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A Systematic Review of Pharmacological Treatments of Pain Following Spinal Cord Injury

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Abstract

Objective—To conduct a systematic review of published research on the pharmacological treatment of pain after spinal cord injury (SCI).

Data Sources—Medline, CINAHL, EMBASE and PsycINFO databases were searched for articles published 1980 to June 2009 addressing the treatment of pain post SCI. Randomized controlled trials (RCTs) were assessed for methodological quality using the PEDro assessment scale, while non-RCTs were assessed using the Downs and Black evaluation tool. A level of evidence was assigned to each intervention using a modified Sackett scale.

Study Selection—The review included randomized controlled trials and non-randomized controlled trials which included prospective controlled trials, cohort, case series, case-control, pre-post and post studies. Case studies were included only when there were no other studies found.

Data Extraction—Data extracted included the PEDro or Downs and Black score, the type of study, a brief summary of intervention outcomes, type of pain, type of pain scale and the study findings..

Data Synthesis—Articles selected for this particular review evaluated different interventions in the pharmacological management of pain post SCI. 28 studies met inclusion criteria: there were 21 randomized controlled trials of these 19 had Level 1 evidence. Treatments were divided into five

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categories: anticonvulsants, antidepressants, analgesics, cannabinoids and antispasticity medications.

Conclusions—Most studies did not specify participants' types of pain; hence making it difficult to identify the type of pain being targeted by the treatment. Anticonvulsant and analgesic drugs had the highest levels of evidence and were the drugs most often studied. Gabapentin and pregabalin had strong evidence (five Level 1 RCTs) for effectiveness in treating post-SCI neuropathic pain, as did intravenous analgesics (lidocaine, ketamine and morphine) but the latter only had short term benefits. Tricyclic antidepressants only showed benefit for neuropathic pain in depressed individuals. Intrathecal baclofen reduced musculoskeletal pain associated with spasticity; however there was conflicting evidence for the reduction in neuropathic pain. Studies assessing the effectiveness of opioids were limited and revealed only small benefits. Cannabinoids showed conflicting evidence in improving spasticity related pain. Clonidine and morphine, when given together, had a significant synergistic neuropathic pain-relieving effect.

Keywords

pain; spinal cord injury; paraplegia; tetraplegia; pharmacological treatments

Introduction

Pain is a frequent complication of spinal cord injury (SCI). Studies examining pain prevalence have noted on average, two-thirds of people with SCI report some form of pain and nearly one-third rate their pain as severe. These estimates have been confirmed in at least two studies[1,2], with several recent studies reporting estimates of prevalence as high as 77%–86%.[3–7] However, it is notable that individual reports of incidence and prevalence vary widely, due to differences in methodology and/or the populations being studied.[8,9]

Pain has often been reported as an important factor in decreased quality of life, and has been shown to adversely impact function and participation in a variety of activities (e.g., sleep, activities of daily living (ADLs), community re-integration) in persons with SCI.[3,10–13] Nepomuceno et al.[10] noted that 23% of individuals with cervical or high thoracic SCI and 37% of those with low thoracic or lumbosacral SCI reported being willing to sacrifice sexual and/or bowel and bladder function, as well as the hypothetical possibility of a cure of their SCI in exchange for pain relief.

The Task Force on Pain Following SCI, sponsored by the International Association for the Study of Pain (IASP), introduced a taxonomy based upon expert consensus of presumed etiology (Sidall et al. 2000); this classification scheme has been widely accepted (Bryce et al. 2006). In this schema, SCI-related pain is classified as either pain caused by the activation of nociceptors which are primary sensory neurons for pain (nociceptive) or pain caused by damage to the sensory system itself (neuropathic). Nociceptive pain can originate from the skin or musculoskeletal system or visceral organs; while neuropathic pain can involve the peripheral nervous system or in the case of spinal cord injury, the central nervous system. The majority of persons complaining of chronic pain report pain onset within the first 6 months of their injury, irrespective of the type of pain.[5,10,14–16] Some studies have reported more delayed pain onset with visceral pain.[5,16] Preliminary longitudinal studies

have shown relatively stable pain patterns over time in persons with chronic SCI, with few individuals reporting dramatic changes in pain location, type or intensity.[17]

Despite impressive gains in limiting bladder, skin, cardiovascular and respiratory complications after SCI, chronic pain post SCI has proven to be largely refractory to medical management.[18–20] This lack of treatment efficacy has been complicated by an incomplete understanding of pain in individuals with SCIs and, until recently, the lack of a standardized framework upon which to classify SCI-related pain.[21] Currently the International Association for the Study of Pain taxonomy sub-committee is in the process of reviewing the pain classification post SCI.

Pharmacological interventions remain the mainstay of treatment for SCI-related pain. Not unexpectedly, Widerstrom-Noga and Turk[22] found that SCI patients with more severe pain were more likely to use pain treatments. The use of simple non-opioid analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen and non-opioid 'muscle relaxants' is common clinical practice in treating SCI pain. Unfortunately, these medications often are ineffective in providing consistent significant pain relief for neuropathic pain and have potential risks, such as gastrointestinal, renal and hepatic toxicity, with prolonged heavy use. For neuropathic or 'central' pain seen following SCI, anticonvulsants and psychotropic drugs, i.e. antidepressants, are reportedly the most commonly used.[23] However, despite increasing popularity, few of these drugs have regulatory approval for use in neuropathic pain, and their use in individual patients is largely based on anecdotal evidence of off-label use. This systematic review was conducted in order to assess the research evidence of treatment approaches currently used in the pharmacological management of pain in persons with SCI. This study is part of the Spinal Cord Injury Rehabilitation Evidence (SCIRE) project (http://www.scireproject.com)[24], an evidence-based review of the literature assessing rehabilitation interventions in SCI patients. SCIRE was first available in 2006 and is currently in its second edition.

Methods

Literature Search Strategy

A systematic review of all relevant literature, published from 1980 to June 2009, was conducted using multiple databases (MEDLINE, CINAHL, EMBASE, PsycINFO). Key words included: pain, pain treatment, pharmacology, pain management, secondary complications, anticonvulsants, cannabinoids, antidepressants, medications, anaesthetic, analgesic, and antispastic. Retrieved references were scanned for relevant citations that might have been missed by the searches of the various databases.

Study selection

Studies were included for analysis if they met the following criteria based on the previously established SCIRE methodology.[25] Studies were only included for analysis if at least 50% of subjects had a SCI, there were at least three subjects with a SCI, and there was a definable intervention being studied. Only studies published in English language were included. For the following review of pharmacological interventions for pain post SCI, 28 of 814 studies

met inclusion criteria. Studies examining all types of pain post SCI (nocioceptive, neuropathic and mixed) were examined.

Study Appraisal

A methodological quality assessment was conducted for each article by two reviewers, using either the Physiotherapy Evidence Database (PEDro) scoring[26] system for randomized controlled trials (RCTs), or the Downs and Black (D&B) tool[27] for non-randomized studies. Scoring discrepancies were resolved by a third blind reviewer.

The PEDro was originally developed for assessing RCTs and systematic reviews in physiotherapy. Individual item level and total PEDro scores have been shown to have good agreement between raters.[28] The PEDro assessment consists of 11 questions with a maximum score of 10. External validity is measured by the first item, while the other 10 items relate to the study's internal validity. Foley et al.[28] have arbitrarily defined the following criteria for rating the methodological quality of a study: 9–10 excellent; 6–8 good; 4–5 fair; <4 poor.

In an evaluation of 194 different tools, the Downs and Black tool was one of only 6 tools identified as suitable for use in systematic reviews[29] for assessing methodological quality in non-randomized studies. In an analysis of 18 tools, Downs and Black (D&B) tool was found to be the best to assess the quality of nonrandomized trials due to its reliability and validity. [30] The D&B tool contains 27 items assessing reporting, external validity, internal validity (bias), internal validity (confounding) with a maximum score of 28.

Higher methodological quality for each study was determined by a higher score on either tool. In the present methodology, a PEDro score of 5 or lower was used to designate "poor" quality RCTS, which corresponds to a marginally lower score than the approximate mean value over all RCTs in the PEDro database conducted over the latest reported time periods (i.e., 1995–2002).[28]

Data Synthesis

Investigations involving similar interventions were grouped and tabulated. Tables containing summaries of each study included the PEDro or Downs and Black score, the type of study, a brief summary of intervention outcomes, type of pain, type of pain scale and the study findings. A modified Sackett scale, with 5 levels of evidence, was used to determine the strength of evidence for each intervention[31] (see Table 1). The modified scale was created in order to simplify the 10 subcategories present in the Sackett scale into a system with 5 Levels. Level 1 included RCTs with a PEDro score of greater than or equal to 6, while RCTs with scores lower than 6 were given a Level 2 evidence. Prospective controlled trials and cohort studies were also included in Level 2 evidence. Level 3 evidence consisted only of case control trials. Prepost studies, post test and case series were considered Level 4 evidence. Lastly, Level 5 evidence consisted of observational studies, clinical consensus, and case reports.

Results

Most pharmacological interventional studies which met our inclusion criteria were supported by strong levels of evidence. 21 of 28 studies were RCTs of which 19 provided Level 1 evidence. When indicated, most studies specifically examined individuals with neuropathic pain post SCI; however, many studies did not distinguish between neuropathic and musculoskeletal pain. Though studies utilized a varying array of pain assessment tools, the two most commonly used scales were the Visual Analogue Scale (VAS; n=17) and the McGill Pain Questionnaire (MPQ; n=8).

Anticonvulsants in SCI Pain

Anticonvulsant medications often are utilized in the treatment of neuropathic pain following SCI, as well as a number of other medical conditions.

Gabapentinoids (gabapentin and pregabalin), are now considered to be first-line treatment for post-SCI neuropathic pain.[32] Gabapentinoids mimic the neurotransmitter GABA; however, unlike baclofen they don't act directly with the GABA receptor. Instead, therapeutic effectiveness for neuropathic pain is believed to be through interaction with voltage gated N-type calcium ion channels at the $\alpha_2\delta$ subunit and also indirectly with the NMDA receptor. Both of these drugs have been shown to increase the activity of inhibitory neurons resulting in a decrease in transmission of nociceptive signals. [33,34]

Rintala et al.[35] conducted a RCT comparing the effects of gabapentin, amitriptyline, and an active control (diphenhydramine) on pain intensity post SCI in individuals with neuropathic pain. At 8 weeks gabapentin, when compared to amitriptyline or diphenhydramine, was not more effective in reducing pain intensity in participants scoring high (≥10) or low (<10) baseline scores on the Center for Epidemiologic Studies Depression Scale-Short Form (CESD-SF).

In a RCT conducted by Siddall et al.,[36] those in the treatment group (n=70) receiving 150 to 600 mg/daily (BID) of pregabalin experienced a significantly greater improvement in pain and sleep than those in the control group (n=67). In a RCT conducted by Vranken et al.,[37] patients in the treatment group received escalating doses of pregabalin (150–600 mg daily), while those in the control group received a placebo. Subjects in the treatment group reported a significant decrease in pain ($p<0.01$), along with improvements in the EQ-5D VAS and utility scores ($p<0.01$), as well as the Bodily Pain subscale of the SF-36 ($p<0.05$), relative to the control group.

Levendoglu et al.,[38] in a cross-over study involving 20 paraplegics with neuropathic pain more than 6 months, found gabapentin was more effective ($p<0.05$) than placebo at reducing neuropathic pain. Tai et al.[39] studied the impact of gabapentin on pain in a small RCT involving only 7 patients. There was a significant reduction in 'unpleasant feelings' with gabapentin vs. placebo ($p=0.028$), while reduction in 'pain intensity' and 'burning pain' only trended towards significance ($p=0.094$ and 0.065, respectively). No differences were detected for other pain descriptors, such as 'sharp', 'dull', 'cold', 'sensitive', 'itchy', 'deep', or 'surface'.

To et al.[40] studied the impact of gabapentin in a case series of 44 SCI patients with neuropathic pain, and reported a significant decrease in pain ($p<0.001$) as measured by the visual analog scale (VAS) in 76% of subjects. Ahn et al.,[32] in a before and after trial of SCI patients with pain, found gabapentin was effective ($p<0.05$) in decreasing neuropathic pain refractory to conventional analgesics. The impact was greater among those patients whose pain had been present for less than 6 months. Putzke et al.[41] found that, among the 21 patients who answered their questionnaire, 67% (n=14) reported a reduction in pain while on gabapentin.

Lamotrigine, a voltage-gated Na^+ channel acting anticonvulsant, was utilized by Finnerup et al.[42] in a 9 week RCT to treat neuropathic pain post SCI in 22 patients. This study found no significant improvement in overall pain post SCI; however, a subgroup of patients with incomplete SCI reported a significant reduction in their at- or below-level neuropathic pain.[42]

Valproic acid is a broad spectrum anticonvulsant sometimes used in the treatment of pain. Studies indicate it works directly on voltage-gated Na^+ channels, resulting in the suppression of high frequency firing neurons. It also indirectly increases GABA concentrations in the brain.[43] In a double-blind cross-over study (n=20), Drewes et al.[44] examined the effects of a 3 week treatment course of valoproic acid on chronic central pain in individuals who had sustained a SCI. Overall, they found no significant differences between the control and treatment groups; however, there was a trend towards improvement in the treatment group.

Levetiracetam is an oral anticonvulsant, with structure and mechanism unrelated to other anticonvulsants. It has multiple analgesic mechanisms of action such as inhibition of N-type voltage gated calcium channels and acts as a $GABA_A$ agonist.[45] Finnerup et al.[45] conducted a randomized, double blind, crossover trial of levetiracetam in SCI individuals with pain. Participants were either placed in the levetiracetam or placebo group for 5 weeks and then crossed over after a 1 week washout period. The study found no significant difference between the levetiracetam and the placebo treatment group in improving pain intensity ($p=0.46$).

Conclusions on Anticonvulsanats in SCI Pain—There is Level 1 evidence that gabapentin and pregabalin improve neuropathic pain post SCI. There is Level 4 evidence that gabapentin is more effective when SCI pain has been present for < 6 months versus > 6 months. There is Level 2 evidence that lamotrigine is effective in reducing neuropathic pain in individuals with incomplete SCI. There is Level 1 evidence that valproic acid does not significantly relieve neuropathic pain post SCI; however a non-significant trend toward improvement in pain was seen; this warrants further study. One Level 1 study showed levetiracetam is not more effective in reducing neuropathic pain post SCI than placebo.

Antidepressants for Post-SCI Pain

Both trazodone and amitriptyline are commonly used antidepressants, which act on adrenergic and $5HT_{2A}$ receptors respectively, resulting in increased serotonin and/or norepinephrine concentrations in the central nervous system.[46] Sandford et al.[47] have speculated that tricyclic antidepressants exert an analgesic effect by increasing serotonin in

the CNS, thereby potentiating the inhibition of afferent pain signals. These properties have resulted in significant pain reduction in a number of clinical conditions.

Amitriptyline is a tricyclic antidepressant which is thought to modulate pain by inhibiting the synaptic reuptake of norepinephrine and serotonin in the central nervous system (CNS). Therefore, amitriptyline has effects on both the adrenergic and 5HT receptor signal transduction pathway. Rintala et al.[35] conducted a RCT comparing the effects of amitriptyline, gabapentin, or an active control (diphenhydramine) in the treatment of neuropathic pain post SCI. At 8 weeks, pain intensity in the amitriptyline group was significantly lower than in the gabapentin (p=0.03) or the diphenhydramine groups (p=0.012). The study found amitriptyline was significantly more effective in treating neuropathic pain in individuals with high (≥10) baseline score of CESD-SF when compared to the active placebo (p=0.035); however, no such difference was seen when compared to gabapentin (p=0.61). Furthermore, no significant improvement in pain intensity was seen in participants with low (<10) baseline CESD-SF scores. In an earlier RCT, Cardenas et al.,[48] compared amitriptyline's efficacy against an inactive control in a mixed group of SCI patients with either neuropathic or nociceptic pain. The study found no significant difference in SCI patients randomized to receive either amitriptyline or placebo given 1–2 hours before bedtime for a period of 6 weeks.

Trazodone is reported to selectively inhibit serotonin and norepinephrine reuptake in a ratio of 25:1, and is thought to produce greater analgesia and less anti-cholinergic side-effects than more non-selective agents like amitriptyline. Davidoff et al.[49] found, in a 6 week double-blind placebo-controlled trial, that trazodone was ineffective at relieving pain in 18 SCI patients with chronic neuropathic pain (see Table 3). Heilporn,[50] using combinations of melitracin (a previously available antidepressant) and TENS, reported relief of pain in 8 of 11 SCI patients with neuropathic pain.

Conclusions on Antidepressants in SCI Pain—There is Level 1 evidence that the tricyclic antidepressant trazodone does not reduce post-SCI neuropathic pain more than placebo. There is Level 1 evidence that amitriptyline is effective in the treatment of post-SCI pain, but only in depressed individuals.

Analgesics for SCI Pain

Given the severity and intractability of post-SCI pain, treatments such as lumbar epidural and subarachnoid infusions of analgesics have been studied. Loubser and Donovan [51] conducted a within subject RCT involving 21 patients, administering a placebo and 5% lidocaine injection in a randomized sequence. Following the lidocaine injections, 13 patients reported a significant mean reduction in pain from baseline averaging 2 hours when compared to placebo (p<0.01). Attal et al.,[52] reported on 15 patients who received lidocaine intravenously and experienced a greater reduction in pain than those who received placebo, with an effect lasting up to 45 minutes post injection, and a reduction in the intensity of brush-induced allodynia and mechanical hyperalgesia. In a RCT study by Finnerup et al.,[53] those patients who received lidocaine intravenously (n=24) in two treatment sessions 6 days apart reported significantly less pain than those who did not receive lidocaine.

Chiou-Tan et al.[54] provided 15 SCI individuals with either oral **mexiletine** (an orally administered derivative of lidocaine) or placebo (150mg 3 × daily) in a double-blind cross-over RCT. There was no appreciable improvement in pain severity, as measured either on a VAS or using the McGill Pain Questionnaire, within either group.

Ketamine is a NMDA receptor antagonist sometimes used to treat neuropathic pain. Two studies have looked at the effect of ketamine on post-SCI pain. In one RCT of 10 subjects, Kvarnstrom et al.[55] found ketamine was successful in reducing spontaneous neuropathic pain post SCI. Eide et al.[56] in another small RCT (n=9), compared intravenous ketamine hydrochloride (an NMDA receptor antagonist), alfentanil (a μ-opioid receptor agonist) and placebo as either a combination bolus or continuous intravenous infusion. The bolus dose was administered for 60 seconds and the continuous intravenous infusion was started simultaneously for 17–21 minutes during testing. A significant reduction in allodynia was noted for the ketamine and alfentanil treatments relative to placebo. Alfentanil and ketamine reportedly reduced wind-up pain when compared to placebo, but not when compared to each other. Wind-up pain is produced by repeated stimulation of c-nociceptive afferents resulting in temporal summation of pain perception.[56] There was a high correlation between the serum concentration of ketamine and the degree of reduction in continuous and wind-up pain.

Morphine is an opium-derived analgesic which acts directly on the central nervous system (CNS) to relieve pain by binding and activating the mu opioid receptor (MOR).[57] There are many endogenous opioids including endorphins, endomorphins and nociceptin produced naturally within the human central nervous system and even more opioids manufactured as analgesics. The mu opioid receptor (MOR) is often targeted pharmacologically for its analgesic effects as the MOR reduces the presynaptic release of GABA.[58] The anti-nociceptive effects of clonidine are thought to be mediated via inhibitory interaction with pre- and post-synaptic primary afferent nociceptive projections in the dorsal horn,[59] and possibly by inhibition of substance P release.[60, 61] Clonidine is a central acting alpha-2 agonist; Ackerman et al.[59] have demonstrated that selective alpha-2 adrenergic antagonists (e.g. Yohimbine) can reverse clonidine-induced analgesia.

Siddall et al.[62] conducted an RCT/cross-over trial of **intrathecal morphine, clonidine** or placebo given at the lumbar level in 20 subjects with post-SCI neuropathic pain. Once a subject achieved satisfactory pain relief or suffered drug side effects with one of the three treatments, that subject was treated with a mixture of clonidine and morphine. Both morphine and clonidine given alone demonstrated a trend towards pain reduction; however, when the combination of morphine and clonidine was administered, there was a significant reduction in pain. Siddall et al.[62] postulated that administering half the effective minimum dose of clonidine and morphine together resulted in a synergistic benefit and reduction in pain.

Uhle et al.[63] reported on 10 SCI patients who were given 0.01mg morphine (1ml) followed by clonidine (30μg) intravenously. If there was no significant reduction in pain, an additional 50μg of clonidine was given. When given clonidine, patients reported good to excellent reductions in pain. Eight of the 10 patients had pumps implanted to ensure continuous

intrathecal administration of clonidine. The average daily dose of clonidine stabilized at 44μg. The authors concluded that combining intrathecal clonidine and opioids reduced pain.[63]

Attal et al.[64] in a RCT administered either saline or **morphine** bolus injections in 15 SCI individuals. The study found morphine significantly reduced dynamic mechanical allodynia pain for up to 90 minutes ($p<0.01$); however, it had no effect on other types of pain. Patients receiving morphine also experienced significantly greater side effects than those receiving the placebo ($p=0.005$); however these adverse effects were mild and reversible.

Tramadol is a low affinity μ opioid agonist which also acts as a weak monoamine reuptake inhibitor. Norrbrink and Lundeberg[65] conducted a double-blind RCT to assess the efficacy of tramadol in 35 SCI individuals diagnosed with at- or below-level neuropathic pain. The authors reported significant differences between the two group pain ratings ($p<0.05$). Tramadol was also found to be effective in improving anxiety, global life satisfaction and sleep quality in post-SCI individuals ($p<0.05$). However, no significant improvement was seen in pain unpleasantness and depression levels.

Capsaicin is a vanilloid receptor 1 (VR1) agonist which has been used for decades to relieve pain. Vanilloid receptors, specifically the VR1, are neuronal membrane recognition sites that are stimulated by capsaicin, noxious heat (>43°C) and low pH; as such they have been identified as an integrator of chemical and physical stimuli that elicit pain.[66] Capsaicin works by activating distinct sensory neurons (noiciceptors) which then transmit nociceptive information back to the CNS and release substance P.[67] The excitation of these neurons is followed by long lasting desensitization periods due to the depletion of substance P. In a survey of 8 patients with pain at or just below the level of injury, Sandford and Benes[67], reported that capsaicin topical cream reduced post-SCI radicular pain symptoms in most patients after 6 months.

Conclusions on Analagesics in SCI Pain—There is Level 1 evidence that lidocaine, delivered through a subarachnoid lumbar catheter, provides more short-term neuropathic pain relief than placebo. There is Level 1 evidence that either intravenous ketamine or alfentanil significantly reduces neuropathic pain relative to placebo. There is Level 1 evidence from 1 RCT and Level 2 evidence from a prospective controlled trial (PCT) that a combination of intrathecal morphine and clonidine results in a significant reduction in neuropathic pain. There is Level 1 evidence that intravenous morphine alone significantly improves dynamic mechanical allodynia pain post SCI. There is Level 1 evidence that tramadol is effective in reducing neuropathic pain post SCI. There is Level 1 evidence that mexilitene does not improve SCI neuropathic pain when compared to placebo. There is Level 5 evidence that capsaicin topical cream may reduce post-SCI pain.

Cannabinoids for SCI Pain

Cannabinoid receptors bind endogenous ligands such as endocannabinoids and exogenous ligands known as **cannabinoids**. These receptors modulate a variety of physiological processes including pain, mood and memory.[68] Tetra hydrocannabinol (THC), a cannabinoid, is the active compound in cannabis and is one of the most common compounds

used to target cannabinoid receptors during drug therapy. THC binds and activates the cannabinoid receptor type 1 (CB_1).[69] It has been anecdotally noted that the use of marijuana provides benefits for central neuropathic pain in some patients.

Hagenbach et al.[70] conducted a study primarily examining the effectiveness of THC in improving spasticity and secondarily, in improving pain with SCI individuals. In the first phase of the study, 22 individuals received 10mg of oral THC which was then dose titrated until maximum tolerance or treatment dose was reached for 6 weeks. The study found a significant reduction in SCI individuals' pain post treatment ($p=0.047$). The third phase of the study, involved a double blind randomized control trial which included 13 of the previously mentioned individuals receiving either individual maximum treatment dosage previously determined or a placebo dose. In this phase, Hagenbach et al.[70], found individuals in the treatment group had no significant pain reduction compared to those in the placebo group.

Conclusions on Cannabinoids in SCI Pain—There is conflicting evidence for the use of THC in reducing spastic pain in SCI individuals.

Anti-Spasticity Medications for SCI Pain

Baclofen is a $GABA_B$ receptor agonist that acts at the level of the spinal cord to suppress spasticity in SCI patients.[71] GABA is known to be involved in several analgesic pathways,[72] and experimentally-induced allodynia can be suppressed by baclofen[73]; however, baclofen appears to be most effective in reducing the musculoskeletal pain associated with spasticity. Continuous intrathecal infusion of baclofen has been shown to further reduce post-SCI spasticity and/or pain (whether it be neuropathic, musculoskeletal, or neuropathic)[74,75] (see Table 6).

In a RCT, Herman et al.[75] found intrathecal baclofen significantly suppressed neuropathic (burning) pain among 6 of 7 subjects ($p<0.001$), while only 1 of the 2 patients in the non-RCT group receiving placebo reported that their neuropathic pain was abolished. Intrathecal baclofen appeared to have an impact on post-SCI neuropathic pain, in addition to treating spasticity. In contrast, Loubser and Akman[76] performed a before-and-after study of implanted baclofen infusion pumps provided for spasticity. Twelve of the 16 patients who had pre-existing chronic pain experienced a reduction on VAS measuring severity of neuropathic pain at 6 and 12 months; however, this difference was not statistically significant ($p=0.26$). In contrast to neuropathic pain, there was a significant decrease in musculoskeletal pain at both 6 and 12 months ($p<0.005$) following intrathecal baclofen pump insertion.

Botulinum toxin (BTX) is a naturally occurring neurotoxin. Many clinicians now use botulinum toxin for the treatment of pain associated with focal spasticity. One study[77] examined the effects of BTX injection given for spasticity control in SCI individuals and reported dramatic improvements in pain following treatment.

Conclusions on Antispastic Medications in SCI Pain—There is conflicting evidence (Level 1 and a Level 4 study) that intrathecal baclofen reduces neuropathic pain

post SCI. There is Level 4 evidence that intrathecal baclofen reduces musculoskeletal pain post SCI, in conjunction with spasticity reduction. There is Level 4 evidence that botulinum toxin results in reduction of post-SCI pain associated with spasticity. Oral baclofen has not been studied in the treatment of pain post SCI.

Discussion

This systematic review assessed the efficacy of pharmacological treatments on post-SCI pain. Despite the fact that the total number of studies exploring pain management after SCI was small, over 70% of the studies reviewed were RCTs. Pharmacological interventions tend to lend themselves well to RCTs. Most studies lacked evidence of numbers to treat and effect size calculations. Most studies assessed pain using primarily two assessment tools, the Visual Analogue Scale and the McGill Pain Questionnaire. Both these tools have been shown to be reliable and valid in the assessment of pain and both are well accepted by pain researchers and clinicians.[78,79] However, neither has been specifically validated for assessment of post-SCI pain. In the end, a more specific and standardized post-SCI pain scale may be of greater value.

Table 7 summarizes the effectiveness of the treatments with respect to the types of SCI pain. There was strong evidence supporting the use of anticonvulsants in the treatment of pain post SCI, particularly central or neuropathic pain. Gabapentin[32,38–40] and pregabalin[36,37] have both been shown to be effective in reducing such pain post SCI. Siddall et al.[36], in a high quality Level 1 study, found pregabalin was not only significantly effective in reducing pain post SCI but also in improving sleep and anxiety. These drugs are relatively well tolerated, with few and largely transient side effects.[36] They also have the benefit of limited interactions with other medications and lack organ toxicity.[38]

Several of the studies reviewed were unblinded. One area of concern with unblinded studies is the patients' awareness they were receiving the active medication likely biased their responses to the drug or their reporting of pain post SCI. Although several studies reported gabapentin as effective in pain management, Rintala et al.[35] in a RCT found gabapentin had no significant effect on pain post SCI when compared to an active control. This was a relatively small study and with more positive studies in favor of using gabapentin we did not feel that it negated the usefulness of this agent. However, it does raise the idea that use of the active control medication makes it more difficult for the patient to distinguish between the interventional medication and the control, thereby reducing bias. Larger studies using active controls may be needed.

Other anticonvulsants which have been studied included: lamotrigine, levetiracetam, and valproate. Lamotrigine was found effective in the sub-group of incomplete SCI. Levitiracetam and Valproate have shown some effect in treating neuropathic pain in other pain populations, but failed to show effect in SCI pain. Both of these agents have more negative side effect profiles than either gabapentin or pregabalin[80] and this makes them a less desirable treatment choice overall. Older but still commonly used anticonvulsants, such as phenytoin (Dilantin) and carbamazepine (Tegretol) have long been used to treat neuropathic pain; however, these drugs have not been studied in post-SCI pain. They have

significant side effects and even in neuropathic pain they are increasingly being supplanted by gabapentin and pregabalin.[80]

Antidepressants have been used to treat pain in a number of populations[81] and have been shown to have some benefit in conditions such as neuropathic pain and fibromyalgia but not low back pain; however, only a limited number of studies have examined their use in post-SCI pain. Tricyclic antidepressants (TCA) have been shown to be partially effective in some SCI patients with neuropathic pain although it is still uncertain whether this is due to an antinociceptive effect or whether the diminished reports of pain are related to the antidepressant effect. Sandford et al.[47] noted that pain and depression may be linked; depression can lower an individual's pain threshold or pain tolerance, thereby increasing the patient's experience of pain. Rintala et al.[35] found similar results with amitriptyline being effective in reducing pain in depressed individuals; while ineffective in treating pain in the general SCI population. Trazodone proved to be ineffective in treating pain in SCI individuals. Given the often problematic side effect profile of the tricyclic antidepressants, further research into the use of these medications in post-SCI pain is likely not warranted; however, the use of newer, less toxic antidepressants such as the selective serotonin re-uptake inhibitors,(SSRIs) and serotonin norepinephrine re-uptake inhibitors (SNRIs) may be helpful.

Lidocaine, an intravenously administered analgesic drug, was shown to be effective in treating post-SCI pain,[51–53] with one exception.[55] The one exception may be due to the fact the study's authors used only half the dosage seen in the other studies with a small sample size. One important disadvantage of intravenous lidocaine is it is not selective for pain specific sodium channel subtypes which may result in a higher risk of adverse effects.[55] The other is that as an intravenous therapy it is not a practical long term management solution.

Mexiletine was found to be ineffective as a treatment for post-SCI pain. This could be due to the use of a relatively smaller dose (450 mg/day) than the 750 mg/day shown to be beneficial in patients with chronic non-SCI neuropathic pain.[54]

There was strong evidence that intravenous ketamine is effective in the treatment of post-SCI central or neuropathic pain.[55,56] Ketamine has been shown to be especially effective in treating wind-up pain, which may be due to the fact that temporal summation of pain (wind-up pain) is mediated by NMDA receptors. Eide et al.[57] provided strong evidence that central pain after SCI is dependent on the activation of NMDA receptors. However, intravenous treatment for chronic pain is not practical and oral ketamine has not been studied in the SCI population.

Tramadol is a more recent analgesic which has become quite popular. A previous Cochrane review assessed its effectiveness in treating neuropathic pain.[82] This review found 3 trials showing significant overall pain relief when compared to placebo or baseline measures; however no differences were seen when comparing it to clomipramine or morphine. One RCT[65] examined the effect of tramadol in improving pain post SCI. The study demonstrated that tramadol was not only effective in reducing pain post SCI, but also other secondary outcomes such as anxiety, global life satisfaction and sleep quality.

It is not uncommon when treating any difficult pain state to use more than one type of analgesic medication. Two studies[62,63] have demonstrated the synergistic effects of intrathecal morphine and clonidine. Their findings suggest that different subtypes of neuropathic pain may respond differently to pharmacological interventions; pain localized to the level of the SCI may be more susceptible to drugs directed at the spinal level, while pain below the level of the SCI may be associated with changes at the thalamic (central) level.[62] Accordingly, deafferent and dysaesthetic neuropathic pain may also respond differently to specific treatments although there are challenges in distinguishing between the two; moreover, most studies did not specify the type of neuropathic pain and hence effectively evaluating treatments was not possible.

One concern with opioids is the potential for addiction or opioid abuse, particularly in younger patients with a history of substance abuse, and clinical trials have not yet been designed to evaluate this.[83] Unfortunately oral opiates have not been studied in the SCI pain setting and therefore cannot be commented on despite their frequent use. Oral Clonidine has also not been studied in individuals post SCI, however, Remy-Neris et al.[84] found that given clonidine's lipophilic nature intrathecal clonidine is not likely to be more effective than the oral or transdermal method of delivery.

Use of capsaicin to relieve radicular pain was supported by Level 5 evidence; however, more studies need to be conducted using larger sample sizes in order to fully understand its effectiveness in post-SCI pain.

Cannabinoids have increasingly been used in the management of pain given that they have been shown to be relatively safe.[84,86] Hagenbach et al.[70], showed that THC may have some analgesic properties to help SCI patients with spasticity related pain. Wade et al.[87] conducted an RCT of sublingual 2.5 mg THC and/or cannabidiol and found that it significantly reduced pain, muscle spasm, spasticity and sleep difficulties in a group consisting largely of multiple sclerosis patients with neuropathic pain. Unfortunately, only a small number of the patients in this study had a SCI, so it did not meet our inclusion criteria. There is anecdotal evidence that marijuana smoking is not uncommon among patients post SCI, and that it may be of some benefit in the management of post-SCI pain; however, there remain social and legal concerns with regard to its use, as well as potential medical concerns about smoking as a delivery system. Oral and sublingual cannabinoids are safe and effective in other populations with chronic pain. They should be furthered studied in the SCI setting.

The antispasticity medication, baclofen, appears to improve chronic post-SCI pain, though the actual mechanism behind the pain relief has not been fully established. There is evidence that baclofen infusion pumps may be helpful for both neuropathic and musculoskeletal pain post SCI.[76] However, studies have shown that intrathecal baclofen only reduces SCI pain when the pain is related to muscle spasms.[88,89] There is need for confirmatory research, due to the small sample size and lack of significant improvement in a later before and after trial. Oral baclofen has not been studied as an antinocioceptive agent in SCI.

Marciniak et al.[77] noted a decrease in pain post botulinum injection in SCI individuals. This decrease was likely attributable to a decrease in spasticity due to botulinum injection;

however, boulinum has been shown to inhibit the release of substance P and other pain neuromodulators and the analgesic effect of botulinum may be more than just the reduction in muscle tone. More research using botulinum in post-SCI pain needs to be conducted in order to understand its mechanism and effectiveness.

Summary

There was strong evidence supporting the use the anticonvulsants such gabapentin or pregabalin for post-SCI neuropathic pain. Other anticonvulsants had limited or lack of evidence for their use with the exception of lamotrigine in the setting of incomplete SCI. Tricyclic antidepressants were supported by limited evidence in those patients with superimposed depression. They have been shown to be effective in other neuropathic pain states; however side effects can be quite significant. There was evidence that some local anaesthetics, such as lidocaine infused into the lumbar subarachnoid space or ketamine given intravenously, provide pain relief; however their effect appeared to be short lived and the impractibility of the delivery system was not conducive to long-term community management. Intrathecal baclofen has been shown to reduce neuropathic pain post SCI, and to reduce musculoskeletal pain associated with post-SCI spasticity. Opioids are commonly used for both musculoskeletal and neuropathic pain; however there was only limited research into their intravenous use in individuals with post-SCI pain and no research on oral use in SCI. Given the frequency of opioid use in SCI pain additional research seems warranted. Tramadol is a newer oral analgesic which shows some promise in SCI pain. Intrathecal clonidine appears to work synergistically with morphine for neuropathic or central pain. Cannabinoids has been shown to have some potential for use post SCI, given evidence supporting their use in other neuropathic pain conditions; however, clinical trials in SCI are lacking.

Pain is an important complication of SCI which leads to decreased function and quality of life. There remain large gaps in the evidence for the treatment of both nociceptive and neuropathic pain following SCI. Future research needs to examine response of specific pain subtypes in spinal cord injured populations, using larger sample sizes and utilizing SCI specific pain assessment tools. Future research should also include a multi-modal approach to treating pain post SCI as it is being increasingly recognized as important due to the multi-factorial nature of pain post SCI. Non-pharmacological treatments in these circumstances can be used as an effective adjunct to pharmacological interventions, enhancing the overall impact of pain-relieving interventions for the SCI patient. Behavioral approaches are also often applied in pain management and can be used alone or in conjunction with pharmacological and physical therapies.

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Table 1

Levels of evidence

Level 1	RCTS with a PEDro score ≥ 6
Level 2	RCTS with a PEDro score < 6, Cohort and Non-RCTS
Level 3	Case-Control studies
Level 4	Pre-Post or Post interventions and Case series,
Level 5	Case reports, Clinical Consensus or Observational studies

Straus et al. 2005[31]

Table 2

Anticonvulsants for SCI Pain

Author Year Country Score (PEDro/D&B)	Population	Intervention	Results	
Gabapentin/Pregabalin				
Rintala et al. 2007[35] USA RCT PEDro=10	**N:**22 **Type of pain:** Individuals with neuropathic pain	**Treatment:** Patients were randomized into 1 of 6 groups: 1) gabapentin-amitriptyline-diphenhydramine (n=7), 2) gabapentin-diphenhydramine-amitriptyline (n=6), 3) amitriptyline-gabapentin-diphenhydramine (n=6), 4) amitriptyline-diphenhydramine-gabapentin (n=6), 5) dephenhydramine-gabapentin-amitriptyline (n=7), 6) diphenhydramine-amitriptyline-gabapentin (n=6). Each drug was administered for 9 wks with 1 washout week before and after each drug treatment, for a total of 31 weeks. The maximum doses were 50mg, 3x/day for amitriptyline; 1200mg, 3x/day for gabapentin; 25mg, 3x/day, diphenhydramine (control). **Pain Scale:** VAS, NRS.	**1**	In subjects with high (≥ 10) baseline Center for Epidemiologic Studies Depression Scale-Short Form (CESD-SF) scores at 8 weeks: **a.** Amitriptyline was significantly more effective in reducing pain intensity than diphenhydramine (p=0.035); but not gapapentin (p=0.61). **b.** No significant difference in pain intensity was seen in effectiveness of gabapentin over diphenhydramine (p=0.97).
			2	Subjects with low (< 10) baseline CESD-SF scores showed no significant difference among the medications. rd
Siddall et al. 2006[36] Australia RCT PEDro=9	**N:**137 **Type of pain:** Individuals with neuropathic pain	**Treatment:** Those in treatment group (n=70) received 150 to 600 mg/daily of pregabalin, while those in control group (n=67) received a placebo. **Pain Scale:** VAS, SFMPQ	**1**	Those in treatment group, once dose stabilized, averaged 460 mg/d at end of 3 week.
			2	Pregabalin more effective than placebo at reducing pain by end of study (p<0.001).
			3	Pain reduction noted both with incomplete (p<0.001) and complete SCI (p<0.05).
			4	The number who reported either a ≥ 30% or ≥ 50% reduction in pain from baseline to final assessment were more likely to be in the pregabalin group (p<0.001 and p<0.05, respectively).
			5	Those in pregabalin group also noted reduction in sleep problems (p<0.021), and an improvement in sleep quality (p<0.05) compared to the control group.
Vranken et al. 2007[37] Netherlands RCT PEDro=9	**N:**40 **Type of pain:** Individuals with neuropathic pain	**Treatment:** Those in treatment group received escalating doses of pregabalin (150, 300, or 600 mg/daily), while control group received placebo. **Pain Scale:** VAS, PDI	**1**	82.5% of subjects completed the study.
			2	Those in the treatment group experienced a decrease in pain (p<0.01) compared to control group.
			3	With respect to health status and quality of life, treatment group experienced a statistically-significant improvement, in particular on the EQ-5D VAS and EQ-5D utility scores (p<0.01).
			4	Scores on the SF-36 showed significant improvement in the bodily pain domain (p<0.009) for the treatment group, but not in other domains.
Levendoglu et al., 2004[38] Turkey RCT PEDro=9	**N:**20 **Type of pain:** Individuals with neuropathic pain	**Treatment:** Subjects randomized to gabapentin or placebo for a 4-week titration period. Following this 4-week period, subjects continued to receive max tolerated doses. After 2-week washout period, treatments were switched in a crossover design.	**1**	Placebo and gabapentin improved pain scores for the following: intensity (p<0.000), shape (p<0.000), hot (p<0.001), unpleasantness (p<0.000), deep and surface pain (p<0.001), at 4th week and again at 8th week of administration.

Author Year Country Score (PEDro/D&B)	Population	Intervention	Results	
		Pain Scale: VAS, NPS	**2**	Intensity of pain decreased significantly for gabapentin groups during treatment ($p<0.001$) and intensity of pain differed between two groups at all time points ($p<0.001$).
			3	VAS scores indicated significant pain relief, which began at week 2 and continued until week 6 ($p<0.001$).
			4	There was a significant difference between the VAS scores for the two groups at the end of the stable dosing periods ($p<0.001$).
			5	More subjects had side effects in the treatment group than in the placebo group ($p<0.05$).
Tai et al., 2002[39] USA RCT PEDro=6	**N:**7 **Type of pain:** Individuals with neuropathic pain	**Treatment:** SCI subjects with neuropathic pain were treated with gabapentin or placebo. **Pain Scale:** NPS	**1**	Significant reduction in 'unpleasant feeling' with gabapentin vs. placebo (p=0.028).
			2	Trend towards reductions with gabapentin vs. placebo for 'pain intensity' (p=0.094) and 'burning sensation' (p=0.065).
			3	No other differences for any other pain descriptors, including '"sharp', 'dull', 'cold', 'sensitive', 'itchy', 'deep', 'surface'.
To et al., 2002[40] Australia Case Series D&B=18	**N:**38 **Type of pain:** Individuals with neuropathic pain	**Treatment:** SCI patients were treated with gabapentin for neuropathic pain. **Pain Scale:** VAS	**1**	76% of subjects reported improvement in pain after taking gabapentin.
			2	The VAS decreased from 8.86 pre-treatment to 4.13 post-treatment (6mo later) ($p<0.001$), with a significant curvilinear trend (p=0.001).
Ahn et al., 2003[32] Korea Case cohort D&B=17	**N:**31 **Type of pain:** Individuals with neuropathic pain	**Treatment:** SCI patients were started on 300 mg of gabapentin, which was increased over 18 days to 1500 mg, followed by a 5-week maintenance period. If pain score did not decrease over this time period, meds were increased to 2400–3600 mg/ day. Group 1 had <6 mo of pain; group 2 > 6 mo. **Pain Scale:** VAS	**1**	Both groups (1 & 2) experienced lower mean scores for pain and sleep interference ($p<0.05$).
			2	Mean pain score decreased more for Group 1 than Group 2 ($p<0.05$).
			3	Mean pain score decreased more for Group 1 during weeks 2–8 than for Group 2 ($p<0.05$).
			4	Mean sleep interference score decreased more for Group 1 than Group 2 ($p<0.05$).
Putzke et al. 2002[41] USA Observational D&B=8	**N:**21 **Type of pain:** Not stated	**Treatment:** Participants were asked to complete a survey (or interview). **Pain Scale:** NRS	**1**	67% of patients reported having had a favorable response to gabapentin.
			2	Among those reporting a favorable response, side effects were forgetfulness & sedation.
			3	Among those interviewed a second time, most who reported a favorable response were using other medications and gabapentin for pain.
			4	Side effects like sedation and forgetfulness were common.
Lamotrigine				
Finnerup et al. 2002[42] Denmark RCT	**N:22** **Type of pain:** Individuals with neuropathic pain	**Treatment:** Following a 1-week baseline period, two 9-week treatment periods, consisting of either lamotrigine or placebo. Once the first 9-week period ended, a 2-week wash-out period began,	**1**	No significant effect on pain intensity across total sample (p=0.11).
			2	For incomplete lesions, lamotrigine reduced pain (p=0.002) when compared to placebo; however, medication had no effect on those with a complete injury.

Author Year Country Score (PEDro/D&B)	Population	Intervention	Results	
PEDro=9		followed by a second 9-week treatment phase. For those on lamotrigine, subjects were started on 25 or 100 mg and this was increased gradually to 400 mg/day. Dose was decreased if the patient could not tolerate the 400 mg/day; dose not allowed to drop below 200 mg/day. **Pain Scale:** MPQ.		Lamotrigine did not change any of the secondary endpoints. No differences were noted on the SF-36 or MPQ.
Levetiracetam				
Finnerup et al. 2009[45] Denmark RCT PEDro=7	**N=24** **Type of pain: Individuals with neuropathic pain**	**Treatment:** Patients were randomized and blinded into two 5 week treatment groups receiving either levetiracetam or placebo tablets. After a 1 week washout period, individuals were crossed over to the 2nd group. Patients received 500mg × 2 for the first week to 1000mg × 2 for the second week, 1500mg × 2 for the 3rd-5th week. Patients were assessed at baseline, end of each treatment and 6 months follow-up. **Pain Scale:** NPSI, NRS.	**1** **2** **3** **4**	No significant difference was seen between levetiracetam and placebo treatment in the median pain intensity (p=0.46) or in secondary outcome measures. Patients treated with concomitant pain medication and patients without concomitant pain medication found no difference in pain reduction. No difference in pain reduction was seen between patients treated with gabapentin and/or pregabalin and patients without gabapentin/pregabalin treatment (p=0.95). There was a trend towards greater adverse events in patients during levetiracetam treatment rather than the placebo treatment; however no significant difference was seen (p>0.075).
Valproate				
Drewes et al., 1994[44] Denmark RCT PEDro =5	**N:**20 **Type of pain:** Individuals with neuropathic pain	**Treatment:** Subjects were administered 600mg of valproate or placebo twice daily. Daily dose of valproate was increased (on an individual basis) if pain persisted and no side effects were reported. First treatment phase lasted 3 weeks, followed by a 2-week washout period, followed by 3 weeks of cross-over treatment. **Pain Scale:** MPQ	**1**	A trend toward improvement was noted among those in the valproate group; however, differences between the two groups were not significant.

Abbreviations: CESD-SF = Center for Epidemiologic Studies Depression Scale-Short Form; D&B = Downs and Black quality assessment scale score[27]; EQ = EuroQoL; MPQ = McGill Pain Questionnaire; NPS = Neuropathic Pain Scale; NPSI = Neuropathic Pain Symptom Inventory; NRS = 11 Point Numeric Rating Scale; PDI = Pain Disability Index; PEDro = Physiotherapy Evidence Database rating scale score[26]; SF-36 = Short Form 36 Health Survey; SFMPQ = Short Form McGill Pain Questionnaire; VAS = Visual Analogue Scale

Table 3

Antidepressants in Post-SCI Pain

Author Year Country Score (PEDro/D&B)	Population	Intervention	Results	
Trazadone				
Davidoff et al. 1987[49] USA RCT PEDro=6	**N:**18 **Type of pain:** Individuals with neuropathic pain	**Treatment:** Subjects underwent a 2-week placebo lead-in period with a 6-week randomization to 150 mg trazadone per day or placebo. **Pain Scale**: MPQ, SPI; PAD	**1**	No significant differences were noted between groups on MPQ, SPI, or PAD.
			2	More subjects reported side effects in experimental group ($p<0.05$).
			3	More subjects in placebo group completed the 8-week study ($p<0.01$).
Amitriptyline				
Rintala et al. 2007[35] USA RCT PEDro=10	**N:**22 **Type of pain:** Individuals with neuropathic pain	**Treatment:** Patients were randomized into 1 of 6 groups: 1) gabapentin-amitriptyline-diphenhydramine (n=7), 2) gabapentin-diphenhydramine-amitriptyline (n=6), 3) amitriptyline-gabapentin-diphenhydramine (n=6), 4) amitriptyline-diphenhydramine-gabapentin (n=6), 5) dephenhydramine-gabapentin-amitriptyline (n=7), 6) diphenhydramine-amitriptyline-gabapentin (n=6). Each drug was administered for 9 wks with 1 washout week before and after each drug treatment, for a total of 31 weeks. The maximum doses were 50mg, 3x/day for amitriptyline; 1200mg, 3x/day for gabapentin; 25mg, 3x/day, diphenhydramine (control). **Pain Scale:** VAS, NRS	**1**	In subjects with high (≥10) baseline Center for Epidemiologic Studies Depression Scale-Short Form (CESD-SF) scores at 8 weeks: **a.** Amitriptyline was significantly more effective in reducing pain intensity than diphenhydramine ($p=0.035$); but not gabapentin ($p=0.61$). **b.** No significant difference in pain intensity was seen in effectivenessin e of gabapentin over diphenhydramine ($p=0.97$).
			2	Subjects with low (< 10) baseline CESD-SF scores showed no significant difference among the medications.
Cardenas et al. 2002[48] USA RCT PEDro=9	**N:**84 **Type of pain:** Mixed group	**Treatment:** Subjects were randomized to either amitriptyline or placebo group for a period of 6 weeks. **Pain Scale:** SFMPQ, BPI	**1**	There were no significant differences between the 2 groups at baseline or at 6 weeks for any measure except satisfaction with life, with higher scores noted in the placebo group ($p=0.004$).
			2	Among those who remained on two medications, those on amitriptyline rated spasticity significantly higher ($p=0.005$) than controls.

Abbreviations: BPI = Brief Pain Inventory; D&B = Downs and Black quality assessment scale score[27]; MPQ = McGill Pain Questionnaire; NRS = 11 Point Numeric Rating Scale; PAD = Zurg Pain and Distress Index; PEDro = Physiotherapy Evidence Database rating scale score[26] ; SFMPQ = Short Form McGill Pain Questionnaire; SPI = Steinback Pain Intensity; VAS = Visual Analogue Scale

Table 4

Analgesic Medication for Post-SCI Pain

Author Year Country Score (PEDro/D&B)	Population	Intervention	Results	
Lidocaine				
Finnerup et al. 2005[53] Denmark RCT PEDro=10	**N:**24 **Type of pain:** Individuals with neuropathic pain	**Treatment:** SCI patients participated. Subjects initially divided into two groups: those with and without evoked pain. In this cross-over design, each group then was subdivided (experimental vs. controls) with experimental group receiving 5 mg of lidocaine infused over 30 min; controls received placebo. **Pain Scale:** MPQ	**1** **2** **3**	In the total sample of patients, lidocaine reduced pain vs. placebo ($p<0.01$). Assessing those with and without evoked, lidocaine still superior to placebo at reducing pain ($p<0.01$ and $p<0.048$, respectively). More patients reported pain relief with at level and below-level pain while receiving lidocaine vs. placebo.
Attal et al. 2000[52] France RCT PEDro=10	**N:**16 **Type of pain:** Individuals with neuropathic pain	**Treatment:** Patients participated, 6 who had had a stroke and 10 post SCI. Subjects given 5mg of lidocaine or saline over a 30-min period. Treatments given in separate sessions, 3 weeks apart. Order of sessions randomized. **Pain Scale:** VAS, MPQ	**1** **2** **3** **4**	Effects of lidocaine on pain were greater than effects of placebo, starting at end of injection, and lasting for up to 45 minutes post injection ($p<0.05$). More people received pain relief with lidocaine than with placebo; however, relief waned by 60 min post injection. Lidocaine reduced pain in 11 patients; and, in 6 of 12 patients, burning pain totally or partially relieved. For those with brush-induced allodynia (n=8), lidocaine produced a reduction in intensity of allodynia 15 min post injection, and this lasted up to 30 minutes post injection.
Kvarnstrom et al. 2004[55] Sweden RCT PEDro=10	**N:**10 **Type of pain:** Individuals with neuropathic pain	**Treatment:** SCI patients were recruited for participation. Ketamine (0.4mg/kg) vs. lidocaine (2.5mg/kg) vs. saline placebo administered intravenously over 40 min. **Pain Scale:** VAS	**1** **2** **3**	VAS scores were significantly reduced in ketamine vs. the placebo group ($p<0.01$). Comparing lidocaine and placebo group, no significant difference noted ($p=0.60$). Pain relief was not linked to altered temperature thresholds or other changes in sensory function.
Loubser & Donovan 1991[51] USA RCT PEDro=8	**N:**21 **Type of pain:** Not stated	**Treatment:** SCI patients with pain received 2 separate injections (placebo vs. 5% lidocaine in dextrose) through a lumbar subarachnoid catheter. **Pain Scale:** VAS	**1** **2** **3**	All 21 patients tolerated injections (anaesthetics and placebo) well. Negative placebo response was noted in 17 pts. Following lidocaine (n=13), patients showed a mean reduction in pain ($p<0.01$) for an average of 123.1± 95.3 min. Pain reduction post injection significant ($p<0.01$) for the treatment group only
Ketamine				

Author Year Country Score (PEDro/D&B)	Population	Intervention	Results	
Kvarnstrom et al.,2004[55] Sweden RCT PEDro=10	**N:**10 **Type of pain:** Individuals with neuropathic pain	**Treatment:** SCI patients were recruited for participation. Ketamine (0.4mg/kg) vs. lidocaine (2.5mg/kg) vs. saline placebo administered intravenously over 40 min. **Pain Scale:** VAS	**1** **2** **3**	VAS scores were significantly reduced in ketamine vs. the placebo group ($p<0.01$). Comparing lidocaine and placebo group, no significant difference noted ($p=0.60$). Pain relief was not linked to altered temperature thresholds or other changes in sensory function.
Eide et al., 1995[56] Norway RCT PEDro=7	**N:**9 **Type of pain:** Individuals with neuropathic pain	**Treatment:** SCI patients were given ketamine hydrochloride, alfentanil or a placebo as combination of bolus and continuous IV infusions. Bolus dose was administered for 60 seconds and the continuous intravenous infusion started simultaneously for 17 to 21 minutes while testing was performed. **Pain Scale:** VAS	**1** **2** **3** **4** **5** **6**	Freidmann's two-way analysis by ranks revealed differences between various treatments ($p=0.005$). Alfentanil and ketamine were significantly better than placebo ($p<0.01$ & $p<0.04$, respectively) No significant differences were noted between ketamine and alfentanil (Wilcoxon $p=0.19$). Significant differences were noted between the treatment groups ($p=0.008$). Allodynia was not changed more with ketamine vs. alfentanil (Wilcoxon $p=0.93$). Alfentanil reduced wind-up-like pain ($p=0.014$) compared to placebo. On ketamine, wind-up-like pain was not significantly reduced ($p=0.07$). A high correlation between the serum concentration of ketamine and the size of reduction in continuous pain ($r=0.78$, $p<0.002$) and reduction in wind-up-like pain ($r=0.83$, $p<0.002$) was noted.
Alfentanil				
Eide et al., 1995[56] Norway RCT PEDro=7	**N:**9 **Type of pain:** Individuals with neuropathic pain	**Treatment:** SCI patients were given ketamine hydrochloride, alfentanil or a placebo as combination of bolus and continuous IV infusions. Bolus dose was administered for 60 seconds and the continuous intravenous infusion started simultaneously for 17 to 21 minutes while testing was performed. **Pain Scale:** VAS	**1** **2** **3** **4** **5** **6**	Freidmann's two-way analysis by ranks revealed differences between various treatments ($p=0.005$). Alfentanil and ketamine were significantly better than placebo ($p<0.01$ & $p<0.04$, respectively) No significant differences were noted between ketamine and alfentanil (Wilcoxon $p=0.19$). Significant differences were noted between the treatment groups ($p=0.008$). Allodynia was not changed more with ketamine vs. alfentanil (Wilcoxon $p=0.93$). Alfentanil reduced wind-up-like pain ($p=0.014$) compared to placebo. On ketamine, wind-up-like pain was not significantly reduced ($p=0.07$). A high correlation between the serum concentration of ketamine and the size of reduction in continuous pain ($r=0.78$, $p<0.002$) and reduction in wind-up-like pain ($r=0.83$, $p<0.002$) was noted.
Clonidine/Morphine				

Author Year Country Score (PEDro/D&B)	Population	Intervention	Results	
Siddal et al. 2000[62] Australia RCT PEDro=8	**N:**8 **Type of pain:** Individuals with neuropathic pain	**Treatment:** Placebo, morphine or clonidine was delivered via catheter into lumbar intrathecal space in 8 SCI patients. Each was first given either: 0.2–1mg of morphine, 50 to 100 mcg of clonidine or placebo; dosage increased if the subject had no side effects and no pain relief. Patients could receive up to 1.5-times the initial drug dosage if necessary. Once each received satisfactory pain relief (or developed side effects from drug they were on), he or she was given a mixture of morphine and clonidine. **Pain Scale:** NPRS, VPR	**1** **2**	The administration of morphine or clonidine resulted in a mean reduction in pain levels; however, this was not statistically significant compared to the effects of placebo. When mixture of morphine and clonidine was administered, there was a significant reduction in pain vs. that achieved on placebo (p=0.008).
Uhle et al. 2000[63] Germany Prospective Controlled Trial D&B=9	**N:**10 **Type of pain:** Mixed group	**Treatment:** Subjects were implanted with an intrathecal pump, originally were given 3 ml saline followed by 1 ml morphine; this was followed by a second dose of morphine (0.02 mg) provided that no side effects or benefits had been noted. This was followed by clonidine (30 ug in 1 ml); then, depending on side effects, a final dose of Clonidine (50 ug in 1 ml). **Pain Scale:** VAS	**1** **2**	Subjects reported good to excellent pain reduction following clonidine administration. After clonidine bolus, subjects experienced the optimum pain reduction. Average initial dose of clonidine was 53 ug/day; this decreased (or stabilized) to 44 ug/day.
Morphine				
Attal et al. 2002[64] France RCT PEDro=10	**N:**15 **Type of pain:** Mixed group	**Treatment:** Initially, patients received IV morphine titrated up to the maximal tolerated dosage using successive bolus injections of 2 mg morphine every 10 minutes. Double blind phase began 3 weeks after titration phase. IV morphine or saline was administered. **Pain Scale:** VAS	**1** **2** **3** **4** **5** **6** **7**	Spontaneous pain scores decreased immediately after the end of the infusion of morphine and placebo for up to 120 minutes in both group. The effects of the morphine did not differ significantly from those who were given the placebo post injection. Those who reported pain relief from the treatment was higher (3x) after the morphine than after the placebo was given from 15 to 60 minutes post injection. Burning pain was weakened by the morphine in 7 pts and by placebo in 4 pts. When looking at the effects of morphine on mechanical allodynia it could be seen that the morphine produced a reduction in intensity. The saline treatment did not have an effect. The morphine significantly reduced (p<0.01) dynamic mechanical allodynia but not other pains.
Tramadol				
Norrbrink & Lundeberg 2009[65] Sweden RCT PEDro=8	**N:**35 **Type of pain:** Individuals with neuropathic pain	**Treatment:** Patients were randomized in a 2:1 ratio (tramadol/placebo) and treatment was administered for 4 weeks. Both patients and staff were blind to the treatments. Each patient was given 50mg tramadol or placebo 3 times daily. The daily dose was increased by 1 tablet every 5 days to a max dose of 8 tablets. **Pain Scale:** MPI-S	**1** **2**	Significant differences were seen in between group pain ratings (p<0.05). Patient Global Impression of Change rating was significantly higher in the tramadol group than the control group.

Author Year Country Score (PEDro/D&B)	Population	Intervention	Results	
			3	Significant improvements were seen in ratings of anxiety, global life satisfaction and sleep quality ($p<0.05$).
			4	No significant changes were seen in pain pleasantness, depression, or on the MPI scales pain interference, perceived life control, affective distress or social support.
Mexiletine				
Chiou-Tan et al. 1996[54] USA RCT PEDro=8	**N:**15 **Type of pain:** Individuals with neuropathic pain	**Treatment:** Following a 1-week washout period, SCI subjects given either 150 mg of mexiletine or placebo (150mg-3 × daily) followed by another 1-week washout period; subjects then crossed over to opposite treatment. **Pain Scale:** VAS, MPQ	**1**	No significant inter-group differences in average pain over preceding week or pain at time of testing.
			2	No difference in McGill Pain scores.
			3	No changes in level of function.
Capsaicin				
Sandford et al., 2000[67] USA Case Studies D&B=4	**N:**8 **Type of pain:** Not stated	**Treatment:** Charts reviewed for individuals given capsaicin to reduce pain. **Pain Scale:** Not stated	**1**	Patients reported a reduction in pain following the administration of capsaicin.

Abbreviations: D&B = Downs and Black quality assessment scale score[27] ;IV = Intravenous; MPI-S = Multidimensional Pain Inventory MPQ = McGill Pain Questionnaire; NPS = Neuropathic Pain Scale; NPSI = Neuropathic Pain Symptom Inventory; NRS = 11 Point Numeric Rating Scale; PEDro = Physiotherapy Evidence Database rating scale score[26]; VAS = Visual Analogue Scale; VPR = Verbal Pain Rating

Table 5

Cannabinoids for Post-SCI Pain

Author Year Country Score (PEDro/D&B)	Population	Intervention	Results	
Hagenbach et al.2007[70] Switzerland RCT (Phase 3) PEDro=4	**N:**13 **Type of pain:** Spastic pain	**Treatment:** In a double blind manner, SCI patients from phase 1 of the study were randomly assigned to either maximum oral THC doses (6 participants) or placebo doses (7 participants) for 6 weeks. **Pain Scale:** Self ratings	**1** **2**	No significant improvement in pain post SCI was seen compared to placebo on day 8 and 43. Individuals in the oral THC group showed no significant difference in mood or attention compared to the placebo group or to baseline.
Hagenbach et al., 2007[70] Switzerland Pre-Post (Phase 1) D&B=16	**N:**22 **Type of pain:** Spastic pain	**Treatment:** Patients received 10mg oral THC on day 1. Dose titration began on day 2 until the maximum tolerated dose or treatment aim was achieved and maintained for 6 weeks. **Pain Scale:** Self ratings	**1**	Significant improvement in pain was seen on day 1 compared to baseline measures (p=0.047).

Abbreviations: D&B = Downs and Black quality assessment scale score[27]; EDro = Physiotherapy Evidence Database rating scale score[26]

Table 6

Antispastic Medications for Post-SCI Pain

Author Year Country Score (PEDro/D&B)	Population	Intervention	Results	
Baclofen				
Herman et al. 1992[71] USA RCT PEDro=8	**N:**10 **Type of pain:** Mixed group	**Treatment:** Baclofen and placebo were randomly administered into L1-2 inter-space of each of 7 SCI patients. In the non-RCT group only 2 subjects were enrolled in the study. **Pain Scale:** Not stated	**1**	Intrathecal baclofen significantly suppressed neurogenic (burning quality) pain among 6 of the 7 RCT subjects ($p<0.001$).
			2	Pinch inducted pain was not affected by either placebo or Baclofen.
Loubser and Akman 1996[76] USA Pre-Post D&B=13	**N:**16 **Type of pain:** Mixed group	**Treatment:** Baclofen infusion pump was implanted into SCI patients. **Pain Scale:** VAS	**1**	12/16 patients described chronic pain prior to procedure.
			2	No significant differences were noted between VAS at the 6 and 12-month assessments following pump implantation.
			3	For those with neuropathic pain symptoms, ANOVA revealed a non-significant effect of intrathecal baclofen on pain at both 6 and 12 months. ($p=0.26$).
			4	In 5 of 6 patients with musculoskeletal pain symptoms, pain severity decreased in conjunction with control of spasticity. Musculoskeletal pain responded to baclofen infusion, while neuropathic pain did not.
Botulinum Toxin				
Marciniak et al. 2008[77] USA Case series D&B=12	**N:**28 **Type of pain:** Mixed group	**Treatment:** Botulinum toxin (BTX) type A injection for focal spasticity control. **Pain Scale:** Not stated	**1**	Improvement was seen post-injection in: • Ambulation, 56%. • Positioning, 71%. • Upper-extremity function, 78%. • Hygiene, 66.6%. • Pain, 83.3%.
			2	The effectiveness of the BTX injections was not influenced by early use of BTX injections (less than a year after onset of symptoms) vs. late use.
			3	Improvement in those with upper arm compared to lower arm injections was similar. Also, level of completeness of the SCI did not effect improvement.

Abbreviations: D&B = Downs and Black quality assessment scale score[27]; EDro = Physiotherapy Evidence Database rating scale score[26]; VAS = Visual Analogue Scale

Table 7

Treatment Effectiveness Summary

Treatment	Type of pain	Effectiveness	Level of Evidence
Gapapentin	Neuropathic	+	1
Pregabalin	Neuropathic	+	1
Lamotrigine	Neuropathic	+*	2
Valproic acid	Neuropathic	−	1
Levetiracetam	Neuropathic	−	1
Trazodone	Neuropathic	−	1
Amitriptyline	Neuropathic	+**	1
Lidocaine	Neuropathic	+***	1
Intravenous Ketamine	Neuropathic	+	1
Intravenous Alfentanil	Neuropathic	+	1
Intrathecal Morphine/Clonidine	Neuropathic/Mixed	+	1/2
Intravenous Morphine	Mixed	+	1
Tramadol	Neuropathic	+	1
Mexilitene	Neuropathic	−	1
Capsaicin	Mixed	+	5
Cannabinoids	Spastic	+/−	2/4
Intrathecal Baclofen	Neuropathic	+/−	1/4
Intrathecal Baclofen	Musculoskeletal/Spastic	+	4
Botulinum Toxin	Spastic	+	4

Abbreviations:+ = Effective; − = Not effective; +/− = conflicting;

*
only in individuals with incomplete SCI;

**
only in depressed individuals;

***
short term