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Pharmacologic therapies of pain in patients with spinal cord injury: a systematic review

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STUDY DESIGN: Systematic review.

OBJECTIVES: This systematic review evaluates all randomized clinical trials (RCTs) conducted on assessing the efficacy and safety of pharmacologic therapies for the treatment of Spinal Cord Injury (SCI)-associated pain.

METHODS: The PubMed/Medline, EMBASE, and Cochrane library online databases were searched from 1946 to May 2019 using specific search terms for SCI, pain, and RCTs meeting predetermined inclusion criteria. The efficacy outcome of interest was pain reduction, discontinuations, and adverse events (AEs).

RESULTS: Of 2746 records identified through database searching, 703 duplicates were deleted. 1814 were excluded, the full text of the remaining 230 articles was reviewed, and finally, 28 papers were selected for drafting. The most studied medications were pregabalin, gabapentin, amitriptyline, and ketamine. Pregabalin, gabapentin, and amitriptyline reduced VAS by more than 30%, and ketamine reduced VAS by 40%. Oxcarbazepine, lamotrigine, alfentanil, tramadol, and morphine added to clonidine, baclofen, and botulinum toxin type A (BTA) significantly reduced pain compared with placebo. On the other hand, valproate, levetiracetam, trazodone, and duloxetine did not significantly alleviate SCI-associated pain compared to placebo. The risks of AEs and discontinuations in anticonvulsants were the least, while it was highest in analgesics.

CONCLUSIONS: Studies of SCI-associated pain were few, small, heterogenic in measures and values, and did not allow quantitative comparisons of efficacy. However, available data suggested pregabalin and gabapentin led to a more marked reduction in SCI-associated pain with fewer AEs. Additional clinical studies are needed to assess the effect of established and novel management options.

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INTRODUCTION

Pain is a common sequela of spinal cord injury (SCI), with an estimated pooled prevalence of 53% in SCI patients [1]. The disability and distress caused by pain profoundly affect patients' functionality, quality of life, and psychological wellbeing [2, 3].

The SCI pain classification, proposed by Bryce et al., presents four types of pain, including nociceptive pain, neuropathic pain, other pain, and unknown pain. Nociceptive pain is defined as the pain arising from activation of a sensory receptor that responds to noxious stimuli, which subdivides into musculoskeletal pain (e.g., spinal fractures, muscle injury, muscle spasms), visceral pain (constipation, urinary tract infection, bowel impaction), or other nociceptive pain (e.g., pressure sores, autonomic dysreflexia headache) [4]. Neuropathic pain (NP) is defined as "pain caused by a lesion or disease of the somatosensory nervous system" which is usually described as burning, prickling, tingling, pins and needles, sharp, shooting, squeezing, painful cold, or electric shock-like pain. They are classified as at-level SCI pain, below-level SCI pain, and other neuropathic pain [4, 5].

The management of neuropathic pain has been an ongoing challenge for healthcare professionals. There are pharmacological and non-pharmacological intervention options, but there is conflicting evidence for their use in reducing neuropathic pain.

Non-pharmacological options for the management of SCI pain generally have no significant adverse effects (AEs), but they have been used as combination therapy with pharmacological treatments or when the patient is refractory to the pharmacological treatments.

The pharmacological treatments that have been used to manage SCI pain are numerous and could be classified into five categories [6]:

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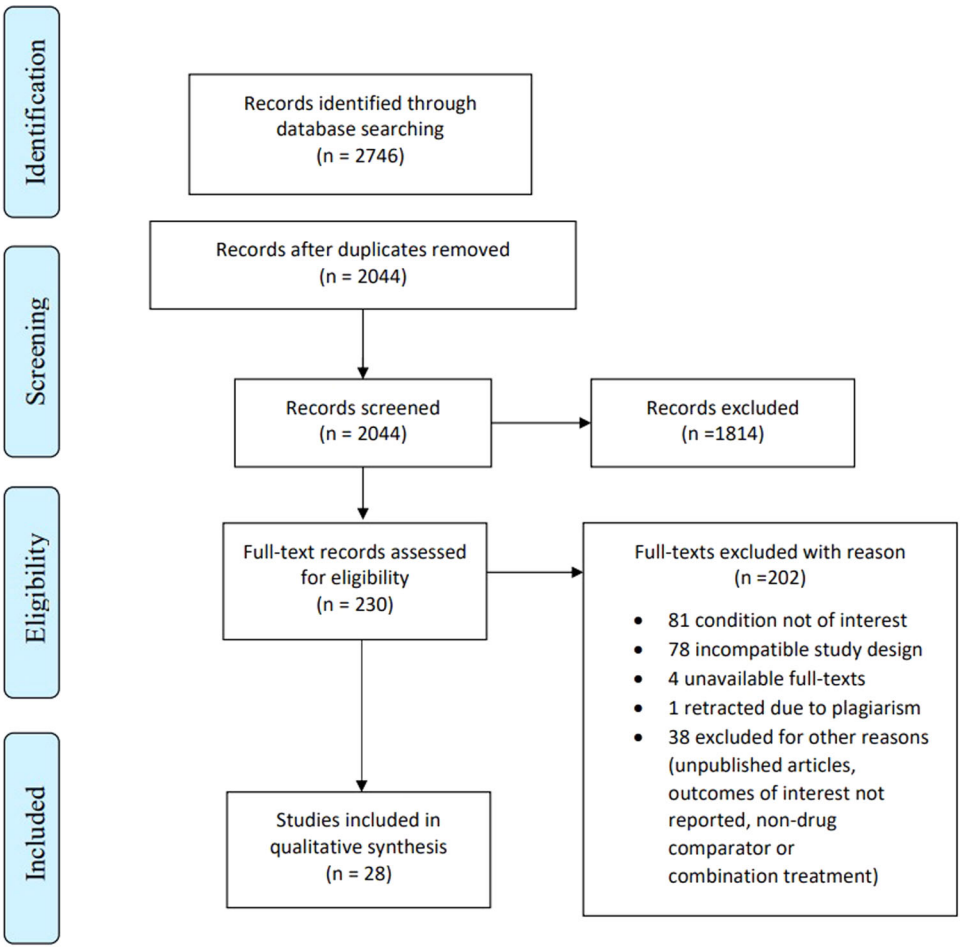

Fig. 1 Literature search flow diagram.

1. Analgesics, which include lidocaine, intravenous ketamine, intravenous alfentanil, intrathecal morphine or clonidine, tramadol, oxycodone, and capsaicin
2. Anticonvulsants, which include gabapentin, pregabalin, valproic acid, levetiracetam, lamotrigine
3. Antidepressants, which include trazodone, amitriptyline, duloxetine, venlafaxine
4. Antispastics, which include intrathecal baclofen, phenol blocks, botulinum toxin
5. Cannabinoids, which include dronabinol and tetrahydrocan nabinol (THC)

Despite various medications being tested for treatment, only pregabalin has gained the US Food and Drug Administration (FDA) approval for SCI pain [7]. This systematic review aimed to appraise the evidence of randomized clinical trials (RCTs) conducted on assessing the efficacy and safety of pharmacologic therapies for the treatment of SCI pain.

METHODS

Research approach

The PubMed/Medline, EMBASE, and Cochrane library online databases were searched from 1946 to May 2019 using specific search terms for (1) SCI, (2) pain, and (3) RCTs. The search terms were adjusted to meet the requirements of the databases. Appendix 1 in the supplemental material contains a detailed search strategy. Furthermore, the reference checking of the included papers was performed to identify the potentially missed items in the original search. Our systematic review was conducted according to the PRISMA 2020 Checklist [8].

Study criteria

Studies had to meet the following criteria in order to be included in our review: (1) ≥50% participants were SCI patients, or the results were stratified by population type (2) RCTs in adults aged ≥18 years (3) Any intervention that involved pharmacological treatment in alleviating pain. Studies that used drugs in combination with nonpharmacological modalities or food supplements were excluded. There were no exclusion criteria based on the type of post-SCI pain (i.e., nociceptive, neuropathic, mixed), specific etiology, or language. Two independent researchers (M.A. D.O and H.Y) reviewed the titles and abstracts of articles. Potentially eligible trials were selected through a consensus process, with conflicts concerning the inclusion or exclusion of studies being resolved by a third reviewer (S.B.J). Full texts of the eligible studies were retrieved. Figure 1 provides an outline of the retrieval and selection of studies.

Data extraction

Four researchers (M.H,A, M.A.D.O, H.Y, and T.I.P), two by two, extracted data independently. The data describing study characteristics, including characteristics of participants, interventions, comparisons, outcomes, analysis approach, results, and study sponsorship were extracted. The relevant statistical significance for each drug comparison is summarized in Table 2. The risk of bias was also evaluated by two researchers independently (H.Y and S.B.J). The third blinded reviewer (V.R.M) resolved the discrepancies.

Outcomes

The primary endpoint of this study was the efficacy of pain reduction in response to pharmacological options for SCI-related pain. This pain reduction is defined as the mean and standard deviation of the change of pain score of an outcome assessment tool for pain such as Numeric Pain Scale (NPS) or Visual Analog Scale (VAS), or other pain-related

questionnaires. Furthermore, we assessed the percentage of patients who experienced more than 30% or 50% pain reduction during the study period. The adverse effects of each drug and the proportion of patients who discontinued a drug were our endpoints regarding drug safety. In studies that did not provide the percentage of pain reduction, we computed it using the difference between the pre-and post-intervention pain scores with the following formula:

((pre-treatment pain score-post-treatment)/pre-treatment pain score) multiply by100

Assessment of methodological quality

We used the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) (9) for risk of bias assessment. This tool categorizes five domains of bias into (1) bias arising from the random sequence generation and allocation concealment (selection bias); (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data (attrition bias); (4) bias in the measurement of the outcome and (5) bias in the selection of the reported result.

We assessed attrition bias as follows: the study was qualified as low-risk if the number of participants who were randomly assigned but withdrew or dropped out did not exceed 20%. If the intention-to-treat analysis was used for studies with more than a 20% dropout rate, we qualified them as high-risk, with some concerns, or low-risk based on their descriptions.

Selective outcome reporting was assessed as follows: studies were qualified as low-risk if (1) they had a pre-trial registration on a clinical trial registry and (2) their published report was consistent with the registered form.

Ethical approval

This study was approved by the Ethics Committee of Sina Trauma and Surgery Research Center, Tehran University of Medical Sciences, with reference number 96-01-38-295.

RESULTS

Results of the search

A total of 2746 records were identified through database searching, of which 703 duplicates were deleted. 1814 out of 2043 studies were excluded at the title and abstract screening phase. The full text of the remaining 230 articles was reviewed in detail, and 202 full-texts were excluded according to the following reasons: type of study ($n = 78$), not related ($n = 81$), unavailable full-texts ($n = 4$), other reasons ($n = 39$). Finally, 28 papers met the inclusion criteria and were selected for drafting (Fig. 1).

Effects of anticonvulsant on SCI associated pain

Among different anticonvulsants, only RCTs conducted on pregabalin [9–13], gabapentin [9, 13–18], lamotrigine [19, 20], valproic acid [21] and levetiracetam [22] met the inclusion criteria for our review (Tables 1 & 2). Pregabalin and gabapentin are the most studied drugs against neuropathic pain following SCI.

Seven studies have evaluated the efficacy of prescribed gabapentin with the dose, ranging between 300 and 3600 mg/ day on SCI-associated pain [9, 13–18]. Five RCTs showed a 32–54% reduction in VAS in groups treated with gabapentin compared to the baseline [9, 13, 14, 16, 17], while two RCTs showed conflicting results [15, 18] (Tables 1 & 2).

Pregabalin has been studied in five RCTs with prescribed doses ranging between 150 and 600 mg/ day, which showed that pregabalin is more effective than placebo or significantly reduced SCI associated pain compared to baseline, with a 32–65% reduction in VAS [9–12, 23].

Lamotrigine was evaluated in two RCTs using 25–400 mg/day doses in patients with SCI-associated pain [19, 20]. Near one-third of patients reported moderate or good pain relief. Lamotrigine was shown to be effective on neuropathic pain in patients suffering from incomplete injury, unlike complete injury [19]. In the second study, although they reported a 0.2–0.4 difference in Short-Form McGill Pain Questionnaire (SFMPQ) scores through follow-ups (day 7, 14, 21), the authors did not divide the study population between complete and incomplete SCI [20]. Only one study evaluated Levetiracetam which showed no reduction in pain intensity measured by Numeric Rating Scale (NRS), and 75% of patients reported no pain relief at all [22]. In another study, 30% of patients taking sodium valproate reported improvement, yet there was no significant effect on SCI-associated NP compared to placebo [21].

No serious adverse event was reported among patients treated with anticonvulsants. Only a few mild to moderate side effects were reported, summarized in Table 2.

Effects of antidepressants on SCI associated pain

Among different antidepressants, only RCTs conducted on trazodone, amitriptyline, and duloxetine met the inclusion criteria for our review (Tables 1 & 2). Apart from amitriptyline, on which three RCTs have been conducted, only one RCT was included in our systematic review for each of the other antidepressants. They showed no significant difference in decreasing SCI-associated pain compared to placebo. On the other hand, amitriptyline, a tricyclic antidepressant that has been investigated in three RCTs [15, 20, 24], was found to be effective in two studies. Amitriptyline was associated with VAS average pain reduction by 40% and decrease in SFMPQ by 0.2–0.4 scores; furthermore, 50% of patients reported more than 30% pain relief with amitriptyline [15, 20], while one of the included studies found no significant difference and did not confirm this effect [24]. Although all three of them were RCTs, there were a few differences in the method of the aforementioned studies, including the prescribed doses (varying between 10 and 150 mg), study design (cross over or parallel), and pain measurement tools (NRS, Short-Form McGill Pain Questionnaire (SFMPQ), Brief Pain Inventory (BPI), VAS) which makes it impossible to compare them directly. Mild to moderate adverse effects such as xerostomia, drowsiness or tiredness, constipation, urinary retention, and increased spasticity were reported in all three studies but their frequency increased in the study administering higher doses [15].

Effects of analgesics on SCI associated pain

Analgesics are potent medications whose indications include the treatment of post-SCI intractable pain. Among different analgesics, only the RCTs conducted on ketamine [18, 25, 26], intravenous alfentanil [26], intrathecal morphine [27, 28], or clonidine [28], tramadol [29], and lidocaine (26) met the inclusion criteria for our review (Tables 1 & 2).

Three RCTs were found for ketamine [18, 25, 26], Ketamin was adminsterated intravenously in all three studies however the dosage protocol was different. Eide et al. used a single bolus dose of 0.18 mg/kg (60 µg/kg followed by 6 µg/kg/min continuous infusion for 17–21 min), however Kvarnström et al. used 0.4 mg/kg which is nearly 2 times higher than the dose used in the previous study. Amr et al. adminstrated a low dose ketamine infusion (80 mg with a rate of 16 mg/h) for 7 days. All three studies showed more than 40% reduction in VAS (Table 1) as well as significantly higher side effects in patients who received ketamine, but no severe side effects were reported (Table 2). Dizziness and short-lasting delusion were the most reported side effect among the three studies (Table 2).

Alfentanil was evaluated only in one RCT [26], which reported 20%, 80% and 70% pain reductuin in VAS from baseline for continuous pain, allodynia and wind-up-like pain respectively.

A randomized placebo-controlled study conducted on 35 patients with neuropathic pain due to SCI showed that tramadol administration results in greater than 25% pain reduction in general and worst pain intensity and about 16% reduction in MPI (pain severity), with more than 55% of patients reporting much (33%) or minimal improvement (25%) [29]. However, significant

Table 1. Demographic and Baseline Features of Randomized Clinical Trials (RCTs) for Pain Following Spinal Cord Injury (SCI).

Author, year	Country	Design	Intervention and Sample Size (n.)	Total Sample Size	Dropout	Age, year (Mean ± SD/ Median (range))	Gender (M/F)	Pain Duration before Entering the Study (Mean ± SD/ Median (range))
Anticonvulsants								
Agarwal, 2016 [20]	India	Parallel	Lamotrigine ($n = 73$) vs. Amitriptyline ($n = 74$)	147	7	109 (74%) patients were in the age group of 18–40	136/11	Not mentioned
Amr, 2010 [18]	Egypt	Parallel	Ketamine and gabapentin ($n = 20$) vs. placebo and Gabapentin ($n = 20$)	40	0	Group1: 48.6 ± 10.1 Group II: 48.7 ± 9.7	Group1: 16/4 Group2: 17/3	Group I: 8 (6–17) Group II: 9 (7–18)
Amr, 2011 [14]	Egypt	Parallel	Group I: Ketamine and Gabapentin ($n = 20$) Group II: placebo and Gabapentin ($n = 20$)	40	0	Group I: 48.6 ± 10.1 Group II: 48.7 ± 9.7	Group I: 16/4 Group II: 17/3	Group I: 8 (6–17) m Group II: 9 (7–18) m
Cardenas, 2013 [10]	Multi country[a]	Parallel	Pregabalin ($n = 112$) vs. placebo ($n = 108$)	220	Pregabalin:19 placebo:17	Group I: 46.1 ± 12.7 Group II: 45.6 ± 13.8	Group I: 84/27 Group II: 92/16	pregabalin: 97.8 (5.0–396.0) m placebo: 97.5 (3.0–497.0) m
Drewes, 1994 [21]	Denmark	Crossover	Valproate vs. placebo	20	0	32.5 (18–75)	15/5	>1 m
Finnerup, 2002 [19]	Denmark	Crossover	Lamotrigine vs. placebo	30	Lamotrigine: 4 placebo: 4	49 (27–63)	18/4	7 (1–31) y
Finnerup, 2009 [22]	Denmark	Crossover	Levetiracetam vs. placebo	36	Levetiracetam: 8 placebo: 4	51 ± 11.2	21/3	>3 m
Kaydok, 2014 [9]	Turkey	Crossover	Pregabalin vs. Gabapentin	28	Gabapentin: 3 Pregabalin: 6	42.8 ± 12.3	14/5[b]	29.3 ± 25.8 m
Levendoglu, 2004 [16]	Turkey	Crossover	Gabapentin vs. placebo	20	0	35.9 ± 9.8	13/7	15.8 ± 9.0 m
Min, 2016 [12]	South Korea	Crossover	Oxcarbazepine vs. Pregabalin	55	0	51.7 ± 10.2	44/11	2458.3 ± 3128.1 d
Rintala, 2007 [15]	US	Triple Crossover	Gabapentin vs. Amitriptyline vs. placebo	38	14[c]	42.6 ± 12.6	20/2	7.3 ± 7.7 y
Tai, 2002 [17]	US	Crossover	Gabapentin vs. placebo	14	7	33 (27–48)	6/1	24.7 y (1 m- 20 y)
Vranken, 2008 [11]	Netherlands	Parallel	Pregabalin ($n = 20$) vs. placebo ($n = 20$)	40[d]	Pregabalin: 3 placebo: 4	Pregabalin: 54.2 ± 9.4 placebo: 54.7 ± 9.7	Group 1: 11/9 Group 2: 10/10	>6 m
Yilmaz, 2014 [13]	Turkey	Crossover	Pregabalin vs. Gabapentin	30	Gabapentin: 4 Pregabalin: 5	33.7 ± 11.8	25/5	30.3 ± 65.9 m[e]
Antidepressants								
Agarwal, 2016 [20]	India	Parallel	Amitriptyline ($n = 74$) vs. lamotrigine ($n = 73$)	147	7	109 (74%) patients were in the age group of 18–40	136/11	Not mentioned
Cardenas, 2002 [24]	US	Parallel	Amitriptyline ($n = 44$) vs. placebo (Benztropine mesylate) ($n = 40$)	84	0	Amitriptyline: 41.0 ± 10.3 placebo: 41.9 ± 9.8	Amitriptyline: 32/12 placebo: 35/5	Amitriptyline: 152.8 ± 117.8 m[f]

Table 1. continued

Author, year	Country	Design	Intervention and Sample Size (n.)	Total Sample Size	Dropout	Age, year (Mean ± SD/ Median (range))	Gender (M/F)	Pain Duration before Entering the Study (Mean ± SD/ Median (range))
								placebo: 183.7 ± 106.8 m
Davidoff, 1987 [32]	US	Parallel	Trazodone ($n = 9$) vs. placebo ($n = 9$)	18	6	Trazodone: 39.4 ± 4.6 placebo: 38.8 ± 2.4	16/2	Trazodone: 47.6 ± 9.8 m placebo: 51.0 ± 19.2 m
Rintala, 2007 [15]	US	Triple Crossover	Amitriptyline vs. Gabapentin vs. placebo	50	14	42.6 ± 12.6	20/2	7.3 ± 7.7 y
Vranken, 2011 [40]	Netherlands	Parallel	Duloxetine ($n = 24$) vs. placebo ($n = 24$)	48	0	Mean: 50.4	Duloxetine: 14/9 placebo: 15/6	>6 m
Analgesics								
Amr, 2010 [18]	Egypt	Parallel	Ketamine and Gabapentin ($n = 20$) vs. placebo and Gabapentin ($n = 20$)	40	0	Group1: 48.6 ± 10.1 Group II: 48.7 ± 9.7	Group1: 16/4 Group2: 17/3	Group I: 8 (6–17) Group II: 9 (7–18)
Attal, 2002 [28]	France	Crossover	Morphine vs. placebo	16[g]	1[h]	53.9 ± 12. 5	6/9	>6 m
Eide, 1995 [26]	Norway	Crossover	Ketamine vs. Alfentanil vs. placebo (N/S[i])	9	0	41(25–72)	8/1	28 (14–94) m
Finnerup, 2005 [41]	Denmark	Crossover	Lidocaine vs. placebo (N/S)	26	2	With evoked pain: 51.5 (32–61) Without evoked pain: 54.5 (28–66)	With evoked pain: 10/2 Without evoked pain: 7/5	With evoked pain: 4.5 (1–13) y Without evoked pain: 6.5 (2–12) y
Kvarnstrom, 2004 [25]	Sweden	Crossover	Ketamine and Lidocaine vs. placebo	10	0	45(30–60)	9/1	9 (2–35) y
Norrbrink, 2009 [29]	Sweden	Parallel	Tramadol ($n = 23$) vs. placebo ($n = 12$)	35	Tramadol: 11 placebo: 2	Tramadol: 51.4 ± 11.6 placebo: 51.2 ± 9.7	28/7	Tramadol: 14.0 ± 12.4 y placebo: 15.7 ± 9.4 y
Siddall, 2000 [42]	Australia	Crossover	Morphine vs. Clonidine vs. placebo vs. Morphine + Clonidine	15	0	50 (26–78)	Not mentioned	>7 m
Antispastics								
Han, 2016 [31]	South Korea	Parallel	BTA[j] ($n = 18 + 2$) vs. placebo ($n = 18 + 2$)	40	BTA: 2 placebo: 2	Group I: 53.1 ± 9.1 Group II: 48.9 ± 14.2	Group I: 15/5 Group II: 14/6	Group I: 46.06 ± 49.1 (3–151) m Group II: 50.26 ± 46.1 (12–192) m
Kumru, 2018 [30]	Spain	Parallel	Baclofen ($n = 8$) vs. placebo ($n = 5$)	13	2	Group I: 49.87 ± 11.36 Group II: 40.8 ± 8.17	All Male	Group I: 15 ± 4.9 m Group II: 12 ± 2 m
Other								
Andresen, 2016 [43]	Denmark	Parallel	PEA[k] ($n = 36$) vs. placebo ($n = 37$)	73	10	56.3 ± 11.6	54/19	>3 m

Table 1. continued

Author, year	Country	Design	Intervention and Sample Size (n.)	Total Sample Size	Dropout	Age, year (Mean ± SD/ Median (range))	Gender (M/F)	Pain Duration before Entering the Study (Mean ± SD/ Median (range))
Chiou-Tan, 1996 [44]	United States	Crossover	Mexiletine vs. placebo	15	4	44 ± 11	9/2	>6 m
Potter, 1998 [45]	US	Crossover	Fampridine vs. placebo	29	3	40.6 ± 10.0	28/1	152.7 ± 105.4 m

[a]Chile, China, Columbia, the Czech Republic, Hong Kong, India, Japan, the Philippines, the Russian Federation, and the United States.
[b]This information pertains to the 19 patients who completed the study. Nine of the twenty-eight patients declined to continue the trial, and the study did not disclose their gender.
[c]Out of 38 randomized participants, 22 completed all 3 phases; 26 completed the gabapentin phase, 28 the amitriptyline phase, and 25 the diphenhydramine phase.
[d]This study included 21 SCI patients and 19 non-SCI patients.
[e]The mean time since injury was reported. The mean time for pain duration was not reported in this study.
[f]These are the mean duration of SCI (The study did not mention the mean duration of pain).
[g]Twenty-one patients suffering from pain caused by poststroke or SCI were recruited consecutively in this study. Five patients were excluded. One patient was withdrawn. Finally, 15 patients completed the trial (poststroke = 6 patients and SCI = 9 patients).
[h]The dropout was among SCI participants and not post strokes.
[i]Normal Saline (NaCl 0.9%).
[j]Botulinum toxin type A.
[k]Palmitoylethanolamide.

AEs were reported for tramadol (more than 90% of patients); therefore, caution should be taken when considering its use (Table 2).

In a crossover RCT in patients with neuropathic pain, intravenous morphine reduced spontaneous ongoing pain (~46%, from 61.6 to 33), however the difference between patients who were administered morphine and the placebo group was not statistically significant [28]. The proportion of patients who benefitted from total or partial (a reduction greater than or equal to 50% in VAS score) pain relief from the treatment was 46% with morphine vs. 13% with placebo [28]. Morphine significantly reduced the intensity of brush-evoked allodynia (but did not affect other evoked pains) [28]. There was a correlation between the magnitude of initial allodynia and the effects of morphine on this symptom [28]. The results of IV morphine were correlated with those of oral morphine at one month [28]. However, in another RCT involving 15 patients, when morphine was given intrathecally together with clonidine, a 37% reduction in the mean pain level was observed compared to the placebo group ($p = 0.0084$) [27], while only a 20% and 17% reduction in the mean pain level was observed, respectively, for morphine or clonidine when they were administered alone. This difference was not statistically significant compared to the placebo group [27]. Significant side effects were reported for morphine in both RCTs, the most frequent being sedation, somnolence, nausea, and headache.

Intravenous lidocaine (2.5 mg/kg), was studied only in one RCT [25], and 10% pain relief was reported for lidocaine, but this difference was not significant.

Effects of antispastics on SCI associated pain

Among the different antispastics reviewed, only baclofen [30] and botulinum toxin A (BTA) [31] were reported in RCTs. Only one RCT has been conducted on baclofen for evaluation of NP which reported >49% reduction in NRS, > 36% in continuous pain, >35% in BPI, and diminished interference of neuropathic pain with activities of daily living [30]. Moreover, one RCT published on BTA showed >20% significant pain relief in SCI patients [31].

Quality of studies

Table 3 shows the result of quality assessments. Figure 2 represents judgments about each item in assessing the risk of bias presented as percentages across studies.

Eighteen of the twenty-eight studies properly reported their randomization and concealment methods. However, nine studies did not mention their randomization or concealment procedure. One study was found to have a high risk of bias due to randomization or concealment. This study was an open-label study in which 21 of the 55 participants were not randomly assigned.

Only a single study was not blinded (open-label). All other studies claimed to be blinded, although five of them did not mention the blinding process. Even though the blinding process was reported in seven publications, the method of analysis for individuals who were excluded from the analysis was not addressed.

All studies used at least one valid outcome measure for pain intensity at comparable time points for patients and controls. However, because patients were the outcome assessors in our study and, in some studies, the patients were not blinded, we qualified such studies as high-risk.

Only five studies had pre-trial registration and therefore were considered low-risk regarding Selective Outcome Reporting. All studies reported at least a clinically relevant pain scale.

DISCUSSION

Our systematic review identified twenty-eight RCTs, which is the highest number of included studies compared to other published

Table 2. Study Characteristics and Primary and Secondary Outcomes of Randomized Clinical Trials (RCTs) for Pain Following Spinal Cord Injury (SCI).

Author, year	Intervention, the root of administration and dosage	Active Drug Treatment Duration[a]	Outcome measure	Outcome	Adverse effects
Anticonvulsants					
Agarwal, 2017 [20]	Amitriptyline (25, 50, 100 mg, D) vs. Lamotrigine (50, 100, 200 mg, BID)	3 w	SFMPQ2[b]	Lamotrigine and Amitriptyline significantly reduced the score at each follow-up compared to baseline, but there was no significant difference between the two groups. (Mean scores difference: Lamotrigine: Day 7 (0.2048), Day14 (0.3622), Day21 (0.4432); Amitriptyline: Day7 (0.2149), Day14 (0.3593), Day21 (0.4312)	Amitriptyline: 10/74 patients reported one or more side effects at doses exceeding 50 mg once daily. The most common side-effects reported were dry mouth and drowsiness. Lamotrigine: none
Amr, 2010 [18]	Group I: Ketamine (80 mg, IV[c] diluted in 500 cc N/S, daily) + Gabapentin (300 mg, TDS) Group II: Placebo infusion + Gabapentin (300 mg, TDS)	1 w	VAS[d]	VAS reduction in group I was ~48% (3 weeks after stopping of infusion) to ~83% (7th day of infusion). VAS reduction in group II was ~13.5% (1st day of infusion) to ~52% (5th day of infusion). At all time periods examined, pain scores in both groups were significantly lower compared with pre-treatment values ($P < 0.05$). Group I showed a significantly higher reduction in pain scores at all time periods than group II ($P = 0.0001$) except the third and fourth weeks after discontinuing the infusion ($P = 0.54$ and $P = 0.25$, respectively). After infusion termination, the group receiving ketamine experienced an increase in pain scores (3 weeks after infusion termination compared to its values at 2 weeks after, $P < 0.0001$).	Gabapentin: two (5%) patients reported dizziness (one in each group); three (7.5%) patients reported fatigue and lack of coordination (2 patients in group I and one in group II). Ketamine: Three patients (15%) reported short-lasting delusions, and two patients (10%) reported an increase in baseline heart rate during Ketamine infusion.
Amr, 2011 [14]	Group I: 0.2 mg/Kg of preservative-free Ketamine (2 ml) single bolus epidural injection and Gabapentin 300 mg TDS vs. Group II: Isotonic saline 0.9%(2 ml) single bolus epidural injection and Gabapentin 300 mg TDS	60 d	VAS	Pain levels were significantly decreased in both groups when compared to the baseline. Depending on the treatment period, this reduction ranged from 40% to 68% in group I and from 37% to 43% in group II. At 7, 15, and 30 days after injection, VAS scores were significantly lower in Group I than in Group II ($P = 0.02$, 0.0001, =0.0001, respectively). Still, no statistically significant difference was found between groups at 45 and 60 days post-injection.	Ketamine: no side effects that could be detected. Gabapentin: fatigue and lack of coordination were observed by 6 (15%) of patients. There was no statistically significant difference regarding the incidence of side effects in both groups.
Cardenas, 2013 [10]	Pregabalin (150–600 mg/day, PO) vs. Placebo	16 w	DAAC[e], PGIC[f]	Pregabalin improved DAAC during the 16-week treatment period compared with placebo ($p = 0.003$). Mean pain score from baseline to endpoint ($p = 0.007$), percentage of patients achieving a 30% decrease in mean pain score at the endpoint ($p = 0.039$), PGIC scores (full scale) at the endpoint ($p = 0.001$) were improved as well. 78% of patients who received pregabalin reported improvement (7% very much improved, 33% much improved, and 38% minimally improved).	When comparing pregabalin with placebo, significant differences was found in AEs including somnolence (33% vs. 13%), dizziness (18% vs. 5.6%), edema (11.6 vs. 2.8), dry mouth (8% vs. 2.8%), fatigue (7% vs. 0.9%), and blurred vision (6.3% vs. 0).

Table 2. continued

Author, year	Intervention, the root of administration and dosage	Active Drug Treatment Duration[a]	Outcome measure	Outcome	Adverse effects
				29.5% of the pregabalin group reported ≥ 50% decrease in pain vs. 15.2% in the placebo group (OR:2.24 $p = 0.026$).	
Drewes, 1994 [21]	Valproate (600mg-2400mg BID) vs. Placebo	3 w	DMPQ[g]	There was no significant difference (6 patients reported improvement receiving valproate vs. 4 patients receiving placebo)	Valproate: Dizziness (4(20%)) Placebo: none
Finnerup, 2002 [19]	Lamotrigine (25–400 mg/day, D or BID) vs. Placebo	9 w	MPQ[h]	Lamotrigine significantly reduced pain compared to placebo in patients with incomplete SCI lesions ($P = 0.02$), while it did not occur in patients with complete injury. ~31% of patients taking lamotrigine reported a moderate or good pain relief vs. ~13% in the Placebo group (p:0.06).	No significant difference was observed between Lamotrigine ($N = 27$) and Placebo ($N = 28$). Only one patient was withdrawn because of a rash during the placebo period.
Finnerup, 2009 [22]	Levetiracetam (500–1500 mg BID) vs. Placebo	5 w	DMPQ	Median pain intensity was the same as the baseline, with no significant difference. 18 (75%) reported no pain relief, while 3 (12.5%) patients reported that their pain got worse	No serious adverse events were reported. Seven patients were withdrawn because of side effects during levetiracetam treatment and two during placebo treatment ($P = 0.21$). Levetiracetam: the number of adverse events during treatment was 34, and most frequents were somnolence, Nausea/constipation, and Dizziness. Placebo: the number of adverse events during treatment was 32. There were no statistically significant differences between the two treatment periods.
Kaydok, 2014 [9]	Pregabalin (150–600 mg/day[i], PO, divided BID vs. Gabapentin (300–3600 mg/day), PO, divided TDS	16 w	VAS, NPS[j], LT[k]	Compared to baseline, VAS was reduced by almost 44% and 54% in the gabapentin group at weeks 4 and 8, respectively; it was also reduced by 54% and 58% in the pregabalin group. The difference was only significant when comparing the 4th week to the baseline ($p = 0.045$). The improvement of NPS score was 52.1 ± 18.1% for the gabapentin group and 54.5 ± 17.8% for the pregabalin group ($p > 0.05$). The improvement of the Lattinen pain frequency was 21.41 ± 28.09% for the Gabapentin group and 28.0 ± 26.3% for the Pregabalin group compared to the baseline. No significant difference was found between Gabapentin and Pregabalin groups ($p > 0.05$).	Gabapentin: 16 (66.7%) patients experienced one or more side effects. Drowsiness (29.2%) and somnolence (25%) were the most common. Other were edema, xerostomia, cognitive dysfunction, hepatic dysfunction, gait disturbance, hemoptysis, and dyspepsia. Pregabalin: 21 (88%) patients experienced one or more side effects. Drowsiness (48%) and somnolence (44%) were the most common. Others were edema, xerostomia, cognitive dysfunction, hepatic dysfunction, gait disturbance, allergic reaction, vertigo, constipation, and paresthesia. No significant difference was found between the two groups.
Levendoglu, 2004 [16]	Gabapentin (900–3600 mg/day, PO divided TDS) vs. Placebo	8 w	VAS, NPS, LQ[l]	Gabapentin provided a mean pain relief of 60.7% vs. 10.3% in the placebo group ($p < 0.000$). At the 4th week, there was a significant reduction in all types of pain compared to baseline, and this trend remained until the 8th week ($P < 0.05$). Although the itchy, dull, sensitive, and cold types of pain (NPS) did not respond differently to gabapentin and placebo, gabapentin provided more pain relief for all other descriptors of pain compared to placebo (reduction in pain intensity:	Placebo: five (25%) patients (6 side effects in total) Gabapentin: 13 (65%) patients (17 side effects in total) ($P < 0.05$). Weakness (25%), itching (10%), edema (15%), vertigo (15%), sedation (15%), and headache (5%) were the most frequent side effects reported for gabapentin. There was no significant difference between Placebo and gabapentin treatment regarding each type of side effect.

Table 2. continued

Author, year	Intervention, the root of administration and dosage	Active Drug Treatment Duration[a]	Outcome measure	Outcome	Adverse effects
				~62%, hot: ~52.8%, sharp: ~56.7%, unpleasantness: ~55.5%, deep pain: ~54%. And surface pain: ~56.3%) Analysis of LQ showed more than 50% reduction in subjective pain intensity and disability due to pain and more than 18% reduction in pain frequency in the gabapentin group.	
Min, 2016 [12]	Pregabalin (150–300 mg/day PO divided BID) vs. Oxcarbazepine (300–600 mg/day PO divided BID)	4 w	VAS	Pregabalin significantly decreased VAS of electrical pain (~38%), burning pain (~42%), pricking pain (40%), numbness (~35%), allodynia (33%), and pressure hyperalgesia (~18). Oxcarbazepine significantly decreased VAS of electrical pain (~35%), burning pain (~45%), pricking pain (40%), numbness (~36%), allodynia (10%), and pressure hyperalgesia (~18). Oxcarbazepine was significantly more effective for patients without evoked pain than in those with it for electrical, burning, and pricking pain. The effect of pregabalin was not different regarding the presence or absence of evoked pain for all pain categories, except burning pain. Pregabalin was significantly more effective for electrical pain, allodynia, and heat hyperalgesia than oxcarbazepine in patients with evoked pain. 15 (27.3%) patients preferred oxcarbazepine, 35 (63.6%) preferred pregabalin, 3 (6.1%) patients were satisfied with both medications, and 2 (4.1%) patients were unsatisfied with both medications.	There were no emergencies associated with the adverse events during the study. Oxcarbazepine: dizziness ($n = 2$), rash ($n = 2$), elevated liver enzymes ($n = 2$). Pregabalin: skin edema ($n = 1$) Three patients reported better spasticity relief with Pregabalin than oxcarbazepine ($n = 3$).
Rintala, 2007 [15]	Group I: Amitriptyline (50 mg, TDS) Group II: Gabapentin (1200 mg, TDS) Group III: Placebo (diphenhydramine, 25 mg, TDS)	8 w	VAS	Amitriptyline was significantly more effective in reducing pain than gabapentin and diphenhydramine ($P = 0.03$). Among participants in the low CESD-SF group, 50% of patients in the amitriptyline group reported at least a 30% decrease in pain from baseline, 42.9% in the gabapentin group, and 35.7% in the diphenhydramine group. Among participants in the high CESD-SF group, the percentages were 62.5, 12.5, and 25, respectively. Gabapentin decreased VAS ~14 to ~18%, yet there was no difference between Gabapentin and diphenhydramine groups.	Gabapentin: most reported AEs were dry mouth (38.8%), drowsiness (22.9%), fatigue (22.4%), dizziness (11.5%) and constipation (10.9%). Amitriptyline: During amitriptyline therapy, five side effects— dry mouth, constipation, difficulty emptying the bowel, nausea, and difficulty emptying the bladder—were significantly more frequent than during therapy with the other two medications. Increased spasticity was reported significantly less often during gabapentin therapy than with the other two medications.
Tai, 2002 [17]	Gabapentin (300–1800 mg/day divided TDS) vs. Placebo	4 w	NPS	There was a significant decrease in "unpleasant feeling" by the 4th week of gabapentin treatment ($p = 0.028$) and a trend toward a significant difference in the reduction of both the "pain intensity" ($p = 0.094$) and "burning sensation" ($p = 0.065$) between gabapentin, and placebo.	urinary retention ($n = 1$)

Table 2. continued

Author, year	Intervention, the root of administration and dosage	Active Drug Treatment Duration[a]	Outcome measure	Outcome	Adverse effects
Vranken, 2008 [11]	Pregabalin (150–600 mg/day, PO, divided BID) vs. Placebo	4 w	VAS, PDI[m], EQ-5D, SF-36[n]	VAS was significantly reduced in the pregabalin group compared to placebo (32.9% vs. 1.3%, $p = 0.01$). VAS-score difference from placebo was: 2.18 with 95% confidence of interval: 0.57–3.80; $P = 0.01$. PDI showed a nearly 10% decrease in the pregabalin group, but there was no significant difference in PDI between the placebo and pregabalin groups. EQ-5D utility and EQ-5D VAS showed an almost 2 and 1.08-fold improvement, significantly higher than placebo. Pregabalin showed a significant improvement (50%) in the bodily pain domain of the SF-36.	Three patients in the placebo and three patients in the pregabalin group withdrew due to AE. The most frequent AEs were somnolence (45%), confusion (35%), dizziness (35%), decreased cognitive performance (30%), and nausea (30%). There was no statistically significant difference regarding the incidence of side effects in both groups.
Yilmaz, 2014 [13]	Pregabalin (up to 300 mg/day, PO, divided BID) vs. Gabapentin (up to 1800 mg/day PO, divided TDS)	16 w	VAS, PDI	Both medications significantly reduced the pain measured by VAS and PDI, and there was no significant difference between pregabalin and gabapentin. Pregabalin decreased the pain VAS by ~45.6% in the first period (before cross over) and ~65.9% in the second period (after cross over). Gabapentin decreased the pain VAS by ~32.1% in the first period and ~41.9% in the second period. Pregabalin decreased the PDI by ~15.2% in the first period and ~48% in the second period Gabapentin decreased PDI by ~35.9% in the first period with no decrease in the second period.	Dizziness and nausea ($n = 2$) were reported in the Pregabalin group.
Antidepressants					
Agarwal, 2017 [20]	Amitriptyline (25,50,100 mg, D) vs. lamotrigine (50,100,200 mg, BID)	3 w	SFMPQ2	Lamotrigine and amitriptyline significantly reduced the score at each follow-up compared to baseline, but there was no significant difference between the two groups.	Lamotrigine: none Amitriptyline: 10/74 patients reported one or more side effects at doses exceeding 50 mg once daily. The most common side-effects reported were dry mouth and drowsiness.
Cardenas, 2002 [24]	Amitriptyline (10–125 mg, PO) vs. Placebo (Benztropine mesylate, 0.5 mg, PO)	6 w	NRS, SF-MPQ, BPI[o]	There were no significant differences between the groups in pain intensity or pain-related disability in either intent-to-treat analyses or analyses of study completers.	Most reported AEs were dry mouth 17 (38.6%), drowsiness/tiredness/fatigue 17 (38.6%), constipation 14 (31.8%), increased spasticity 11 (25%), urinary retention 5 (11.4%), and sweating 5 (11.4%). There were no statistically significant differences between amitriptyline and placebo in side effects or severity except for a significantly higher severity rating for increased spasticity in the amitriptyline group (25% vs. 15%, $P = 0.005$).
Davidoff, 1987 [32]	Trazodone hydrochloride (50–150 mg) vs. Placebo (diphenhydramine)	8 w	MPQ, SPI[p]	No significant difference	Drowsiness was significantly higher in patients on trazodone ($n = 4$, ~44%) than Placebo ($n = 1$).

Table 2. continued

Author, year	Intervention, the root of administration and dosage	Active Drug Treatment Duration[a]	Outcome measure	Outcome	Adverse effects
Rintala, 2007 [15]	Group I: Amitriptyline (50 mg, TDS) Group II: Gabapentin (1200 mg, TDS) Group III: Placebo(diphenhydramine) (25 mg, TDS)	8 w	VAS	Amitriptyline reduced VAS average pain by 40%. The average VAS with amitriptyline therapy was significantly lower than with gabapentin (P:0.03) and diphenhydramine therapy (p:0.012). Pain intensity during amitriptyline therapy was significantly lower than during diphenhydramine therapy within the high CESD-SF group only (40.6% reduction in VAS, p:0.035) and not the low CESD-SF group. Among participants in the low CESD-SF group, 50% of patients in the amitriptyline group reported at least a 30% decrease in pain from baseline, 42.9% in the gabapentin group, and 35.7% in the diphenhydramine group. Among participants in the high CESD-SF group, the percentages were 62.5, 12.5, and 25, respectively.	Out of 210 times patients completed the checklist during amitriptyline therapy, five side effects—dry mouth (63.8%), constipation (29.2%), difficulty emptying the bowel (11.4%), nausea (9%), and difficulty emptying the bladder (5.2%) were significantly more frequently reported than during therapy with the other two medications. Increased spasticity was reported significantly less often during Gabapentin therapy than with the other two medications.
Vranken, 2011 [40]	Duloxetine (60–120 mg/day) PO, Once Daily vs Placebo	8 w	VAS, PDI, PGIC, EQ-5D, SF-36	Pain intensity in the duloxetine group decreased more than 30% following treatment, but this difference was not significant. Follow-up observation showed no significant difference in PDI, EQ5D, and the SF36 between the two groups. Brush evoked VAS and Acetone drop VAS was the only indexes that showed a significant difference between the duloxetine and placebo groups (both showed a reduction of about 53% in the duloxetine group).	12 (50%) patients reported somnolence, 5 (~20%) nausea-vomiting, and 4 (~16%) dizziness, yet, there was no statistically significant difference regarding the incidence of side-effects in both groups except for Somnolence which was more frequent in the duloxetine group (50% vs. 8%, $p = 0.003$).
Analgesics					
Amr, 2010 [18]	Group I: Ketamine (80 mg, IV diluted in 500 cc N/S, daily) + Gabapentin (300 mg, TDS) Group II: Placebo infusion + Gabapentin (300 mg, TDS)	1 w	VAS	VAS reduction in group I was ~48% (3 weeks after stopping of infusion) to ~83% (7th day of infusion). VAS reduction in group II was ~13.5% (1st day of infusion) to ~52% (5th day of infusion). At all time periods examined, pain scores in both groups were significantly lower compared with pre-treatment values ($P < 0.05$). Group I showed a significantly higher reduction in pain scores at all time periods than group II ($P = 0.0001$) except the third and fourth weeks after discontinuing the infusion ($P = 0.54$ and $P = 0.25$, respectively). After infusion termination, the group receiving ketamine experienced an increase in pain scores (3 weeks after infusion termination compared to its values at 2 weeks after, $P < 0.0001$).	Ketamine: Three patients (15%) reported short-lasting delusions, and two patients (10%) reported an increase in baseline heart rate during Ketamine infusion. Gabapentin: two (5%) patients reported dizziness (one in each group); three (7.5%) patients reported fatigue and lack of coordination (2 patients in Group I and one in Group II).

Table 2. continued

Author, year	Intervention, the root of administration and dosage	Active Drug Treatment Duration[a]	Outcome measure	Outcome	Adverse effects
Attal, 2002 [28]	Morphine (9–30 mg, mean dosage: 16 ± 6.1 mg, IV) vs. N/S (same Volume as Morphine, IV)	2 sessions 2 weeks apart	VAS	Morphine showed more than a 45% reduction in spontaneous ongoing pain, but it was not significant compared to placebo.	Morphine: ($n = 9$), the most frequent side effect was somnolence (5 (~33%)), then nausea (3 (20%)), dizziness (3 (20%)), and headache (3 (20%)). Placebo ($n = 6$). The side effects were significantly greater in patients receiving morphine than those treated with placebo ($p = 0.005$).
Eide,1995 [26]	Ketamine (6 µg/kg/min after a bolus dose of 60 µg/kg, IV) vs. alfentanil (0.6 µg/kg/min after a bolus dose of 7 µg/kg, IV) vs. placebo (0.9% NaCl) I0056	SD[q]	VAS	Ketamine showed ~40%, and alfentanil showed a 20% reduction in VAS (continues pain). Ketamine showed ~60%, and alfentanil showed ~80% reduction in VAS (allodynia). Ketamine showed ~60%, and alfentanil showed a ~70% reduction in VAS (wind-up-like pain). Both continuous and evoked pain was significantly reduced by ketamine or alfentanil compared to the placebo but had no significant effect on heat pain sensation. No significant difference was found between ketamine and alfentanil.	The reduction of pain was not associated with severe side effects. The most common side effect of both ketamine (~55%, 4 modest, 1 bothersome), and alfentanil (~55%, 4 weak, 1 modest) was dizziness.
Finnerup, 2005 [41]	Group I: Lidocaine (5 mg/kg, IV) Group II: Placebo (N/S, IV)	3 w	MPQ, VAS	Lidocaine reduced pain compared to placebo ($p < 0.01$). The median difference in pain reduction between lidocaine and placebo was 36%. 9 (37.5%) patients obtained 50% pain relief with lidocaine. 19 (79.16%) patients reported pain relief of their total pain.	Lidocaine increased blood pressure and pulse rate compared to placebo ($P < 0.05$). The most common AEs were somnolence (11 (45%)), dizziness (7 (29%)), dysarthria (7 (29%)), and lightheadedness (7 (29%)).
Kvarnstrom, 2004 [25]	Ketamine (0.4 mg/kg, IV) vs. Lidocaine (2.5 mg/kg, IV) vs. Placebo (N/S, IV)[ϕ]	SD	VAS	The mean value for maximal pain reduction from baseline was 38% for ketamine, 10% for lidocaine, and 3% for placebo. 50% of patients who took ketamine and 10% of patients who took lidocaine reported more than 50% reduction in VAS. However, only ketamine vs. placebo showed a significant difference ($P = 0.025$, McNemar's test) and not lidocaine ($P = 0.31$).	Ketamine: 9 patients (90%), 39 total side effects. Most common AEs were (70%) patients reported somnolence (7 (70%)), dizziness (7 (70%)), and change in vision (7 (70%)). Lidocaine: 5 patients (50%), 13 total side effects. Most common AEs were somnolence (5 (50%)), out-of-body sensation (2 (20%)), and paranesthesia (2 (20%). Placebo: 1 patient (10%), 2 total side effects.
Norrbrink, 2009 [29]	Tramadol (150–400 mg PO, divided TDS) vs. Placebo	4 w	CR-10[r], PGIC	There was a 25% reduction in "general pain intensity", a 28% reduction in "worst pain intensity", and a 16% reduction in "MPI[s]-pain severity". The tramadol group experienced no change in "present pain intensity", while the placebo group experienced a 9% increase. PGIC: in the tramadol group: 33.5% reported "much improved", 25% "minimally improved", and 41.5% reported no change.	Tramadol: 21 (91%) patients, the most reported adverse events were tiredness (17 (74%)), dry mouth (12 (52%)), and dizziness (12 (52%)) Placebo: 7 (58%) patients, the most commonly reported side-effect was constipation (4 (33%)).

Table 2. continued

Author, year	Intervention, the root of administration and dosage	Active Drug Treatment Duration[a]	Outcome measure	Outcome	Adverse effects
Siddall, 2000 [42]	Group I: Morphine (0.2–1 mg, IT) Group II: Clonidine (50–100 mcg, IT) Group III: N/S as Placebo (IT) Group IV: Morphine + Clonidine	3 d	NRS, NPRS, VPR	Morphine: 20% reduction in the mean pain level (not significant vs. placebo) Clonidine: 17% reduction in the mean pain level (not significant vs. placebo) Morphine + Clonidine: 37% reduction in the mean pain level (significant vs. placebo, p:0.0084)	Gp I: Oxygen desaturation (8 (50%)), sedation (8 (50%)), pruritus (6 (38%)), nausea (2 (13%)), and hypotension (1 (6%)). Gp II: hypotension (8 (53%)), nausea (6 (40%)), sedation (5 (33%)), oxygen desaturation (5 (33%)), and dry mouth (3 (20%)). G III: sedation (13%), oxygen desaturation (13%) Gp IV: hypotension (9 (56%)), oxygen desaturation (7 (44%)), pruritus (4 (25%)), dry mouth (4 (25%)), and sedation (3 (19%)).
Antispastics					
Han, 2016 [31]	Group I: BTA[t] (200U in 4 ml Group II: Placebo (N/S, 4 ml)	SD	VAS KSF-MPQ[u]	Botulinum had a significant effect in the 4th week ($p = 0.0027$) and 8th week ($p = 0.0053$) of assessment (mainly on below-level neuropathic pain). BTA significantly reduced VAS, ~22% in 4 weeks and ~25% in 8 weeks. 30% of patients (BTA) reported more than 30% pain relief at 4 and 8 weeks, 10% and 20% reported more than 50% pain relief at 4 and 8 weeks, respectively. reduction in SF-MPQ: Total SF-MPQ: ~23% (4 weeks),14% (8 weeks) Sensory: ~24% (4 weeks), ~15% (8 weeks) Affective: ~17% (4 weeks), ~9.5% (8 weeks) Present pain intensity: ~13% (4 weeks), ~16% (8 weeks)	No adverse effect
Kumru, 2018 [30]	Group I: Baclofen (50 µg, IT [v]at L3–L4) Group II: Placebo (1 ml N/S, SC at L3–L4)	SD	NRS, NPSI[w], BPI	Baclofen significantly reduced the NRS (~49%-~57%), continuous pain (~36%-59%), paroxysmal pain (~92%), and allodynia (~68%-~81%). BPI: there was a significant improvement in maximum, average, minimum, and current pain (more than 35%). The mean percentage of improvement following treatment with baclofen ranged from 50% (24 h later) to 68%. (4 h later).	Not mentioned
Other					
Andresen, 2016 [43]	Sublingual PEA[x]-um microgranules (600 mg, BID) vs. Placebo	12 w	NRS	There were no significant effects on SCI pain. However, participants who received PEA had significantly less need for rescue medications than the placebo group.	Serious adverse events were urinary tract infection, paralytic ileus, cholecystolithiasis, and erysipelas, causing hospitalization in 3 patients treated with PEA-um and 1 treated with Placebo No significant difference between PEA and placebo.
Chiou-Tan, 1996 [44]	Mexiletine (450 mg/day, PO, once daily) vs. Placebo	4 w	VAS, MPQ	The VAS decreased by 4.9 percent (at the time of the test) and 11.6 percent (during the previous week); however, the difference was not significant compared to the placebo group. Internal pain was reduced by 21% with MPS, but there was no significant difference between the placebo and mexiletine groups.	Not mentioned

Table 2. continued

Author, year	Intervention, the root of administration and dosage	Active Drug Treatment Duration[a]	Outcome measure	Outcome	Adverse effects
Potter, 1998 [45]	Fampridine (12.5–17.5 mg BID) vs. Placebo	2 w	MPQ	Seven patients (27%) reported less pain following fampridine-SR, and an equal number did so following Placebo. No significant difference (p: >0.999). ~30% of patients reported a wish to continue fampridine.	Fampridine: mild and transient lightheadedness (~19%), some mild agitation, and some mild gastric upsets.

[a]Treatment duration for cross-over studies has been reported based on one arm of the trial. For example, if the study was trialed for 5 weeks of placebo and valproate and crossed for another 5 weeks, the treatment period is reported as 5 weeks. The washout period is not included as the treatment period.
[b]Short–form MC Gill Pain Questionnaire-2.
[c]Intravascular.
[d]Visual Analog Scale.
[e]Duration-adjusted average change.
[f]Patient Global Impression of Change.
[g]Danish version of the McGill Pain Questionnaire.
[h]McGill Pain Questionnaire.
[i]The dosage provided in the parentheses means that the prescribed dose gradually increased from the minimum amount written to the maximum.
[j]Neuropathic pain scale.
[k]Lattinen test.
[l]A questionnaire derived from the Lattinen test.
[m]Pain Disability Index.
[n]Short-form Health Survey questionnaire 36.
[o]Brief pain inventory.
[p]Stembach Pam Intensity Scale.
[q]Single dose.
[r]Borg's Category Ratio.
[s]Multidimensional Pain Inventory.
[t]Botulinum toxin type A.
[u]Korean version of the short-form McGill Pain Questionnaire.
[v]Intrathecal.
[w]Neuropathic Pain Symptom Inventory.
[x]Palmitoylethanolamide.

Table 3. Risk of Bias Assessment of Included Studies.

Intention-to-treat	Unique ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall		
	Yilmaz,2014	Pregabalin	Gabapentin	Pain intensity	!	-	+	-	!	-	+	Low risk
	kaydok,2014	Pregabalin	Gabapentin	Pain intensity	!	-	+	-	!	-	!	Some concerns
	Cardenas,2013	Pregabalin	Placebo	Pain intensity	+	+	+	+	+	+	-	High risk
	Vranken,2008	Pregabalin	Placebo	Pain intensity	+	+	+	+	!	!		
	Min,2016	Pregabalin	Placebo	Pain intensity	-	-	+	-	!	-	D1	Randomization process
	Amr,2011	Ketamine	Placebo	Pain intensity	+	!	+	+	!	!	D2	Deviations from the intended interventions
	Amr,2010	Ketamine	Placebo	Pain intensity	+	!	+	+	!	!	D3	Missing outcome data
	Levendoglu,2004	Gabapentin	Placebo	Pain intensity	+	!	+	+	!	!	D4	Measurement of the outcome
	Rintala,2007	Gabapentin, Amitriptylin	Placebo	Pain intensity	+	+	+	+	!	!	D5	Selection of the reported result
	Tai,2002	Gabapentin	Placebo	Pain intensity	+	!	-	+	!	-		
	Drewes,1994	Valproate	Placebo	Pain intensity	!	+	+	+	!	!		
	Finnerup,2002	Lamotrigine	Placebo	Pain intensity	+	+	+	+	!	!		
	Finnerup,2009	Levetiracetam	Placebo	Pain intensity	+	+	+	+	+	+		
	Agarwal,2017	Lamotrigine	Amitriptyline	Pain intensity	!	!	+	-	!	-		
	Cardenas,2002	Amitriptyline	Placebo	Pain intensity	+	+	+	+	!	!		
	Davidoff,1987	Trazodone hydrochloride	Placebo	Pain intensity	!	-	-	-	!	-		
	Vranken,2011	Duloxetine	Placebo	Pain intensity	+	+	+	+	!	!		
	kvarnstrom,2004	Lidocaine, Ketamine	Placebo	Pain intensity	+	+	+	+	!	!		
	Eide,1995	Ketamine, Alfentanil	Placebo	Pain intensity	!	!	+	+	!	!		
	Norrbrink,2009	Tramadol	Placebo	Pain intensity	+	+	+	+	!	+		
	Attal,2002	Morphine	Placebo	Pain intensity	+	!	+	+	!	!		
	Siddal,2000	Morphine, Clonidine	Placebo	Pain intensity	!	!	+	+	!	!		
	Finnerup,2005	Lidocaine	Placebo	Pain intensity	+	+	+	+	!	!		
	kumru,2018	Baclofen	Placebo	Pain intensity	+	+	+	+	+	+		
	Potter,1998	Fampridine	Placebo	Pain intensity	!	!	+	+	!	!		
	Andersen,2016	Ultramicronized Palmitoylethanolamide	Placebo	Pain intensity	+	+	+	+	+	+		
	Chiou-Tan,1996	Mexiletine	Placebo	Pain intensity	!	-	-	-	!	-		
	Han,2016	Botulinum toxin	Placebo	Pain intensity	+	+	+	+	+	+		

reviews of RCTs on the pharmacologic management of pain due to SCI. Unlike other published reviews, only randomized clinical trials are included in this study. Moreover, we included studies that greater than 50% of their participants were suffering from SCI, and following utilizing the formula mentioned in the method section, we calculated pain reduction for each trial using the reported data, if available. Our results show that there is still an insufficient number of clinical studies and comparative data among the identified pharmacologic options. While the included studies have a good quality level according to our risk of bias assessment, the reported data are often missing uncertainty measures, such as confidence interval or standard error surrounding the mean outcomes, which resulted in the impossibility to perform a meta-analysis.

Pregabalin was the only drug evaluated by four different studies [9, 10, 12, 23] and had the strongest impact on pain reduction of all the evaluated medications, with an 11-point NRS treatment effect. Interestingly, one of the pregabalin studies [10] also included the largest sample of patients ($n = 220$) of all the studies, which might justify identifying statistically significant results.

A risk of all-cause discontinuations greater than placebo was not observed in any of the included studies. However, for several

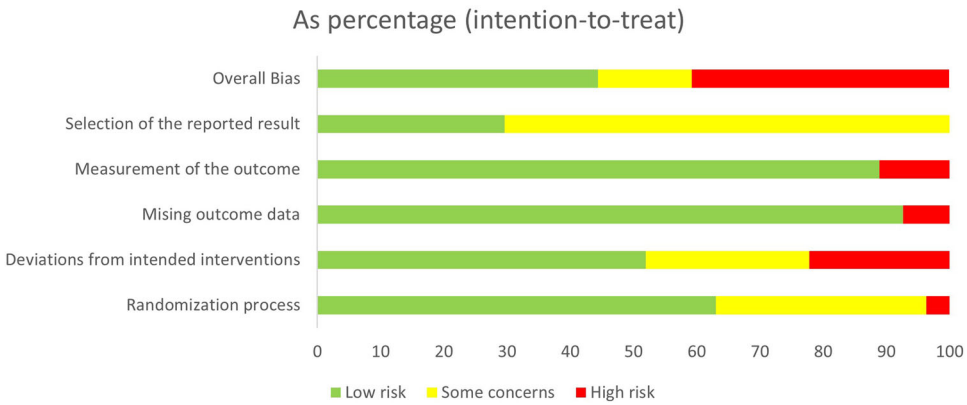

Fig. 2 The overall risk of bias assessment of studies.

treatments, the risk of AEs was significantly higher compared to placebo. A possible reason for this finding could be related to patients deciding to remain on therapy as the beneficial effects outweigh the AEs.

It should be noted that two studies used diphenhydramine as a placebo [15, 32] to mirror some of the AEs experienced by patients when taking their active comparators. Hence, the severity of AEs and the level of discontinuations between diphenhydramine and the active comparators (amitriptyline, gabapentin, and trazodone) may be inferior to what was observed in other studies comparing actual placebo and active treatments.

A systematic review [33] published in 2013 reported that pregabalin, followed by amitriptyline, was the most effective of all medications used to reduce post-SCI NP, compared to placebo. Our review also showed that pregabalin and amitriptyline were evaluated in four [9, 10, 12, 23] and three [15, 20, 24] studies, respectively. Two studies, one on levetiracetam and one on pregabalin, reported the proportion of patients experiencing a decrease in pain by >30% and >50% compared to baseline [33]. Patients on pregabalin were more than twofold likely to experience >30% (risk ratio of 2.6 (95% CI 1.4–4.7)) and >50% (risk ratio of 2.9 (95% CI 1.1–7.6)) pain reduction compared to placebo [33]. On the other hand, the effect of levetiracetam could be considered similar to placebo, as the associated relative risks approximated 1 [33]. Our review also showed no significant difference in levetiracetam and placebo in terms of pain improvement [22].

According to another review study [34], amitriptyline, gabapentin, and pregabalin should be considered the first choice in managing neuropathic pain after SCI. The available clinical trials show that using higher doses leads to more and more severe AEs. Moreover, they suggested that a combination of various medications or measures, albeit scarcely investigated as an option, is likely to have a more pronounced effect than the administration of one single drug. Our review also found that combination therapies may be more effective than monotherapy in improving SCI-associated pain. For instance, combination therapy of ketamine and gabapentin decreased pain significantly compared to gabapentin alone [18]. Similarly, another study [27] showed that a mixture of clonidine and morphine was more effective than either drug administered alone. Studies examining the effect of combined treatment compared to monotherapy may lead to a better approach to pain management which takes a multidisciplinary perspective into account. In this regard, a non-randomized clinical trial involving ten patients reported a 70–100% reduction in chronic neuropathic pain by intrathecal administration of clonidine (average dose of 44 µg/day), combined with opioids [35].

Previous guidelines on pain management recommended the use of antidepressants and anticonvulsants as first-line treatment for this condition [36–38]. Our review found that amitriptyline was ineffective in reducing SCI-related pain in one study [24] and significantly improved pain in two studies [15, 20]; at the same time trazodone made no difference in pain improvement [32]. However, Mehta et al. reported that most antidepressants (i.e., amitriptyline, duloxetine, trazodone, and venlafaxine) were not effective in decreasing pain due to SCI [34] but were effective in reducing pain in people with SCI who are also experiencing a significant comorbid depressive disorder [34].

Most anticonvulsants reviewed in our study were effective in reducing post-SCI pain. No significant difference was observed in levetiracetam [22] and valproate [21], even though not enough RCTs were conducted on either. Gabapentin, the most studied anticonvulsant in improving post-SCI pain, was found to be effective in most studies. However, one study did not report data on whether gabapentin led to an improvement in pain symptoms compared to the baseline. This strengthens the current evidence that gabapentin could become the first choice to manage SCI-induced pain.

LIMITATIONS

There are certain limitations to this review that should be mentioned. Among the number of studies included in our review, sample sizes were generally limited. Moreover, only RCTs were included in order to minimize bias, however results may differ from what is usually observed in clinical practice; for instance, the duration of many of the RCTs did not exceed 12 weeks, while patients are usually treated for a longer period of time in the clinical setting. However, we did not consider the aforementioned example a limitation when interpreting the study results as most studies assessing pain have demonstrated pain improvement within one to three weeks [39]. As the study's primary outcome, pain relief was evaluated in most studies by using McGill Pain Questionnaire (MPQ), NPS, VAS, or Verbal Numeric Scale (VNS), which are relatively subjective tools and may be affected by multiple unknown factors. Meta-analysis was not possible due to different methodologies, heterogeneity of the data reported, different routes of administration, and lack of sufficient studies for each drug.

In some studies, patients could not discontinue their standard medication regimens. In those cases, the observed result might have derived from the synergistic effect of the prescribed intervention medication and the patients' self-consumed drugs instead of the prescribed intervention alone, despite the baseline being not significantly different between the studied groups.

CONCLUSION

Our systematic review collects the best available evidence on the treatment of SCI-related pain, demonstrating the need for more studies comparing different pharmacologic options for this condition. To this end, considering sample size, study design (parallel or crossover), statistical analysis methods, and efficacy outcomes for each study included in the review is paramount.

According to the most updated evidence, the use of anticonvulsants such as gabapentin and pregabalin in the management of pain due to SCI is supported. Their mechanism and optimal administration, including dose, duration, and onset time, need to be explored by future studies.

Local anesthetics are still recognized as an effective option for short-term pain management, and current evidence is still supporting the use of cannabinoids, intrathecal baclofen, and botulinum toxin for the treatment of nociceptive or spasticity-related pain. Future studies conducting sub-analyses based on pain subtypes may shed more light on treatment effectiveness, not to mention the need for more studies evaluating the consequences of multiple treatments combined.

Presently, we are unable to demonstrate a possible lack of efficacy for the other identified treatments as the data reported in the included studies were limited. Our systematic review suggests investigating new treatment options with fewer side effects that afford longer pain relief durations.

DATA AVAILABILITY

All data is available within this manuscript.

REFERENCES

1. Burke D, Fullen BM, Stokes D, Lennon O. Neuropathic pain prevalence following spinal cord injury: a systematic review and meta-analysis. Eur J Pain. 2017;21:29–44.
2. Carrard V, Kunz S, Peter C. Mental health, quality of life, self-efficacy, and social support of individuals living with spinal cord injury in Switzerland compared to that of the general population. Spinal Cord. 2021;59:398–409.
3. Tran J, Dorstyn D, Burke A. Psychosocial aspects of spinal cord injury pain: a meta-analysis. Spinal Cord. 2016;54:640–8.
4. Bryce TN, Biering-Sørensen F, Finnerup N, Cardenas D, Defrin R, Lundeberg T, et al. International spinal cord injury pain classification: part I. Background and description. Spinal Cord. 2012;50:413–7.
5. Jensen TS, Baron R, Haanpää M, Kalso E, Loeser JD, Rice AS, et al. A new definition of neuropathic pain. Pain. 2011;152:2204–5.
6. Di Stefano G, Di Lionardo A, Di Pietro G, Cruccu G, Truini A. Pharmacotherapeutic Options for Managing Neuropathic Pain: A Systematic Review and Meta-Analysis. Pain Res Manag. 2021;2021:6656863.
7. Saulino M, Averna JF. Evaluation and management of SCI-associated pain. Curr Pain Headache Rep. 2016;20:1–9.
8. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
9. Kaydok E, Levendoglu F, Ozerbil M, Karahan A. Comparison of the efficacy of gabapentin and pregabalin for neuropathic pain in patients with spinal cord injury: a crossover study. Acta Med Mediterr. 2014;2014:1343–8.
10. Cardenas DD, Nieshoff EC, Suda K, Goto S, Sanin L, Kaneko T, et al. A randomized trial of pregabalin in patients with neuropathic pain due to spinal cord injury. Neurology. 2013;80:533–9.
11. Vranken J, Dijkgraaf M, Kruis M, Van der Vegt M, Hollmann M, Heesen M, et al. Pregabalin in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. Pain.2008;136:150–7.
12. Min K, Oh Y, Lee S-H, Ryu JS. Symptom-based treatment of neuropathic pain in spinal cord-injured patients: a randomized crossover clinical trial. Am J Phys Med Rehabilitation. 2016;95:330–8.
13. Yilmaz B, Yasar E, Omac OK, Goktepe AS, Tan AK. Gabapentin vs. pregabalin for the treatment of neuropathic pain in patients with spinal cord injury: A crossover study. Turk J Phys Med Rehab. 2014;61:1–5.
14. Amr YM. Epidural ketamine in post spinal cord injury-related chronic pain. Anesthesia, Essays Res. 2011;5:83.
15. Rintala DH, Holmes SA, Courtade D, Fiess RN, Tastard LV, Loubser PG, et al. Comparison of the effectiveness of amitriptyline and gabapentin on chronic neuropathic pain in persons with spinal cord injury. Arch Phys Med Rehab. 2007;88:1547–60.
16. Levendoglu F, Ögün CÖ, Özerbil Ö, Ögün TC, Ugurlu H. Gabapentin is a first line drug for the treatment of neuropathic pain in spinal cord injury. Spine. 2004;29:743–51.
17. Tai Q, Kirshblum S, Chen B, Millis S, Johnston M, DeLisa JA. Gabapentin in the treatment of neuropathic pain after spinal cord injury: a prospective, randomized, double-blind, crossover trial. J Spinal Cord Med. 2002;25:100–5.
18. Amr YM. Multi-day low dose ketamine infusion as adjuvant to oral gabapentin in spinal cord injury related chronic pain: a prospective, randomized, double blind trial. Pain Physician. 2010;13:245–9.
19. Finnerup NB, Sindrup SH, Bach FW, Johannesen IL, Jensen TS. Lamotrigine in spinal cord injury pain: a randomized controlled trial. Pain. 2002;96:375–83.
20. Agarwal N, Joshi M. Effectiveness of amitriptyline and lamotrigine in traumatic spinal cord injury-induced neuropathic pain: a randomized longitudinal comparative study. Spinal Cord. 2017;55:126–30.
21. Drewes A, Andreasen A, Poulsen L. Valproate for treatment of chronic central pain after spinal cord injury. A double-blind cross-over study. Spinal Cord. 1994;32:565–9.
22. Finnerup N, Grydehøj J, Bing J, Johannesen IL, Biering-Sørensen F, Sindrup S, et al. Levetiracetam in spinal cord injury pain: a randomized controlled trial. Spinal Cord. 2009;47:861–7.
23. Yilmaz B, Yasar E, Omac O, Goktepe A, Tan A. Pregabalin for the treatment of neuropathic pain in patients with spinal cord injury: a cross-over study. Eur J Pain Suppl. 2011;5:239.
24. Cardenas DD, Warms CA, Turner JA, Marshall H, Brooke MM, Loeser JD, et al. Efficacy of amitriptyline for relief of pain in spinal cord injury: results of a randomized controlled trial. Pain. 2002;96:365–73.
25. Kvarnström A, Karlsten R, Quiding H, Gordh T. The analgesic effect of intravenous ketamine and lidocaine on pain after spinal cord injury. Acta Anaesthesiol Scand. 2004;48:498–506.
26. Eide PK, Stubhaug A, Stenehjem AE. Central dysesthesia pain after traumatic spinal cord injury is dependent on N-methyl-D-aspartate receptor activation. Neurosurgery. 1995;37:1080–7.
27. Siddall PJ, Molloy AR, Walker S, Mather LE, Rutkowski SB, Cousins MJ, et al. The efficacy of intrathecal morphine and clonidine in the treatment of pain after spinal cord injury. Anesthesia Analgesia. 2000;91:1493–8.
28. Attal N, Guirimand F, Brasseur L, Gaude V, Chauvin M, Bouhassira D. Effects of IV morphine in central pain: a randomized placebo-controlled study. Neurology. 2002;58:554–63.
29. Norrbrink C, Lundeberg T. Tramadol in neuropathic pain after spinal cord injury: a randomized, double-blind, placebo-controlled trial. Clin J Pain. 2009;25:177–84.
30. Kumru H, Benito-Penalva J, Kofler M, Vidal J. Analgesic effect of intrathecal baclofen bolus on neuropathic pain in spinal cord injury patients. Brain Res Bull. 2018;140:205–11.
31. Han ZA, Song DH, Oh HM, Chung ME. Botulinum toxin type A for neuropathic pain in patients with spinal cord injury. Ann Neurol. 2016;79:569–78.
32. Davidoff G, Guarracini M, Roth E, Sliwa J, Yarkony G. Trazodone hydrochloride in the treatment of dysesthetic pain in traumatic myelopathy: a randomized, double-blind, placebo-controlled study. Pain. 1987;29:151–61.
33. Snedecor SJ, Sudharshan L, Cappelleri JC, Sadosky A, Desai P, Jalundhwala YJ, et al. Systematic review and comparison of pharmacologic therapies for neuropathic pain associated with spinal cord injury. J Pain Res. 2013;6:539–47.
34. Hagen EM, Rekand T. Management of neuropathic pain associated with spinal cord injury. Pain Ther. 2015;4:51–65.
35. Uhle E-l, Becker R, Gatscher S, Bertalanffy H. Continuous intrathecal clonidine administration for the treatment of neuropathic pain. Stereotact Funct Neurosurg. 2000;75:167–75.
36. Tan T, Barry P, Reken S, Baker M; Guideline Development Group. Pharmacological management of neuropathic pain in non-specialist settings: summary of NICE guidance. BMJ. 2010;340:c1079.
37. Moulin D, Boulanger A, Clark A, Clarke H, Dao T, Finley G, et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. Pain Res Manag. 2014;19:328–35.
38. Hatch MN, Cushing TR, Carlson GD, Chang EY. Neuropathic pain and SCI: identification and treatment strategies in the 21st century. J Neurological Sci. 2018;384:75–83.
39. Egbunike IG, Chaffee BJ. Antidepressants in the management of chronic pain syndromes. Pharmacotherapy: J Hum Pharmacol Drug Ther. 1990;10:262–70.
40. Vranken JH, Hollmann MW, van der Vegt MH, Kruis MR, Heesen M, Vos K, et al. Duloxetine in patients with central neuropathic pain caused by spinal cord injury or stroke: a randomized, double-blind, placebo-controlled trial. Pain.2011;152:267–73.

41. Finnerup NB, Biering-Sørensen F, Johannesen IL, Terkelsen AJ, Juhl GI, Kristensen AD, et al. Intravenous lidocaine relieves spinal cord injury pain: a randomized controlled trial. Anesthesiology. 2005;102:1023–30.
42. Siddall PJ, Molloy AR, Walker S, Mather LE, Rutkowski SB, Cousins MJ. The efficacy of intrathecal morphine and clonidine in the treatment of pain after spinal cord injury. Anesthesia Analgesia. 2000;91:1493–8.
43. Andresen SR, Bing J, Hansen RM, Biering-Sørensen F, Johannesen IL, Hagen EM, et al. Ultramicronized palmitoylethanolamide in spinal cord injury neuropathic pain: a randomized, double-blind, placebo-controlled trial. Pain. 2016;157:2097–103.
44. Chiou-Tan FY, Tuel SM, Johnson JC, Priebe MM, Hirsh DD, Strayer JR. Effect of mexiletine on spinal cord injury dysesthetic PAIN1. Am J Phys Med Rehabilitation. 1996;75:84–7.
45. Potter PJ, Hayes KC, Segal JL, Hsieh JT, Brunnemann SR, Delaney GA, et al. Randomized double-blind crossover trial of fampridine-SR (sustained release 4-aminopyridine) in patients with incomplete spinal cord injury. J Neurotrauma. 1998;15:837–49.

AUTHOR CONTRIBUTIONS

M.H.A was responsible for writing the protocol and report, screening potentially eligible studies, extracting and analyzing data, interpreting results, creating 'summary of findings' tables, discussing the results, and article drafting. S.B.J was responsible for, extracting and analyzing data, interpreting results, and assessing the risk of bias of included studies. A.B was responsible for extracting and analyzing data, creating a summary of findings, and revising the manuscript. T.I.P, M.A.D.O, and H.Y were responsible for screening potentially eligible studies and extracting data. Z.Gh was responsible for revising the manuscript, communicating with team members and the corresponding author. M.M was responsible for pharmacological supervision of the manuscript and defining the pharmacologic categories for included RCTs. V.R.M was responsible for the study's conception, designing the review protocol, and supervising the whole process. All authors provided feedback on the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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