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Scientific Review

Pain following spinal cord injury

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Chronic pain is an important problem following spinal cord injury (SCI) and is a major impediment to effective rehabilitation. The reported prevalence of chronic SCI pain is variable but averages 65% with around one third of these people rating their pain as severe. The mechanisms responsible for the presence of pain are poorly understood. However, evidence from clinical observations and the use of animal models of SCI pain suggests that a number of processes may be important. These include functional and structural plastic changes in the central nervous system following injury, with changes in receptor function and loss of normal inhibition resulting in an increased neuronal excitability. A number of specific types of SCI pain can be distinguished based on descriptors, location and response to treatment. Nociceptive pain can arise from musculoskeletal structures and viscera and neuropathic pain can arise from spinal cord and nerve damage. The role of psychological and environmental factors also needs to be considered. Accurate identification of these pain types will help in selecting appropriate treatment approaches. Current treatments employ a variety of pharmacological, surgical, physical and psychological approaches. However, evidence for many of the treatments in use is still limited. It is hoped that future research will identify effective treatment strategies that accurately target specific mechanisms.
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Historical overview

Chronic pain is a major problem in those who have sustained a spinal cord or cauda equina injury.[1] These patients usually have devastating neurological deficits. A significant proportion also suffers from chronic pain. Riddoch[2] addressed the problem of pain after SCI in his 1917 paper although Munro's classic paper on spinal cord injuries in 1943 did not even mention the issue of chronic pain.[3] After WW II, Botterell *et al.*[4] described chronic pain in 12/103 SCI patients and 11 of these 12 had cauda equina injuries. Kuhn[5] reported that 0.234% of the injuries in WW II involved the spinal cord and that 22.5% of 113 patients with SCI had chronic pain.

Prevalence/incidence

Since then, there have been numerous reports regarding the incidence and prevalence of pain following SCI. In 1962, Kaplan[6] attempted to classify SCI pains and stated that 37% of 52 SCI patients had chronic pain 1 year after injury and this increased to 50% by 5 years after injury. Davis[7] reported an incidence of 27% in 471 SCI patients. Richards *et al.*[8] claimed that 77% of 88 SCI patients had chronic pain and that psychosocial variables predicted about 1/2 of the variance. Woolsey[9] identified less than a 20% incidence of chronic pain in a group of 100 SCI patients.

A number of more recent studies have all contributed data on the incidence and prevalence of pain after SCI.[10–17] The methodology and the patient population being studied appear to greatly influence the reported incidence of SCI pain but across studies it appears that an average of 65% of people with SCI experience pain and in nearly one third of these people the pain is rated as severe.

Although it has been demonstrated that pain is a relatively common problem for people following SCI,[18–20] the various factors that are involved in the development of SCI pain are unclear. With regard to injury level, it has been alleged that injury at all cord levels, including cervical,[21] thoracolumbar[22] and conus medullaris and cauda equina[4,18,23] are most likely to be associated with the presence of pain, but none of

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these suggestions have been supported by existing evidence. It has also been stated that injuries resulting in damage to the spinal cord from gunshot wounds are more likely to result in pain.[18,24] Several studies have proposed from clinical observation that pain is more common in people with incomplete lesions[25,26] and this has been supported by findings at autopsy.[27]

Despite these studies, which suggest a relationship with physical factors following SCI, other studies have found that there is no significant relationship between the presence or severity of pain and the level or completeness of SCI.[8,10,28] It was concluded from these studies that psychosocial rather than physical factors were more closely associated with the experience or severity of pain following SCI. It has also been demonstrated that chronic pain is associated with more depressive symptoms and more perceived stress.[29] Cluster analysis of data obtained from questionnaires in another study revealed a relationship between pain, spasticity, 'abnormal nonpainful sensations' and sadness.[30]

There is little question that severe pain is likely to interfere with the rehabilitation potential of patients who have sustained a SCI.[30–32] Collating these reports suggests that more than 1/2 of patients who sustain a SCI suffer from chronic pain severe enough to interfere with rehabilitation and the activities of daily living and therefore reduce quality of life. Attempts to alleviate pain after SCI consume significant amounts of health care but are often unsuccessful. In the past two decades, there has been increased interest in the physiological mechanisms underlying pain after SCI and in the development of useful classification schemes. Some types of pain in SCI patients can be treated with widely accepted standardized forms of therapy when their aetiology has been properly classified. New treatments may offer the hope of pain relief in specific types of pain after SCI.

Mechanisms of pain

Plasticity

It is now well established that the central nervous system undergoes dramatic changes in response to either peripheral nerve or spinal cord injury. Central processes of primary afferents sprout and may develop connections to new populations of neurons.[33] Second-order neurons lose their synaptic input and enter into new structural relations with glia. Trophic substances play a large role in modulating this type of plasticity, which could underlie some of the pain syndromes that follow SCI.[34,35] Damage to neurons from excitatory amino acids has also been proposed as a mechanism for the development of pain.[36] Even without structural changes, loss of normal inhibitory processes contributed by opioids, monoamines, GABA and glycine following SCI may result in functional changes such as increases in spontaneous and evoked neuronal activity.[37–39] Eide has proposed that up-regulation of neuronal activity is the cause of both spontaneous and evoked pain after SCI.[40] He stated that increased glutamatergic excitatory activity involving NMDA receptor activation is the primary cause and that this can lead to changes in voltage sensitive Na^+ channels. In fact, so many changes occur in the spinal cord after injury that it is difficult to ascertain which ones are specifically relevant to the development of pain. It is also unclear why a significant proportion of patients do not have the complaint of pain after an apparently identical injury.

Central pattern generation

Another concept for SCI pain was proposed by Melzack and Loeser.[41] Based on the clinical evidence that cordotomy and cordectomy were usually not effective for the relief of diffuse, below level neuropathic SCI pain (see classification scheme below), they proposed that structures rostral to the level of injury were essential for the genesis of this type of pain. Melzack[42] has carried this theme forward to develop the concept of the neuromatrix: the brain contains widely distributed parallel processing neural networks that create an image of self through genetic programs and memories of past experience. Afferent inputs act upon this neuromatrix and produce output patterns that lead to the report of pain. This concept points to an unresolved issue about pain after SCI: is the apparatus essential to produce the report of pain located at or near the site of injury, or does it lie in more rostral structures? The presence of SCI pain in patients who have very high cervical spinal cord lesions seems to indicate that suprasegmental structures may play a critical role. There have been few, if any, experimental studies that address this issue. This concept does not negate the role of neural changes at the level of injury, but it does state that the genesis of the pain is from suprasegmental structures, not the injury site.

Experimental models

A large body of literature exists on the effects of spinal cord lesions on the development of behaviours that suggest chronic pain.[43] Research studies have generally focused upon the effects of deafferentation via dorsal rhizotomy or direct SCI by cordotomy or trauma to the spinal cord. They are, therefore, relevant only to neuropathic SCI pain, and do not have much relevance to the other types of pain described below. Indeed, those models that lead to alterations in, but not the complete loss of, sensation are most applicable to the study of neuropathic pain that occurs at the level of SCI. In contrast, models which produce an interruption of the spinothalamic tract may be most applicable to the study of neuropathic pain occurring below the level of SCI.

Among the early studies of the effects of spinal cord lesions on neuronal activity were those of Loeser.[44] Although all animals that have sustained a SCI manifest neuronal hyperactivity in the dorsal horn,

only a small fraction develops any detectable pain behaviours. There is a species effect on the genesis of pain behaviours after SCI. In addition, within the human species only a fraction of patients will report chronic pain. Of course, the ambiguity of what an animal feels that causes it to chew on or to withdraw an extremity is always present. It remains fairly well demonstrated, however, that lesions of the peripheral nerves and spinal cord can lead to behaviours that suggest both spontaneous and evoked pains such as thermal and mechanical allodynia.

Developing animal models for the pain after SCI is important for the development of successful treatment strategies. Valid models would appear to be those that mimic the histological effects of human SCI. Four are currently utilized: an ischaemic model,[45,46] an excitotoxic model,[47] a spinal cord contusion model,[48] and a hemisection model.[49–51]

The ischaemic model developed by Wiesenfeld-Hallin and her colleagues[46] uses a photochemical method to produce graduated ischemia in the spinal cord. Following ischaemic injury to the spinal cord, there are two distinct periods during which hypersensitivity is seen with stimulation within dermatomes near the injury. An acute period of hypersensitivity (1–5 days) is associated with reduced GABA immunoreactivity[39] and is attenuated by activation of $GABA_B$ receptors.[52] In contrast to acute hypersensitivity after ischaemic SCI, the chronic phase of hypersensitivity, with onset at 7–50 days, does not depend on GABAergic mechanisms[46] but does respond to intrathecal application of opioids[53] and the $alpha_2$ noradrenergic agonist clonidine.[54] Interactions between opiate and cholecystokinin (CCK) segmental modulatory systems may play a role in the development of pain,[55] but this model has not ruled out the effects of altered downstream modulation upon damaged spinal cord segments.

Substantial evidence has accrued that glutamate is responsible for much of the damage seen after SCI.[56] This has led to a series of studies using agonists and antagonists of glutamate and NMDA receptors injected directly into the spinal cord in the absence of trauma.[57] Cavitation within the cord is noted following injections of the excitatory amino acid quisqualic acid (an AMPA receptor agonist), and the animals manifest allodynia and other signs of chronic pain.[58] It is believed that the effects of excitotoxic substances may lead to cell death and altered synaptic connectivity as well as imbalances between different functional systems. Exactly how this produces pain that persists even when the involved cord segments are removed (as in distal cordectomy in humans) is not clear. The abnormal behaviours seen in animals whose spinal cords had been injected with quisqualic acid were reversed by intrathecal adrenal medullary transplants.[59]

The spinal contusion model, usually evoked by dropping a weight on the exposed spinal cord, produces changes in the excitability of neurons that could be relevant to the development of pain after SCI.[60] It has been demonstrated that animals exhibit features of neuropathic pain at the level of SCI with lowered vocalization thresholds in the dermatomes adjacent to the level of injury.[48] In particular, hypersensitivity was observed for lesions restricted to the central grey matter or the dorsal half of the spinal cord, suggesting that spinal grey matter damage contributes to development of at level neuropathic SCI pain. Following spinal cord contusion there is a significant increase in both basal and stimulus-evoked levels of neuronal activity as measured by c-*fos* expression in the spinal dorsal horn immediately above the level of injury.[61]

Lesions of the anterolateral spinal column in monkeys and rats have been shown to produce caudally directed overgrooming/autotomy.[49,51] Christensen and Hulsebosch[50,62] have described a model for neuropathic pain either at or below the level of injury. Their rats developed mechanical and thermal allodynia after a cord hemisection. Dorsal horn neurons were shown to be hyperexcitable in this preparation, suggesting that central sensitization played a role in the development of a pain state after SCI. The same authors also demonstrated that calcitonin gene-related peptide (CGRP), which is normally confined to lamina I and II of the dorsal horn, can be found in lamina III and IV after spinal cord hemisection.[35] This suggests ingrowth of fine primary afferent fibres into nuclear regions where they do not normally occur. The intensity of this response to injury was modulated by levels of nerve growth factor. This suggested a potential strategy for prevention of spinal cord changes after injury that could be related to the genesis of pain. This research suggests that plasticity in the spinal cord could be responsible for the development of pain. However, plastic changes are a response to injury and may or may not be linked to the presence of pain.

Patient evaluation

The assessment of every patient with SCI and chronic pain requires a detailed history that describes the onset of the pain and its quality, distribution, and relieving or aggravating factors. It is also important to ascertain how intervening surgeries and treatment have influenced the pain. The physical examination must precisely describe the patient's neurological status. If this is changing, the relationship to the pain complaint must also be determined. The stability of the traumatized spine must be ascertained through history, physical examination and imaging studies. Electrodiagnostic studies may be useful in determining the exact levels of injury to the nervous system and specific peripheral nerve function when indicated. Diagnostic nerve blocks can also help delineate the level of a painful lesion. On the basis of the history, physical examination and appropriate imaging and electrical studies, it should be possible to classify the pain syndrome as described below. The assignment of the patient to one of these pain classes will permit

optimal treatment planning and implementation. More than one type of pain can be present in the SCI patient.

Pain syndromes

Mechanical instability of the spine
This type of pain is most common after cervical spine injury and is rarer after thoracic or lumbar injury. Most patients who sustain an injury to the spinal cord have also received massive trauma to the vertebral column and its supporting structures. This typically leads to acute pain similar to that seen with musculoskeletal trauma anywhere in the body. It may be present from the time of injury or rarely, it may develop later. This is a type of musculoskeletal pain that is due to the disruption of ligaments or fracture of bones with resultant instability of adjacent structures. It is characterized by the movement of osseous structures in abnormal planes or in abnormal amounts.

Another type of musculoskeletal pain usually commences soon after injury and is related to activity or position. The pain is in the region of the spine, although it may radiate around the trunk or toward an extremity; but, it is not radicular. This type of pain can be seen after spine injury without an associated damage to the spinal cord. Radiographs, computerized tomography (CT) scan, or magnetic resonance (MR) scan will show instability by manifesting abnormal movement.

This type of pain is relieved by immobilization; it is also usually opiate and NSAID sensitive. Immobilization until spontaneous healing has occurred or surgical fusion are both effective treatments in almost all patients. The pain secondary to mechanical instability is almost always alleviated by surgical fusion across the region of instability. Sved *et al*[63] found that early surgery to stabilize the spine did not lead to any alteration in the incidence of chronic pain after SCI.

Muscle spasm pain
This type of pain is found only in patients with partial spinal cord injuries in whom some sensation is preserved but severe muscle spasm develops. The patient reports pain associated with visible and palpable muscle spasm at or below the level of SCI. The pain usually starts well after the SCI. This pain is best relieved by alleviating the muscle spasms; analgesics may be helpful but rarely are adequate. Hence, oral or intrathecal antispasticity medications such as baclofen are the primary treatment for this type of pain.

Secondary overuse or pressure syndromes
This type of pain is very common in paraplegics and much less common in quadriplegics. The pain occurs in normally innervated regions rostral to the level of the SCI. The onset is delayed months or even years after the cord injury. The pain is described as aching in the area of pressure or overuse and is worse with use of involved joints or pressure on the part. It is typically seen in the shoulders and carpal tunnels of those who propel themselves in wheelchairs and therefore use their shoulders as hips.[64] Lal in 1998[65] reported on shoulder joint degenerative changes in 72% of a sample of paraplegics. If the pain is due to nerve compression, electrophysiological studies as well as MR can aid in diagnosis.

Resting the painful part or protecting it from trauma can alleviate this type of pain. Nonsteroidal anti-inflammatory drugs (NSAIDS) or, when needed, opioids are also helpful. This is not a neuropathic pain and is not alleviated by anticonvulsants or antidepressants. Peripheral nerve compression can, when necessary, be alleviated by surgical decompression.

Visceral pain
It is not at all clear that this is a distinct category of chronic pain in patients with SCI. The patient describes burning, cramping, bloating constant but often fluctuating pain. Some patients seem to have intermittent attacks of this type of pain. The onset is usually delayed for months or years after the spinal cord trauma. Visceral pain may be due to normal afferent input via the sympathetic and vagus nerves in paraplegics and the vagus nerves alone in those who are quadriplegic. This pain could be stimulus driven from abdominal myoneural dysfunction, it could result from the imbalance of afferent input, or it could be a form of SCI pain as described above. Davis and Martin[22] believed that this was a pain associated with autonomic phenomena. It was described by Kuhn in 1950[66] in patients with visually inspected cord transections who had preserved recognition of noxious genital stimulation. Komisaruk[67] reported that women with high spinal cord transections could still perceive genital stimulation.

There is virtually no information on the treatment of this type of pain after SCI.

Nerve root entrapment
Nerve root entrapment leads to radicular pain in the distribution of a single nerve root. It may, rarely, be bilateral. This type of pain occurs at the level of spinal trauma, and the pain usually is present from the time of injury. Nerve root entrapment may be associated with mechanical instability, but this is not a necessary concomitant.

This pain is usually described as lancinating, burning, or stabbing. If the involved root contributes to the brachial or lumbosacral plexus, there may be electromyographic (EMG) or somatosensory evoked potential (SSEP) abnormalities. Radiographic, CT or MR evidence of compression of the nerve root in the

foramen by bone or disc is correlated with the location of the pain.

This radiculopathic pain may be relieved by opiates or by neuropathic pain-relieving drugs such as anticonvulsants or tricyclic antidepressants. If it is associated with instability, stabilization will provide relief. If it is associated with bone or disc in the neural foramen, surgical decompression is usually effective.

An important variant of this type of pain is seen after injury to the cauda equina. There are several potential etiologies for pain after such an injury. First, the spinal cord may be significantly deafferented, leading to changes in central connectivity and neuronal activity that could cause pain. Second, the damaged roots of the cauda equina could be spontaneously active and generate signals that are interpreted as pain. The arachnoiditis that follows major injury to the cauda equina may limit the normal movement of the nerve roots and lead to mechanical irritation of the roots with very slight movements.[68] Third, peripheral stimuli could lead to abnormal activity at the site of axonal injury.

The pain is reported in the lower lumbar and sacral dermatomes; it is constant but may fluctuate with activity or autonomic activation. It is usually described as burning, stabbing and hot. Most authors have commented on the refractory nature of pain after cauda equina injury. Spinal cord stimulation has sometimes been successful.

Syringomyelia

Chronic pain may occur in association with the development of a post-traumatic syrinx in the spinal cord.[69] This pain always has a delayed onset, perhaps even may be years after the SCI. The development of a syrinx is characterized by new neurological deficits at a higher level than the original injury. The loss of pain and temperature sensation is typical, but all sensory and motor functions can be effected. Patients describe a constant, burning pain that may be associated with allodynia.

Diagnosis is established by MR scan. The most effective treatment for the syrinx is surgical decompression of the arachnoid scar at the level of injury so that there is free flow of spinal fluid around the spinal cord. Treating the syrinx by inserting a drainage tube that goes either to the subarachnoid space or the peritoneal cavity does not provide as good long-term results. Even though the syrinx may collapse, it is not always the case that pain relief will be obtained. The medications utilized for neuropathic pain (see below) may be helpful when syringomyelic pain persists after collapse of the syrinx.

Transitional zone pain (TZP)

This type of pain has also been labelled girdle zone pain or segmental deafferentation pain. It occurs at the border of normal sensation and anaesthetic skin. Transitional zone pain is described as burning and aching and is often associated with allodynia and hyperpathia in the painful region. The pain is located in a 2–4 segment band that is bilateral and circumferential. As many as 1/3 of SCI patients who have pain will have the segmental deafferentation type, although Beric lumped together radicular pains and transitional zone pains in his report.[70] This type of pain usually develops in the first few months after injury.

Transitional zone pain does not usually respond to opiates, but it may respond to neuropathic pain-relieving medications such as anticonvulsants and antidepressants. Epidural or somatic nerve root blocks that make the painful area anaesthetic may relieve the pain. Dorsal root entry zone (DREZ) lesions usually relieve this pain perhaps by their dorsal rhizotomy effect or perhaps by being an analog of distal cordectomy that raises the sensory level to the top of the painful region. Some have reported pain relief by spinal cord stimulation. If the type of pain was not delineated in a clinical report, it is highly likely that this was the type of pain relieved by whatever treatment is being advocated.

Central dysesthesia syndrome

This is the most difficult to manage of the SCI pain syndromes. It is perceived in anaesthetic regions below the level of injury, although it has also been reported by some patients who do not have a complete cord transection and have some preserved functions. It may be visceral, dysaesthetic, superficial, or complex regional pain syndrome (CRPS)-like. Patients use various descriptors such as tingling, numbness, aching, throbbing, squeezing and sickening. Sometimes there is also a lancinating component. The pain is always ascribed to specific body regions and is usually bilateral. Patients often provide bizarre descriptions. It is constant, but may fluctuate with mood or activity. It is not related to position or activity. The pain usually starts soon after injury and is found in about 1/3 of SCI patients who complain of chronic pain. Beric *et al.*[70] found that 13/102 consecutive traumatic SCI patients with pain had this type of pain. Beric *et al.*[26] suggested that this type of pain was due to loss of spinothalamic systems with the relative preservation of dorsal column function. Other terms used for this type of pain include central pain, phantom pain, central dysesthesia syndrome, and dysesthetic pain.[22,25,26] Beric *et al.*[71] described a double lesion phenomenon occurring in patients with cervical or thoracic cord injuries who developed lower motor neuron signs in the lumbosacral segments.

Concurrent infections or other illnesses may aggravate this central pain state. It responds poorly to oral opioids or any other medications. It may respond to intrathecal opioids, or to a combination of bupivacaine, clonidine and opioid when systemic routes are ineffective. Surgical procedures such as

cordectomy or any other ablative procedure are rarely successful, and it is unlikely to respond to spinal cord or brain stimulation. Most patients with this type of pain do not get significant relief from any of the currently available therapies.

Cognitive, affective and environmental pain syndromes
Any pain syndrome can be modified by cognitive and affective factors as well as environmental influences acting upon the patient. The eight types of pain described above are certainly no exceptions to this general rule. Indeed the disability ascribed to chronic pain is highly likely to be primarily related to these three confounders. It is also possible that the entirety of a patient's pain behaviours can be related to affective or environmental factors, but this is certainly not common. All pain syndromes related to SCI can benefit from the application of psychological management strategies.[28]

Patients who have sustained a SCI are often physically and psychologically devastated. Suffering may be due to pain, alternatively, it can be engendered by other effects of SCI. Lundqvist *et al*.[72] found that pain was the only complication of SCI that lowered quality of life scores. Westgren and Levi[73] reported that pain had more effect upon quality of life scores than the extent of SCI. Biomedically focused physicians tend to ignore the psychological factors that may be leading to pain behaviour. The literature contains repeated references to the role of factors other than SCI itself in the genesis of pain behaviour and disability ascribed to pain.[74]

Taxonomy

Many classification systems have been used to categorise the types of pain described above. However, as yet, no attempts have been made to validate any classification system either on the basis of clinical findings, response to treatments, or putative mechanisms. Burke and Woodward[75] constructed a simple classification of pains seen after SCI and discussed their relationship to phantom phemomena. Waisbrod *et al*[76] believed that there were three types of pain after SCI on the basis of their study of 27 patients. Donovan *et al*.[77] designed a classification scheme for SCI pain in 1982, but subsequent case series either have utilized parochial classifications without the attempt to integrate concepts or did not even attempt to classify types of pain. Recently, Frisbie,[78] Beric[70] and Siddall *et al*.[79] have published classification schemes for pain after SCI.

The most recent taxonomy has been developed and proposed by the SCI Pain Task Force of the International Association for the Study of Pain (IASP) (Table 1).[80] This taxonomy proposes a three tier classification in which pain types are firstly divided into nociceptive and neuropathic and secondly into musculoskeletal, visceral, and above-, at- or below-level neuropathic pain types. The third tier aims to identify a pain type based on specific structures and pathology when this is possible.

Treatment

Pharmacological
There are few properly conducted clinical trials that adequately describe the nature of the patients' pains and utilize effective clinical study techniques. All of the medications used for any type of chronic pain have been tried in uncontrolled fashions for the variety of pain syndromes that occur after SCI.[81] Small sample size, non-controlled, unblinded studies characterize the literature in this area.

Table 1 Proposed classification of pain related to spinal cord injury

Broad type (Tier 1)	*Broad system (Tier 2)*	*Specific structures/pathology (Tier 3)*
Nociceptive	Musculoskeletal	Bone, joint, muscle trauma or inflammation
		Mechanical instability
		Muscle spasm
		Secondary overuse syndromes
	Visceral	Renal calculus, bowel, sphincter dysfunction, etc.
		Dysreflexic headache
Neuropathic	Above level	Compressive mononeuropathies
		Complex regional pain syndromes
	At level	Nerve root compression
		Syringomyelia
		Spinal cord trauma/ischemia (segmental deafferentation, transitional zone, border zone, girdle zone etc.)
		Dual level cord and root trauma (double lesion syndrome)
	Below level	Spinal cord trauma/ischemia (central dysesthesia syndrome, central pain, phantom pain, etc.)

Reproduced with permission from [80]

Opioids Some patients may respond to systemic opioids, but this appears to be the exception rather than the rule. The dysesthetic type of pain which is the most common type of chronic SCI pain is often unresponsive to even high doses of opioid agents. Only one randomized controlled trial (RCT) has evaluated the efficacy of opioids in the management of neuropathic SCI pain. This study found that intravenous infusion of alfentanil (bolus 7 μg followed by 0.6 μg/kg/min) resulted in a significant reduction in the evoked and spontaneous neuropathic pains associated with a spinal cord injury.[82] One non-randomized single blind crossover study found that epidural morphine (5 mg) 'had a pain relieving effect' in five out of 14 patients with neuropathic following SCI.[83] A case series also reports good relief of pain with intrathecal administration of morphine.[84]

α *Adrenergic agonists* As described above, there is some evidence that systemic or spinal administration of opioids may result in relief of neuropathic pain. It has also been suggested that clonidine either alone or administered spinally in combination with morphine is effective. Clonidine has been administered by the epidural route and has been found to be more effective than morphine for pain relief in patients with SCI pain[83] suggesting that alpha-adrenergic agonists may have a useful role in this problem. A case series of 10 subjects found that three out of the six patients with epidural clonidine injections (150 μg) had 50% or greater relief of their pain.[85] One non-randomized single blind crossover study found that epidural clonidine (150 μg) 'had a pain relieving effect' in 10 out of 15 patients with neuropathic pain following SCI.[83] One randomized-controlled trial found that intrathecal morphine and clonidine were ineffective when administered alone but were effective when administered in combination.[86]

Antidepressants There are a number of anecdotal reports that tricyclic antidepressants may be effective in relieving SCI pain and especially neuropathic below level pain[77,87] although it has been sometimes assumed that this effect is due to the mood altering effects of this class.[88] The presumed mechanism of pain relieving action is thought to be their ability to inhibit the reuptake of serotonin and noradrenaline and therefore increase pain inhibitory mechanisms.

One study reports the use of the tricyclic antidepressant melitracen in combination with the dopamine antagonist and antipsychotic drug, flupenthixol for the treatment of below level neuropathic pain.[87] Five out of 11 patients obtained substantial improvement. There is also evidence from a case report that the use of an anticonvulsant (carbamazepine) in addition to a tricyclic antidepressant (amitriptyline) is more effective than the use of these agents by themselves in the management of below level neuropathic pain.[89] One case series has reported that amitriptyline in combination with a number of other treatments (clonazepam, NSAIDs, TENS, 5 hydroxy tryptophan and spinal cord stimulation) was effective in relieving neuropathic pain following SCI.[84] A non-randomized controlled study also suggests that this combination is effective for chronic neuropathic SCI pain.[90] One ramdomized-controlled trial has been performed. This study investigating the effect of the selective serotonin reuptake inhibitor trazodone at a dose of 150 mg/day found no significant difference in relief of pain when compared with placebo.[91]

Anticonvulsants Anecdotally, anticonvulsants such as carbamazepine are more effective in the management of radicular or segmental pain, particularly where there is a sharp, shooting component.[81,92] Extrapolation from other types of pain related to central or peripheral nervous system injury has led to the widespread use of anticonvulsant medications with some success.[89,93] Other anticonvulsants such as sodium valproate[94] and clonazepam are also used although evidence of their effectiveness is limited and in the case of sodium valproate negative. As reported above there are two reports of the efficacy of carbamazepine in the management of neuropathic SCI pain.[89,90] Although both positive, carbamazepine was used in conjunction with amitriptyline and there are no studies which examine its effectiveness as a single agent. Gabapentin is a newer anticonvulsant that has now been used extensively for the management of neuropathic pain following SCI with anecdotal evidence of efficacy.[93] Although one case series includes patients with SCI neuropathic pain who respond positively,[95] there are no series or RCTs that evaluate the efficacy of gabapentin in the treatment of SCI neuropathic pain.

Local anaesthetics Local anaesthetics probably act in a similar manner to anticonvulsants by dampening central aberrant neuronal activity. Two RCTs have evaluated the efficacy of local anaesthetics. Lidocaine administered intravenously[96] has been used with success in the management of SCI pain. Another study administered lidocaine (lignocaine) intrathecally and found a significant reduction in neuropathic below level pain when compared with placebo.[97] However a study evaluated mexiletine and found no significant effect of mexiletine on SCI neuropathic pain.[98]

NMDA receptor antagonists One RCT has evaluated the efficacy of intravenous ketamine infusion in the management of neuropathic SCI pain. This study found that intravenous infusion of ketamine (bolus 60 μg followed by 6 μg/kg/min) resulted in a significant reduction in the evoked and spontaneous neuropathic pains associated with spinal cord injury.[82]

Baclofen While intrathecal baclofen may produce relief in those with muscle spasm pain, it appears to have no effect on neuropathic pain and in fact may increase it.[99]

Neural blockade
Anaesthetic blockade at several levels may be useful in reducing pain following SCI. This may include the use of sympathetic, epidural or spinal blockade. There is anecdotal evidence of spinal blockade resulting in disappearance of dysaesthetic below lesion pain.[100,101] This had led to the suggestion of a 'neural pain generator' which is located spinally at the distal end of the proximal segment. However, pain relief is only temporary and there is no evidence that even multiple local anaesthetic blocks result in long term relief of pain.

Physical
Those pain syndromes that are associated with overuse or pressure can often be managed by physical measures alone. Physicians who specialize in the management of SCI patients are familiar with the problems engendered by paraplegia and quadriplegia and can design prosthetic devices, orthotics, and exercise routines that will aid in the management of these problems. Physical therapies are not useful for neuropathic SCI pains.

Surgical
Orthopaedic and neurosurgical procedures designed to stabilize the spine immediately after trauma and to decompress impinged nerve roots can be very effective at eliminating the pains of instability or nerve root compression.[102] On the other hand, Burke[23] reported that patients who had spinal surgery were more likely to have chronic pain than those who were treated conservatively; this was not congruent with the observations made by Sved.[63] Decompressive surgery with lysis of adhesions at the site of SCI is also effective in the treatment of syringomyelia, although the pain associated with this condition may not remit even though the syrinx is collapsed.

Stimulation techniques

Transcutaneous electrical nerve stimulation (TENS)
Stimulating anaesthetic skin never provides pain relief.

Some patients with neuropathic pain at the level of their injury may get some relief from stimulation in the area of pain and partial sensation. In one study it appeared that TENS was more effective in controlling the pain at the site of injury rather than root pain or diffuse below lesion pain although it is not clear how many of those with pain at the level of injury had musculoskeletal pain.[103] However, another study reported lack of success in treating at-level neuropathic pain which in this case was presumed to be due to nerve root involvement but with no description of how this was identified.[87] It may be more effective in those patients that have incomplete lesions.

Spinal cord stimulation This technique has been reported to be successful in the management of other types of neuropathic pain such as arachnoiditis. It is generally not successful in the management of SCI pain[104] although there are reports that it may be useful if the spinal cord lesion is incomplete.[14,105] It appears to be more effective for transitional zone or radicular pains than below level neuropathic SCI pain.[106]

All the studies that are currently available are case reports or series and usually contain subjects with other conditions, which makes it difficult to analyse SCI pain specifically. An early case series of 10 patients with neuropathic pain reported that only five went on to permanent implantation of DCS and at 12 months only one was obtaining adequate relief.[104] In contrast with use in peripheral neuropathic pain, it was difficult in many cases to obtain paraesthesia in the area of pain and two received pain relief with no sensory perception in the region of pain. Later studies have in some measure confirmed these findings with an initial improvement in 20% to 75% of patients but a decline in long term efficacy of 10% to 40%.[105]

Brain stimulation Electrical stimulation of the thalamus,[107,108] periventricular grey matter,[107] internal capsule[107,109] and motor cortex[110] has been used for the treatment of neuropathic SCI pain and has some utility when all else has failed.[1,111] Most reports of treatment of SCI neuropathic pain are contained within series collected on a number of conditions and it is sometimes difficult to extract information. However, cumulative data from six studies (case series and case reports) demonstrates early relief in some patients but generally long term efficacy is poor.[107–110] The pain in these reports consisted of people with below level neuropathic pain.[107] As with SCS, it is difficult to obtain paraesthesia in the region of pain.[107]

Ablative procedures
Various surgical procedures have been attempted to provide relief to patients with SCI and were strongly advocated for the control of persistent pain with reported success.[4,112] However it is now recognised that the success of these various procedures is often disappointing and does vary according to the nature of the pain[113] and ablative neurosurgical procedures need to be tailored to the type of pain syndrome if they are to be successful.[113] For below level neuropathic SCI pain, ablative surgery, including cordotomy, distal cordectomy and thalamotomy and intrathecal administration of agents such as phenol[114] and alcohol have a low chance of success. Despite this, two procedures may have a limited place in the management of at level neuropathic pain. These are DREZ lesions and cordectomy.

DREZ lesions Dorsal root entry zone (DREZ) lesions that involve two to three spinal segments have been

proposed as being effective in the management of SCI pain.[115–117] However evidence from studies in which this procedure has been used indicate that good outcome is dependent to a large extent on the nature of their pain.[118] Those who have radicular pain or at level neuropathic pain are more likely to have a favourable outcome while those who have the diffuse, distal or burning pain or syrinx are less likely to do well.[102,113,117] The procedure also carries the risk of cerebrospinal fluid leaks, as well as changes in sensory level or motor function.

Cordectomy The use of cordectomy as a pain relieving measure is controversial. Early studies[22] found that cordectomy was unsuccesful in producing long-term relief and more recent cases are described in which pain was felt even after verified total spinal transection.[41] Several anecdotal reports suggest that even with complete anatomical section of the spinal cord there is either poor or no relief of below level neuropathic pain.[101,113] However more recent studies have indicated a better success rate with removal of the cord at least two to three segments above the level of injury[18] and a study of response to high spinal cordotomy indicates that up to 56% of paraplegics obtain relief following this procedure.[119] At level neuropathic pain may also be alleviated in some patients by transecting the spinal cord at a higher level.[120] This success is presumably due to removal of the focus of aberrant neuronal activity in the spinal cord described previously in this article. Despite these reports of pain relief, many spinally injured patients are understandably reluctant to consider removal of sections of their spinal cord.

Other procedures Other surgical procedures that have been used with varying results in the management of SCI pain include anterior spinal cord decompression, commissurotomy and surgical sympathectomy. When it is impossible to decompress a mechanically compromized nerve root, dorsal rhizotomy may be useful.

Psychological treatment

Patients with a major SCI usually have significant psychological distress.[19,29] The patient with SCI undergoes a huge adjustment in relationships, life-style, vocation and self image, which need to be addressed. The superimposition of chronic pain is a major factor that prevents expected rehabilitation and return to employment and function in domestic life. Psychological assessment should be part of the evaluation of every SCI patient with chronic pain of any type.[121] Utilization of pain management strategies and cognitive behavioural therapy can facilitate both pain management, improve mood, help with long term adjustment and return to maximal functional status.[122–124] Association with groups of SCI patients is also a positive step for most patients.

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