Diagnostics and Treatment of Pain in Spinal Cord Injury

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Abstract

Pain has various manifestations in spinal cord injury (SCI) that depend on multiple factors such as the affected tissue. Neuropathic pain is common, and nociceptive pain is frequently seen as a consequence of complications like overstraining of joints or bowel dysfunction and mainly presents as musculoskeletal and/or visceral pain.

Both, peripheral neuropathic pain, as a result of lesions to nerve roots, and central neuropathic pain, due to lesions of the spinal cord occur in SCI. It is classified as at-level or below-level pain. Neuropathic pain, which is not or indirectly related to SCI, such as carpal tunnel syndrome, is termed "other" neuropathic pain. There is limited knowledge of the underlying mechanisms in SCI-related neuropathic pain. It often develops into a chronic condition, having a crucial impact on the patients' quality of life.

Therapy of neuropathic pain includes antidepressants and anticonvulsants. Some patients experience insufficient pain relief and may experience undesirable side effects. Promising non-pharmacological therapeutic approaches beyond psychological support/therapy, like neurostimulation, are being investigated.

For treatment of nociceptive pain, it is important to identify the underlying causes and to tailor the treatment individually. Its therapy may involve different approaches comprising physiotherapy, medical treatment, including spasmolytic drugs, as well as interventional treatment.

This chapter will focus on the most relevant aspects of SCI-related pain, including epidemiology, impact on physical and psychosocial functioning, potentially underlying mechanisms, and important diagnostics. We will discuss the latest scientific knowledge and discuss the prediction, prevention, and treatment of pain in SCI.

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12.1 Background

Pain is one of the most challenging complications of spinal cord injury (SCI), with serious consequences for the patients [1–3]. Once pain has developed, it has a long-term negative impact on the patients' quality of life [3, 4]. The onset of pain is usually within the first year after the injury. The pain frequently increases over time, and more than 50 % of SCI patients develop chronic pain during the course of disease [5, 6]. Three to five years following injury, musculoskeletal pain is present in about 60 % and neuropathic pain in 50–60 % of SCI patients [7, 8]. Depending on the study design and based on considerable heterogeneity in assessing pain in SCI, its prevalence is reported with a wide variance between 26 and 96 % [9, 10]. Patients suffering from cauda equina lesions more frequently complain of severe pain compared with paraplegic patients having a thoracic level of injury or tetraplegic patients [11–13]. Nevertheless, the predictive relevance of aspects such as the level or completeness of injury is still the subject of discussion, especially in neuropathic pain types [7, 10].

12.2 Characterization and Classification of Pain Following SCI

Pain has different qualities or descriptors. The word "aching" is commonly used to describe musculoskeletal pain, whereas "burning" is typically associated with neuropathic pain [11, 14–16]. Nevertheless, this approach is not enough to capture the complex nature of the pain presentation in SCI and cannot be used to differentiate between nociceptive and neuropathic pain, especially since nociceptive pain is represented not only by musculoskeletal but also by visceral pain and other pain subtypes. Furthermore, an overlapping of different pain types and subtypes in SCI patients is a common phenomenon [17–19]. Meanwhile, numerous diagnostic tools have been developed, including questionnaires, physical examination, or even instrument-based tools, addressing a more sophisticated and accurate evaluation of the different pain types (for details please see Sect. 13.5).

Recently, an international consensus classification of pain after SCI "the International Spinal Cord Injury Pain (ISCIP) Classification" was published [20, 21]. The classification is based on three tiers: "pain type," "pain subtype," and "pain source" or "pathology," respectively (Table 12.1). The first tier classifies pain into nociceptive, neuropathic, other, and unknown pain. Other pain is pain that cannot be classified into the categories nociceptive or neuropathic, e.g., irritable bowel syndrome or fibromyalgia. In contrast, unknown pain can neither be assigned to any of the above-listed categories nor be related to a specific pain syndrome. The second tier subdivides nociceptive pain into musculoskeletal, visceral, and other nociceptive pain, and neuropathic pain into SCI-related pain (at level or below level) and other neuropathic pain. Possible underlying causes of all subtypes of pain are accordingly summarized within the third tier.

Table 12.1 The International Spinal Cord Injury Pain (ISCIP) Classification [23]

Tier 1	Tier 2	Tier 3
Nociceptive pain	Musculoskeletal pain	*For example* Articular trouble/joint pain Fracture-associated pain Spasm-related muscle pain Back pain/lumbago Pain related to heterotopic ossification
	Visceral pain	*For example* Angina pectoris Constipation/ileus Cystitis/pyelonephritis
	Other nociceptive pain	*For example* Pressure sore-related pain General wound pain Headache due to migraine or autonomic dysreflexia
Neuropathic pain	SCI-related pain	*For example* Spinal cord contusion/compression Spinal ischemia Nerve root compression Cauda equina compression
	At-level SCI pain	
	Below-level SCI pain	
	Other neuropathic pain	*For example* Brachial plexus injury Entrapment syndromes (i.e., carpal tunnel syndrome, ulnar nerve entrapment) Generalized nerve damages (i.e., metabolic nerve damages, inflammatory polyneuropathies)
Other pain		*For example* Fibromyalgia Complex regional pain syndrome (CRPS)
Unknown pain	Pain that can neither be assigned to any of the above-listed categories nor be related to a specific pain syndrome	

12.3 Nociceptive Pain

Painful stimuli to body tissue, whether mechanical, thermal, or caused by ongoing pathological processes within specific organ structures (e.g., inflammation), activate nociceptors and generate nociceptive pain. For a detailed overview of the neurobiology of pain and peripheral mechanisms of cutaneous nociception in particular, please see [22].

12.3.1 Clinical Characteristics of Nociceptive Pain

Nociceptive pain is the most frequent type of pain in individuals with SCI [7]. It is possible to differentiate between the types of pain by determining pain quality/

characteristic, distribution, clinical course, and responsiveness to any therapeutic approach. Nociceptive pain may respond well to a variety of different therapy strategies including surgical/interventional, pharmacological, and physical therapy. Its etiology can be assigned to three different subtypes:

1. *Musculoskeletal pain* is a leading cause of nociceptive pain in the chronic phase of SCI. It is described as either above, at, or below the neurological level of injury, i.e., the most caudal segment with fully preserved neurological function [23]. This type of pain has various causes and thus could accrue from overuse of joints, ligaments, and tendons, as well as be due to a reduced functional use of joints resulting from a lack of muscular stabilization and/or muscular imbalance in tetraplegic patients [24–27]. It can also present as fracture-related pain, as pain resulting from heterotopic ossification, or as a consequence of spasticity [28]. The perception of musculoskeletal pain is often restricted to the involved body region and lesioned tissue, respectively. This type of pain can usually be provoked by manipulation of the affected region. A related example would be the tenderness on palpation of a fracture.
2. *Visceral pain* is also a common cause of nociceptive pain in the late chronic phase of SCI and is typically located within the chest (thorax) or in abdominal/pelvic structures, as it is attributed to either disinhibited/increased or inhibited/attenuated activation of the circuitries within the autonomous nervous system [3, 23]. Although evidence-based insights in the underlying mechanisms of abdominal pain are still sparse, recent reports support the already existing notion that constipation is a leading factor [29]. This goes in line with the finding that visceral pain has a late onset, often many years after the SCI [7, 30]. Its clinical presentation is generally diffuse and can be highly unspecific after SCI. While individuals with paraplegia may describe visceral pain as "cramping," "dull pressing," or "causing nausea" similar to nondisabled persons, patients with tetraplegia and visceral pain might in contrast present with complaints that are hardly referable [28]. Thus, symptoms may diminish to nonspecific clinical signs like a general feeling of discomfort/malaise. Important information could be derived from instrument-based or laboratory proof of usual triggers of visceral pain, such as the involvement of the bowels (e.g., constipation/ileus) or the urinary tract (e.g., cystitis) [3], but also a temporal link of pain to increased activity of visceral organs (e.g., postprandial pain) could lead the way to the accurate classification. If there are no clear indications of visceral involvement, another type of pain, such as neuropathic pain, could be present. Here, a permanent presence of pain may support the diagnosis of neuropathic pain.
3. *Other nociceptive pain* is pain that cannot be allocated to the aforementioned subtypes. They may be related or unrelated to SCI, but should fulfill the criteria of nociceptive pain [23]. Those, for instance, include pain due to pressure ulcer or headache as a consequence of autonomic dysreflexia.

12.4 Neuropathic Pain

Neuropathic pain represents a significant socioeconomic burden – both at individual and societal levels, as it is associated with high levels of morbidity and large direct and indirect costs [9, 31]. Neuropathic pain is not a term applied to a single underlying mechanism or disease, but describes a syndrome of various sensory symptoms and signs (e.g., spontaneous ongoing pain, allodynia, and painful attacks). Allodynia is pain due to a stimulus that does normally not provoke pain (e.g., pain evoked by light touch or cold) [32]. Hyperalgesia, which is an increased response to a stimulus that is normally painful [32], may also be present on examination and is differentiated according to the test stimulus (e.g., cold, warm, punctuate, or static mechanical). In general, neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system [33]. It is divided into peripheral and central neuropathic pain depending on whether the lesion or disease is in the peripheral (nerve root or nerve) or central (brain or spinal cord) nervous system.

Following SCI, patients may experience central neuropathic pain due to the spinal cord lesion or peripheral neuropathic pain due to a lesion or compression of the nerve roots, including cauda equina. Because of the difficulty in distinguishing between peripheral and central pain in some cases, neuropathic pain following SCI is classified into *at-level* and *below-level* neuropathic pain [23]. Patients with SCI may have *other* neuropathic pain, which is pain that is not caused by the SCI but instead by, e.g., thoracotomy due to intercostal nerve injury or carpal tunnel syndrome due to wheelchair use. Other neuropathic pain can be located at, above, or below injury level.

12.4.1 Clinical Characteristics of Neuropathic Pain

At-level neuropathic pain is located anywhere within the dermatome of the neurological level of injury and/or three dermatomes below this level [23]. Pain caused by damage to the cauda equina is always classified as at-level pain, also in cases where it extends more than three dermatomes below the neurological level. *Below-level* neuropathic pain is located in the region more than three dermatomes below the neurological level of injury, but may extend to the at-level area. Neuropathic pain is often described as shooting, pricking, squeezing, or burning. Allodynia – most often to touch or cold stimuli and hyperalgesia to pinprick or thermal stimuli – may be present.

Neuropathic pain following SCI may occur immediately at the time of injury but may also have a delayed onset up to several months. At-level neuropathic pain often has an earlier onset than below-level pain [7]. Neuropathic pain may diminish or resolve during the first year [34], but often becomes chronic, and patients who experience neuropathic pain at 6 months are likely to have neuropathic pain with the same intensity 5 years after their SCI [7]. Paresthesia, which is described as abnormal sensations that are not painful or unpleasant, and dysesthesia, which is described

as unpleasant abnormal sensations, are often present following SCI, e.g., an ongoing tight sensation or a tingling sensation occurring either spontaneously or evoked by, e.g., touching the area.

Recent studies have found that early sensory hypersensitivity predicts later development of central pain [8, 35]. In one study in incomplete SCI, sensory hypersensitivity (mechanical allodynia and temporal summation of pain) and hyperpathia in the first months after SCI preceded ongoing below-level SCI pain [35], whereas in another study, early (1 month) sensory hypersensitivity (particularly cold-evoked dysesthesia) was a predictor of the development of below-level SCI pain [8]. Interestingly, sensory hypersensitivity did not predict at-level SCI pain, supporting that these two pain types are two different pain phenomena, presumably with different underlying mechanisms [7].

12.4.2 Mechanisms of SCI Neuropathic Pain

The mechanisms involved in SCI neuropathic pain are multiple and only incompletely understood. A SCI allegedly causes irreversible functional changes in the vicinity of the lesion site. These include neuronal hyperexcitability, impaired modulation from interrupted supraspinal control, and destroyed spinal circuitries. Insights from animal models indicate the presence of regenerative processes that are characterized by structural adaptions (e.g., rewiring of axonal connections) and changes in signal transmission on cellular level [36–39]. Besides its assumed linkage to spontaneous recovery after SCI, this so-called plasticity may also cause fundamental changes in the transmission of pain signals and therefore lead to detrimental effects with neuropathic pain as a possible consequence. Such neuronal changes include an increased sensitivity to sensory stimuli and a disturbed balance between excitation and inhibition. Ongoing spontaneous activity in central pain pathways rostral to the site of injury are thought to cause spontaneous pain, and neuronal hyperexcitability may cause increased pain to painful stimuli, decreased pain thresholds, aftersensations, and spread of pain. Central sensitization is defined as increased responsiveness of nociceptive neurons in the central nervous system to normal or subthreshold afferent input [32]. Several molecular changes seem to be involved, including changes in the N-methyl-D-aspartate (NMDA) and other glutamate receptors [40], sodium, calcium, and potassium channel expression [41, 42], glia cell activation and release of pro-inflammatory cytokines [41, 43–45], degeneration of inhibitory dorsal horn interneurons containing γ-aminobutyric acid (GABA) [46], and loss of inhibition from descending pathways, dependent on monoamines such as noradrenaline, serotonin (5-HT), and dopamine. Significant structural changes lead to reorganization, such as intraspinal sprouting of calcitonin gene-related peptides and substance P containing fine primary afferents and Rac1-regulated remodeling of dendritic spines on dorsal horn neurons [47–50].

There is evidence from human studies to support that the changes occurring at the injury site of the spinal cord are important for both at- and below-level pain. In some cases, spinal transection and dorsal root entry zone (DREZ) lesions may relieve both at- and below-level pain, suggesting that the area around the spinal lesion acts as a

pain generator. However, these procedures also carry the risk of development of central pain [51–53]. It has also been shown that sensory hypersensitivity at the level of injury and that the percentage of rostral gray matter lesions are highest in patients with below-level pain [54, 55]. It is hypothesized that ectopic activity arising at the rostral part, transmitted via multisynaptic propriospinal pathways, may also play a role in SCI pain [54]. Activity in residual spinothalamic tract neurons may additionally contribute to the generation of pain after SCI [56]. In addition to changes in neuronal excitability at the spinal cord level, changes can be demonstrated in different brain areas following SCI, e.g., the thalamus [57, 58], anterior cingulate cortex, right dorsolateral prefrontal cortex [59], and the somatosensory S1 cortex [60]. Furthermore, pain may be associated with a specific electroencephalography (EEG) signature with increased power in the theta and alpha bands in the relaxed state [61]. The specific role of these changes in generation or modulation of pain is unknown. In summary, neuronal hyperexcitability at the level of injury, spared polysynaptic pathways, and partially spared spinothalamic tract neurons, together with deafferentation resulting in abnormal neuronal brain activity, are possible mechanisms that are involved in the development and manifestation of SCI neuropathic pain.

Experimental models are crucial for improving our understanding of molecular SCI pain mechanisms and for testing new drugs. Assessing pain-like behavior in animals is, however, challenging [62], particularly after central nervous system lesions [63, 64]. Due to the development of the spastic syndrome, the specific assessment of pain-like behavior in rats with SCI cannot rely on the evaluation of simple reflexes and withdrawal thresholds but requires tests that involve brainstem-dependent responses such as licking, guarding, and escape or more complex, cerebrally mediated behaviors.

12.5 Diagnosis of Pain and Its Clinical Distinction

Considering its different manifestations and bearing in mind the potential overlapping of their symptoms, diagnostics of pain related to SCI are challenging [17–19]. Substantial impairment of sensory function below the level of lesion renders the interpretation of symptoms even more difficult.

Assessing the medical history of patients with pain should comprise an exact evaluation of all aspects of the symptoms including the course, impact, and multidimensional aspects of pain. The distribution of pain should be mapped on body charts. The pain intensity can be assessed using a categorical scale, such as mild, moderate, or severe. Other one-dimensional scales are often used, e.g., an 11-point numeric rating scale (NRS) from 0 to 10, where 0 indicates “no pain” and 10 “worst possible pain” or “most intense pain imaginable.” Average and worst pain is often assessed. Since not all sensory symptoms that could occur in neuropathic pain are constantly rated as pain (e.g., tingling), it may be useful also to assess unpleasantness. The character and quality of pain, its onset and time course, aggravating and alleviating factors, and associated symptoms should be included in the evaluation. The impact of pain on daily life refers to its impact on quality of life, function,

sleep, mood, and social relations. The International Spinal Cord Injury Core Data Set has been developed to assist physicians in collecting relevant data related to pain in a standardized way. The dataset includes classification, location, temporal aspects, intensity, impact, and treatment of pain [65].

Reliable and valid differentiation and classification of pain types are needed. Positive diagnostic criteria and a grading system of definite, probable, and possible presence of neuropathic pain have been published [66]. Four criteria need to be fulfilled for the definite presence of neuropathic pain: (1) a history of a relevant nervous system lesion, (2) at least one test confirming such a lesion, (3) pain located in an area of the body consistent with the location of the lesion, and (4) negative (e.g., hypoaesthesia) and/or positive (e.g., allodynia) sensory perception in the painful area. If the pain is not a primary consequence of movement, inflammation, or other local tissue damages and if it is described as burning, shooting, squeezing, painful cold, or electric shock-like or is associated with allodynia, it is likely to classify the pain as neuropathic pain [23]. Nevertheless, a careful examination to exclude other causes of pain is obligatory, and the correct classification of pain into neuropathic and nociceptive pain may still be challenging.

The neurological examination is essential for the diagnosis of neuropathic pain. The International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) serves as a reliable and valid basis for clinical examination of sensory and motor function [67], but it is recommended to perform additional sensory examinations including sensory thresholds to touch, vibration, pinprick, and thermal stimuli. Dynamic mechanical allodynia can be assessed by brushing the skin lightly using a small brush or cotton wool. Aftersensations, i.e., pain continuing after the stimulation has ceased, may be observed. More sophisticated assessments such as quantitative sensory testing (QST); electrophysiological examination using, e.g., laser evoked or contact heat evoked potentials (LEPs and CHEPS); and imaging (e.g., X-ray, CT, MRI) may provide additional insights [68].

Simple questionnaires have been developed for identifying patients with neuropathic pain. The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) scale [69], the Neuropathic Pain Questionnaire (NPQ) [70], the 10-item questionnaire DN4 [71], IDPain [72], painDETECT [73], and the Pain Quality Assessment Scale (PQAS) [74] are simple patient-based screening questionnaires partially with a short sensory examination that may help to detect the presence of neuropathic pain [75]. Recently, a spinal cord injury pain instrument (SCIPI) has been developed [76]. In most of the questionnaires, pricking pain, electric shocks, burning, numbness, and increased pain to touch are defined as indicators for neuropathic pain. These screening tools seem to have lower psychometric properties when applied to SCI patients than to the general population [77].

12.6 Psychological Aspects of Pain

Psychosocial factors may influence the patients' pain perception and subjective grading of pain. For example, affective disorders, level of independence from caregivers, level of social support, and a lack of efficient coping strategies are of

relevance in this respect and are reported to be associated with greater severity of pain [78–80]. These factors may cause a deterioration of pain or may result in greater psychological distress. It is therefore important to evaluate psychological functioning and the impact of pain on its clinical development. There is also existing evidence for effective psychotherapeutic therapy approaches in complementary treatment and coping of pain, respectively. Such strategies comprise self-hypnosis and biofeedback relaxation training, as well as cognitive behavioral therapy, generally embedded in a multimodal therapy approach [81–84].

12.7 Therapy

Treatment approaches in SCI-related pain range from physiotherapeutic measures through unspecific and specific pharmacotherapy to instrument-based approaches, all with significantly varying levels of evidence for the given indication. The diagnosis of pain type is the first important step. If possible, the underlying cause of pain should be treated, and when this is not possible, symptomatic treatment of the pain and the related disability should be offered. Realistic expectations about the outcome of a given treatment should be discussed with the patient. During the course of pain treatment, the level and character of the pain and side effects should be carefully monitored. When the pain has become chronic and is associated with disability, a multidisciplinary approach is preferred, and it is important to evaluate and treat any associated depression, sleep disturbance, and psychological distress. Disciplines, for instance, could comprise psychologists, physiotherapists, neurologists, and orthopedists/trauma surgeons and, if necessary, specialized pain therapists.

12.7.1 Treatment of Nociceptive Pain

Nociceptive pain is considered to be amenable to certain therapeutic strategies, including interventional but also nonsurgical and instrument-based therapies. The level of evidence for these approaches is varying to a large degree and sometimes it is very low.

Whenever possible, therapy should primarily focus on the elimination of the underlying causes, such as administration of laxatives, fracture treatment, wound care, or reduced stress on overused joints [85]. Surgical interventions addressing arthrosis or ankylosis of the shoulder joint in patients with paraplegia are subject to controversial discussions. Even though reported to be effective following a careful risk-benefit analysis and in consideration of the time and costs for the post-interventional rehabilitation period, such complex interventions should only be considered with caution in SCI patients due to a high risk for recurrent articular complaints [86–89].

The second mainstay of routinely applied therapy strategies is represented by mostly temporary pharmacological treatment. This approach includes nonsteroidal anti-inflammatory drugs (NSAID), such as ibuprofen or diclofenac, as well as other

non-opioid pain drugs, such as metamizole [85]. In markedly severe cases, opioids could also be an option for symptomatic pain therapy. The "WHO Treatment Guidelines on chronic nonmalignant pain in adults" are currently being developed, but not yet published [90]. Until then, the "WHO's cancer pain ladder for adults" may be used as orientation guideline, since it is a widespread clinical tool that is also commonly used in nociceptive pain management [91, 92]. However, there are still no evidence-based treatment recommendations based on randomized clinical trials in SCI, as well as in general pain therapy of adults. Individualized pain management concepts, based on the underlying pathology, should be considered in given cases [92].

Both aforementioned approaches should always be embedded in a multimodal therapy setting that comprehensively addresses the patient's complaints. Such supportive therapies primarily involve physical therapy, including general or symptom-oriented exercise programs [93–98]. Numerous further non-pharmacological and nonsurgical therapy approaches have already been tested in various studies and/or trials. Among them, acupuncture was found to have beneficial effects on musculoskeletal pain in SCI [99, 100]. However, it does not seem to be superior to the control interventions consisting of physical activity and sham acupuncture, respectively. Instrument-based therapies such as transcranial electrical stimulation (TCES) or transcutaneous electrical nerve stimulation (TENS) have also been tested, especially for their effect on general pain relief, which also includes musculoskeletal pain intensity. Thus, TCES and TENS admittedly delivered indications for efficacy in this context, yet existing clinical trials are few, methodically heterogeneous or not focused on SCI pain [101–108]. Furthermore, low or insufficient evidence of efficacy in SCI-related musculoskeletal pain has yet to be stated for conservative methods, such as massage, heat therapy, or behavioral management (e.g., hypnosis or cognitive behavioral therapy) [81, 109–112]. In consequence, if and to what extent such a therapeutical regimen should be added has to be decided on an individual basis.

12.7.2 Treatment of Neuropathic Pain

If possible, the underlying causes should be treated, but often symptomatic treatment is the only option. So far, no treatment has proven successful in preventing neuropathic SCI pain. It is important to exclude other causes of pain such as musculoskeletal pain and to consider factors that may aggravate neuropathic pain such as pressure sores, spasticity, or bladder infection. It is also important to evaluate the impact of pain on daily life, sleep and mood, psychological factors, and risk of suicidal ideation.

12.8 Pharmacological Treatment

The Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP) has recently updated the evidence-based treatment recommendations for neuropathic pain [34]. Based on the Grading of

Recommendations Assessment, Development, and Evaluation (GRADE) system, pregabalin, gabapentin, serotonin-noradrenaline reuptake inhibitors (SNRIs), and tricyclic antidepressants (TCAs) have strong recommendations for use in neuropathic pain. Opioids and a combination of selected first-line agents have weak recommendations, whereas there are weak recommendations against the use of cannabinoids and valproate and strong recommendations against the use of levetiracetam and mexiletine. No studies have examined the efficacy of nonsteroidal anti-inflammatory drugs (NSAID) and paracetamol in neuropathic pain. Certain topical agents are also recommended for peripheral neuropathic pain. Thus, NeuPSIG recommends pregabalin, gabapentin, SNRIs, and TCAs as first-line drugs, tramadol as second-line, and other opioids as third-line treatments for central neuropathic pain [34]. Data for other drugs such as NMDA antagonists and other anticonvulsants were inconclusive. However, a trial of such drugs, e.g., oxcarbazepine or lamotrigine, may be indicated in certain conditions and by pain specialists.

Randomized controlled trials (RCT) in SCI neuropathic pain support these recommendations (Table 12.2). Patients with SCI may, however, be particularly vulnerable to CNS-related side effects, including dizziness and somnolence, which may be due to their frequent use of spasmolytic drugs [113, 114]. It is also important to be aware that pain relief is moderate and only effective in a subgroup of patients.

Table 12.2 Summary of randomized double-blind, placebo-controlled trials with at least ten patients and with a treatment of at least 3 weeks

Study	Drug, final daily dose, number randomized	Outcome	NNT
Antidepressants			
[129]	Amitriptyline 150 mg, 38	p	ns
[130][a]	Duloxetine 60, 120 mg,	n	
Anticonvulsants			
[113]	Pregabalin 600 mg, 137	p	7.0 (3.9–37)
[131][a]	Pregabalin 600 mg, 40	p	3.3 (1.9–14)
[115]	Pregabalin 600 mg, 220	p	7.0 (3.9–31)
[132]	Gabapentin 3600 mg, 20	p	NA
[129]	Gabapentin 3600 mg, 38	n	
[133]	Levetiracetam 3000 mg, 36	n	
[134]	Valproate 2400 mg, 20	n	
[135]	Lamotrigine 400 mg, 30	n	
Miscellaneous			
[114]	Tramadol 400 mg, 36	p	ns
NCT01606202[b]	Sativex spray, 111	n	
[136]	Mexiletine 450 mg, 11	n	

NNT numbers needed to treat to obtain one patient with a 50 % pain reduction, *CPSP* central poststroke pain, *SCI* spinal cord injury, *p* positive, *n* negative, *NA* dichotomous data not available, *ns* no significant difference in numbers of patients with 50 % pain reduction during active and placebo treatment

[a]Included both SCI pain and central poststroke pain

[b]Data from clinicaltrials.gov

Pregabalin and gabapentin, including gabapentin extended release and enacarbil, are structurally related compounds. Their analgesic effect in neuropathic pain is thought to be mediated through antagonism of the $\alpha_2\delta$ subunit of voltage-dependent calcium channels at presynaptic sites. The most common side effects are somnolence and dizziness, which seem particularly bothersome in SCI [113, 115]. Other side effects include peripheral edema, nausea, and weight gain. Gabapentin is administered three times daily with slowly increasing dosage, e.g., starting with 300 mg the first day and increased by 300 mg every 1–7 days. The final daily dose is between 1800 and 3600 mg. Pregabalin is administered twice daily and slowly titrated from 75 or 150 mg daily to 600 mg daily. In SCI individuals with renal impairments, lower doses are used.

Antidepressants have a comparatively weaker body of evidence with regard to RCT but are also used in neuropathic pain treatment. These include TCAs (e.g., amitriptyline, imipramine, and nortriptyline) and SNRIs (duloxetine and venlafaxine), whereas the effect of selective serotonin reuptake inhibitors (SSRIs) is even less certain [34]. Antidepressants block the reuptake of noradrenaline and serotonin, and TCAs also have other actions such as a blockade of sodium channels. Side effects to TCAs include dry mouth, somnolence, constipation, urinary retention, orthostatic hypotension, and sweating. TCAs are contraindicated in patients with epilepsy, heart failure, and cardiac conduction blocks, and an electrocardiogram (ECG) is needed before initiating treatment. There is a large pharmacokinetic variability in the metabolic pathways of TCAs, and the final dose varies considerably among patients. TCAs should be slowly titrated stating with 10 or 25 mg daily up to 50–150 mg daily. Side effects to SNRIs include nausea, somnolence, dizziness, constipation, and sexual dysfunction. Duloxetine can be initiated with 30 mg and increased to 60 mg daily, while venlafaxine can be started at 37.5 mg and increased slowly up to 150–225 mg daily. If treatment with a single drug is only partly effective, combination therapy can be tried. Side effects, e.g., somnolence and dizziness, need to be carefully monitored, and it is important to be aware of specific side effects, e.g., the serotonin syndrome, which, for example, can occur when combining SNRIs such as antidepressants and tramadol. It is characterized by flu-like symptoms, rapid heart rate, high blood pressure, nausea/vomiting, and heavy sweating and can lead to agitation, confusion, hallucination, and muscle rigidity. High fever, irregular heartbeat, seizures, and unconsciousness are eventually symptoms in severe cases of the serotonin syndrome.

In severe refractory neuropathic SCI pain, intrathecal treatment with clonidine and morphine [116] or with ziconotide or morphine, either alone or added to baclofen treatment, may be considered, but there is limited knowledge about long-term efficacy and safety, and usually the effect is unpredictable with only a small percentage of patients responding [117, 118].

12.9 Non-pharmacological Treatment

Neurostimulation techniques such as transcranial direct current stimulation and repetitive transcranial magnetic stimulation or invasive procedures such as motor cortex stimulation and spinal cord stimulation are being tested, but results are

conflicting with very few data on long-term efficacy and safety [119–125]. In a recent study, the combination of transcranial direct current stimulation and visual illusion reduced SCI pain, but the treatments given alone had no or limited effect [126]. Dorsal root entry zone (DREZ) is not recommended [125].

Cognitive behavioral programs have been shown in RCTs to improve the sense of coherence and depression [83] and to reduce anxiety and increase participation in activities [127], although no effect on pain intensity was seen. An exploratory study also found an effect on pain intensity and pain-related disability of a multidisciplinary cognitive behavioral program for coping with neuropathic SCI pain [128]. Such programs as well as other psychological treatments, e.g., hypnosis [84], may thus be valuable additions to the treatment.

Summarizing, although certain non-pharmacological treatment approaches in SCI-related chronic neuropathic pain are believed to be beneficial, a convincing basis of evidence is still lacking [108].

Conclusion

Pain is a common and relevant complication in SCI. Its assessment and therapy can be major challenges. Musculoskeletal pain is common in the acute phase, and musculoskeletal, neuropathic, and visceral pain are the most common types of pain in the chronic phase.

Assessment of pain in SCI, including its characterization and assignment to specific pain types (nociceptive vs. neuropathic), is still being optimized with respect to reliability and validity. While most of the currently established questionnaires have not been developed to specifically assess pain in SCI, recent publications increasingly focus on the verification of appropriate SCI-specific assessments to account for particularities in manifestation of different SCI pain types.

Pain can have a severe impact on the patients' rehabilitation, sleep, mood, and quality of life. A multidisciplinary approach to treatment on an individual basis is thus needed. A better understanding of the underlying mechanisms is needed to develop more promising therapy strategies and to be able to prevent the development of chronic pain. Yet, in all aforementioned SCI-related pain types, clinically established therapy approaches comprise non-pharmacological and/or pharmacological treatments. While interventional and pharmacological therapies of nociceptive and visceral pain are mainly aiming for identification of causalities and their resolution, therapeutic approaches for neuropathic pain are largely focused on an assumed modulation of neuronal hyperexcitability and decreased inhibition. A lot of these options are mainly applied on empirical basis, like the application of laxatives in neurogenic bowel dysfunction to relieve visceral pain. Others, like the administration of antidepressants in SCI-related neuropathic pain, are based on partially scarce evidence. Given this fact, therapeutic decisions should admittedly be made in accordance with current guidelines or, if not applicable, at least be based on publications of national or international associations/societies, which are representing the field of SCI.

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