Management of Neuropathic Pain Associated with Spinal Cord Injury

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ABSTRACT

Spinal cord injury (SCI) is an injury to the spinal cord that leads to varying degrees of motor and/or sensory deficits and paralysis. Chronic pain of both neuropathic and nociceptive type is common and contributes to reduced quality of life. The aim of the review is to provide current clinical understanding as well as discuss and evaluate efficacy of pharmacological interventions demonstrated in the clinical studies. The review was based on literature search in PubMed and Medline with words “neuropathic pain” and “spinal cord injury”. The review included clinical studies and not experimental data nor case reports. A limited number of randomized and placebo-controlled studies concerning treatment options of neuropathic pain after SCI were identified. Amitriptyline, a tricyclic antidepressant and the antiepileptic drugs, gabapentin and pregabalin, are most studied with demonstrated efficacy, and considered to be the primary choice. Opioids have demonstrated conflicting results in the clinical studies. In addition, administration route used in the studies as well as reported side effects restrict everyday use of opioids as well as ketamine and lidocaine. Topical applications of capsaicin or lidocaine as well as intradermal injections of Botulinum toxin are new treatment modalities that are so far not studied on SCI population and need further studies. Non-pharmacological approaches may have additional effect on neuropathic pain. Management of pain should always be preceded by thorough clinical assessment of the type of pain. Patients need a follow-up to evaluate individual effect of applied measures. However, the applied management does not necessarily achieve satisfactory pain reduction. Further clinical studies are needed to evaluate the effect of both established and novel management options.
INTRODUCTION

A spinal cord injury (SCI) is an injury to the spinal cord that leads to varying degrees of motor and/or sensory deficits and paralysis [1]. Although injury of the cauda equina is included, the definition excludes isolated injuries to other nerve roots [2]. The condition may lead to lifelong loss of function, autonomic disturbances and reduced quality of life, as well as increased morbidity and mortality.

Pain is common in patients with SCI [3–5]. The pain may be of nociceptive or neuropathic type or a combination of the two. Neuropathic pain following SCI is caused by damage to or dysfunction of the nervous system, while nociceptive pain is caused by damage to non-neural tissue either musculoskeletal due to bone, joint, muscle trauma or inflammation, mechanical instability or muscle spasm. Pain of visceral origin may develop for instance due to renal calculus, bowel, sphincter dysfunction, headache related to autonomic dysreflexia and secondary overuse syndromes [6, 7].

The pain may be localized above, at or below the level of the SCI and may persist for many years after the acute injury [8–10]. Pain may occur immediately after the acute injury or develop and increase in intensity a long time after the injury [8, 11]. Neuropathic pain is found to contribute to reduced quality of life in patients with SCI [8, 11].

Current review is based on search in PubMed and Medline databases with words “neuropathic pain” and “spinal cord injury”. The review included all clinical studies, but not experimental and case reports, published until December 2015 when the search was conducted. The review included all clinical studies, but not experimental data nor case reports.

The aim is to provide current clinical understanding as well as possible treatment options and initiatives with efficacy evaluation.

This review article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

EPIDEMIOLOGY OF SCI AND NEUROPATHIC PAIN FOLLOWING SCI

There are large variations in incidence, prevalence, gender distribution, mechanisms, level and completeness of SCI worldwide [12–19].

The global incidence of traumatic SCI is estimated to be 23 cases per 1,000,000 persons in 2007 and is dependent on regional results [20]. The reported annual incidence ranges from 2.3 per million in one Canadian study to 83 per million in a study from Alaska [18–21]. Differences in definition, inclusion criteria, classification and procedures for identification of patients as well as geographical and cultural issues may contribute to a vast range of annual incidence reported in the studies [16, 21].

Information about prevalence of traumatic SCI is scarce [18]. The lowest reported prevalence is from India, 236 per million population [22], and the highest from the USA, 4187 per million population [23]. The incidence and prevalence of non-traumatic SCI are very limited and the results are uncertain.

Neuropathic pain is a common complication following SCI. The prevalence of pain in SCI is
reported between 18% and 96%, the variation may be explained by differences in selection of study populations [4, 24]. Pain is usually described as present in 60–69% of the SCI population [5]. Most individuals with chronic pain and SCI report more than one pain problem [24]. Prevalence of chronic pain in individuals with SCI is reported to be 11–94%, and severe, disabling pain in 18–63% [24].

Clinical Characteristics of Neuropathic Pain Following SCI

Neuropathic pain above the level of injury is often caused by concomitant compressive radiculopathies or sometimes by complex regional pain syndromes. Neuropathic pain at the level of injury is caused by nerve-root compression development of complications such as syringomyelia or SCI itself, while neuropathic pain below the level of injury is caused by spinal cord trauma or disease [2].

A recent prospective study followed 90 patients with traumatic SCI 1, 6 and 12 months after the injury [7]. Eighty-eight patients completed the 12-month follow-up. Approximately, 80% of the patients reported any type of pain at all periods evaluated. Neuropathic pain related to SCI increased over time, and musculoskeletal pain decreased slightly, with both being present in 59% of patients at 12 months; other neuropathic pain not related to SCI and visceral pain were present in 1–3%. Early sensory changes (particularly cold-evoked dysesthesia) indicated development of neuropathic pain below the level of injury later [7]. The findings demonstrate that examination of sensation may give additional information about prognosis. Trauma in the spinal cord may result in subsequent central neuropathic pain with localization at or below the level of SCI with allodynia, hyperalgesia and sensory deficit in the pain area [25]. There is usually no relation to movement in neuropathic pain. Different descriptive words indicating neuropathic characteristics of sensation such as burning, tingling, pricking, sharpness, shooting, squeezing, cold, electric or shock-like pain have been used by patients [25]. Neuropathic pain at injury level resolved later in 45% of patients and below injury-level pain resolved in 33% of cases. The findings indicate that majority of SCI patients with pain syndromes have long-lasting problems and need follow-up of pain problems.

CLASSIFICATION OF NEUROPATHIC PAIN IN SCI

Neuropathic pain is defined as proposed by the International Association for the Study of Pain (IASP) as “pain initiated or caused by a primary lesion or dysfunction of the nervous system” [25]. Neuropathic pain is divided into peripheral and central pain [25–27]. Pain after SCI is classified according to type, localization and level of injury [8].

A typical feature of central neuropathic pain following SCI is its localization below the level of the injury combined with sensory phenomena such as allodynia or hyperalgesia in the painful area [8, 9]. Central neuropathic pain may develop months or years after the injury [8–10]. Development of neuropathic pain a long time after SCI may be a sign of post-traumatic syringomyelia [8].

Neuropathic pain above the level of injury is usually not due to the SCI itself. Patients who use a manual wheelchair may experience carpal tunnel syndrome and peripheral neuropathic pain as a result and shoulder pain due to muscular overuse [28, 29]. Peripheral...
neuropathic pain at injury level can be due to concomitant injury to the nerve root.

Both nociceptive and neuropathic pain may vary in intensity and may be dependent on daily activities as well as being affected by the individual’s psychosocial environment [30].

PATHOPHYSIOLOGY

Numerous and complex changes in the nervous system will take place after development of pain following SCI.

A number of molecular changes will occur after SCI including changes in sodium ion-channels, voltage-gated calcium channels, glutamate and gamma-aminobutyric acid metabolism, serotonergic, noradrenergic, N-methyl-D-aspartate (NMDA) and opioid receptors. Drugs such as antiepileptics, tricyclic antidepressants and opioids have an effect on these changes [8, 31]. Neuroplasticity may contribute to both recovery of neuropathic pain and maintenance and chronification of pain after SCI despite for attempts on medical treatment [31].

Neuropathic pain may also develop because of compression of nerve roots after spinal trauma [31, 32]. Clinically, this pain will often be localized above the level of injury [31].

CLINICAL EXAMINATION

A thorough examination is important to identify any possible somatic cause of the pain other than SCI and to classify the type of pain to optimize therapy. The localization, duration, intensity and characteristics of pain are useful information when assessing the pain [8, 32]. The clinical examination must include a neurological status with a mapping of sensory phenomena in the painful area, indicating the presence of neuropathic pain [32]. It is important to collect data regarding previous surgical and medical treatment [8]. Information will help to find possible underlying causes, classify pain type and relate localization to previous SCI correctly as well as choose appropriate modalities of further management.

Pain intensity can be assessed using a visual analog scale (VAS) or numeric rating scales [8, 33]. Pain characteristics can be mapped using descriptive scales, such as the McGill Pain Questionnaire [34]. The International Spinal Cord Injury Pain Basic Data Set represents an international consensus on clinical data and relevant assessments scales required for pain assessment in SCI patients [35].

TREATMENT

Established Pharmacological Treatment

Neuropathic pain after SCI often emerges as a chronic condition and responds poorly to a single drug. However, monotherapy will help to identify effectiveness of a single drug. Information about expected effect, the timeline of treatment and need for follow-up should be clearly explained to patients. Freedom from pain is often not realistic, instead modulation of the neuropathic pain may be a more achievable goal. Pharmacological treatment of neuropathic pain following SCI is in general long-lasting process and both expected effect and side effects should be considered before the start and during follow-up. Table 1 gives an overview of randomized clinical studies performed on patients with neuropathic pain following SCI.
Table 1: Randomized clinical studies for neuropathic pain following spinal cord injury

| References         | Treatment                         | Dosage                          | Study design                                      | Sample size | Active substance | Placebo |
|--------------------|-----------------------------------|---------------------------------|--------------------------------------------------|-------------|------------------|---------|
|                    | **Antidepressants**               |                                 |                                                  |             |                  |         |
| Cardenas et al.    | Amitriptyline vs placebo         | 10–25 mg                        | Randomized controlled Trial                      | 84          | 44               | 40      |
| Rintala et al.     | Amitriptyline vs active placebo vs gabapentin | 150 mg amitriptyline vs 3600 mg gabapentin | Randomized, controlled, double blind, triple crossover | 38          | 38               | 38      |
| Yang et al.        | Lithium vs placebo               | 0.6–1.2 mmol/l                  | Randomized, double-blind, placebo-controlled trial | 40          | 20               | 20      |
| Davidhoff et al.   | Trazodone hydrochloride vs placebo| 50–150 mg                       | Randomized, double-blind, placebo-controlled trial | 18          | 9                | 9       |
| Vranken et al.     | Duloxetine vs placebo            | 60–120 mg                       | Randomized, double-blind, placebo-controlled trial | 48*         | 24               | 24      |
|                    | **Antiepileptics**               |                                 |                                                  |             |                  |         |
| Rintala et al.     | Gabapentin vs active placebo      | 900–3600 mg                     | Randomized, controlled, double blind, triple crossover trial | 38          | 38               | 38      |
| Leventoglu et al.  | Gabapentin vs placebo            | 1800 mg                         | Randomized, double-blind, placebo-controlled, crossover trial | 20          | 20               | 20      |
| Tai et al.         | Gabapentin vs placebo            | 150–600 mg                      | Prospective, randomized, double-blind, crossover trial | 7           | 7                | 7       |
| Ahn et al.         | Gabapentin                       | 1800 mg                         | Evaluation study                                  | 31          |                  |         |
| Siddall et al.     | Pregabalin                       | 150–600 mg                      | Randomized, placebo-controlled, multicentre trial | 137         | 70               | 67      |
| Vranken et al.     | Pregabalin vs placebo            | 150–600 mg                      | Randomized, double-blind, placebo-controlled trial | 40*         | 20               | 20      |
| Cardenas et al.    | Pregabalin vs placebo            | 150–600 mg                      | Randomized, double-blind, placebo-controlled trial | 220         | 112              | 108     |
| Finnerup et al.    | Lamotrigine vs placebo           | 200–400 mg                      | Randomized double blind, placebo-controlled, crossover trial | 30          | 27               | 28      |
| Drewes et al.      | Valproate vs placebo             | 600–2400 mg                     | Double-blind, cross-over, placebo-controlled trial | 20          | 20               | 20      |
| Finnerup et al.    | Levetiracetam                    | 500–3000 mg                     | Randomized, double-blind, placebo-controlled, crossover, multicentre trial | 36          | 18               | 18      |
| Salinas et al.     | Carbamazepine vs placebo         | 600 mg                          | Randomized, double-blind, placebo-controlled trial | 46          | 24               | 22      |
|                    | **Opioids**                      |                                 |                                                  |             |                  |         |
| Norrbrink et al.   | Tramadol                          | 150 mg                          | Randomized, double-blind, placebo-controlled trial | 35          | 23               | 12      |
| Attal et al.       | Morphine vs placebo              | 2 mg morphine every 10 min intravenous | Double-blind, placebo-controlled, crossover trial | 16          | 8                | 8       |
| Siddall et al.     | Morphine and clonidine vs placebo | Individual dosage               | Randomized, double-blind, placebo-controlled trial | 15          | 15               | 15      |
|                    | **Cannabinoids**                 |                                 |                                                  |             |                  |         |
| Rintala et al.     | Dronabinol vs placebo            | 5–20 mg                         | Randomized, controlled, double-blind, crossover trial | 7           | 7                | 5       |
| Wade et al.        | Cannabis vs placebo              | 2.5–120 mg                      | Double-blind, placebo-controlled, crossover trial | 24*         | 24               | 24      |
| Karst et al.       | Synthetic cannabinoid vs placebo | 40 mg                           | Randomized, double-blind, placebo-controlled trial | 21*         | 21               | 21      |
|                    | **Others**                       |                                 |                                                  |             |                  |         |
| References       | Treatment                          | Dosage                                      | Study design                                                                 | Sample size | Active substance | Placebo |
|------------------|------------------------------------|---------------------------------------------|-------------------------------------------------------------------------------|-------------|------------------|---------|
| Eide et al. [66] | Ketamine, alfentanil and placebo   | 60 + 6 µg/kg and alfentanil (7 + 0.8 µg/kg) | Continuous and evoked pain was examined before and after the intravenous infusion of either ketamine, alfentanil or placebo. | 9           | 9                | 9       |
| Amr et al. [65]  | Ketamine + gabapentin vs gabapentin + placebo | 80 mg ketamine + 900 mg gabapentin         | Randomized, controlled, double blind trial                                   | 40          | 29               | 29      |
| Kvarnstrom et al. [67] | Lidocaine vs ketamine vs placebo | 0.4 mg/kg ketamine vs 2.5 mg/kg lidocaine | Randomized, double-blind, three period, three-treatment, cross-over trial    | 10          | 10               | 10      |
| Finnerup et al. [63] | Lidocaine vs placebo | 5 mg/kg | Randomized, double-blind, placebo-controlled, crossover trial | 24          | 24               | 24      |
| Chiou-Tan et al. [64] | Mexiletine vs placebo | 450 mg | Randomized, placebo-controlled, double-blind, crossover trial | 15          | 11               | 11      |

| References       | Time     | Outcomes                                | Adverse effect active substance | Adverse effect placebo | Dropout                          |
|------------------|----------|-----------------------------------------|---------------------------------|------------------------|----------------------------------|
| Antidepressants   |          |                                         |                                 |                        |                                  |
| Cardenas et al. 37 | 6 weeks  | No significant between amitriptyline and placebo | 43                             | 36                     | 0                                |
| Rintala et al. 36 | 8 weeks  | Amitriptyline > gabapentin              |                                |                        | 28 completed the amitriptyline phase |
| Yang et al. 38   | 6 weeks  | Lithium > placebo                       | 16                             | 14                     | 2 in each group                   |
| Davidhoff et al. 39 | 6 weeks  | No significant difference between trazodone hydrochloride and diphenhydramine | 4                              | 1                      | 5 in active drug group, 1 in placebo group |
| Vranken et al. 40 | 6 weeks  | No significant difference between duloxetine vs placebo | 30 AE in total                 | 10 AE in total          | 0                                |

| Antiepileptics    |          |                                         |                                 |                        |                                  |
| Rintala et al. 36 | 8 weeks  | No significant difference between gabapentin and diphenhydramine |                                |                        | 26 completed the gabapentin phase |
| Levendoglu et al. 43 | 18 weeks | Gabapentin > placebo                     | 30 AE in total                  | 6                      |                                  |
| Tai et al. 45     | 10 weeks | Gabapentin > placebo                     |                                | NA                     |                                  |
| Ahn et al. 47     | 8 weeks  | Effect of Gabapentin                     | 15                             | NA                     |                                  |
| Siddall et al. 48 | 12 weeks | Pregabalin > placebo                     | 15                             | 9                      | 21 in active group, 30 in placebo group |
| Vranken et al. 49 | 4 weeks  | Pregabalin > placebo                     | 3                              | 3                      | 3 in active group, 4 in placebo group |
| Cardenas et al. 50 | 17 weeks | Pregabalin > placebo                     | 75                             | 50                     | 6 in active group, 5 in placebo group |
Table 1 continued

| References          | Time     | Outcomes                                      | Adverse effect active substance | Adverse effect placebo | Dropout |
|---------------------|----------|-----------------------------------------------|---------------------------------|------------------------|---------|
| Finnerup et al. [52]| 21 weeks | No significant difference between lamotrigine and placebo | 1                              | 2                      | 3       |
| Drewes et al. [53]  | 8 weeks  | No significant difference between valproate and placebo | 4                              | 0                      | 0       |
| Finnerup et al. [54]| 12 weeks | No significant effect                          | 7                              | 2                      | 9       |
| Salinas et al. [55] | 1 month  | Carbamazepine > placebo only after 1 month<sup>b</sup> | 23                             | 21                     | 1       |
| Dropout             |          |                                               |                                 |                        |         |
| Opioids             |          |                                               |                                 |                        |         |
| Norrbrink et al. [58]| 4 weeks | Tramadol > placebo                            | 21                             | 7                      | 10      |
| Attal et al. [59]   | 20 min each | Morphine > placebo after 1 month              | 5                              | 0                      | 1       |
| Siddal et al. [60]  | 3 days each | Morphine + clonidine > morphine or clonidine or placebo | Morphine 25 AE, Clonidine 27 AE, Morphine/clonidine 27 AE | 4 AE | 0 |
| Cannabinoids        |          |                                               |                                 |                        |         |
| Rintala et al. [68] | 17 weeks | No significant difference between dronabinol and placebo | 30 AE                          | 18 AE                  | 2       |
| Wade et al. [69]    | 10 weeks | Cannabis > placebo                            | 24                             | 21                     | 3       |
| Karst et al. [70]   | 3 weeks  | Synthetic cannabinoid > placebo               | 2                              | 0                      | 2       |
| Others              |          |                                               |                                 |                        |         |
| Eide et al. [66]    | 2 h each | Ketamine + alfentanil > alfentanil or ketamine or placebo | –                              | –                      | –       |
| Amr et al. [65]     | 1 week   | Ketamine + gabapentin > gabapentin + placebo  | –                              | –                      | –       |
| Kvarnstrom et al. [67]| 2 weeks | Ketamine > lidocaine or placebo               | Ketamine 9, Lidocaine 5        | 1                      | –       |
| Finnerup et al. [63]| 2 weeks | Lidocaine > placebo                           | 9                              | 1                      | 0       |
| Chiou-Tan et al. [64]| 10 weeks | No significant difference between mexiletine and placebo | –                              | –                      | 4       |

<sup>a</sup> Patients with several diagnoses were included in the study  
<sup>b</sup> Carbamazepine was used as prophylactic treatment
Antidepressants
Amitriptyline, a tricyclic antidepressant showed effect in one study [36], while another randomized study did not confirm this effect [36, 37]. The applied doses varied between 10 and 150 mg in these studies and the studies were designed differently and direct comparison is not possible between these studies. Known adverse effects such as dry mouth, drowsiness or tiredness, constipation, urinary retention and increased spasticity were reported in both studies [36, 37]. Side effect occurred more frequently in the study applying higher doses of amitriptyline [36].

Another antidepressive drug, lithium, has shown favorable effect on neuropathic pain in a placebo-controlled study exploring possible effect on patients with SCI [38]. Oral lithium was titrated to 0.6–1.2 mmol/l for 6 weeks with subsequently 6-month clinical follow-up. The effect of lithium on neuropathic pain was a secondary outcome in this study. A total of 40 patients were enrolled, half of patients suffered from severe neuropathic pain. Significant improvement, measured by visual analog scale (VAS) was recorded after 6 weeks as well as after discontinuation of the 6 months of treatment [38]. However, further studies on neuropathic pain following SCI are needed to confirm the effectiveness of lithium.

Two oral antidepressives, trazodone (50–150 mg) and duloxetine (60–120 mg) have been studied in the randomized, placebo-controlled double-blinded studies without showing any effect in patients with SCI [39, 40].

Other tricyclic antidepressants such as nortriptyline, imipramine, and desipramine are considered to be first-line choice in management of neuropathic pain in general [41, 42]. Other recommended drugs for neuropathic pain include venlafaxine, selective serotonin reuptake inhibitors such as sertraline, paroxetine, fluoxetine and citalopram [41]. All these drugs are not, however, sufficiently studied neither in patients with SCI nor in patients with neuropathic pain [41]. In individual intractable cases, both well-documented and less documented medication may be considered.

Antiepileptics
Pregabalin and gabapentin are the most studied drugs against neuropathic pain following SCI. The analgesic effect of these drugs has been explained by action through multiple pathways [32]. Several studies have reported on the efficacy of gabapentin. [36, 43–47]. Two studies, including only 27 patients all together, showed better effect than placebo, while two other studies showed conflicting results [36, 43–47]. The administered doses varied between 300 and 3600 mg. Pregabalin have been studied in three randomized placebo-controlled studies in the doses between 150 and 600 mg [48–50]. These studies showed that pregabalin has superior effect to placebo [48, 49]. Both pregabalin and gabapentin have similar adverse effect with somnolence, dizziness, edema, dry mouth, and fatigue [36, 50, 51].

Lamotrigine was studied using doses of 200–400 mg in patients with SCI [52]. Thirty patients with complete and incomplete injury were included in the study. Lamotrigine showed effect on neuropathic pain in the group with incomplete injury [52]. Levetiracetam and sodium valproate have been studied in randomized placebo controlled manner in patients with SCI [53, 54]. There was, however, no significant effect on neuropathic pain recorded in these studies. Carbamazepine has been studied in one placebo controlled study on SCI patients. Carbamazepine was administered up to 600 mg daily to SCI patients without pain.
The conclusion was that carbamazepine may prevent the early, but not the long-term development of neuropathic pain [55]. Other antiepileptic drugs suggested to have effect on neuropathic pain are phenytoin, oxcarbamazepine and lacosamide. However, the evidence of effect is weak or limited to the specific types of syndromes with neuropathic pain and is not studied on patients with SCI [56]. Phenytoin has been effective on trigeminal neuralgia in doses 15 mg/kg. Also, oxcarbamazepine has reduced significantly the neuropathic pain in doses above 770 mg daily and lacosamide has proven efficacy in doses 15 mg/kg [56]. Gabapentin and pregabalin obviously should be used before other antiepileptics in the SCI-related neuropathic pain. Other studied antiepileptics may be considered in individual cases with intractable neuropathic pain as a last resort.

**Opioids**

Opioids are potent drugs and recommended as a medication against intractable pain after SCI [32, 56, 57]. Tramadol has been shown to be effective in the randomized placebo-controlled study on 35 patients with SCI-related neuropathic pain [58].

Intravenously given morphine did not show effect in a crossover study in patients with neuropathic pain due to different conditions including SCI [59]. Clonidine together with morphine given intrathecally has been used in two studies including in total of 23 participants [60, 61]. Both studies concluded favorable effect of treatment [60, 61].

The use of Oxycodone, an oral opioid has demonstrated additional improvement of pain in patients with SCI and neuropathic pain pre-treated with antiepileptic drugs [62]. Use of opioids alone or with other medications may be an option. However, side effects such as constipation, nausea and cognitive deprivation along with the risk of drug abuse may complicate a long-term use.

**Other Anti-Analgesics**

Intravenous lidocaine has shown effect on the patients with SCI and neuropathic pain in a limited study [63]. A per oral analog to lidocaine, mexiletine was, however, not effective in another 4-week placebo-controlled randomized study where only 11 patients completed the study [64].

Ketamine, a NMDA receptor antagonist, was compared with other drugs in three studies [63, 65, 66]. Intravenous ketamine together with oral gabapentin showed better effect than gabapentin and placebo immediately after administration [65]. However, the effect was not present 2 weeks after treatment. Another study compared the effect of ketamine (in dose 0.4 mg/kg) with lidocaine (2.5 mg/kg) and placebo. Ketamine, but not lidocaine, showed significant effect [67]. The third study investigated the effect of ketamine together with μ-receptor agonist alfentanil compared with placebo [66]. This study showed significant effect in patients with SCI and neuropathic pain with dysesthesia. Intravenously administered lidocaine in dosage 5 mg/kg has also shown effect [63]. However, daily intravenous administration will limit the use of these medications on patients with long-lasting pain.

Cannabis-based medications have been studied both in patients with neuropathic pain and also in patients suffering from spasticity related pain in particular. A pilot study on Dronabinol, oral cannabinoid given 5–20 mg daily to patients with SCI and neuropathic pain did not show better effect than placebo [68]. Two studies using cannabis spray on a mixed cohort including patients with SCI.
demonstrated significant effect on neuropathic pain [69, 70]. The studies are so far too limited and efficacy of cannabinoids and opioids is questionable.

Treatment of neuropathic pain after SCI may include use of topical agents [71]. Topical use of 0.025% capsaicin ointments was studied in a retrospective study including only eight patients, proved effective on neuropathic pain [72]. Topical use of lidocaine or high doses of capsaicin (8%) has not been studied on patients with SCI. These drugs have, however, shown effect on the other types of neuropathic pains [56, 73]. Another new approach for treatment of well-localized neuropathic pain is intradermal use of botulinum toxin A injections [73]. This treatment has not been tried on SCI-related neuropathic pain, but it proved effective in the cases with chronic neuropathic pain after surgery or trauma [74]. The treatment should be studied further on patients with SCI-related neuropathic pain in future.

A recent systematic review compared all available pharmacologic therapies for neuropathic pain following SCI and concluded that available studies are small and cause insufficient data for quantitative comparisons [75].

Other Options of Treatment of Neuropathic Pain Following SCI

Two studies examined the effect of transcutaneous electrical nerve stimulation (TENS) on neuropathic pain following SCI [76, 77]. Low-frequency TENS demonstrated a favorable effect on pain [77]. Transcranial electric stimulation either alone or together with visual illusions was studied in several studies [78–81]. Favorable effect was demonstrated in all studies. One observational study exploring the effect of visual illusions demonstrated significant reduction of pain as measured by VAS [82]. Transcranial magnetic stimulation did not however show significant effect in two studies on SCI patients [83, 84]. One study, exploring effect of deep brain stimulation did not demonstrate effect of such procedure [85].

Two studies, one of them a mixed cohort, have shown partial effect of DREZotomy (Dorsal Root Entry Zone—a surgical treatment) on neuropathic pain [86, 87].

One observational study investigated the effect of acupuncture or massage on neuropathic pain following SCI [88]. Comparing pain before and after treatment, reduction of pain was reported with both acupuncture and massage. Osteopathic manipulation did not however show any effect in SCI patients with neuropathic pain [89].

Management of Both Neuropathic Pain and Nociceptive Pain

Both nociceptive and neuropathic pain may occur simultaneously in patients with SCI. Given this, management of both types of pain should be addressed. The effect of single pain medication or combinations against mixed types of pain after SCI has not been systematically studied. Non-steroidal anti-inflammatory drugs and opioid medication is widely clinically used [90]. Acupuncture, manual therapy, hypnosis and biofeedback have demonstrated effect on nociceptive pain and should be considered as possible options of non-pharmacological treatment in the cases with mixed pain [91–93]. Physiotherapy can alleviate nociceptive pain and should be considered, particularly if muscular shoulder pain is present [94–96].
RECOMMENDATIONS

Based on current knowledge, amitriptyline, gabapentin and pregabalin have the best documented effects on neuropathic pain after SCI and should be considered as the first choice. However, the documentation about efficacy is limited on patients with SCI-related pain in most other options and individual variations in response to treatment are observed. In addition, side effects should be considered, particularly if high doses are used. The available clinical trials demonstrate that use of higher doses results in several and more serious side effects. In the cases of intractable pain, treatments effective on other types of neuropathic pain may be considered. A combination of several drugs or measures, although scarcely studied so far, has probably more pronounced effect than administration of one single drug. Maintenance of treatment effect is not systematically studied. Therefore, the patients should be followed up and treatment should be evaluated continuously. Further studies are needed for evaluation of efficacy of those measures on pain after SCI.

CONCLUSIONS

The majority of patients suffer from pain following SCI. Pain has profound impact on many aspects of daily life. The management of pain should be based on clinical findings leading to diagnosis of pain type and evaluation of effect of treatment. Thorough clinical assessment of the condition should precede administration of drugs to make sure of the presence of neuropathic pain.

Evidence of efficacy of pharmacological treatment of neuropathic pain following SCI is limited and available literature does not give enough information about long-term effect or usefulness of combination therapy. Based on current knowledge, tricyclic antidepressant amitriptyline and antiepileptics gabapentin and pregabalin have the best documented effect on neuropathic pain after SCI.

Treatment of topical agents such as capsaicin or lidocaine as well as with intradermal Botulinum toxin injections may be useful approaches but need to be studied on populations with SCI. Further studies are needed for evaluation of efficacy of those measures on pain after SCI.

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Compliance with ethics guidelines. This review article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

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