0.

[2] Ahuja CS, Wilson JR, Nori S, Kotter MRN, Druschel C, Curt A, et al. Traumatic spinal cord injury. Nat Rev Dis Primers 2017;3:17018. https://doi.org/10.1038/nrdp.2017.18.

[3] Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME). Available at: http://ghdx.healthdata.org/gbd-results-tool.

[4] SCI facts and figures. J Spinal Cord Med. 2017;40(6):872-3. https://doi.org/10.1080/10790268.2017.1379938.

[5] Silva NA, Sousa N, Reis RL, Salgado AJ. From basics to clinical: a comprehensive review on spinal cord injury. Prog Neurobiol 2014;114:25–57. https://doi.org/10.1016/j.pneurobio.2013.11.002.

[6] Falavigna A, Quadros FW, Teles AR, Wong CC, Barbagallo G, Brodke D, et al. Worldwide steroid prescription for acute spinal cord injury. Global Spine J 2018;8(3):303–10. https://doi.org/10.1177/2192568217735804.

[7] Zhou H, Lou Y, Chen L, Kang Y, Liu L, Cai Z, et al. Epidemiological and clinical features, treatment status, and economic burden of traumatic spinal cord injury in China. medRxiv 2021 2021.09.27.21264179Doi:. https://doi.org/10.1101/2021.09.27.21264179.

[8] Anderson DB, Luca K, Jensen RK, Eyles JP, Van Gelder JM, Friedly JL, et al. A critical appraisal of clinical practice guidelines for the treatment of lumbar spinal stenosis. Spine J 2021;21(3):455–64. https://doi.org/10.1016/j.spinee.2020.10.022.

[9] Montero-Odasso MM, Kamkar N, Pieruccini-Faria F, Osman A, Sarquis-Adamson Y, Close J, et al. Evaluation of clinical practice guidelines on fall prevention and management for older adults: a systematic review. JAMA Netw Open 2021;4(12) e2138911Doi:. https://doi.org/10.1001/jamanetworkopen.2021.38911.

[10] Erickson J, Sadeghirad B, Lytvyn L, Slavin J, Johnston BC. The scientific basis of guideline recommendations on sugar intake: a systematic review. Ann Intern Med 2017;166(4):257–67. https://doi.org/10.7326/m16-2020.

[11] Lee JL, Matthias MS, Menachemi N, Frankel RM, Weiner M. A critical appraisal of guidelines for electronic communication between patients and clinicians: the need to modernize current recommendations. J Am Med Inform Assoc 2018;25(4):413–8. https://doi.org/10.1093/jamia/ocx089.

[12] Gerber LH, Deshpande R, Prabhakar S, Cai C, Garfinkel S, Morse L, et al. Narrative review of clinical practice guidelines for rehabilitation of people with spinal cord injury: 2010-2020. Am J Phys Med Rehabil 2021;100(5):501–12. https://doi.org/10.1097/phm.0000000000001637.

[13] Liang N, Wu S, Roberts S, Makaram N, Ngwayi JRM, Porter DE. Critical appraisal of paralyzed veterans of America Guidelines in spinal cord injury: an International Collaborative Study Using the Appraisal of Guidelines for Research and Evaluation II Instrument (AGREE II). Mil Med 2021. https://doi.org/10.1093/milmed/usab465.

[14] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535. https://doi.org/10.1136/bmj.b2535.

[15] van Teijlingen E, Hundley V. The importance of pilot studies. Nurs Stand 2002;16(40):33–6. https://doi.org/10.7748/ns2002.06.16.40.33.c3214.

[16] Simon A, Pratt M, Hutton B, Skidmore B, Fakhraei R, Rybak N, et al. Guidelines for the management of pregnant women with obesity: a systematic review. Obes Rev 2020;21(3):e12972. https://doi.org/10.1111/obr.12972.

[17] Yao L, Ahmed MM, Guyatt GH, Yan P, Hui X, Wang Q, et al. Discordant and inappropriate discordant recommendations in consensus and evidence based guidelines: empirical analysis. BMJ 2021;375:e066045. https://doi.org/10.1136/bmj-2021-066045.

[18] Homer CS, Oats J, Middleton P, Ramson J, Diplock S. Updated clinical practice guidelines on pregnancy care. Med J Aust 2018;209(9):409–12. https://doi.org/10.5694/mja18.00286.

[19] Brouwers MC, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ 2010;182(18):E839–42. https://doi.org/10.1503/cmaj.090449.

[20] Khanji MY, Bicalho VV, van Waardhuizen CN, Ferket BS, Petersen SE, Hunink MG. Cardiovascular risk assessment: a systematic review of guidelines. Ann Intern Med 2016;165(10):713–22. https://doi.org/10.7326/m16-1110.

[21] Consortium for Spinal Cord M. Early acute management in adults with spinal cord injury: a clinical practice guideline for health-care professionals. J Spinal Cord Med 2008;31(4):403–79.

[22] Hurlbert RJ, Hadley MN, Walters BC, Aarabi B, Dhall SS, Gelb DE, et al. Pharmacological therapy for acute spinal cord injury. Neurosurgery 2013;72(Suppl 2):93–105. https://doi.org/10.1227/NEU.0-b013e31827765c6.

[23] Zhang Z, Li F, Sun T. An expert consensus on the evaluation and treatment of acute thoracolumbar spine and spinal cord injury in China. Neural Regen Res 2013;8(33):3077–86. https://doi.org/10.3969/j.issn.1673-5374.2013.33.001.

[24] National Clinical Guideline C. National Institute for Health and Care Excellence: Clinical Guidelines. Spinal Injury: Assessment and Initial Management. London: National Institute for Health and Care Excellence (UK); 2016. Copyright © National Clinical Guideline Centre 2016.

[25] Fehlings MG, Wilson JR, Tetreault LA, Aarabi B, Anderson P, Arnold PM, et al. A clinical practice guideline for the management of patients with acute spinal cord injury: recommendations on the use of methylprednisolone sodium succinate. Global Spine J 2017;7(3 Suppl):203s–11s. https://doi.org/10.1177/2192568217703085.

[26] Arnold PM, Anderson PA, Chi JH, Dailey AT, Dhall SS, Eichholz KM, et al. Congress of neurological surgeons systematic review and evidence-based guidelines on the evaluation and treatment of patients with thoracolumbar spine trauma: pharmacological treatment. Neurosurgery 2019;84(1):E36–e8. https://doi.org/10.1093/neuros/nyy371.

[27] Roquilly A, Vigué B, Boutonnet M, Bouzat P, Buffenoir K, Cesareo E, et al. French recommendations for the management of patients with spinal cord injury or at risk of spinal cord injury. Anaesth Crit Care Pain Med 2020;39(2):279–89. https://doi.org/10.1016/j.accpm.2020.02.003.

[28] Takami T, Shimokawa N, Parthiban J, Zileli M, Ali S. Pharmacologic and regenerative cell therapy for spinal cord injury: WFNS Spine Committee Recommendations. Neurospine 2020;17(4):785–96. https://doi.org/10.14245/ns.2040408.204.

[29] Jones J, Hunter D. Consensus methods for medical and health services research. BMJ 1995;311(7001):376–80. https://doi.org/10.1136/bmj.311.7001.376.

[30] Bracken MB, Collins WF, Freeman DF, Shepard MJ, Wagner FW, Silten RM, et al. Efficacy of methylprednisolone in acute spinal cord injury. Jama. 1984;251(1):45–52.

[31] Bracken MB, Shepard MJ, Hellenbrand KG, Collins WF, Leo LS, Freeman DF, et al. Methylprednisolone and neurological function 1 year after spinal cord injury. Results of the National Acute Spinal Cord Injury Study. J Neurosurg. 1985;63(5):704–13. https://doi.org/10.3171/jns.1985.63.5.0704.

[32] Bracken MB, Shepard MJ, Collins WF, Holford TR, Young W, Baskin DS, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National Acute Spinal Cord Injury Study. N Engl J Med 1990;322(20):1405–11. https://doi.org/10.1056/nejm199005173222001.

[33] Bracken MB, Shepard MJ, Collins WF, Holford TR, Baskin DS, Eisenberg HM, et al. Methylprednisolone or naloxone treatment after acute spinal cord injury: 1-year follow-up data. Results of the second National Acute Spinal Cord Injury Study. J Neurosurg 1992;76(1):23–31. https://doi.org/10.3171/jns.1992.76.1.0023.

[34] Otani K, Abe H, Kadoya S, Nakagowa H, Ikata T, Tominaga S, et al. Beneficial effects of methylprednisolone sodium succinate in the treatment of acute spinal cord injury [in Japanese]. Sekitsui Sekizui J. 1994;7:633–47.

[35] Bracken MB, Shepard MJ, Holford TR, Leo-Summers L, Aldrich EF, Fazl M, et al. Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. JAMA 1997;277(20):1597–604.

[36] Bracken MB, Shepard MJ, Holford TR, Leo-Summers L, Aldrich EF, Fazl M, et al. Methylprednisolone or tirilazad mesylate

administration after acute spinal cord injury: 1-year follow up. Results of the third National Acute Spinal Cord Injury randomized controlled trial. J Neurosurg 1998;89(5):699–706. https://doi.org/10.3171/jns.1998.89.5.0699.

[37] Pointillart V, Petitjean ME, Wiart L, Vital JM, Lassié P, Thicoipé M, et al. Pharmacological therapy of spinal cord injury during the acute phase. Spinal Cord. 2000;38(2):71–6. https://doi.org/10.1038/sj.sc.3100962.

[38] Matsumoto T, Tamaki T, Kawakami M, Yoshida M, Ando M, Yamada H. Early complications of high-dose methylprednisolone sodium succinate treatment in the follow-up of acute cervical spinal cord injury. Spine (Phila Pa 1976). 2001;26(4):426–30. https://doi.org/10.1097/00007632-200102150-00020.

[39] Geisler FH, Dorsey FC, Coleman WP. Recovery of motor function after spinal-cord injury−a randomized, placebo-controlled trial with GM-1 ganglioside. N Engl J Med 1991;324(26):1829–38. https://doi.org/10.1056/nejm199106273242601.

[40] Geisler FH, Coleman WP, Grieco G, Poonian D. The Sygen multicenter acute spinal cord injury study. Spine (Phila Pa 1976) 2001;26 (24 Suppl):S87–98. https://doi.org/10.1097/00007632-200112151-00015.

[41] Oxman AD, Schünemann HJ, Fretheim A. Improving the use of research evidence in guideline development: 8. Synthesis and presentation of evidence. Health Res Policy Syst 2006;4:20. https://doi.org/10.1186/1478-4505-4-20.

[42] Schünemann HJ, Fretheim A, Oxman AD. Improving the use of research evidence in guideline development: 9. Grading evidence and recommendations. Health Res Policy Syst 2006;4:21. https://doi.org/10.1186/1478-4505-4-21.

[43] Edejer TT. Improving the use of research evidence in guideline development: 11. Incorporating considerations of cost-effectiveness, affordability and resource implications. Health Res Policy Syst 2006;4:23. https://doi.org/10.1186/1478-4505-4-23.

[44] Oxman AD, Schünemann HJ, Fretheim A. Improving the use of research evidence in guideline development: 12. Incorporating considerations of equity. Health Res Policy Syst 2006;4:24. https://doi.org/10.1186/1478-4505-4-24.

[45] Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ. What is "quality of evidence" and why is it important to clinicians? BMJ 2008;336(7651):995–8. https://doi.org/10.1136/bmj.39490.551019.BE.

[46] Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al. Going from evidence to recommendations. BMJ 2008;336 (7652):1049–51. https://doi.org/10.1136/bmj.39493.646875.AE.

[47] Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336 (7650):924–6. https://doi.org/10.1136/bmj.39489.470347.AD.

[48] Kreiner DS, Shaffer WO, Baisden JL, Gilbert TJ, Summers JT, Toton JF, et al. An evidence-based clinical guideline for the diagnosis and treatment of degenerative lumbar spinal stenosis (update). Spine J 2013;13(7):734–43. https://doi.org/10.1016/j.spinee.2012.11.059.

[49] Fretheim A, Schünemann HJ, Oxman AD. Improving the use of research evidence in guideline development: 3. Group composition and consultation process. Health Res Policy Syst 2006;4:15. https://doi.org/10.1186/1478-4505-4-15.

[50] Schünemann HJ, Fretheim A, Oxman AD. Improving the use of research evidence in guideline development: 10. Integrating values and consumer involvement. Health Res Policy Syst 2006;4:22. https://doi.org/10.1186/1478-4505-4-22.

[51] Hurlbert RJ. Strategies of medical intervention in the management of acute spinal cord injury. Spine (Phila Pa 1976) 2006;31(11 Suppl):S16–21 discussion S36. https://doi.org/10.1097/01.brs.0000218264.37914.2c.

[52] Connolly SM, Baker DR, Coldiron BM, Fazio MJ, Storrs PA, Vidimos AT, et al. AAD/ACMS/ASDSA/ASMS 2012 appropriate use criteria for Mohs micrographic surgery: a report of the American Academy of Dermatology, American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and the American Society for Mohs Surgery. J Am Acad Dermatol 2012;67 (4):531–50. https://doi.org/10.1016/j.jaad.2012.06.009.

[53] Fehlings MG, Chen Y, Aarabi B, Ahmad F, Anderson KD, Dumont T, et al. A randomized controlled trial of local delivery of a rho inhibitor (VX-210) in patients with acute traumatic cervical spinal cord injury. J Neurotrauma 2021;38(15):2065–72. https://doi.org/10.1089/neu.2020.7096.

[54] Ulndreaj A, Badner A, Fehlings MG. Promising neuroprotective strategies for traumatic spinal cord injury with a focus on the differential effects among anatomical levels of injury. F1000Res 2017;6:1907. https://doi.org/10.12688/f1000research.11633.1.

[55] Badhiwala JH, Ahuja CS, Fehlings MG. Time is spine: a review of translational advances in spinal cord injury. J Neurosurg Spine 2018;30(1):1–18. https://doi.org/10.3171/2018.9.Spine18682.

[56] Fehlings MG, Nakashima H, Nagoshi N, Chow DS, 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. 2016;54(1):8–15. https://doi.org/10.1038/sc.2015.95.

[57] Koda M, Hanaoka H, Fujii Y, Hanawa M, Kawasaki Y, Ozawa Y, et al. Randomized trial of granulocyte colony-stimulating factor for spinal cord injury. Brain 2021;144(3):789–99. https://doi.org/10.1093/brain/awaa466.

[58] Chou R, Qaseem A, Snow V, Casey D, Cross JT, Shekelle P, et al. Diagnosis and treatment of low back pain: a joint clinical practice guideline from the American College of Physicians and the American Pain Society. Ann Intern Med 2007;147(7):478–91. https://doi.org/10.7326/0003-4819-147-7-200710020-00006.