Chronic pain following spinal cord injury

Summary

Background. Chronic pain following spinal cord injury is common, and may result in a substantially reduced quality of life. The aim of the paper is to provide an overview of pain conditions resulting from spinal cord injuries and an update on therapy options.

Method. The article is based on literature searches in PubMed review articles for the period 2006–2011, using the search phrases «pain and spinal cord injury/injuries», «chronic pain and spinal cord injury/injuries» and «neuropathic pain and spinal cord injury/injuries». Some key articles on neuropathic pain are also included, irrespective of the year of publication.

Results. Patients with spinal cord injury may develop nociceptive and/or neuropathic pain.The cause, nature and localisation of the pain must be established before therapy is initiated. Neuropathic pain should primarily be treated with amitriptyline, gabapentin or pregabalin. Duloxetine, lamotrigine and tramadol may also be effective. Local treatment with high-concentration capsaicin and lidocaine may relieve localised neuropathic pain. Selected patients with intractable chronic neuropathic pain can be treated with intrathecal medication using an implanted pain pump or by microsurgical DREZotomy (Dorsal Root Entry Zone). Physiotherapy, non-steroidal anti-inflammatory drugs and opioids are most widely used for treating nociceptive pain. Physical exercise and acupuncture may provide relief from shoulder pain.

Interpretation. There may be several causes of chronic pain following spinal cord injury. Different measures have been tested for the management of chronic pain after spinal cord injury, but most studies have been performed on a limited number of patients. Further studies are needed to find more effective means of relieving pain following spinal cord injuries.

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Pain is common in patients with spinal cord injury (SCI). Up to 80 % of SCI patients are reported to suffer from chronic pain (1). The pain may be of nociceptive or neuropathic type or a combination of the two. Neuropathic pain is caused by damage to or dysfunction of the nervous system, while nociceptive pain is caused by damage to non-neural tissue. The pain may be localised above, at or below the level of the spinal cord injury and may persist for many years after the acute injury (2–4). Pain may occur immediately after the acute injury or develop and increase in intensity long after the injury, and reduce the quality of life (2, 5). The characteristics of pain depend on the extent and level of the injury and on the anatomical structures involved (2, 6). Psychological and social factors may have a pain-modulating effect (2). In this article, we provide an overview of the various pain conditions and an update on the management options available.

Method

This article is based on literature searches in PubMed review articles, using the search phrases «pain and spinal cord injury/injuries», «chronic pain and spinal cord injury/injuries» and «neuropathic pain and spinal cord injury/injuries». The search was limited to articles published in English during the period 2006–2011. The keyphrase «pain and spinal cord injury/injuries» resulted in 994 hits, 226 of which were review articles. Searches using the keyphrase «chronic pain and spinal cord injury/injuries» gave 237 hits, 83 of which were review articles. Searches on «neuropathic pain and spinal cord injury/injuries» resulted in 208 hits, 77 of which were review articles. The search was concluded on 12 November 2011.

Only articles dealing with individuals with spinal cord injury were included in the study. Case studies and experimental studies were excluded. In addition, a review was made of key articles on neuropathic pain, irrespective of the year of publication. Relevant articles were selected and data extracted by the first author.

Pain classification

Pain is classified according to type and localisation in relation to the level of the spinal cord injury (2). There are two main types of pain – nociceptive and neuropathic. The current classification of pain following SCI proposed by the International Association for the Study of Pain (IASP) is presented in Table 1.

Nociceptive pain

Musculoskeletal pain is the most common type of nociceptive pain experienced by individuals with SCI (2). In more than 50 to compensate for loss of function in arms and legs (2, 7). Using a manually operated wheelchair increases the risk of developing shoulder pain (7). Where injury is above the T6 level, headache may be indicative of autonomic dysreflexia (2). Abdominal pain in patients with SCI may have complex causes, and requires broad clinical examination.

Neuropathic pain

SCI patients may develop both central and peripheral neuropathic pain (Table 1). A typical feature of central neuropathic pain is its localisation below the level of the injury combined with sensory phenomena such as allodynia or hyperalgesia in the painful area (2, 3). The pain may develop months or

Main points

- Chronic pain is a frequent, disabling complication of spinal cord injury (SCI)
- SCI patients may have nociceptive or neuropathic-type pain or a combination of the two
- The therapeutic strategy depends on the cause, type and localisation of the pain
- The first-line pharmacological therapy for neuropathic pain includes amitriptyline, gabapentin or pregabalin
- Targeted exercise and acupuncture can provide relief from shoulder pain

years after the injury (2–4). The development of neuropathic pain may be a sign of post-traumatic syringomyelia (2).

Neuropathic pain above the injury site is frequently unconnected with the spinal cord injury itself, for example carpal tunnel syndrome owing to overuse of the wrist in manual wheelchair users. Neuropathic pain at injury level can be indicative of, amongst other things, trauma-related 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 (8).

Table 1 Proposed classification of pain following SCI by the International Association for the Study of Pain (IASP) (2)

Type	System	Involved structures and pathological changes
Nociceptive pain	Musculoskeletal	Bone, joint, muscle trauma or inflammation
		Mechanical instability
		Muscle spasm
		Secondary overuse syndromes
	Visceral	Renal calculus, bowel, sphincter dysfunction, etc. Dysreflexic headache
Neuropathic pain	Above injury level	Compressive mononeuropathies
		Complex regional pain syndromes
	At injury level	Nerve-root compression (including cauda equina)
		Syringomyelia
		Spinal cord trauma
		Spinal cord ischaemia
	Below injury level	Spinal cord trauma
		Spinal cord ischaemia

Pathophysiology of neuropathic pain following spinal cord injury

There are a number of changes and mechanisms which contribute to the development of chronic pain following spinal cord injury. The actual trauma can cause damage to nerve roots, which leads to the generation of nerve impulses giving rise to pain and the development of peripheral neuropathic pain (so-called peripheral pain generators) (2).

Pain at and below injury level may be caused by post-traumatic changes in the spinal cord itself. Clinical observations of pain relief at and above injury level after a spinal anaesthetic block led to the development of the theory of a spinal pain generator in the spinal cord which increases sensitivity to peripheral stimuli. A number of molecular changes occur post-injury, such as up-regulation of sodium ion channels, changes in glutamate receptors, and inhibition of serotonergic, noradrenergic, opioid and gamma-aminobutyric acid receptors (2). Drugs against neuropathic pain have an effect on these mentioned changes (2, 9). In addition, the damage leads to activation of microglia and production of cytokines such as TNF-α, interleukin-1β and interleukin-6 (10).

Changes in supraspinal structures probably also play an important role in the development of central neuropathic pain (supraspinal pain generator) (2, 4). Reorganization in the thalamic neurons and function contributes to the development of central neuropathic pain. Changes in neuroplasticity in the cortex and in spinothalamic cortical paths are probably involved in modulating the intensity of neuropathic pain (2, 4).

Clinical examination

Because it has consequences for the therapy that will be applied, a thorough examination is important both in order to identify any possible somatic cause of the pain other than spinal cord injury and to classify the type of pain. To assess pain it is necessary to establish the localisation, duration, intensity and characteristics of the pain (2). The clinical examination must include the neurological status with mapping of sensory phenomena. All previous surgical and medical treatment must be studied (2). An international consensus has been developed to establish the data required for pain assessment (11).

Pain intensity can be assessed using a visual analogue scale (VAS) or numeric rating scales (2, 11). Both types of scale are one-dimensional and based on the patient's subjective assessment of the pain. Pain is considered mild if the intensity on the VAS or numeric rating scale is scored 1–3, moderate if the score is 5–7, and severe if the score is 7 or over (12). Both over- and underestimation of pain can occur, but a longitudinal evaluation can provide information about pain variation over time and the effect of pain relief and pain management measures (11).

Pain characteristics can be mapped using descriptive scales, such as the McGill Pain Questionnaire, which has been validated in Norwegian (13). The screening tool DN4 (Douleur Neuropathique en 4 Questions) has the highest sensitivity for distinguishing between nociceptive and neuropathic pain, while LANSS (the Leeds Assessment of Neuropathic Symptoms and Signs) and NPQ (the Neuropathic Pain Questionnaire) have the highest specificity (14). Because it is not always possible to make a definite diagnosis of neuropathic pain, a grading system has been introduced with the categories «possible», «probable» and «definite» (15). The grading is based on clinical examination and the results of supplementary tests (15). Quantitative sensibility tests and neurography are examples of supplementary tests that can be used to diagnose neuropathic pain (16). Multidimensional pain rating scales can provide information about both the type and intensity and the psychosocial consequences of pain (17).

Management

Treating chronic pain can be a challenge because the pain condition rarely responds to one single type of measure, and the efficacy of treatment varies from one individual to another. Neuropathic pain can in general only be modulated, and patients should be informed that it is not possible to achieve complete freedom from pain. The treatment is generally long-term. Nociceptive pain should be treated with time-limited measures, and generally with pain relief medication combined with non-pharmacological treatment, for example physiotherapy.

Non-steroidal anti-inflammatory drugs and opioids are most frequently used in clinical practice to treat individuals with nociceptive pain following SCI (18), but no studies exist on the efficacy of such treatment for this group of patients. An overview of clinical studies of pain therapies for SCI patients is presented in tabular form below.

Neuropathic pain

Antidepressants. Tricyclic antidepressants such as amitriptyline have long been used to treat chronic pain. Two studies of amitriptyline have shown conflicting results (19, 20). In two placebo-controlled studies of, respectively, SCI patients (21) and a mixed cohort of patients with central neuropathic pain (22), the two antidepressants trazodone and duloxetine showed no effect. Earlier studies have, however, demonstrated the effect of duloxetine on peripheral neuropathic pain (23).

Antiepileptics. Amongst antiepileptic drugs, the most studied are gabapentin and pregabalin. The analgesic effect is related to multiple mechanisms of action. Three studies have studied the effect of gabapentin in

Table 2 Overview of studies of drug therapies for neuropathic pain following SCI

Treatment	First author (reference)	Daily dose, form of administration	Type of study	Number of persons included	Main results
Antidepressants					
Amitriptyline	Cardenas (19)	10–125 mg per- orally	Randomised, placebo-controlled	84	Amitriptyline = placebo
Amitriptyline vs gabapentin	Rintala (20)	150 mg vs 3 600 mg perorally	Randomised, placebo-controlled	38	– Amitriptyline > placebo – No significant trend for amitriptyline > gabapentin
Trazodone	Davidoff (21)	50–150 mg perorally	Randomised, placebo-controlled, double-blind	19	Trazodone = placebo
Duloxetine	Vranken (22)	60–120 mg perorally	Randomised, placebo-controlled, double-blind	48[1]	Duloxetine = placebo
Antiepileptics					
Gabapentin[2]					
	Levendoglu (24)	900–3 600 mg perorally	Randomised, placebo-controlled, cross-over	20	Gabapentin > placebo
	Tai (25)	1800 mg perorally	Randomised, placebo-controlled, double-blind, cross-over	7	Gabapentin > placebo
	Putzke (26)	300–3 600 mg perorally	Observational study	27	67 % reported effect
Pregabalin					
	Siddall (27)	150–600 mg perorally	Randomised, placebo-controlled	137	Pregabalin > placebo
	Vranken (28)	150–600 mg perorally	Randomised, placebo-controlled	40[1]	Pregabalin > placebo
Lamotrigine	Finnerup (30)	200–400 mg perorally	Randomised, placebo-controlled, double-blind, cross-over	30	Lamotrigine = placebo. In incomplete SCI: – Lamotrigine > placebo
Levetiracetam	Finnerup (31)	500–3 000 mg perorally	Randomised, placebo-controlled, double-blind, cross-over	36	Levetiracetam = placebo
Valproate	Drewes (32)	600–2 400 mg perorally	Randomised, placebo-controlled, double-blind, cross-over	20	Valproate = placebo
Opioids					
Tramadol	Norrbrink (33)	150 mg perorally	Randomised, placebo-controlled, double-blind	36	Tramadol > placebo
Morphine	Attal (34)	9–30 mg intravenously	Randomised, placebo-controlled, double-blind, cross-over	24	Morphine = placebo
Morphine and clonidine	Siddall (43)	Individual dosage intravenously	Randomised, placebo-controlled, double-blind	15	Morphine + clonidine > morphine or clonidine or placebo
Oxycodone	Barrera-Chacon (35)	Not stated, supplemental treatment to anti-epileptics	Observational study	54	Oxycodone + antiepileptics > antiepileptics
Others					
Mexiletine	Chiou-Tan (39)	450 mg perorally	Randomised, placebo-controlled, double-blind	15	Mexiletine = placebo
Ketamine and gabapentin	Amr (41)	80 mg ketamine intravenously + 900 mg gabapentin perorally	Randomised, placebo-controlled, double-blind	40	Ketamine+ gabapentin > gabapentin + placebo. After 2 weeks: – Ketamine+ gabapentin = gabapentin + placebo
Lidocaine	Finnerup (38)	5 mg/kg intravenously	Randomised, placebo-controlled, double-blind	24	Lidocaine > placebo
Lidocaine vs ketamine	Kvarnström (40)	0.4 mg/kg^{-1} ketamine intravenously vs 2.5 mg/kg^{-1} lidocaine intravenously	Randomised, placebo-controlled, double-blind	10	Ketamine > lidocaine > placebo
Baclofen	Loubser (44)	Individual dosage intrathecally	Retrospective observational study	16	No effect on neuropathic pain. Effect in 83 % of patients with musculoskeletal pain
Capsaicin	Sandford (42)	0.025 % ointment	Retrospective observational study	8	Effect
Cannabis	Wade (36)	2.5–120 mg, spray	Randomised, placebo-controlled, double-blind	24[1]	Cannabis > placebo
Dronabinol	Rintala (37)	5–20 mg perorally	Randomised, placebo-controlled, double-blind, cross-over	7	Dronabinol = placebo

[1] Patients with different diagnoses included

[2] See also reference 20 under Antidepressants and reference 41 under Other analgesics

Table 3 Overview of studies of non-medicinal treatment of neuropathic pain following SCI

Treatment	First author (reference)	Measure	Type of study	Number of participants	Effects
DREZotomy	Spaic (45)	Surgical intervention	Observational study	26	Immediate effect in 88 % of patients, prolonged effect in 69 %
DREZotomy	Kanpolat (46)	Surgical intervention	Observational study	55[1]	Immediate effect in 72.5–77 % depending on operation level
Transcranial magnetic stimulation (TMS)	Kang (49)	1 000 stimuli daily for 5 days; 500 impulses	Randomised, double-blind, cross-over	13	TMS = simulation
Transcranial magnetic stimulation (TMS)	Defrin (50)	500 impulses	Randomised, double-blind, placebo-controlled	12	TMS = simulation
Transcranial electrical stimulation (TES)	Tan (48)	100 μ A, 1 hour per day for 21 days	Randomised, observational study, placebo-controlled	38	TES > simulation
Transcranial electrical stimulation (TES)	Fregni (47)	2 mA, 20 mins per day for 5 days	Randomised, double-blind, placebo-controlled	17	TES > simulation
Transcranial electrical stimulation (TES) and visual illusions	Soler (53)	2 mA, 10 x 20 mins in the course of 14 days + virtual walking	Randomised, observational study, placebo-controlled	39	TES+ Visual illusions > TES or visual illusions
Visual illusions	Moseley (52)	Virtual walking, video film or guided imagery of walking	Observational study	5	Significant reduction in VAS
Deep brain stimulation	Rasche (51)	Surgical implantation of stimulator	Double-blind observational study	56[1]	No effect
Transcutaneous electrical nerve stimulation	Norrbrink (54)	2 weeks 80 Hz 3 daily or 2 weeks 2 Hz 3 daily	Observational study, cross-over	24	No effect
Acupuncture vs massage	Norrbrink (56)	6 weeks' treatment	Observational study	30	Acupuncture = massage > prior to treatment
Osteopathic manipulation	Arienti (55)	3 weeks' treatment	Observational study	47[2]	No effect

[1] Patients with different diagnoses included
[2] Patients with combined neuropathic and nociceptive pain included

Table 4 Overview of studies of treatment for nociceptive pain following SCI

Treatment	First author (reference)	Treatment	Indication	Type of study	Number of participants	Effect
Nitroglycerin	Giner-Pascual (64)	1.25 mg transdermally	Pain and tendinopathy in shoulders	Randomised, placebo-controlled	45	Nitroglycerin > placebo
Hypnosis vs EMG biofeedback	Jensen (59)	10 x hypnosis vs 10 x EMG biofeedback	Chronic pain	Observational study	37	Hypnosis > EMG biofeedback
Exercise	Mulroy (60)	12-week exercise programme	Shoulder pain	Randomised, placebo-controlled	80	Exercise > without exercise
Exercise	Nawoczenski (62)	8-week exercise programme	Shoulder pain	Observa-tional study	41	Exercise > without exercise
Exercise	Kemp (63)	12-week exercise programme	Shoulder pain	Observa-tional study with control group	58	Exercise > without exercise
Exercise	Curtis (61)	6-month exercise programme	Shoulder pain	Randomised, placebo-controlled	42[1]	Exercise > without exercise
Acupuncture	Dyson-Hudson (57)	10 treatments	Shoulder pain	Randomised, placebo-controlled	17	Acupuncture = simulation > prior to treatment
Acupuncture vs manual therapy	Dyson-Hudson (58)	5 weeks' treatment	Shoulder pain	Randomised	20	Acupuncture = manual therapy > prior to treatment

[1] Patients with different diagnoses included

SCI patients. Two studies, one with varying doses of gabapentin and one with few study participants, demonstrated a reduction of pain intensity and pain frequency, as well as improved quality of life (24, 25), while in one study gabapentin was not shown to have any effect (20). A non-blinded study showed a positive effect of gabapentin in 67 % of SCI patients (26). Even though the results vary, Baastrup & Finnerup recommend gabapentin against neuropathic pain in SCI patients in their review article (9).

Pregabalin showed better effect than the placebo in two studies (27, 28). There are no comparative studies on the efficacy of gabapentin and pregabalin (29). Lamotrigine is a drug which may have an analgesic effect by blocking sodium ion channels and inhibiting the release of glutamate from presynaptic neurons (9). In one study no statistically significant effect of the drug was found, although subanalyses revealed pain relief in patients with incomplete SCI and neuropathic pain (30).

Levetiracetam and sodium valproate have shown no effect in studies (31, 32).

Opioids. Opioids are much used to treat intractable post-SCI pain in both the acute and the chronic phase (18). Tramadol has proven effective in treating neuropathic pain in SCI patients (33), while in another study intravenous morphine had no demonstrable effect (34). Oxycodone has been effective in combination with antiepileptic drugs. (35).

The effect of cannabis products has been investigated in two studies, one of which demonstrated the effect of cannabis spray (36), while the other on the cannabis derivative dronabinol found no effect (37). The effect of cannabis products on patients with central neuropathic pain has been studied and shown to have positive results (23)

Other analgesics. Intravenous lidocaine has in one study been shown to have an effect on neuropathic pain and allodynia (38). Treatment with mexiletine has not been effective (39). Ketamine administered intravenously has proven more effective than lidocaine (40) and gabapentin (41). A retrospective study has demonstrated the effect of transcutaneously administered capsaicin (42). Local treatment with high-concentration capsaicin and lidocaine is recommended according to international guidelines as the first-line therapeutic option for localised peripheral neuropathic pain (23).

Pain pumps for intrathecal drug delivery or surgical intervention. Where pain is intractable and does not respond to conventional measures, intrathecal drug delivery or surgical intervention should be considered. Intrathecal clonidine combined with morphine has provided effective pain relief for four hours in SCI patients in one study (43). Intrathecally delivered baclofen is used primarily to treat spasticity. One study reported effective pain relief in patients with the combination musculoskeletal pain and spasticity (44). Surgical treatment such as DREZotomy (*D*orsal *R*oot *E*ntry *Z*one) may modulate pain, probably because of an improved balance between inhibitory and excitatory sensory impulses at the injury site (45). The operation involves the destruction of areas carrying pain impulses in the spinal cord at the dorsal root entry zone. Two observational studies report a demonstrable effect (45, 46). Postoperatively, patients may develop muscular weakness, sensory impairment, sexual dysfunction and bladder dysfunction.

Two studies have demonstrated that electrical stimulation can modulate neuropathic pain in SCI patients (47, 48). Magnetic cortical stimulation and deep brain stimulation have had no demonstrable effect (49–51).

Visual illusions. In 2007, Moseley published a study on the use of the visual illusion of walking as a possibility for modulating neuropathic pain in paraplegic patients (52). The experiments were based on the hypothesis that neuropathic pain can be caused by disrupted cortical proprioceptive representation and a mismatch between motor and sensory signals in SCI patients. The effect of visual illusions was examined by having the patient look at a monitor with a constructed virtual image of the patient's trunk combined with an actor's legs walking on a treadmill. Also studied was the effect of guided imagery of walking, undertaken by a psychologist. Another positive study used visual illusions combined with transcranial electrical stimulation (53).

Other measures for treating neuropathic pain

Norrbrink studied transcutaneous electrical nerve stimulation as a method of managing neuropathic pain in SCI patients, without demonstrating any effect (54). Nor was osteopathic manipulative treatment shown to have an effect on neuropathic pain or neuropathic and nociceptive pain in combination (55). Acupuncture and massage therapy may be effective in some individuals: 53 % of those who received acupuncture and 60 % of those who were treated with massage reported immediate relief from pain (56). A prolonged effect was reported two months later in 40 % of the?acupuncture group and 6 % of the?massage group. An overview of clinical studies on neuropathic pain following SCI is presented in Table 2 and Table 3.

Nociceptive pain

An overview of clinical studies on nociceptive pain following SCI is presented in Table 4. Nociceptive pain should, as mentioned, be treated with time-limited measures, generally with a combination of medication and non-pharmacological therapies. The effect of analgesics on nociceptive pain following SCI has not been specifically studied. Non-steroidal anti-inflammatory drugs and opioids are the medications most widely used (18). Acupuncture, manual therapy, hypnosis and EMG biofeedback have been shown to have some effect in some studies (57–59). Targeted physical exercise programmes have proven to be effective in four studies on shoulder pain (60–63). Transdermal nitroglycerin has been shown to have an effect on nociceptive shoulder pain (64).

Conclusion

Chronic pain can develop after spinal cord injury and may result in a substantially reduced quality of life. Thorough clinical examination is necessary prior to treatment. Most studies on the treatment and management of pain following SCI are small-scale. Based on current knowledge, we would recommend amitriptyline, gabapentin or pregabalin as the first-line drugs for peroral treatment of neuropathic pain. Local treatment with high-concentration capsaicin and lidocaine may modulate localised neuropathic pain. Physiotherapy combined with analgesics may relieve nociceptive pain.

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