Journal of the Neurological Sciences 384 (2018) 75–83

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Review Article

Neuropathic pain and SCI: Identification and treatment strategies in the 21st century

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ARTICLE INFO

Keywords:
Spinal cord injury
Neuropathic pain measures
Neuropathic pain
Pain classification
Pain management
SCI pain treatment
ISCIP

ABSTRACT

Pain is a common complication in patients following spinal cord injury (SCI), with studies citing up to 80% of patients reporting some form of pain. Neuropathic pain (NP) makes up a substantial percentage of all pain symptoms in patients with SCI and is often complex. Given the high prevalence of NP in patients with SCI, proper identification and treatment is imperative. Indeed, identification of pain subtypes is a vital step toward determining appropriate treatment. A variety of pharmacological and non-pharmacological treatments can be undertaken including antiepileptics, tricyclic antidepressants, opioids, transcranial direct current stimulation, and invasive surgical procedures. Despite all the available treatment options and advances in the field of SCI medicine, providing adequate treatment of NP after SCI continues to be challenging. It is therefore extremely important for clinicians to have a strong foundation in the identification of SCI NP, as well as an understanding of appropriate treatment options.

Here, we highlight the definitions and classification tools available for NP identification, and discuss current treatment options. We hope that this will not only provide a better understanding of NP for physicians in various subspecialties, but that it will also help guide future research on this subject.

1. Introduction

Spinal cord injury (SCI) is a devastating condition that results in the loss or damage of sensory, motor and autonomic functions which leads to several secondary complications. Although some complications are more severe than others, minor complications can be equally or even more, disabling [1]. The ability to manage these complications can significantly impact ones quality of life [1,2]. Pain is one of the most common secondary conditions found in people with SCI and its impact is significant [3–5]. Recent statistics in studies with large sample sizes indicate that approximate that 65 to 85% of all SCI patients will experience pain, and about a third of these patients will experience severe/excruciating pain [6]. Indeed, pain was ranked as one of the top 5 perceived difficulties after SCI in a large study assessing patients' perception in dealing with the major consequences of SCI [7]. A cross sectional study on patients with SCI also showed that pain was associated with patients' perceptions of their cognitive, physical, and emotional functionality after an SCI [8]. Chronic pain has also been significantly associated with depression, chronic fatigue and a decreased quality of life [9,10].

For patients with SCI, pain is one of the most difficult conditions to treat [9]. The fundamental problem is that pain after SCI is often complex and multifactorial. This is especially true for neuropathic pain (NP) which is known to be chronic and refractory to many of the treatments that are currently available [1]. Recent data states that 30–50% of SCI patients suffer from NP within a year after injury [6,11]. With the prevalence of SCI increasing, and the chronic nature of this type of pain, the demand for pain management in this specific population will continue to increase. Due to the complexity of NP in patients with SCI management requires updated information that is often unfamiliar or difficult for physicians who do not routinely manage chronic pain or post-SCI patients to keep up with.

The goal of this review is to provide a current overview for identification, classification, and treatment of SCI NP (Table 1). Although other reviews on SCI NP exist, this review is the only to combine classification, treatments and recommendations within one paper. Additionally, we have incorporated the Neuropathic Pain Special Interst Group (NeuPSIG) recommendations [12], as well as other recommendations by the NIH and SCI specialized researchers [12–15]. We hope that the information provided here will educate and inform

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https://doi.org/10.1016/j.jns.2017.11.018
Received 29 November 2016; Received in revised form 8 September 2017; Accepted 14 November 2017
Available online 16 November 2017
0022-510X/

Table 1
Summary of review article outline and specific items that are discussed in each section.

NP in SCI review outline	
1. Introduction	
2. Pain Terminology	
3. Pain Assessments	Items discussed
3.1 Pain classification	*Cardenas SCI pain taxonomy, IASP taxonomy, Bryce-Ragnarsson taxonomy, ISCIP classification*
3.2 Pain Measures	*DN4, NPS, LANSS, NPQ, NPSI, SCIPI*
4. Pain Treatment	Items Discussed
4.1 Antiepileptics	*Pregabalin, Gabapentin, Phenytoin, Carbamazepine, Phenobarbital, Valproic acid, Lamotrigine, Topiramate*
4.2 Tricyclics	*Amitriptyline*
4.3 Opioids	*Methadone, Tramadol*
4.4 Cannabinoids	
4.5 Advanced therapies	*Intrathecal pumps*
4.6 Invasive and surgical options	*Nerve blocks, DREZ, Spinal cord stimulation,*
4.7 Other non-pharmacological options	*tDCS, TMS, TENS, behavioral therapy/psychological therapy*
5. Conclusions/recommendations	

others on proper identification, and enable a more informed decision regarding current treatment for SCI patients with NP.

2. Pain-related terminology

To properly diagnose NP in patients with SCI, it is crucial to first identify the different types of pain that can be present in these patients. This requires proper understanding and use of the terms used in various clinical tools and pain classification systems.

2.1. Terminology and definitions

There are various ways that pain can be generated in the body. The first important distinction to understand is the difference between nociceptive and NP. Nociceptive pain is defined as pain generated from the activation of nerve endings, or nociceptors, in peripheral tissues. Nociceptive pain can be found in a number of different tissues, including skin, muscles, tendons, bones, and ligaments and is often described as dull, achy, crampy, or throbbing [16,17]. Nociceptive pain can be further subdivided into musculoskeletal pain and visceral pain. Musculoskeletal pain is a common, and frequently-experienced, form of

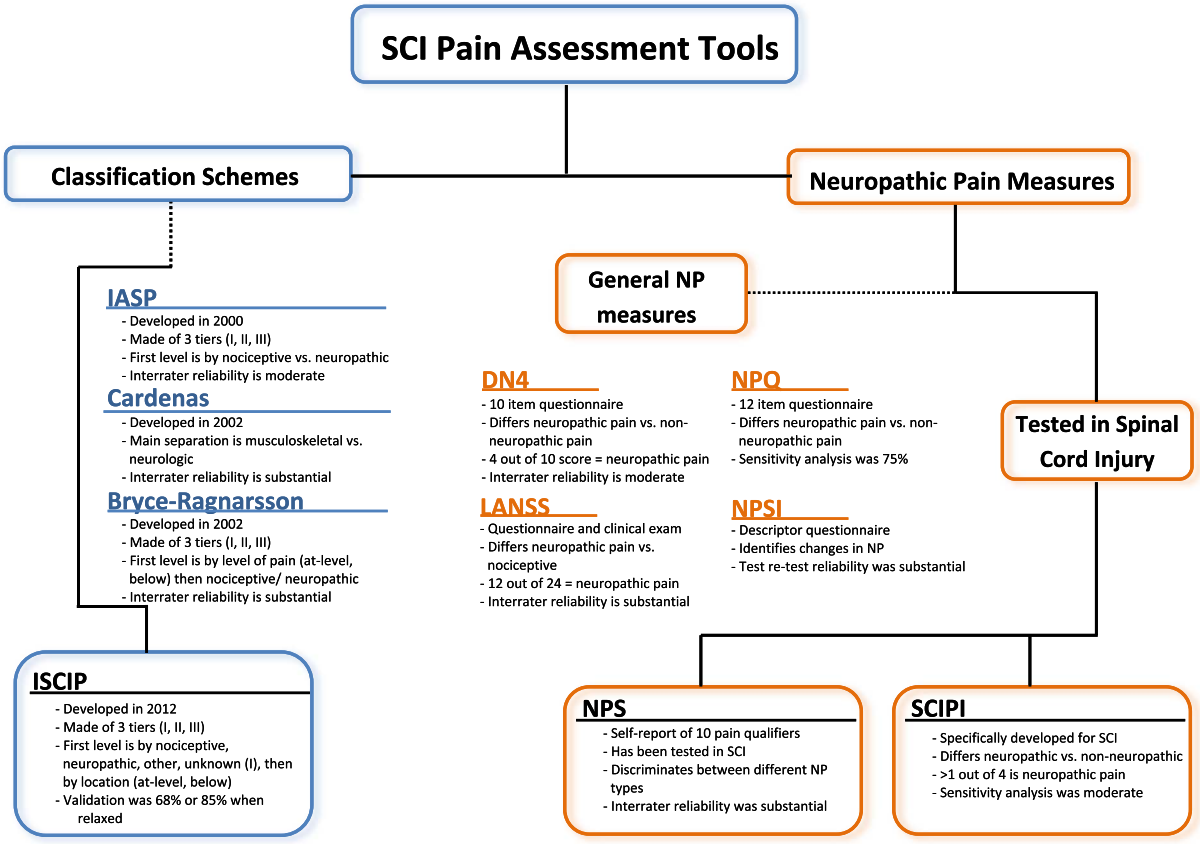

Fig. 1. Flow chart of current classification schemes and neuropathic pain measures available for persons with SCI. The circled assessments on the bottom indicate those that have been specifically tested or developed in the SCI population.

pain due to trauma or inflammation in bones, joints, muscles, or other connective tissue. It can also arise from mechanical instability, muscle spasms, or overuse syndromes like tendonitis or bursitis. For this class of pain, it is necessary for the patient to have at least some preserved sensation where the pain is located. The patient should also be able to accurately localize the pain to a discrete area, or region. Evidence of musculoskeletal pathology underlying the pain must also exist [7]. Visceral pain is typically poorly localized, and is the result of activation of nociceptors in the abdominal, thoracic, or pelvic organs and tissues. This pain is often associated with diagnoses such as myocardial infarctions, cholecystitis, and kidney stones. It can be activated by stimuli such as distension, compression, inflammation, and ischemia affecting the visceral organs [7].

In contrast, NP arises as a direct consequence of a lesion or disease affecting the somatosensory system. In other words, NP develops due to injury of the nerves themselves. People who experience NP frequently describe the pain as tingling, burning, electric shock-like, cold, pricking, pins and needles, squeezing, sharp, itchy, and/or shooting [7,16,17]. Furthermore, patients describe it as spontaneous (arising without a definable stimulation), and evoked (an abnormal response to stimuli) [16]. NP can be further divided into peripheral NP and central NP. A lesion of the peripheral nerve generates peripheral NP. This includes the entire peripheral nervous system, including the most distal terminals of the nerves. In contrast, a lesion in the central nervous system generates central NP. In general, individuals with SCI have central NP, however those that have an SCI due to trauma may also have peripheral NP [7]. Regardless of the origin of NP, treatment options are identical.

3. Clinical SCI pain assessment/classification

Historically there has been no consensus on how to define and classify pain, thus leading to a large number of different classification schemes and tools that were built on differing definitions. This produced wide variances of reported SCI pain prevalence. The lack of consistent definitions and classifications also made comparisons between SCI NP studies nearly impossible, contributing to confusion within the field. In this section, we have focused on the most common NP tools currently available (many of which are included in the SCI common data elements for pain). For clarity, we grouped these tools into [1] pain classification schemes, and [2] NP measures (Fig. 1). Psychometric results were included when available.

3.1. Pain classification schemes

Classification schemes typically categorize different types (and subtypes) of pain, and they often require clinical expertise to interpret and use correctly. In this way, they are different than the NP measures or scales discussed in the next section. Here, we only describe the most recently developed classification schemes.

3.1.1. Cardenas SCI pain taxonomy

This classification scheme was published in 2002 and was developed largely based on the presumed pathology of SCI pain. It is categorized first by pain location and distribution relative to the level of injury, and then how it is related to activity, positioning and light touch [18]. This scheme has 2 major pain categories: *musculoskeletal* and *neurologic*. *Musculoskeletal pain* is divided into mechanical spine pain and overuse pain. *Neurologic pain* has 4 subcategories: SCI, transition zone, radicular and visceral pain. SCI pain is identified as pain felt below the lesion in areas without normal sensation; and related to activity and touch but not affected by position. It should be noted that SCI pain using this taxonomy refers only to diffuse pain below the level of injury. Interrater reliability using this taxonomy was found to be substantial (kappa value of 0.66) when subjects were interviewed in person.

3.1.2. International Association for the Study of Pain taxonomy

In 2000 The International Association for the Study of Pain (IASP) organized a working group to establish a standardized classification scheme for SCI pain. Much of the schema was based on Siddall's pain classification which came out almost simultaneously with the original Bryce-Ragnarsson SCI classification system (see below). The Siddall classification was composed of 4 main categories or systems (Axis 1); *Musculoskeletal, Visceral, Neuropathic, and Other* [19]. NP was then further divided into 'at level' and 'below level' (Axis 2), with pain descriptors. The final Axis of NP (Axis 3) was then further divided based on the source (radicular or central). In this way, this system first classifies pain based on the 'system' and then by the 'localization' of the pain. Although the IASP pain taxonomy was based on the Siddall classification of 1997, there are only 2 major categories of pain; *Nociceptive* and *Neuropathic* (Tier I) in the IASP taxonomy. *Nociceptive* is further divided into musculoskeletal and visceral (Tier II), and *Neuropathic* is further divided into above, at and below level pain. The last tier (Tier III) involved the structural causes of pathology of Tier II subcategories. This classification is a bit more comprehensive than the Siddall system in that it classifies first on system of pain (*nociceptive* and *neuropathic*), and then regional localization (at, above, or below). One study has shown the interrater reliability of this scheme to be only moderate with kappa values from 0.33 to 0.65.

3.1.3. Bryce-Ragnarsson SCI pain taxonomy

This classification system attempts to consider all the existing classifications before its time, as well as new clinical and research insights for SCI pain of that time. This system classifies pain first based on regional location, Tier I (at, above or below level pain relative to the level of injury), and then by type (*nociceptive* or *neuropathic*; Tier II). Tier III then stratifies tier II by various subtypes. This classification scheme is more detailed than the Cardenas classification, and it is similar to the IASP classification except it reverses Tiers I and II. The authors believe that classifying SCI in this way is comprehensive and easy to understand, making it possible for non-SCI specialists to readily use it. The interrater reliability for this scheme was reported to be substantial with a kappa average of 0.70 (the study range was 0.55–0.91) [20].

3.1.4. International spinal cord injury pain (ISCIP) classification

A few years after the publication of the above schemes a group of SCI pain experts developed a consensus SCI pain classification scheme. The resulting scheme was a marrying of the IASP and Bryce-Ragnarsson schemes but with important modifications [16]. This classification is organized into 3 main tiers: Tier I includes the types of pain; *nociceptive, neuropathic, other* and *unknown*; Tier II includes various subtypes of pain for the nociceptive and neuropathic pain categories; and tier III is used to specify the primary pain source and/or pathology. For the *other pain* category, tier III is used to specify recognized pain entities that do not fit the *nociceptive* or *neuropathic pain* categories. The panel felt that this new SCI pain classification scheme was simple, as well as comprehensive. Initial validation of the ISCIP showed an overall correctness in determining pain type to be 68% when strict criteria were used and jumped to 85% when criteria were maximally relaxed [21]. During ISCIP development, clinicians reported feeling very confident in their judgments, but they also noted that certain subtypes of pain were more difficult to classify than others (i.e. vignettes with autonomic dysreflexia headaches, or abdominal pain). The authors indicated that some of these issues could have been caused by the ambiguity in certain definitions. The ISCIP requires further validation, along with reliability testing, before it can be universally used as the preferred taxonomy for SCI pain. It is, however, the first universal classification tool developed thus far.

3.2. Neuropathic pain measures

NP screening tools are different than the complex classification schemes above in that they were designed to be used by those with limited expertise to screen for certain pain types. These are also preferred when tracking or documenting pain during clinical studies. In this section, we will limit our discussion to two types of neuropathic pain measures: (1) those that help discriminate between NP and NNP (DN4, NPQ, SCIPI), and (2) those that assess the status or changes in neuropathic pain (NPS, NPSI).

3.2.1. Douleur neuropathique 4 questions (DN4)

This tool was first developed in France and discriminates between NP and NNP [22]. It is a 10-item questionnaire based on sensory descriptors and an exam. Each item is scored on a binary scale with a minimum score of 4 out of 10 for the diagnosis of NP. An even shorter 7-item questionnaire is available as well (the DN4-interview), with a cut-off score of 3 out of 10 for NP diagnosis. Although the DN4 has been translated into English, psychometric tests have only been performed in France and formal validation and reliability tests on the English version are needed. However, initial data did show substantial inter-rater reliability (kappa of 0.70–0.96) and strong face validity (90–95%). This questionnaire indicates that sensory descriptors alone may be sufficient for NP vs. non-NP diagnosis, and it is significantly different than the Neuropathic Pain Questionnaire (NPQ) and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) discussed below.

3.2.2. Neuropathic pain scale (NPS)

This scale was developed to track and measure different NP qualities or descriptors such as intense, sharp, hot, dull, cold, sensitive, itchy [23]. Using these subjective pain descriptors, the authors suggest that the NPS can determine the status or change in NP. This scale is a self-report of 10 different pain quality items rated on a 1 to 10 scale; with one item related to the time quality of the pain. Each item was originally designed to be used independently and not summed into a total score, but later studies by this group used composite scores [24]. Initial results of the NPS show that it is able to discriminate between different categories of NP, and is sensitive enough for use in treatment studies [24–26]. Additionally, initial studies showed positive descriptive validity and substantial reliability with a Cronbach's alpha of 0.86–0.92 [24]. This scale has been used in a large number of NP patients in general, and it has also been tested specifically in the SCI population for changes in NP states [27]. There is also a Neuropathic Pain Scale-Revised (NPS-R) that includes 7 additional pain qualities than those in the original NPS. This scale does not discriminate between NP and NNP (or nociceptive pain).

3.2.3. Leeds assessment of neuropathic signs and symptoms (LANSS)

This pain scale was developed in the UK to differentiate NP from nociceptive pain using several sensory pain descriptors and a bedside sensory dysfunction examination. It consists of 7 yes/no items with scale scores associated with each yes answers. Five items are self-report with the other two involving clinical examination. A score of 12 or higher out of 24 signifies NP. Initial validity showed that the LANSS scale was able to correctly identify 82% of patients with 85% sensitivity and 80% specificity. There is also a self-completed version of the LANSS (S-LANSS) available with similar specificity and sensitivity (74% and 75% respectively) [28]. Interrater reliability was substantial with a Cronbach alpha of 0.72–0.81. However, due to the potentially impaired sensation in SCI patients, this scale has been questioned as whether it is valid or not for SCI patients with NP.

3.2.4. Neuropathic pain questionnaire (NPQ)

This 12- item questionnaire is like the NPS, with a few additional descriptors. In addition to discriminating between NP and NNP, it also has areas for changes in pain severity and change [29]. Initial studies showed that the predictor variables with sensitivity of 74.7% and a specificity of 77.6%. Although the authors designed this questionnaire to also test NP changes, to date, there are no published reports regarding its sensitivity or reliability. There have been no specific studies using this questionnaire for SCI patients with NP, but it has been noted that 2 persons with SCI were included in the sampling groups during the development of the questionnaire [30]. There is also a 3-item version of this questionnaire called the NPQ-short form (NPQ-SF) [31]. This is used for NP vs NNP discrimination only and includes the bare bones of pain descriptors.

3.2.5. Neuropathic pain symptom inventory (NPSI)

This self-administered questionnaire was developed by French authors to satisfy the need for a simple, and easy-to-understand tool that is able to evaluate the different parameters of NP [32]. The NPSI consists of 10 descriptors specific to NP and 2 items that assess the duration of spontaneous ongoing and paroxysmal pain. Scores are then summed for a total intensity score (out of 100). In this regard the authors suggest that the NPSI is sensitive to pain treatment effects/changes. Although the NPSI looks like the NPS, it differs in several specific pain descriptors, and the authors recommend its use for documenting pain treatment effects/changes and should be used in parallel to the NPS. Psychometric analysis from the initial study indicated that it had good face validity and both the short and long term test-retest reliability of the NPSI was very high with intraclass correlation coefficients ranging from 0.81–0.98 for each of the items. The NPSI has been translated and validated in a few other studies with good results, but it has not specifically been validated in the SCI population [33–35].

3.2.6. Spinal cord injury pain instrument (SCIPI)

This is the most current screening tool for differentiating NP from NNP in the SCI population [36]. In many regards the SCIPI has significant overlap to the DN4, LANSS and NPQ. What distinguishes it from the others is the inclusion of pain characterization specific to those with SCI (i.e. pain is characterized as being constant, unchanged and/or occurring in insensate areas). A score of 1 is given for each positive answer with a total score of 4. A score of ≥ 1 indicated the presence of NP but a cutoff of ≥ 2 was mentioned to be more appropriate for maximizing sensitivity in practice. The initial study indicated sensitivity and specificity to be 0.72 and 0.76, respectively. Although the DN4 has stronger overall psychometrics, the authors mention that the major advantage of the SCIPI over the DN4 in SCI patients is that it does not require in person screening. It is also important to note that this tool determines the presence of NP, and cannot measure or assess different NP states. Further studies are required before this tool can be universally accepted.

4. Treatment of neuropathic pain in SCI

There is a broad range of pharmacological and non-pharmacological treatments available to patients with SCI and NP. Each of these treatments has different cost/benefit profiles and they target different parts of the pain pathway. Due to the complex nature of NP, this means that there is no ‘one size fits all’ approach when it comes to treatment. Although many of the medications for NP are frequently well-tolerated, some of them also have harmful or uncomfortable side-effects. Caution must always be exercised when dealing with such medications. Similarly, non-pharmacological treatments such as spinal injections, intrathecal pumps, and other surgical procedures should only be considered after pharmacological treatment attempts. In this section, we discuss some of the most widely known pharmacological and non-pharmacological treatments available for SCI NP.

4.1. Antiepileptics

Gabapentin and pregabalin are two of the most popular drugs

currently used within this group, replacing older agents such as valproate, carbemazepine, and phenytoin. These older agents can still be used, but their administration is complicated by higher risk of serious side effects, and they often need frequent toxicology monitoring.

Pregabalin is currently approved for the treatment of NP in > 100 countries. In the United States, it has been FDA approved for the treatment of pain due to diabetic peripheral neuropathy, postherpetic neuralgia, fibromyalgia, and as of 2012, NP related to SCI. A few studies have demonstrated the efficacy of pregabalin over placebo in patients with NP and SCI and it is generally well tolerated [37,38]. Pregabalin does have a black box warning for the rare, but serious, side effect of suicidal ideation in a very small percentage of patients. Despite this, pregabalin is still considered a first line treatment.

Gabapentin is also widely used for SCI patients with NP. Various studies have been conducted to examine the effectiveness of gabapentin in the treatment of NP after SCI, however results have been mixed. A recent systematic review was able to demonstrate large improvements for NP using gabapentin monotherapy in patients with SCI [39]. Furthermore, like pregabalin, gabapentin has an improved safety profile over the older antiepileptic agents. Common adverse reactions of gabapentin are also like those of pregabalin and caution must be exercised in patients with renal insufficiency when dosing gabapentin. Dosing adjustments must be made once creatinine clearance falls below 60 mL/min [40]. Recently, the combination of intravenous ketamine and oral gabapentin was evaluated in a double-blind, randomized, controlled trial in SCI patients with NP [41]. This study showed a marked improvement in average pain scores in comparison to the placebo group [41,42]. It has also been suggested that morphine and gabapentin are beneficial for NP in general [43].

Lamotrigine was considered a first-line agent in NP [44] prior to the emergence of pregabalin and gabapentin. A randomized controlled trial (RCT) on lamotrigine in SCI patients with NP was able to demonstrate a reduction in spontaneous and evoked pain in patients with incomplete SCI only [45].

Anticonvulsants (phenytoin and carbamazepine) along with other older-generation anti-epileptics (phenobarbital and valproic acid) have fallen out of common use due to their unfavorable metabolic and interaction profiles. Moreover, there is limited evidence that any of these medications can exert significant, lasting benefits for patients with SCI and NP [44]. Topiramate is a broad-spectrum anti-convulsant. One case study has suggested that topiramate may be an effective treatment in the SCI population [46], but more studies are needed before its' efficacy for SCI NP can be determined. Interestingly, a side-effect of topiramate is significant weight loss [47] and patients taking topiramate may also experience parasthesias, which can further complicate the clinical picture in patients with SCI.

4.2. Tricyclic antidepressants

Tricyclic antidepressants (TCAs) lead to increases of serotonin, norepinephrine and weak NMDA negative allosteric modulators in the CNS, thereby modulating afferent pain signal pathways. Tricyclics have been found to be effective in the treatment of a number of chronic pain conditions and are also considered to be first-line treatments in patients with NP [48,49]. While these medications tend to be well tolerated, physicians and patients should be aware of various side-effects which are associated with the serotonergic, noradrenergic, and antihistaminergic properties of TCAs such as bladder retention, prolonged QT interval and sedation. Dosing these medications at night can minimize the interference of these side effects on a patient's daily life. Additionally, patients who are taking TCAs concomitantly with other antidepressants such as selective serotonin reuptake inhibitors (SSRIs), or the codeine analog tramadol, are at higher risk of developing serotonin syndrome. Precaution should be taken when prescribing tricyclics under these conditions. The only documented TCA that has been studied in patients with SCI is amitriptyline. One RCT in patients with both neuropathic and musculoskeletal SCI pain found no significant differences in pain intensity, or pain-related disability between groups treated with amitriptyline versus placebo [50]. Another, more recent study, found amitriptyline to be efficacious in relieving at-level or below-level NP, but only in a subgroup of patients with high scores for depression [51]. Given that amitriptyline is relatively well tolerated and safe, it is considered a viable option for SCI patients. Secondary amine tricyclics (nortriptyline and desipramine) cause less sedation and fewer anticholinergic effects compared to amitriptyline, but they have not been studied in SCI patients.

4.3. Opioids

Opioids are one of the most classically used pain medications and they exert their therapeutic effects through modulation of both central and peripheral pain pathways via inhibition of pain perception. While opioid medications are potent analgesics, their use in both chronic pain and NP remains controversial due to various physiological, pathological, and psychosocial issues that can arise with their use. In general, opioids are not commonly recommended for the treatment of patients with SCI and NP [52]. However, a randomized controlled trial using intravenous morphine and alfentanil were able to demonstrate significant reductions in NP following SCI [53]. Methadone has also been cited as a promising treatment for its NMDA antagonist action and it has been shown to be effective for NP that is resistant to conventional analgesics [54,55]. However, a recent Cochrane review stated that methadone use for non-cancerous pain is controversial [56,57]. Indeed, the evidence is sparse regarding the use of specific oral or transdermal opioids in the treatment of NP from SCI.

The use of chronic opioid analgesic therapy must be approached cautiously due to a range of negative side effects. The most common adverse events reported with opioid use include constipation, sedation, development of tolerance, physical and psychological dependence, development of opioid-induced hyperalgesia, and the possibility of death due to overdose. Moreover, patients using long-term opioids may develop endocrine abnormalities, including decreased testosterone, progesterone, estradiol, and reduced cortisol response to stress [58].

Tramadol, considered to be a less potent opioid agonist with less abuse potential and an effective analgesic, is a potential replacement for traditional opioids. One RCT performed on patients with at-or-below level NP after SCI was able to demonstrate improvements in pain when taking tramadol, versus placebo [59]. The authors suggested that tramadol might be a second-line option for SCI patients with NP who have not responded to gabapentin, pregabalin, or other TCAs. However, tramadol lowers the seizure threshold and can contribute to the development of serotonin syndrome when combined with SSRIs, SNRIs, or TCAs. Therefore, caution should be taken when considering its use especially for patients with depression. Older patients and those with renal or hepatic impairment should be treated with reduced dosages as well.

4.4. Cannabinoids

Cannabinoid receptors modulate a variety of physiologic processes, including pain, mood, and memory. Cannabinoids have received a lot of attention in recent years because a number studies have shown its analgesic effects for non-cancerous pain [60]. While cannabinoids tend to be well-tolerated with mild, transient side effects, questions remain about its use for NP following SCI. One study comparing dronabinol against an active placebo (diphenhydramine) found no significant difference in relief of below-level NP [61]. Yet another study using a cannabinoid analog showed significant improvements in NP, although those with SCI NP were small (n = 3) [62]. For now, this class of medications continues to remain unproven as a reliable analgesic for NP following SCI.

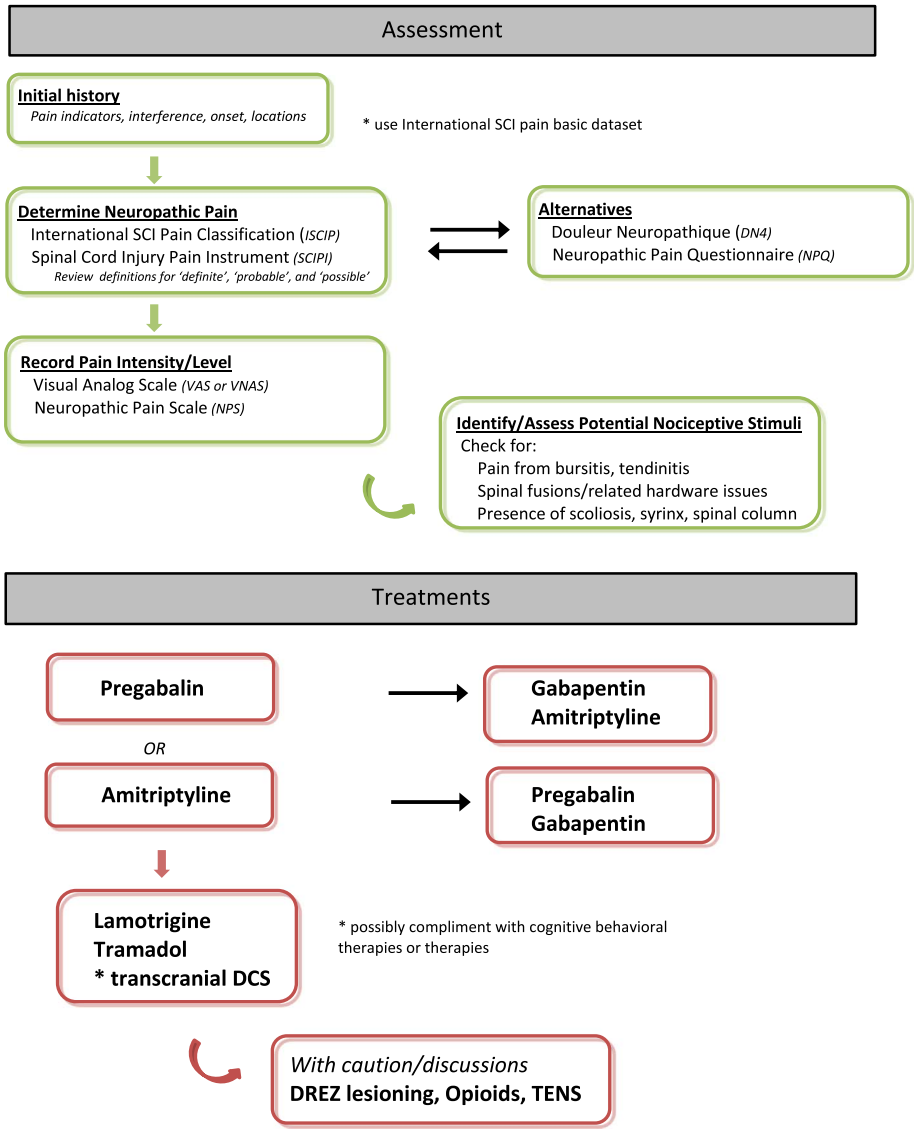

Fig. 2. Assessment & Treatment Recommendations for Neuropathic Pain due to Spinal Cord Injury.

4.5. Advanced interventional therapies

Following the success of intrathecal delivery of baclofen for treatment of spasticity associated with SCI [63], intrathecal pumps started being used for NP as well. However, a recent systematic review stated that although intrathecal baclofen has been shown to be beneficial for musculoskeletal pain associated with spasticity in SCI patients, its effectiveness for NP is still largely conflicting [64]. Interestingly one study on the administration of intrathecal clonidine and oral baclofen did show some benefits in pain management [65]. Two other studies have indicated that combinations of intrathecal medications besides baclofen may be of benefit to SCI patients with NP. Notably, combining intrathecal hydromorphone and ziconotide in SCI patients with NP was found to significantly reduce pain [66], and another study found synergistic analgesic effects on both at-level and below-level NP using intrathecal delivery of morphine and clonidine [67]. Although these results are compelling, they are both case reports and insufficient evidence exists at this time to recommend its use for NP in SCI patients [68].

4.6. Invasive and surgical procedures

Pharmacotherapy may not be sufficient to relieve pain in all SCI patients with NP. In these cases, the use of invasive and surgical procedures may be effective in producing more definitive pain relief.

Nerve block injections (epidurals, stellate blocks, lumbar sympathetic blocks, peripheral nerve blocks) have long been established as providing highly effective, albeit transient, pain relief in NP secondary to spinal conditions such as radiculopathy and spinal stenosis. This procedure appears to confer the most benefits to SCI patients who have at-level NP, or when used to treat NP from radiculopathies above the level of injury [69]. The longevity of the analgesic effect, however, is often limited to less than a year and carries several metabolic, endocrine, immunologic, and psychological side effects. This treatment must be used with caution, or avoided altogether, in patients with underlying diabetes mellitus, osteoporosis, cancer, immunocompromised states, and psychiatric illness. In addition, any procedure involving the spine always carries a small risk of further iatrogenic neurologic injury from the procedure itself.

Dorsal root entry zone (DREZ) ablation treatments, such as DREZ lesioning and microsurgical DREZotomy provide pain relief by targeting the nociceptive fibers of the lateral horn of the dorsal rootlet, the medial portion of the Lissauer tract, and the deafferentiated neurons of the dorsal horn [70]. One caveat to the use of this procedure is that it is only considered a treatment option in patients with complete SCI, as patients with incomplete SCI would have a high risk of losing preserved

function below the level of injury [71]. A systematic review of the use of the DREZ procedure for NP after SCI showed that this treatment may be most effective in patients with specific segmental (dermatomal) pain, as opposed to diffuse pain [72].

Spinal cord stimulation (SCS) is a minimally invasive and reversible therapy for the treatment of NP in SCI [73,74]. A systemic review found that SCS are more effective than conventional medical management in patients with NP from a variety of disorders [75–77]. However, the data on the use of SCS for NP after SCI is limited, making the use of this treatment controversial [78].

4.7. Other non-pharmacologic treatments

The long-term use of medications often increases their potential for adverse or side effects. As such, there is great interest in non-invasive interventions. However, recent analysis shown that many do not have strong evidence yet to support recommended use in SCI NP [79,13,80]. However, here we mention a few worth discussing.

A few clinical studies exist on the use of transcranial direct current stimulation (tDCS) in patients with SCI-related NP [81–83]. Two studies show significant reductions in pain intensities compared to controls [81,82], however one on those with long-term NP showed no difference [83]. It is possible that tDCS is most beneficial in those with acute or newly diagnosed NP.

Recent studies in transcranial electrical stimulation (TES) and transcranial magnetic stimulation (TMS) have demonstrated a modest improvement in post-SCI pain. A systematic review of multiple types of physical treatments stated that TES and TMS may be very promising techniques in providing short and long-term pain relief in patients with NP after SCI but evidence is weak or conflicting at this point [68,79,84,85]. This same study also stated that, while generally considered safe for use, treatments such as osteopathy, acupuncture, and transcutaneous electrical nerve stimulation (TENS) have not demonstrated definitive benefit. This review also showed that psychological therapies such as cognitive behavioral therapy, hypnosis and visual imagery may be of use in alleviating psychological distress associated with pain.

5. Conclusion and recommendations

NP continues to negatively influence the lives of a high percentage of patients with SCI. Despite various treatment attempts, it is still a very difficult condition to treat and many patients continue to live with persistent pain. At this point in time, there is no singular or definitive treatment plan for patients who suffer from NP. However, we have provided recommendations for NP assessment, and treatment (Fig. 2) accompanied by our discussion below. Please note that these are not evidence-based decisions, as more research is required for that. However, our recommendations for identifying and treating NP were based on current scientific evidence, clinical experience and recently published recommendations from specialty pain groups. Multidisciplinary recommendations that incorporate non-pharmacological treatments, like cognitive behavioral therapy, have also been recently published [86], but is beyond the scope of this review.

5.1. Recommendations

In 2014 the National Institute of Neurological Disorders and Stroke (NINDS) developed data collection standards for clinical studies being performed in SCI. These Common Data Elements (CDEs) are classified as core, highly recommended, supplemental, or exploratory and span SCI patient histories, physical or laboratory assessments, and a wide range of outcomes [87]. Although designed for research purposes, many of the recommended CDEs for SCI and pain should also be collected when first identifying NP (and a few when tracking treatment efficacy). When identifying NP for the first time in an SCI patient, a complete and detailed history of the patient's pain should be obtained. This includes pain indicators, pain inference, onset, and location(s). All of these can be recorded using the most recent version of the International SCI pain basic dataset [14].

The second, and most critical, step is the distinction between nociceptive and neuropathic pain. This can be particularly difficult because SCI patients can experience multiple types of pain at a single time [5,88]. The ISCIP classification scheme or SCIPI measurement tool should be used for NP determination. If this is not possible for some reason, the DN4, or NPQ (in that hierarchal order) can be used as substitute. Additionally, because identifying NP is so problematic, a review of the ‘definite’, ‘probable’ and ‘possible’ grading system developed by Treede and colleagues is highly suggested [89,90]. As mentioned in a recent review, it is important to note that abnormal sensations below the level of injury are common in SCI patients regardless of nociceptive or neuropathic pain, and so not all pain located below the level of injury should be labeled as ‘definite’ NP (an illustrative example is provided in the paper) [80]. After the identification of pain type, pain intensity via visual numeric scale (or a related pain scale), as well as the NPS for NP states should be recorded. These will help determine a baseline prior to treatments.

The next step in SCI NP management is to prevent windup or plasticity changes in the central nerve system that may lead to chronic NP. Any reversible nociceptive stimuli such as musculoskeletal pain from bursitis, tendinitis, etc. should be addressed first. In situations where spinal fusion has been performed, the integrity of the fusion site as a possible pain generator should be assessed prior to pharmacological treatments. Pain may arise from the hardware or the fusion itself that can complicate a patients overall clinical picture. Evaluations for spinal abnormalities such as scoliosis, post-traumatic syrinx and spinal column scarring may also be warranted. In some of these situations surgical interventions to correct these might be considered before continuing with progressive NP management in SCI patients.

Once these have been assessed or corrected, pharmacologic agents may be introduced. We typically use newer antiepileptics such as pregabalin and gabapentin, or low-dose TCAs such as amitriptyline or nortriptyline (please see cautions for TCAs in above sections) as the first line of pharmacologic agents. These recommendations are consistent with NeuPSIG recommendations [12] as well as other SCI expert groups [13,80,91]. If the pain is not sufficiently controlled by one of these agents, we recommend switching to a medication within the same class to see whether one type works better than another. For example, we typically start with pregabalin or amitriptyline If the patient experiences unsatisfying relief of pain with one of these, we would first switch from pregabalin to gabapentin (or possibly lamotrigine), and then cross categories (i.e. antiepileptics to amitriptyline or vice versa). If these fail, even after dose escalations, then we move to tramadol. Although some have recommended tDCS as a fourth-line treatment [13,80], until further studies are done we recommend limiting its use for now [92]. We reserve opioids as a last resort, used only after various medications or therapy failures. If medications and alternative therapies do not adequately control the pain, or if side effects from medications are intolerable, a discussion with the patient regarding invasive interventions such as intrathecal pump, injections, or other surgeries, is warranted. Indeed, for complete injuries DREZ lesioning could be extremely beneficial. Although there is some talk that these surgeries and treatments may have a place in first line NP management, research doesn't exist to support this yet.

Since pain often has a psychological component, we also believe that cognitive behavioral therapies (CBTs) will make their way into NP pain management in SCI. Studies indicating the effectiveness of therapies, like mindfulness and other CBT, for those with chronic conditions are just now emerging [86,93,94]. Although it is unlikely that these will be effective in significantly reducing NP for SCI individuals on their own, it could be an impactful addition to a patient's overall pain management plan.

6. Final thoughts

Although the hope is that one, or more, of the recommendations above enables reliable pain relief, the reality is that many SCI patients continue to suffer from NP despite ongoing treatments. The reason for this is multifold. The first issue is the translational barrier between jumping from effective treatments in animal models to human efficacy. Current animal models for NP in SCI do not properly mirror the clinical condition. These issues are discussed in eloquent detail in a recently published review [15]. In short, there are significant differences in the way SCI NP in animals are modeled and assessed. For example, animal models predominately use thoracic injuries (93%), yet recent studies show majority of SCI patients have cervical injuries [95]. Indeed, a larger portions of individuals with tetraplegia report NP compared to paraplegia (50% vs 18%) [6]. Additionally, majority of NP animal models focus on below-level allodynia (72%), yet recent clinical studies report ~37% and 35% of SCI patients have at-level and below-level NP respectively [6,96]. Animal models also lack the ability to assess spontaneous pain, of which as much as 86% of SCI patients report as spontaneous [96]. Animal models also almost completely ignore the accompaniment of traumatic brain injury, or peripheral nerve damage that occurs in clinical SCI, both of which impact or influence NP.

Variations in the delineation of origin and pathophysiology of NP also exist. Complicating the situation is that both central and peripheral mechanisms have been implicated in NP and we have limited knowledge on where and how the central and peripheral mechanisms crossover and contribute to pain. Without this, the identification of more precise (and possibly more efficacious) medications or surgical procedures cannot be reliably determined. Instead, we are left with several medications that work on the general pathways of pain (not even NP specifically). This is the contributing factor in why some medications work for small subsets of SCI patients. There are also studies that show persistent NP results in anatomical changes in the brain (specifically in the pain regions) [97,98]. This may permanently alter a patient's ability to respond to various pharmacological agents or therapies. Thus, intervening prior to these “windup” or alterations is extremely important. More research on the pathophysiology of NP, especially in the context of SCI, is clearly needed.

The second issue relates to the variable nature by which clinicians and researchers define, classify and measure pain. As noted earlier, an ever-expanding number of different classifications systems and measurement tools for NP have been developed in the past, and almost none of them were specific for the SCI population. These differences in pain definitions and identification leads to differences in pain diagnoses, which can significantly change a patients' pain management plan, and subsequently their potential for proper pain relief. It also makes findings from clinical studies and trials almost impossible to compare. The recent development of the ISCIP and SCIPI will go a long way to fill these gaps by unifying the field in defining and diagnosing NP, but only if they are adopted universally.

The last issue that we will mention is this review is the difficulty in running clinical trials for SCI patients with NP. Even with the advent of better classification tools, better knowledge of the evolution of NP, and more directed therapies, running the large-scaled clinical trials needed is very difficult. This is partially because there are very few places with specialized SCI care. Thus, to meet the standards of a large sample size, a concerted effort must be spent on recruitment. The other limitation lies in the fact that the number of people with SCI (and NP) for recruitment into a trial is relatively small in comparison to other diseases. Large scaled, well-designed clinical trials are therefore possible, but will take longer to run in this population. There is also discussion as to whether smaller, more focused, trials on the various subsets of SCI NP patients would be more beneficial [80,99].

Despite these challenges, the field is still making beneficial progress as many clinicians and researchers are currently tackling these issues. Indeed, the field seems to be making a concerted effort to work together to help move the advent of newer, better therapies and treatments for NP forward.

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