Recommendations for the Management of Neuropathic Pain due to Spinal Cord Pathologies

Multidisciplinary Panel on Neuropathic Pain*

I. Classification, Pathophysiology and Epidemiology

Pain is a common symptom of several spinal cord pathologies, including traumatic spinal cord injuries (SCI), intramedullary tumours, syringomyelia and multiple sclerosis.1 (Table 1) Spinal cord pain is most commonly the result of trauma, such as from motor vehicle accidents.2 Other causes of chronic spinal cord pain include iatrogenic pain (such as from surgery), inflammation, tumour, vascular disease and congenital conditions.3

Pain associated with spinal cord lesions may be classified into four types: musculoskeletal, visceral, neuropathic and other.3,4 These recommendations focus on neuropathic forms of spinal cord pain, which may be further divided into radicular and central pain.5

Investigators classify neuropathic pain as ‘at level’ or ‘below level’ to help distinguish between central and radicular pain.2,5 Neuropathic at-level pain occurs at the level of the spinal cord lesion or two segments

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*Table 1. Spinal cord pathologies that may cause neuropathic pain*

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<tr>
<th>Compressive lesions</th>
<th>Noncompressive lesions</th>
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<td>Spinal cord injury</td>
<td>Spinal cord infarction</td>
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<td>Spinal stenosis</td>
<td>Arteriovenous malformation</td>
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<td>Hematomyelia</td>
<td>Infectious myelitis, including neurosyphilis</td>
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<td>Syringomyelia</td>
<td>Acute transverse myelitis and multiple sclerosis</td>
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<td>Primary and metastatic intramedullary tumours</td>
<td>Vitamin B12 deficiency</td>
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<td></td>
<td>Idiopathic progressive necrotic myelopathy</td>
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<td>Familial spinal paraplegia</td>
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<td>Latrogenic causes</td>
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Patients with SCI may also experience dysesthesia and allodynia. Considered together, the prevalence of pain or dysesthesia may reach 77%, and allodynia may be present in almost half of patients. Neuropathic pain associated with allodynia is more common in patients with incomplete spinal cord lesions, central cord syndrome or cervical cord involvement. Pain develops in around 60% to 70% of patients following SCI, and about one third will report severe pain. The pain is generally chronic and debilitating, with 60% to 65% of those with severe pain continuing to suffer for more than 6 months. Patients who develop neuropathic pain soon after injury are more likely to develop ongoing pain, and the pain is more likely to be severe. Spinal cord pain is also associated with poor quality of life, stress, depression and other psychological problems.
II. Assessment

- The Transverse Myelitis Consortium Working Group has proposed a diagnostic algorithm for acute transverse myelitis, which can help to identify patients with neuropathic pain due to spinal cord lesions. (Figure 1)
- A thorough clinical history, physical examination and neurological examination should be conducted on all patients with neuropathic pain symptoms, which can help to determine the nature of the spinal cord lesion.
- Emergent conditions (e.g., spinal cord compression) should be
promptly identified and managed. Assessment should then be directed at localizing the lesion (ie, neurological level) and qualifying and quantifying pain, which includes distinguishing at-level from below-level pain. Sensory testing should be considered.

- Diagnostic imaging procedures, such as magnetic resonance imaging (MRI), preferably with gadolinium contrast, or computed tomography (CT)-myelography, should be part of the initial evaluation to determine the presence of a structural cause.
- In the absence of any contraindication, a lumbar puncture (with analysis of cerebrospinal fluid [CSF] cell count, differential count, protein, glucose, intrathecal antibodies and cytological analysis) may be performed to distinguish an inflammatory from a non-inflammatory cause. The presence of inflammatory conditions may warrant further examinations to identify demyelination in the spinal cord or elsewhere. Other ancillary diagnostic procedures may be performed whenever indicated.

### III. Management

- Treatment of neuropathic pain due to spinal cord lesions includes primary treatment of the underlying cause (eg, surgery for certain structural abnormalities) and other neurological sequelae (eg, motor deficits, incontinence).
- Spinal cord injury causing compression should be treated within 8 hours of compression, if possible. Methylprednisolone may be given as a 30 mg/kg-bolus dose, then maintained at a dose of 5.4 mg/kg/hour. If initiated within 3 hours, treatment should be maintained for 24 hours; maintain treatment for 48 hours if initiated between 3 and 8 hours after injury. If neuropathic pain is due to direct compression by tumour, antineoplastic treatment may reduce the size of the tumour and provide pain relief.
- Although surveys indicate non-steroidal anti-inflammatory drugs are one of the most common medications prescribed to SCI patients, there is very little evidence of their benefit for pain due to spinal cord lesions to merit their mention in these recommendations.
- Anticonvulsants and opioids are perceived by SCI patients as the most effective analgesics, and either may be used as first-line treatment for neuropathic pain due to spinal cord lesions. Patients receiving opioids or other analgesics may also be given an add-on anticonvulsant.

## Appendix 1: Evidence-based Management of Neuropathic Pain due to Spinal Cord Pathologies

Several spinal cord pathologies may cause neuropathic pain. (Table 1) However, published evidence on the management of spinal cord-associated neuropathic pain is mostly focused on pain due to SCI, whereas literature on other aetiologies mostly consists of case reports. Hence, efficacy of treatment for neuropathic pain due to spinal cord pathologies is mostly inferred from SCI studies.

**Pharmacological Treatment**

### I. Anticonvulsants

Anticonvulsants such as gabapentin and carbamazepine are effective for various neuropathic pain syndromes, and may also be useful in neuropathic pain due to spinal cord pathologies. However, the efficacy of different anticonvulsants in this condition may vary.

A randomized, placebo-controlled, crossover trial involving 30 SCI patients with neuropathic pain showed lamotrigine (maximum dose, 400 mg) significantly reduced pain only in patients with incomplete SCI, but had no significant effect in the total patient population. Another crossover study demonstrated valproate had no significant analgesic effects on severe chronic central pain in SCI patients even though high serum drug concentrations were achieved.

In contrast, the efficacy of gabapentin is better established by clinical studies. A retrospective study showed 76% of SCI patients treated with gabapentin for neuropathic pain reported pain reduction. Mean pain score was measured on a 10-cm visual analogue scale and progressively improved from 8.86 (baseline) to 5.23 (after 1 month of treatment), and then to 4.13 by month 6. The efficacy of gabapentin is further supported by two prospective, randomized, placebo-controlled, crossover trials involving patients with neuropathic pain related to SCI, demonstrating that gabapentin reduced neuropathic pain associated with SCI.
A third prospective study (n=31) evaluated the efficacy of gabapentin according to the duration of patients’ pain (ie, pain >6 months vs <6 months). This study included SCI patients with neuropathic pain that was unrelieved by maximal therapy using other drugs, such as antidepressants, opioids and other anticonvulsants. Significant reductions in mean pain and sleep interference scores were observed after 2 and 4 weeks of gabapentin treatment. After 8 weeks, the reduction in mean pain score for gabapentin-treated patients with pain for <6 months was from 7.3 to 3.0, and for those with pain for >6 months was from 7.6 to 5.1 (p<0.05 for both groups).

Pregabalin has anticonvulsant, analgesic and anxiolytic properties. Some studies demonstrate analgesic efficacy after the first day of treatment. Pregabalin is effective in either twice- or three-times daily dosing (total daily dose 150-600 mg).

A randomized, double-blind, placebo-controlled trial evaluated the efficacy of pregabalin in patients with central neuropathic pain due to traumatic SCI of ≥1 year duration and with a nonprogressive stage of ≥6 months. Patients received either pregabalin (titrated based on tolerability and efficacy up to 600 mg/day; n=70) or placebo (n=67). Concomitant medications were allowed, including opioids, antidepressants, anticonvulsants and muscle relaxants. After 12 weeks of treatment, pregabalin significantly reduced endpoint mean pain scores compared with placebo (-28.3% vs -7.5%; p <0.001). Pregabalin also significantly reduced sleep interference and improved Patient Global Impression of Change scores and Short-Form McGill Pain questionnaire rating.

II. Opioids
Two studies, both using a randomized, double-blind, placebo-controlled, crossover design, demonstrated the efficacy of opioids in neuropathic pain due to spinal cord lesions. However, both used intravenously administered opioids. The first study involved nine post-SCI patients with central dysaesthesia pain. Alfentanil 0.6 µg/kg/minute after a 7.0 µg/kg bolus dose reduced continuous and evoked pain, and treatment was not associated with severe side effects. However, alfentanil may be inappropriate for chronic neuropathic pain because of its rapid onset and short duration of action.

The second trial involved fifteen patients with central pain syndromes (six poststroke patients and nine SCI patients). Although morphine (9-30 mg; mean dose, 16 mg) had similar efficacy to placebo in controlling ongoing pain and had no effect on certain types of evoked pain (ie, static mechanical and thermal allodynia/hyperalgesia), it reduced the intensity of brush-induced allodynia. This suggested morphine may have analgesic effects on some components of central neuropathic pain.

III. Antidepressants
Antidepressants are effective in certain neuropathic pain syndromes, such as PDN, PHN and atypical facial pain. However, evidence supporting their role in neuropathic pain due to spinal cord lesions is not convincing. A systematic review showed only one of three studies on central pain had data suitable for analysis. Although this study suggested benefit from antidepressants, a clinical trial (n=84) revealed amitriptyline did not improve SCI-associated chronic pain intensity and related disability.

A randomized, double-blind, placebo-controlled trial showed patients with dysaesthetic pain syndrome secondary to traumatic myelopathy and treated with trazodone (a selective serotonin uptake inhibitor) 150 mg/day had pain measures that were similar to placebo-treated patients. Significantly more trazodone-treated patients complained of side effects and prematurely stopped taking the test medication.

IV. Membrane Stabilizers
Many membrane-stabilizing agents have been used for various neuropathic pain syndromes, but their role in neuropathic pain due to spinal cord lesions may be extremely limited. A randomized, double-blind, crossover trial (n=10) showed intravenous lidocaine 2.5 mg/kg infused over 40 minutes had no significant analgesic effect in patients with neuropathic pain after SCI.

Oral mexiletine, an antiarrhythmic drug and analogue of lidocaine, may also be ineffective. Fifteen patients with spinal cord dysaesthetic pain were treated for 4 weeks with either mexiletine 450 mg/day or placebo. Results showed mexiletine has no significant effect on dysaesthetic pain scores (via the McGill pain questionnaire and visual analogue scales [VAS]) and functional scores (via the Barthel index).

V. Ketamine
Two randomized, double-blind, crossover trials demonstrated ketamine may have significant analgesic effect in spinal cord-associated neuropathic pain. The first study involved nine patients with central dysaesthesia pain after SCI. Spontaneous continuous and evoked pain were both markedly reduced after intravenous infusion of ketamine (60 µg/kg bolus dose then 6 µg/kg/min).

The second study involved ten SCI patients with neuropathic below-level pain. Ketamine was infused at 0.4 mg/kg over 40 minutes. Although treatment was associated with significant side effects, half of ketamine-treated patients reported a 50% reduction in pain visual analogue scales scores. In contrast, no placebo-treated patient reported a similar reduction.
Appendix 1: Evidence-based Management of Neuropathic Pain due to Spinal Cord Pathologies

Nonpharmacological Treatment

I. Neuraxial Drug Administration

When conventional and less invasive routes of drug delivery are ineffective, direct neuraxial delivery may be attempted, using opioids, clonidine, baclofen and other agents. A case series (n=33) found that continuous intrathecal morphine infusion afforded effective analgesia to SCI patients with chronic, resistant pain. However, analgesia from intrathecal opioids alone may be suboptimal. A randomized, double-blind, placebo-controlled trial (n=15) found that post-SCI neuropathic pain was relieved more effectively by combined intrathecal clonidine and morphine than morphine alone. The degree of pain relief significantly correlated with cervical CSF drug concentrations.

Baclofen may also be useful in treating pain due to spinal cord lesions. Baclofen was evaluated in a double-blind design on seven patients (four multiple sclerosis patients, one patient with spinal cord compression and two transverse myelitis patients) and in a nonblinded fashion on two SCI patients. All patients had chronic spinal lesions and function-limiting spasticity refractory to oral medications, including baclofen. Results revealed baclofen 50 µg, when instilled into the L1-L2 interspace, significantly suppressed dysesthetic pain and spasm-related pain.

Membrane stabilizers may also be used via direct intrathecal administration. In a double-blind study involving patients with SCI-related chronic pain, significantly more patients responded to intrathecal lidocaine injection (13/21) compared with placebo (4/21). Patients who responded to lidocaine reported a 37.8% mean reduction in pain intensity for a median duration of 123.1 minutes.

II. Neurostimulation

Neurostimulatory techniques, such as SCS and deep-brain stimulation (DBS), are usually reserved for selected patients with chronic intractable pain that is resistant to conventional noninvasive therapies. However, studies specifically evaluating the efficacy of neurostimulation on neuropathic pain due to SCI are generally poor in quality. Poorly defined study populations, unclear data, weak study designs and heterogeneity of outcome measures may limit accurate evaluation.

Theoretically, the analgesic effects of DBS are due to inhibition of nociceptive pathways within the brain and modulation of descending inhibitory pathways. However, evidence of its usefulness is not convincing and is limited to case studies and reports.

A multidisciplinary approach should be taken to rehabilitation. Many patients achieve significant pain relief from physical therapy.

References:

11. Transverse Myelitis Consortium Working Group. Proposed diagnostic criteria and nosology of acute...
In turn, SCS may produce analgesia by inhibiting nociceptive input from Aδ and C fibres as a result of selective Aδ- and Aδ-fibre stimulation, and by stimulating dorsal nerve roots and the dorsal columns that may activate inhibitory networks within the spinal cord. SCS may also cause the release of pain-suppressing neurochemical mediators. A systematic review indicated that 50% to 70% of patients treated with SCS experienced initial improvement, but a decline in efficacy is found in 19% to 41% upon follow-up. A cost-benefit analysis further showed that SCS may reduce physician office visits, nerve blocks, radiological imaging, emergency room visits, hospitalization and surgical procedures in patients with intractable chronic neuropathic pain. Studies indicate transcutaneous electrical nerve stimulation does not significantly reduce neuropathic and musculoskeletal pain in post-SCI patients. However, a retrospective study (n=36) found that 67% of patients with central neuropathic pain due to traumatic and nontraumatic SCI improved after electroacupuncture therapy. Patients with constant, bilateral or symmetric pain were more likely to benefit from this technique.

III. DREZotomy

Refractory pain due to SCI and cauda equina injuries are not responsive to classic neurosurgical procedures. Instead, DREZotomy has been used to relieve post-SCI central pain, with modest to good outcomes in small nonrandomized trials. Systematic review of literature indicates approximately 75% of post-SCI patients treated with DREZotomy experience good pain relief immediately after surgery, 48% to 52% with good pain relief after 1 year, and 41% to 52% after 3 years. However, considerable caution is warranted when interpreting these results, as the evidence for DREZotomy is weak and largely comprises data from observational studies without control groups.

While recognizing these reservations about the current evidence, DREZotomy may in fact offer some benefits to particular subsets of patients. Good long-term outcomes were achieved more frequently in patients with segmental pain distribution than those with below-level pain (68% vs 0%); and in patients with paroxysmal pain than those with continuous pain (88% vs 26%). Despite the preponderance of benefit towards segmental pain, DREZotomy may also have a role in central pain. Outcomes of patients with central pain may be improved through operative intramedullary electrophysiological guidance. In a study involving SCI patients with central pain (n=41), electrophysiological guidance was done via recording of DREZ-related spontaneous electrical hyperactivity in nine patients, and additional recording of DREZ-induced evoked electrical hyperactivity during transcutaneous C-fibre stimulation in 32 patients. Using these techniques, 88% of patients achieved 50% to 100% relief of pain, with 84% achieving 100% relief. However, DREZotomy may be associated with adverse effects, the most common being motor and sensory deficits. Other potential complications associated with this procedure include CSF leakage and wound infections.