

FULL PAPER

Investigation of the effect of Duloxetine on pain status of patients with spinal cord injuries: A systematic review of drug therapy

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Duloxetine is a series of tricyclic antidepressants that have the potential inhibitory properties of histamine H1 and H2 receptors. The present study aimed at evaluating the effect of a Systematic Review of Investigating the Effect of Duloxetine on the pain status of patients with SCIs. The present systematic review was conducted observing principles of publication ethics and guidelines of systematic reviews and meta-analyses (PARISMA) aimed to investigate the effect of duloxetine on the pain status of patients with SCIs during 2010-2021. Two researchers who were proficient in SCIs and reviewed review articles performed the search. A checklist including the author's name, publication date, Outcomes, Control, Intervention, Population, and Study design was used for data collection. Using Excel 2007 Software, the collected data were classified and the final report. The result showed that 202 articles were included in the study in the first stage. In the first stage, 154 articles were deleted due to the irrelevance of the title and method of the article. Also, 34 articles were done due to duplication of articles, and 8 articles were done due to non-human studies. Finally, 6 articles entered the systematic review stage. In all reviewed articles, it was shown that doxepin effectively reduces pain and can reduce pain. While in the placebo group, patients' pain did not decrease. Due to the effect of duloxetine on reducing pain in patients with SCIs, it is suggested that duloxetine can reduce pain in patients.

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KEYWORDS

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Introduction

Spinal cord injuries (SCIs) are among the most traumatic events worldwide, which often cause disabilities in patients, affecting and reducing the quality of life [1,2]. These spinal cord injuries may be well treated at the early stages and not severe. However, suppose the injury is severe, in addition to numerous primary problems such as reduced mobility permanent muscle paralysis below the lesion. In that case, these patients may have

secondary complications such as pain, pressure ulcers (bedsores), reduced physical activity, reduced social participation, and/or even job loss [3-5].

The most common problems of patients with SCIs are paralysis, atrophy, pain, and spasticity. Still, if no proper treatment is taken for the patient, the patient may suffer from long-term renal and musculoskeletal complications such as pain and osteoporosis [6,7]. Pain is one of the significant problems of patients with SCIs, so a study conducted by

Hunt *et al.* on 37 published articles showed that the chronic pain prevalence was 68%, the prevalence of neuropathic pain was 58%, the prevalence of musculoskeletal pain was 56%. The prevalence of visceral pain was 20% [8]. Neuropathic pain is a recurrent complication of spinal cord injury that may have unknown mechanisms, but major interventions should be performed to reduce it [9,10].

There are various methods to reduce patients' pain with spinal problems, mentioned in previously published articles, pharmacological and non-pharmacological methods [11,12]. There are a variety of drugs available to reduce the pain of patients with spinal problems, including steroidal anti-inflammatory drugs (prednisolone, dexamethasone, methylprednisolone, triamcinolone, and betamethasone) and nonsteroidal anti-inflammatory drugs (diclofenac, brufen, naproxen, and piroxicam) [13,14]. Duloxetine is a series of tricyclic antidepressants that have the potential inhibitory properties of histamine H1 and H2 receptors. It seems that duloxetine can effectively reduce patients' pain by increasing serotonergic and noradrenergic activities [15,16]. Duloxetine is a serotonin and reuptake inhibitor of norepinephrine as a pain inhibitor used in lower back pain, fibromyalgia, orthopedic surgery, knee pain, and for the treatment of diseases with psychiatric disorders [17,19].

Objectives

Due to the importance of reducing the pain of patients and the role of physicians in

TABLE 1 Search terms

Search Term	Boolean Keywords
Outcome term	Pain
Population term	Patients with SCIs in worldwide
Descriptive term	Duloxetine OR spinal cord lesion OR spinal cord injury OR spinal surgeries OR central neuropathic pain OR chronic pain OR spinal cord OR spinal fixation OR spinal drug

Inclusion and exclusion criteria

Inclusion criteria included articles published with the spinal group in which the effect of

identifying the types of drugs needed to reduce pain, it is necessary to conduct further studies. Also, since there was no systematic review in this field. For this reason, the present study was conducted aimed to evaluate the effect of duloxetine on the pain status of patients with SCIs by systematic review.

Methods

Study protocol

The present systematic review was conducted observing principles of publication ethics and guidelines of systematic reviews and meta-analyzes (PARISMA) [20] aimed to investigate the effect of duloxetine on the pain status of patients with SCIs during 2010-2021.

Search strategy and selection of studies

Two researchers who were proficient in SCIs (Assistant Professor of Neurosurgery) performed the search and reviewed review articles. The search was performed in all domestic databases in Iran (SID, Iran Doc, RICST), Google Chrome search engine, and the following international databases. Such as the Web of Science, Science Direct, Scopus, Embase, PubMed/Medline, EBSCO, CINAHL, Cochrane Library, EMBASE.

The "All Fields" option was used for the search, and the searched keywords are described in Table 1. In Persian language databases inside Iran, Persian equations of English keywords were used, and a search was performed.

duloxetine on pain status was investigated. Also, the scope of the article search was during 2010-2021 in Persian and English. Articles on

other groups of patients with incomplete data, qualitative studies, review studies, case report studies, case series studies, and articles on the non-human group were excluded from the study.

Data extraction

A checklist including author's name, publication date, Outcomes, Control, Intervention, Population, and Study design was used for data collection.

Statistical synthesis

Using Excel 2007 Software, the collected data were classified, and the final report is given in Table 2.

Results

Search results and features

According to Figure 1, 202 articles were included in the study in the first stage. 154 articles were deleted due to the irrelevance of the title and method of the article. Also, 34 articles were done due to duplication of articles, and 8 articles were done due to non-

human studies. Finally, 6 articles entered the systematic review stage.

Demographic characteristics articles reviewed

Out of 64 reviewed articles, 6 articles entered the systematic review (Altiparmak *et al.* [21], Prabhala *et al.* (2019) [22], Tsuji *et al.* [23], Samadi *et al.* (2021) [24], Hyer *et al.* (2015) [25], and Vranken *et al.* (2011) [26]). Except for the article published by Tsuji *et al.* [27], which was a retrospective observational type, the rest of the published articles were RCT type. In all 6 articles, the total sample size was 298 patients, and most of the patients were female. Regarding the effect of duloxetine on the pain status of patients with spinal cord problems in all 6 articles, the results showed that duloxetine can reduce patients' pain. The flowchart of articles entered the systematic review is shown in Figure 1.

Role of doxepin in reducing pain

In all reviewed articles, it was shown that doxepin effectively reduces pain and can reduce pain. While in the placebo group, patients' pain did not decrease.

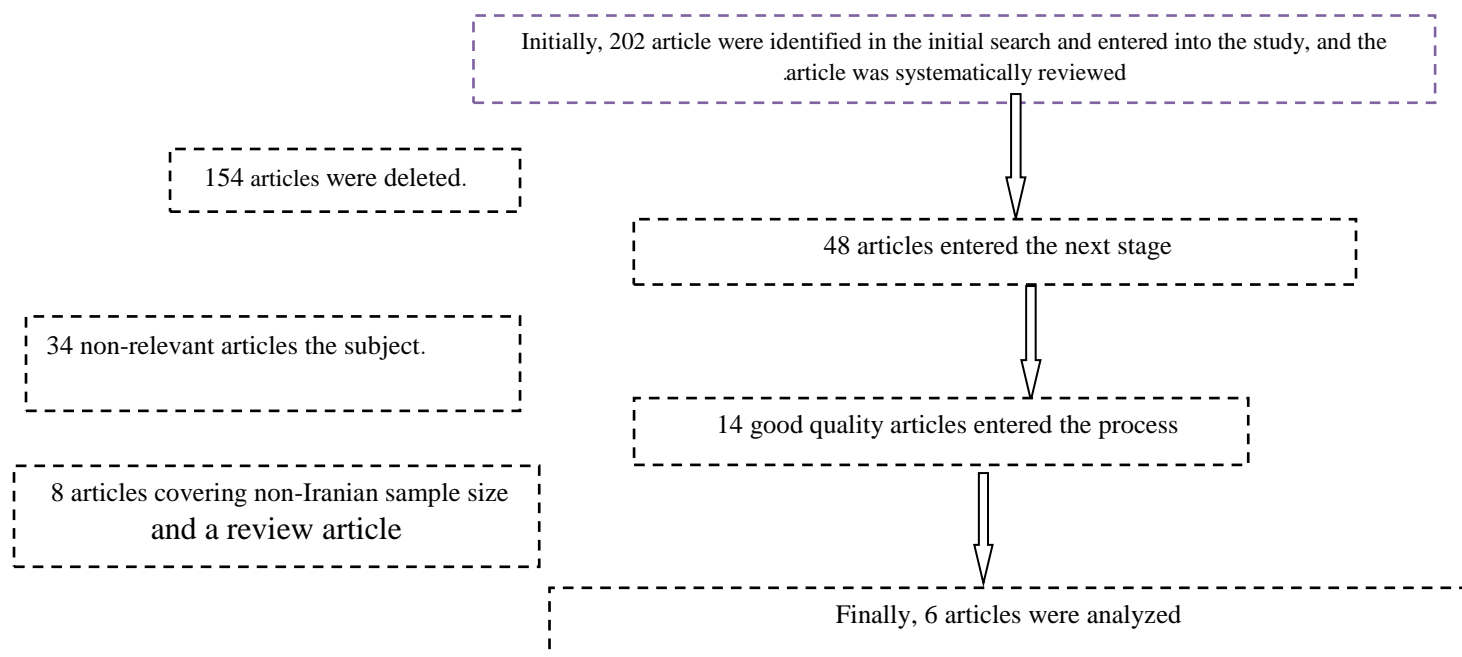


FIGURE 1 Flowcharts for systematic review

TABLE 2 Specifications of articles entered in the systematic review

-	Author	Study design	Population	Intervention	Control	Outcomes
1	Altiparmak <i>et al.</i> (21)	RCT	N = 64 (IG: n = 31, CG: n = 33); Female (%), 64% Age: 18-65 Years Type of disease: spinal surgery.	Duloxetine, oral, 60 mg, 1 hour before and 24 th after surgery	Matching micro cellulose, oral, 1 hour before and 24 th after surgery	The reduction rate in the duloxetine group was 1.16±0.82 and in the control 0.49 ± 0.61.
2	Tsuji <i>et al.</i> (23)	Retrospective observational	N = 24 (IG: n = 19, CG: n = 5); Male (%), 62.5% Age: 66.9±11.2 Years Type of disease: spinal surgery.	Duloxetine, oral, 20-60 mg, more than 90 days	Placebo	Patients with CP: reduced pain in all of them. Patients with PCN: pain in 18 patients had a significant reduction in die. It also had no effect on their pain in 5 patients.
3	Vranken <i>et al.</i> , (2011) (26)	RCT	N = 48 (IG: n = 24, CG: n = 24); Type of disease: SCI or stroke	Duloxetine, oral, 60-120 mg, once daily	Placebo, oral, 60-120 mg, once daily	IG: 29.6% Reduction in pain (from 7.2 ± 0.8 to average reduction 6.1 ± 1.7). CG: 15% Reduction in pain (from 7.1 ± 0.8 to average reduction 5.0 ± 2.0).
4	Prabhala <i>et al.</i> , (2019) (22)	-	N = 64 (IG: n = 41, CG: n = 71); Female (%), 61.8% Age: 58.0±10.6 Years Type of disease: Spinal cord stimulation (SCS).	Duloxetine, oral, 30-60 mg	Placebo	According to the findings, administration of duloxetine can significantly reduce the pain of patients before SCS.
5	Samadi <i>et al.</i> , (2021) (24)	RCT	N = 30 (IG: n = 15, CG: n = 16); Female (%), 58% Age: 18-65 Years Type of disease: PSF surgery.	Duloxetine, oral, once-daily 30 mg, after PSF surgery	Placebo, oral, once-daily 30 mg, after PSF surgery	The M(SD) of pain in the experimental group was 5.20(1.47) and, in the control, group was 6.81(1.64), which showed a statistically significant difference in pain between the two groups(P<0.05).
6	Hyer <i>et al.</i> , (2015) (25)	RCT	N = 68 Type of disease: spine surgery	Duloxetine + opioid, oral	placebo + opioid, oral	Patients were evaluated from 2 weeks before surgery to 3 months after surgery. The use of duloxetine reduced the pain of patients in the experimental group compared to patients in the control group.

Discussion

The present study was conducted aimed to investigate the effect of duloxetine on pain status in patients with spinal cord injuries. According to the study results, duloxetine can effectively reduce the pain of patients with spinal cord injuries. This study was conducted for the first time in the world on a group of patients with spinal cord injuries, so the results will be compared with other studies in which duloxetine has been used on the pain of other patients. Patients with spinal cord injuries experience a lot of pain, and finding ways to reduce pain is one of the objectives of experts in this field [27]. Regarding the presence of pain in patients with spinal cord injuries, the results of Hatefi *et al.*'s meta-analysis showed that pain in patients with SCI in Iran was 65.9%, indicating a high prevalence of pain in these patients [28].

According to the study results, it reduces patients' pain with spinal cord injuries. A study by Hirase *et al.* on 5 articles prescribing duloxetine to 832 patients with CLBP showed that in all studies, patients' pain was reduced after taking duloxetine and a significant difference between was the pain of the patients who received duloxetine and the placebo group [17]. Another meta-analysis investigating the effect of duloxetine on pain was published in a study by CHEN *et al.* on 2059 patients showed that their pain was reduced after taking this drug [29]. Duloxetine is also prescribed to reduce pain in patients with neuropathy and fibromyalgia. According to a study by Sultan *et al.* duloxetine has been prescribed as a placebo for 1510 patients for 12-13 weeks. According to the results, prescribing this drug has reduced patients with painful diabetic neuropathy [30], which is consistent with the study results.

One of the limitations of this study is not conducting a meta-analysis study and reporting the data in a systematic review. It is suggested to conduct a meta-analysis study for another intervention in this field and obtain

more results. Other limitation of this study is the heterogeneity of the articles reviewed and the questionnaire used. For this reason, the study results were reported in a systematic review. One of the strengths of this study is the novelty of the study, which no study has been conducted in this field so far, and therefore can be helpful as a suitable clinical finding.

Conclusion

Due to the effect of duloxetine on reducing pain in patients with SCIs, it is suggested that duloxetine can reduce pain in patients.

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Abbreviations

RCT: double-blind randomized controlled trial
IG: Intervention group
CG: Control group
CP: Chronic Pain
PCN: Postsurgical chronic numbness
SCS: Spinal cord stimulation
PSF: Posterior spinal fixation
CLBT: chronic low back pain
R: systematic review and meta-analysis
SCIs: Spinal cord injuries
RICST: Regional Information Center for Science and Technology
SID: Scientific Information Database
Iran Doc: Iranian Research Institute for Information Science and Technology

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