SCIRE

SPINAL CORD INJURY REHABILITATION EVIDENCE

Pain Following Spinal Cord Injury

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Key Points

Pain post SCI has a significant effect of quality of life.

Post-SCI pain is common and often severe beginning relatively early post-injury.

Post-SCI pain is most commonly divided into neuropathic or musculoskeletal pain.

Massage may not be helpful for post-SCI neuropathic and musculoskeletal pain.

Osteopathy alone may not be helpful for post-SCI neuropathic pain.

Acupuncture may reduce post-SCI neuropathic and musculoskeletal pain.

Electrostimulation acupuncture is effective in improving neuropathic pain in SCI pain.

Regular exercise reduces post-SCI neuropathic and musculoskeletal pain.

A shoulder exercise protocol reduces post-SCI nociceptive shoulder pain intensity.

MAGIC wheels 2 gear wheelchair reduces nociceptive shoulder pain.

Hypnosis may reduce neuropathic and musculoskeletal pain intensity post SCI.

Biofeedback may reduce neuropathic and musculoskeletal pain intensity post SCI.

Cognitive behavioral therapy combined with pharmacological treatment may result in improvement in secondary outcomes among SCI individuals with chronic pain.

Cognitive-behavioral pain management programs alone do not alter post-SCI pain.

Visual imagery may reduce neuropathic pain post SCI

Transcranial electrical stimulation is effective in reducing post SCI neuropathic pain.

Static field magnet may reduce nociceptive shoulder pain post SCI.

Transcutaneous electrical nerve stimulation may reduce pain at site of injury in patients with thoracic but not cervical injury.

Transcranial magnetic stimulation reduces post-SCI neuropathic pain.

Gabapentin and pregabalin improve neuropathic pain post SCI.

Combined osteopathy and pregabalin may improve pain post SCI.

Lamotrigine may improve neuropathic pain in incomplete spinal cord injury

Levetiracetam is not effective in reducing neuropathic pain post SCI.

Valproic acid does not reduce neuropathic pain post SCI.

Amitriptyline is effective in reducing neuropathic pain in depressed SCI individuals.

Duloxetine may improve neuropathic pain post SCI

Trazodone does not reduce post-SCI neuropathic pain.

Lidocaine through a subarachnoid lumbar catheter and intravenous Ketamine improve post-SCI neuropathic pain short term.

Mexilitene does not improve SCI dysesthetic pain.

Intrathecal Baclofen improves musculoskeletal pain post SCI and may help dysethetic pain related to spasticity.

Motor point phenol block reduces spastic shoulder pain.

Botulinum toxin injections for focal spasticity improves pain.

Intravenous morphine reduces mechanical allodynia.

Tramadol reduces neuropathic pain.

Alfentanil reduces chronic pain post SCI.

Alfentanil is more effective in reducing wind up like pain post SCI than ketamine.

Oxycodone and anticonvuslants may improve neuropathic SCI pain.

Cannabinoids are a potential new treatment for post-SCI pain in need of further study.

Dronabinal is not effective in reducing pain post SCI.

Intrathecal Clonidine alone does not appear to provide pain relief although it may be helpful in combination with Intrathecal Morphine.

Topical capsaicin reduces post-SCI radicular pain.

Spinal cord stimulation may improve post-SCI neuropathic and musculoskeletal pain.

Dorsal longitudinal T-myelotomy procedures reduce pain post SCI.

DREZ surgical procedure reduces pain post SCI.

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Pain Following Spinal Cord Injury

1.0 Executive Summary

Pain is a common concern among persons with spinal cord injury. Incidence of pain following SCI can range anywhere from 48 to 92% (Britell & Mariano 1991; Cohen et al. 1988; Mariano 1992; Modirian et al. 2010; Rose et al. 1988Pain often starts immediately after SCI and can continue to increase over time among 47% of individuals; while it decreases in only 7% Turner et al. (2001).). It is estimated that 30-40% of patients with SCI experience severe disabling pain (Burke & Woodward 1976). Pain is often reported as the most important factor for decreased quality of life. Most studies of chronic SCI pain have focused on the medical causes and clinical manifestations of pain while much less is understood about how psychosocial factors impact SCI pain (Summers et al. 1991). Pain itself was found to be associated with greater emotional distress than the SCI itself. Hence treatment of post-SCI pain should involve these multidimensional aspects.

How is it classified?

Recently, an international group of clinicians and researchers developed a consensus for an SCI pain classification, International Spinal Cord Injury Pain Classification (ISCIP Classification). The ISCIP classification incorporates common pain pathology after SCI even those not necessarily related to SCI itself (Bryce et al. 2012). The system classifies pain at three tiers. Tier 1 includes pain types such as nociceptive, neuropathic, other pain, or unknown pain. Tier 2 provides a subtype of each type, nociceptive pain consists of musculosketal, visceral, and other nociceptive pain types. Neuropathic pain consists of at level, below level, and other neuropathic pain. The last tier defines the primary source of the pain or its related pathology.

What are the management options for pain post SCI?

Currently, anticonvulsants such as gabapentin and pregabalin are considered first line treatment for neuropathic pain post SCI. Other pharmacological approaches to manage pain post SCI pain include tricyclic antidepressants (e.g. amitriptyline), anesthetics (eg. lidocaine), antispastics (e.g. baclofen), opioids, and cannabinoids. There is evidence for the use of several non-pharmacological approaches to pain post SCI including massage, osteopathy, acupuncture, transcranial direct current stimulation, transcranial electrical stimulation, transcutaneous electrical nerve stimulation, transmagnetic stimulation, neuromuscular electrical stimulation, functional electrical stimulation, diet, and physical activity. Behavioural management of SCI related pain include approaches such as visual illusion, biofeedback, hypnotic suggestion, mindfulness, and cognitive behaviour therapy. Surgical approaches are considered last line of management strategies used to treat intractable pain. These include spinal cord stimulation, dorsal longitudinal t-myelotomy, and dorsal rhizotomy.

Gaps in the Evidence

Though the pain experience is multidimensional, there is surprisingly a lack of evidence for multimodal approaches to pain management. Studies evaluating the combination of non-pharmacological, behavioural, and pharmacological approaches should be evaluated. There is a lack of evidence on which approaches work best for each type of pain. Studies targeting treatments to specific types of pain are warranted. Lastly, there is a lack of evidence on the effectiveness of several treatments over long term follow-ups, with most studies limiting follow-ups to months.

2.0 Introduction

The last few decades have witnessed increasing sophistication and advances in the rehabilitation of spinal cord injured (SCI) patients with marked improvements in the quality of care accompanied by significant reductions in morbidity and mortality. Despite these impressive gains in bladder, skin, cardiovascular and respiratory care, the treatment of chronic pain in SCI has proven largely refractory to medical management. This lack of treatment efficacy has been complicated by an incomplete understanding of pain in individuals with spinal cord injuries and lack of a standardized framework upon which to classify these injuries (Burchiel & Hsu 2001).

3.0 Incidence, Quality and Significance

3.1 Incidence of Pain Post SCI

Pain is a frequent complication of traumatic spinal cord injury. Reported estimates of the incidence of pain following SCI range anywhere from 48 to 92% (Britell & Mariano 1991; Cohen et al. 1988; Mariano 1992; Modirian et al. 2010; Rose et al. 1988). These wide ranging estimates are felt to be a reflection of significant heterogeneity in defining pain in this population. Bonica (1991) reviewed data contained in 10 reports that surveyed 2,449 SCI patients (Botterell et al. 1953; Britell 1986; Burke 1973; Davis & Martin 1947; Kaplan et al. 1962; Munro 1950; Nepomunceno et al. 1979; Richards et al. 1980; Rose et al. 1988; Woolsey 1986). Chronic pain was present in 1,695 (69%) and in 30% of these patients it was rated as severe. Six of the reports (Botterell et al. 1953; Burke 1973; Davis & Martin 1947; Nepomunceno et al. 1979; Rose et al. 1988; Woolsey 1986) analyzed the different types of pain. Out of a total of 1,965 patients, 608 (31%) of the patients had central pain, dysesthesia, or phantom limb pain, 219 (12%) had root pain, and 198 (10%) had visceral pain caused by a central mechanism. There were 1,028 (53%) SCI patients with deafferented pain.

3.2 Impact on Quality of Life

It is estimated that 30-40% of patients with SCI experience severe disabling pain (Burke & Woodward 1976). Pain is often reported as the most important factor for decreased quality of life. Nepomuceno et al. (1979) noted that 23% of individuals with cervical or high thoracic SCI and 37% of those with low thoracic or lumbosacral injury would trade the loss of sexual and/or bowel and bladder function as well as hypothetical possibility for cure to obtain pain relief.

Rose et al. (1988) sent a questionnaire to 1,091 spinal cord injured individuals. Pain, which was reported as constant in 43%, was considered severe at some point in the day in half the sample and mild to moderate in 21% of respondents. Prior to the SCI, 595 of the sample were employed; afterwards only 325 were employed. Interestingly 98 SCI individuals (11%) reported it was the severity of their pain and not their paralysis, which stopped them from working. Of the 325 SCI subjects (83%) who were employed, 269 reported that the pain interfered with their

work. A total of 118 SCI subjects found that the pain was severe enough to stop social activity. Pain appeared to be more severe in the evening and at night, interfering with sleep in 325 of respondents (37%). This study clearly pointed out the importance of chronic pain in determining disability and morbidity in SCI patients (Rose et al 1988). Another survey in the Netherlands found 63.8% of respondents experienced high pain levels (Heutnik et al. 2011). NSW ACI Pain Network (2013) found that neuropathic pain was the most distressing for people with SCI.

Pain post SCI has a significant effect of quality of life.

3.3 Severe Pain and SCI Location

Persons with SCI who complain of severe pain are more likely to have low spinal cord or cauda equina lesions (Botterell et al. 1953; Davis & Martin 1947; Nepomuceno et al. 1979; Ragnarsson 1997). Severe pain was noted in 10-15% of persons with quadriplegia; 25% of those with thoracic paraplegia and 42-51% of those with lesions of the cauda equina (Ragnarsson 1997)

3.4 Natural History of SCI Pain

Turner et al. (2001) examined the timing of the development of pain post-SCI noted that in 901 patients with SCI, pain started immediately after SCI in 34%, within the first year in 58%, pain increased over time in 47% and decreased over time in 7%. Turner et al. (2001) noted that pain most often started within the first 6 months following SCI. This has also been noted in several other studies (Nepomuceno et al. 1979; Siddall et al. 1999; Stormer et al. 1997; Turner & Cardenas 1999).

Conclusion

For many SCI patients, pain has a significant impact on quality of life.

Over 50% of SCI patients develop chronic pain. Severe pain is more common the lower down the lesion in the spinal cord. Pain post SCI most often begins within the first 6-12 months post-SCI.

Post-SCI pain is common and often severe beginning relatively early post-injury.

4.0 Location and Quality of SCI Pain

Widerstrom-Noga et al. (2001) conducted a careful analysis of the relationship between the location of the pain and the patients' description of the pain. In this study 217 of 330 patients reporting chronic pain in a previous survey agreed to participate in the study. Participants had been injured for an average of 8.2±5.1 years and 55.4% were quadriplegic. Most subjects in this study marked multiple areas on a pain drawing with the back area being most frequently implicated (61.8%). 59.9% complained of a burning pain while 54.9% described an aching pain. Interestingly burning pain was significantly associated with pain localized to the front of the torso and genitals, buttocks and lower extremities. In contrast, aching type pain was significantly associated with pain localized to the neck, shoulders and back.

Widerstrom-Noga et al. (2001) noted that the descriptor “burning” is often associated with neuropathic pain (Fenollosa et al. 1993; Ragnarsson 1997; Siddall et al. 1999) whereas “aching” is often associated with musculoskeletal pain (Siddall et al. 1999; Tunks 1986). However, since there is a significant overlap in the quality of pain types it is difficult to establish a definitive clinical relationship (Bowsher 1996; Eide 1998; Widerstrom-Noga et al. 2001). Widerstrom-Noga et al. (2001) suggest that musculoskeletal-type pain (best characterized by the aching pain in the neck, shoulders and back) is potentially amenable to therapeutic interventions and aggressive attempts should be made to ameliorate this type of pain. All of this underscores the need for a reproducible classification system of the pain experienced following SCI. Bennett et al. (2007) have noted that the increasing reliance on validated screening tools may help “form the basis of forthcoming clinical diagnostic criteria”.

Conclusion

The most common types of pain post SCI are: 1) a burning pain (likely neuropathic) usually localized to the front of torso, buttock or legs or 2) an aching pain (likely musculoskeletal) usually localized to the neck, shoulders and back.

Post-SCI pain is most commonly divided into neuropathic or musculoskeletal pain.

5.0 Classification of SCI Pain

Siddall et al. (1997) noted that one of the concerns regarding SCI-related pain was a lack of consensus over a classification system for SCI pain. This has led to considerable variation in incidence and prevalence rates for pain post SCI depending on the classification system used. Twenty-eight classification schemes have been published between 1947 and 2000. A Task Force on Pain Following Spinal Cord Injury of the International Association for the Study of Pain has introduced a taxonomy, which classified SCI pain based on presumed etiology (Burchiel & Hsu 2001; Siddall et al. 2000). Recently, an international group of clinicians and researchers developed a consensus for an SCI pain classification, International Spinal Cord Injury Pain Classification (ISCIP Classification). The overall structure of the ISCIP classification is similar to that developed by the previous IASP classification of pain related to SCI. However, the new system has merged and improved on previously published SCI classification systems. The ISCIP classification incorporates common pain pathology after SCI even those not necessarily related to SCI itself (Bryce et al. 2012).

Table 1 International Spinal Cord Injury Pain Classification (Bryce et al. 2012)

Tier 1: Pain type	Tier 2: Pain subtype	Tier 3: Primary pain source and/or pathology
Nociceptive	Musculoskeletal	e.g. glenohumeral arthritis, lateral epicondylitis, comminuted femur fracture, quadratus lumborum muscle spasm.
	Visceral	e.g. myocardial infarction, abdominal pain due to bowel impaction, cholecystitis.
	Other nociceptive pain	e.g. autonomic dysreflexia headache, migraine headache, surgical skin incision.
Neuropathic	At Level SCI pain	e.g. spinal cord compression, nerve root compression, cauda equine compression
	Below level pain	e.g. spinal cord ischemia, spinal cord compression
	Other neuropathic pain	e.g. carpal tunnel syndrome, trigeminal neuralgia, diabetic polyneuropathy.
Other pain		e.g. fibromyalgia, Complex Regional Pain Syndrome type I, interstitial cystitis, irritable bowel syndrome

Tier 1: Pain type	Tier 2: Pain subtype	Tier 3: Primary pain source and/or pathology
Unknown pain		

Table 2 Previous IASP Classification of Pain Related to SCI (Burchiel & Hsu 2001)

Broad Type (Tier 1)	Broad System (Tier 2)	Specific Structure/Pathology (Tier 3)
Nociceptive	Musculoskeletal	Bone, joint, muscle trauma, or inflammation Mechanical instability Muscle spasm Secondary overuse syndromes
	Visceral	Renal calculus, bowel, sphincter dysfunction, etc. Dysreflexic headache
Neuropathic	Above Level	Compressive mononeuropathies Complex regional pain syndromes
	At Level	Nerve root compression (including cauda equine) Syringomyelia Spinal cord trauma/ischemia (transitional zone, etc.) Dual-level cord and root trauma (double lesion syndrome)
	Below Level	Spinal cord trauma/ischemia (central dysesthesia syndrome, etc.)

Table 3 SCI pain types according to major classification*

Bryce/Ragnarsson	Cardenas	Donovan	ISAP	Tunks
Above level 1) Nociceptive 2) Neuropathic At level 3) Nociceptive 4) Neuropathic Below level 5) Nociceptive 6) Neuropathic	Neurologic 1) Spinal cord 2) Transition zone 3) Radicular 4) Visceral Musculoskeletal 5) Mechanical spine 6) Overuse	1) Segmental 2) Spinal cord 3) Visceral 4) Mechanical 5) Psychogenic	Nociceptive 1) Musculoskeletal 2) Visceral Neuropathic 3) Above level 4) At level 5) Below level	Above level 1) Myofascial 2) Syringomyelia 3) Non-spinal cord injury At level 4) Radicular 5) Hyperalgesic border reaction 6) Fracture 7) Myofascial (incomplete) Below level 8) Diffuse burning 9) Phathom 10) Visceral 11) Myofascial (incomplete)

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Table 4 Reliability of SCI pain classification systems

	Kappa coefficient[1]	Percent agreement
Bryce and colleagues	.70	Unavailable
Cardenas	.68	Unavailable
Donovan	.55	50%-62%
IASP	.49	52%
Tunks	.49	27%

[1]Kappa coefficient is the proportion of agreement controlling for change agreement, with 1.0 representing perfect agreement between raters. Kappa coefficients greater than .60 or .70 reflect substantial interrater agreement.

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6.0 Musculoskeletal or Mechanical Pain

Musculoskeletal or mechanical pain occurs at or above the level of the lesion and is due to changes in bone, tendons or joints (Guttmann 1973). This is referred to as *nociceptive pain* caused by a variety of noxious stimuli to normally innervated parts of the body (Ragnarsson 1997). Overuse of remaining functional muscles after spinal cord injury or those recruited for unaccustomed activity may be of primary importance in some patients (Farkash & Portenoy 1986). Pain may also be secondary to spinal osteoporosis or facet arthropathy (Farkash & Portenoy 1986). Instability of the vertebral column may also be a problem (Farkash & Portenoy 1986). Pain is usually dull and aching in character and although more common soon after SCI, it may become chronic.

Sie et al. (1992) studied 239 SCI outpatients for the presence of upper extremity pain. Of the 136 patients with quadriplegia, 55% reported upper extremity pain, most commonly at the shoulder (46% of all subjects). In the case of shoulder pain, 45% were orthopedic-related including tendonitis, bursitis, capsulitis and osteoarthritis. Of the 103 paraplegics, 66 reported upper extremity pain with two-thirds reporting symptoms of carpal tunnel syndrome and 13 reporting musculoskeletal-related shoulder pain. Dalyan et al. (1999), in a questionnaire returned by 130 SCI patients, found that 58.5% of patients reported upper extremity pain. Of these, 71% had shoulder pain, 53% wrist pain, 43% hand pain, and 35% elbow pain. Pain was most likely to be associated with pressure relief, transfers, and wheelchair mobility. Subbarao et al. (1995), in a survey of 800 SCI patients, found that 72.7% of responders reported some degree of chronic pain at the wrist and shoulder, with wheelchair propulsion and transfers being responsible for most of the pain. McCasland et al. (2006) noted that in their survey, 70% of SCI had shoulder pain, one-third had a previous injury to their shoulder and 52% reported a bilateral pain. Quadriplegics were more likely to have shoulder pain (80%). Previous shoulder trauma increased the risk of having shoulder pain.

7.0 Central or Neurogenic Dysesthetic Pain

"Central" dysesthesia or "deafferentation" pain is the most common type of pain experienced below the level of SCI and is generally characterized as a burning, aching and/or tingling sensation. In many cases this dysesthetic or deafferentation pain has defied a pathophysiological explanation (Britell 1991) although most researchers firmly support a central nervous system origin for this pain. Nashold (1991) goes as far as stating that except for radicular pain, all other pains of paraplegia are central or deafferentation in origin. This pain is most often perceived in a generalized manner below the level of the lesion, often a diffuse burning type of pain (Britell 1991; Tunks 1986). Burning pain is reportedly most common with lesions at the lumbar levels, although it may be found with SCI at thoracic and cervical levels (Tunks 1986). Nashold (1991) reported this pain occurred almost immediately after SCI and persisted.

Beric (1997) refers to this pain as central dysesthetic pain (CDP) and found dissociative sensory loss and absence of spinothalamic-anterolateral functions, with different degrees of dorsal column function preservation present almost exclusively in incomplete SCI patients. CDP takes weeks or months to appear and is often associated with recovery of some spinal cord function. Paradoxically CDP is often characterized by complete loss of temperature, pinprick, and pain perception below the level of the lesion. It rarely occurs in spinal cord Injuries with complete sensory loss or loss of both sensory and motor functions below the level of the lesion. Davidoff et al. (1987a) concurred and further noted dysesthetic pain was more likely to be found in incomplete paraplegia resulting from penetrating wounds of the spinal cord, and in spinal fractures treated with conservative management.

A number of factors may contribute to exacerbations of these "central" pain syndromes; these include visceral diseases or disturbances, movement, smoking or alcohol, emotional factors, fatigue, and even weather changes (Botterell et al. 1953; Davis & Martin 1947; Davis 1975; Tunks 1986). Pressure sores, particularly if infected, or an occult injury such as a fracture, may result in an increase in burning, dysesthetic pain. These stimuli often provoke autonomic dysreflexic-like symptoms and simultaneously also may aggravate this "burning" pain.

8.0 Borderzone or Segmental Pain

Individuals with SCI frequently experience a band of pain and hyperalgesia at the border zone between diminished or abnormal and preserved sensation (Botterell et al. 1953; Davis 1975; Heliporn 1978; Kaplan et al. 1962; Maury 1978; Melzack & Loeser 1978; Michaelis 1970; Tunks 1986). In the more recent literature, this segmental pain is further described as occurring at or just above the level of sensory loss in the cutaneous transition zone from the area of impaired/lost sensation to areas of normal sensation, involving at least one to three dermatomes (Friedman & Rosenblum 1989; Nashold 1991; Ragnarsson 1997) and is often associated with spontaneous painful tingling or burning sensations in the same area. Ragnarsson (1997) also noted that in an individual with a cervical cord injury, segmental pain may be described as tingling, burning or numbing pain in the shoulders, arms or hands, those with a thoracic cord injury frequently describe a circumferential, feeling of tightness and pain around the chest and abdomen while lumbar lesions tend to be localized to the groins and different parts of the lower extremities. According to Nashold (1991) paraplegics often complain that touching the skin in the pain region activates the pain causing it to radiate into the lower parts of the body, especially the legs. Pain can be triggered by stroking and/or touching the skin in adjacent painful dermatomes (Nashold 1991). Even light touch or the pressure of clothing or bed sheets over this region may provoke marked discomfort (Tunks 1986). It may be accompanied by sweating or vasodilation at or below the level of hyperalgesia. Segmental pain is generally symmetrical although a partial spinal cord injury with asymmetrical neurological involvement will produce asymmetries (Nashold 1991).

This pain has also been described as "neuropathic at level pain" (Siddall et al. 1997)
Although several theories have been proposed (Levitt 1983; Matthew & Osterholm 1972; Melzack & Loeser 1978; Nashold & Bullitt 1981; Pollock et al. 1951; Tunks 1986) the neurological mechanism responsible for this area of hyperalgesia after spinal injury is not well understood (Farkash & Portenoy 1986). Although radicular pain is most severe in incomplete SCI lesions, it is also seen in transected cauda equina lesions which are by definition radicular types of pain (Heaton & Coates 1965; Siddall et al. 1997). It may also be secondary to spinal cord instability by facet or disc material, or to direct damage to the nerve root during the initial injury (Burke 1973; Nashold 1991). This “radicular” pain is associated with sensory change in the involved painful dermatome (Nashold 1991) and is most common to cervical or lumbosacral nerve roots. Non-neural structures, such as the dura mater, have also been suggested as a source of radicular pain (Cyriax 1969; Farkash & Portenoy 1986). In addition, it has been suggested that central borderzone pain may be generated in the damaged spinal cord just proximal to the spinal cord injury (Nashold 1991; Pollock et al. 1951). Unfortunately, unless there is definitive evidence on imaging of nerve root damage, it is difficult to distinguish between these various mechanisms of pain.

To reflect this uncertainty Siddall et al. (1997) in their proposed classification of SCI pain note that this "neuropathic at level pain" is divided into radicular and central pain. Radicular pain is due to nerve root pathology while central pain is due to changes within the spinal cord or

possibly supraspinal structures. Pain attributable to nerve root damage is suggested by features of neuropathic pain (i.e. burning, stabbing, shooting, electric-like pain, allodynia) and increased pain with spinal movement. Sjolund (2002) notes that this pain is thought to occur from nerve root entrapment and may occasionally benefit from decompression.

However, pain, which appears radicular in nature, may occur in the absence of nerve root damage. This leads to the second grouping of borderzone pain, namely central pain or that which is due to pathology within the spinal cord thought to be the result of damage to the gray matter of the dorsal horn of the spinal cord (Ragnassaron 1997; Woolsey 1995). According to Ragnassaron (1997), such an injury *"has been said to result in hyperactivity of the nociceptor cells within the dorsal horn* (Nashold & Bullitt 1981; Nashold & Ostdahl 1979) *which can be electrically recorded* (Nashold & Alexander 1989)*."* Sojlund (2002) notes that this second type of at level neuropathic pain is experienced as a girdle pain uni- or bilaterally in 2-4 segments of the transitional region. This pain is described as stimulus independent, often accompanied by troublesome allodynia or hyperalgesia and thought to arise from segmental deafferentation (Sjolund 2002).

9.0 Psychological Factors

Most studies of chronic SCI pain have focused on the medical causes and clinical manifestations of pain while much less is understood about how psychosocial factors impact SCI pain (Summers et al. 1991). Pain itself was found to be associated with greater emotional distress than the SCI itself. A negative psychosocial environment along with increased age, depression, anxiety and intellect were found to be associated with reports of greater post-SCI pain severity interfering with activities of daily living (Richards et al. 1980). Greater pain severity was not associated with physiological factors such as injury level, completeness of injury, surgical fusion and/or instrumentation or veteran status. The authors were unable to distinguish whether the psychological factors were a consequence of, or contributors to, greater pain severity. Summers et al. (1991) studied 54 SCI patients (19 with quadriplegia and 35 with paraplegia) and of these, 42 patients assessed with the Pain questionnaire found that anger and negative cognitions were associated with greater pain severity. Severity of pain was higher in patients who reported pain in response to a question on general well-being, those that were less accepting of their disability and those that perceived that a significant other would express punishing responses to their pain behaviours. The authors concluded that the experience of pain was associated with psychosocial factors. Hence treatment of post-SCI pain should involve these multidimensional aspects.

Cohen et al. (1988) found that patients with complete SCIs reported significantly less severe pain than did pain clinic patients. However, they did not differ from patients with incomplete lesions. Patients with complete SCIs and pain clinic patients showed a significantly more disturbed Minnesota Multiphasic Personality Inventory(MMPI) profile than did patients with incomplete SCIs. It was hypothesized that those patients with complete lesions view themselves as more functionally limited than patients with incomplete lesions, and the completeness of the SCI may be more important in determining psychosocial adjustment than pain per se. Rintala et al. (1998) in community-based men with SCI found that chronic pain was associated with more depressive symptoms, more perceived stress and poorer self-assessed health.

Wollaars et al. (2007) administered questionnaires to persons with a SCI. Of the potential 575 subjects, 49% provided responses. SCI pain prevalence was 77%. Factors associated with less pain intensity included more internal pain control and coping, less catastrophizing, a higher level of lesion and a non-traumatic SCI cause. More pain was associated with greater pain-related

disability. Lower catastrophizing was related to better health. Factors related to greater well-being included less helplessness and catastrophizing, greater SCI acceptance and lower anger levels. Greater levels of depression were associated with higher levels of SCI helplessness, catastrophizing and anger. The authors noted that chronic SCI pain and quality of life were both largely associated with several psychological factors of which pain catastrophizing and SCI helplessness were more important. Surprisingly, pain intensity showed no independent relationships with health, well-being and depression (Wollaars et al. 2007).

Widerström-Noga et al. (2007) studied 190 patients with SCI and chronic pain and were able to identify three subgroups. The first group was described as 'dysfunctional', characterized by higher pain severity, life interference, affective distress scores, and lower levels of life control and activities scores. The second group was described as 'interpersonally supported', characterized by moderately high pain severity, and higher life control, support from significant other, distracting responses, solicitous response, and activities scores. The final group was described as 'adaptive copers', characterized by lower pain severity, life interference, affective distress, support from significant others, distracting responses, solicitous responses, activities and higher life control scores. Compared with dysfunctional subgroup, the interpersonally supported group reported significantly greater social support (Widerström-Noga et al. 2007).

9.1 Catastrophizing and Pain Post SCI

When pain post SCI is refractory to pharmacological and surgical treatment, it is important to fully understand the negative impact of the patient's psychosocial environment prior to undertaking more invasive approaches to treatment.

Table 5 Catastrophizing and Pain Post SCI

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Giardino et al. 2003 USA Case Series N=74	**Population:** Age=21-64 yr; Gender: males=60, females=13. **Treatment:** Questionnaire. **Outcome Measures**: Coping Strategies Questionnaire (CSQ), Short form McGill Pain Questionnaire (SF-MPQ), West Haven-Yale Multidimensional Pain Inventory (WHYMPI) solicitous subscale and CES-D scale.	1. CSQ catastrophizing was associated with WHYMPI ($p<0.05$), CES-D ($p<0.001$), SF-MPQ (sensory pain) ($p<0.01$) and CSQ SF-MPQ (affective pain) ($p<0.001$). 2. Catastrophizing also accounted for significant variance in sensory pain scores ($t=2.63$, $p<0.05$). An interaction between relationship type and catastrophizing was also found ($p<0.05$). 3. A significant relationship was noted between affective pain score and solicitousness ($p<0.05$) and catastrophizing and solicitousness ($p<0.05$). 4. Catastrophizing itself accounted for a significant amount of variance in affective pain scores ($p<0.01$).

Giardino et al. (2003) noted that pain-related catastrophizing, or exaggerating the negative consequences of a situation, has been associated with greater pain intensity, emotional distress and functional disability in patients with chronic pain conditions and SCI. This was thought to provide partial support for a "communal coping" model of catastrophizing, where catastrophizing

in persons with pain may function as a social communication directed toward obtaining social proximity, support or assistance.

10.0 Non-Pharmacological Management of Post-SCI Pain

Before moving to pharmacological and surgical interventions, it is important to deal with those factors which may intensify or worsen the experience of pain. As mentioned previously, SCI pain may be worsened by decubitus ulcers, a urinary tract infection or stone, autonomic dysreflexia, increased spasticity, anxiety, depression, psychosocial factors and other contributors to post-SCI pain (Davis et al. 1998; Tunks 1986). There are a number of non-pharmacological interventions for post-SCI pain which have been studied from massage to hypnosis.

10.1 Massage

Massage are used primarily to treat musculoskeletal pain. Their benefit is well known in a number of musculoskeletal pain disorders, although there are significant differences among therapists as to how treatment is delivered.

Table 6 Massage in Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Lovas et al. 2017 Australia RCT PEDro=4 N=40	**Population:** Mean age=46.0±11.6 yr; Gender: males=34, females=6; Time since injury=18.4±12.1 yr; Level of injury: paraplegia=30, tetraplegia=9; Severity of injury: complete=20, incomplete=19; Type of pain=neuropathic and musculoskeletal. **Intervention:** Participants were randomized to either a Swedish upper body massage group (MT) or n active concurrent control guided imagery (GI) relaxation group for 5 wks with one session per wk. **Outcome Measures:** Short-form McGill pain questionnaire (MPQ) and Chalder's fatigue scale (CFS).	1. No significant differences between groups for pain severity scores ($p>0.05$). 2. Pain scores reduced significantly over time from pre-treatment to post-treatment in both groups ($p<0.01$). 3. No significant interaction effect between groups and intervention over time ($p<0.05$). 4. No significant between-group differences in overall CFS scores ($p>0.05$). 5. Fatigue scores reduced significantly over time ($p<0.01$). 6. No significant interaction effect between groups and intervention over time ($p>0.05$).
Chase et al. 2013 USA RCT PEDro=5 N=40	**Population:** Age=40.24 yr. Sex: Males=33, Females=7; Mean time since injury was 69.35days. Severity of injury: complete=23. Incomplete=17. Type of pain=neuropathic and musculoskeletal **Intervention:** SCI individuals in rehabilitation facility were randomly assigned to receive broad compression massage (BCM) or light contact touch (LCT) 3 times a week for 2 weeks and then crossed over to the alternative treatment after a 1 week wash-out period. **Outcome Measures:** Brief Pain Inventory (BPI); PHQ9.	1. Pain intensity reduced significantly more in the individuals receiving LCT first compared to the BCM group, $p=0.01$). 2. No significant difference between the groups was seen in PHQ9.
Norrbrink & Lundeberg 2011 Sweden	**Population:** Age=47.1 yr. Mean time since injury was 11.9 yr. Type of pain=neuropathic.	1. Worst pain intensity and pain unpleasantness improved

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Prospective Controlled Trial N=30	**Intervention:** Participants were placed in one of two groups to receive acupuncture or massage therapy. Both groups consisted of 6 weeks with treatment twice a week. **Outcome Measures:** Visual Analogue Scale.	significantly in the acupuncture group compared to the massage group. 2. However, no significant differences were seen in pain intensity between the two groups.

No significant difference in pain intensity reduction post SCI was seen among those that received massage compared to guided imagery (Lovas et al. 2017) or acupuncture (Norrbrink & Lundeberg 2011). In a crossover RCT, Chase et al. (2013) found that patients that received light touch and then massage were more likely report reduction in pain intensity than those that received massage and then light touch. The study did not examine the effectiveness of either treatment compared to the alternative; hence, it is difficult to examine if one treatment itself is more effective than the other.

Conclusion

There is level 2 evidence that massage therapy is equally as effective as guided imagery and acupuncture in reducing pain intensity post SCI.

Massage is as effective as guided imagery or acupuncture at reducing mixed pain post SCI.

10.2 Osteopathy

Osteopathy treatment has been shown to be effective in the relief of chronic pain in individuals with osteoarthritis and inflammatory conditions. Osteopathy's effect on pain is related to its influence on the release of beta-endorphin and reduction in serotonin (Degenhardt et al. 2007).

Table 7 Osteopathy in Post-SCI Pain

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
Arienti et al. 2011 Italy RCT PEDro=6 N=47	**Population:** Severity of injury: AIS A=33, B, C and D=14; Level of injury: paraplegia=19, tetraplegia=7. Type of pain=neuropathic. **Intervention:** Patients were randomly placed into three groups: pharmacological group received 600mg per day of pregabalin. The pharmacological and osteopathic group received 600mg per day of pregabalin and osteopathical treatment once a week for the first month, once every fortnight for the second month, once during the third month all for 45 min each by an osteopathic physician. The osteopathic	1. Rates of improvement based on the VNS scores were similar across the two treatments (p=0.26). 2. The highest pain relief was seen in the combined pharmacological and osteopathic group compared to the pharmacological alone (p=0.05) and the osteopathic alone (p=0.001).

Author Year Country Score Research Design Total Sample Size	Methods	Outcome
	group received on the osteopathic treatment described above. **Outcome Measures:** Verbal numeric scale (VNS).	

Arienti et al. (2011) examined the use of osteopathic treatment in reducing neuropathic pain post SCI. Participants were randomized into one of three groups: the pharmacological group received 600 mg of pregabalin per day; the combined pharmacological and osteopathy group received osteopathic treatment once a week for the first month, once every fortnight for the second month and once during the third month for 45 minutes along with the pharmacological treatment; the osteopathic group received only the osteopathic treatment schedule described and the combined group received both active treatments. The study found verbal numeric scale (VNS) ratings were not significantly different among the groups from baseline to eight weeks. However, the combined treatment group had the highest pain relief compared to the pharmacological alone ($p=0.05$) and the osteopathic alone ($p=0.001$) groups from 13 to 24 weeks.

Conclusion

There is level 1b evidence (from one randomized controlled trial; Arienti et al. 2011) that osteopathy alone was as effective as pregabalin in improving neuropathic pain post SCI.

There is level 1b evidence (from one randomized controlled trial; Arienti et al. 2011) that osteopathy combined with pregabalin is more effective in reducing neuropathic pain post SCI than osteopathy alone.

Osteopathy alone is as effective at reducing neuropathic pain as pregabalin post-SCI.

Osteopathy in combination with pregabalin is effective at reducing neuropathic pain post SCI

10.3 Acupuncture

Acupuncture is a component of traditional Chinese medicine that has been used for the treatment of pain for thousands of years and is based on the premise that illness arises from the imbalance of energy flow (Qi) through the body (Dyson-Hudson et al. 2001). Needle acupuncture involves inserting fine needles into specific points to correct these imbalances (Dyson-Hudson et al. 2001; NIH Consensus Conference 1998; Pomeran 1998; Wong & Rapson 1999). Acupuncture has been shown to activate type II and type III muscle afferent nerves or A delta fibers, blocking the pain gate by stimulating large sensory neurons as well as releasing endogenous opioids, neurotransmitters and neurohormones (Dyson-Hudson et al. 2001; Pomeran 1998; Wong & Rapson 1999).

Table 8 Acupuncture in Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Estores et al. 2017 USA RCT Crossover PEDro=5 N=21	**Population:** Immediate treatment group (n=12): Mean age=41.1 yr; Gender: males=10, females=2; Time since injury=7.6 yr; Level of injury: C3-T12 for all; Severity of injury: AIS A=4, B=1, C=4, D=3; Type of pain=neuropathic. Delayed treatment group (n=8): Mean age=46.1 yr; Gender: males=6, females=2; Time since injury=13 yr; Level of injury: C3-T12 for all; Severity of injury: AIS A=1, B=1, C=2, D=4; Type of pain=neuropathic. **Intervention:** Participants were randomized to either an 8-wk once daily 10-needle battlefield acupuncture (BFA) group or a delayed-entry control group, then after the first BFA group finished, the delayed-entry group completed the BFA protocol. **Outcome Measures:** Change in pain severity (numeric rating scale (NRS)) and global impression of change (GIC).	1. Mean baseline pain scores were significantly higher in the acupuncture group than the control group (p=0.027). 2. BFA group reported significantly more pain reduction than the delated entry control group (p=0.014). 3. Significant difference between GIC scores from baseline to post-intervention between groups, with the BFA group showing a larger improvement (p=0.011).
Yeh et al. 2011 Taiwan RCT PEDro=6 N=99	**Population:** Age: 60.4 yr; Type of pain=undifferentiated. **Treatment:** Patients who previously underwent surgery for non-traumatic SCI were randomized to 3 groups: 1) received true acupoint intervention through electrical stimulation; 2) received sham acupoint; 3) received no acupoint stimulation. **Outcome Measures:** Visual Analogue Scale (VAS), Brief Pain Inventory (BPI)	1. Significant difference was seen in pain intensity between the true acupoint group and sham group ($p<0.03$) and the true acupoint group and control group ($p<0.02$). 2. A significant reduction was also seen in the impact of pain on sleep in the true acupoint group compared to the other two groups ($p<0.05$).
Dyson-Hudson et al. 2007 USA RCT PEDro=9 N=17	**Population:** Mean age=39.9 yr; Gender: males=18, females=5; Level of injury: tetraplegia=8, paraplegia=15; Type of pain=nociceptive musculoskeletal. **Treatment:** Individuals received 10 treatments, 2x/wk (acupuncture or sham acupuncture) for 5 weeks. **Outcome Measures:** Wheelchair User's Shoulder Pain Index (WUSP)I, Numeric Rating Scale (NRS)	1. Both groups experienced significant reduction in shoulder pain ($p<0.005$), as indicated by WUSPI. 2. Greater reduction in pain in acupuncture group vs. sham acupuncture group (66% vs. 43%) was noted; however there was no statistically significant difference in pain reduction between the two groups on WUSPI. 3. No significant differences in NRS between the two groups, though both had significant pain reduction.
Dyson-Hudson et al. 2001 USA RCT	**Population:** Age=28-69 yr; Gender: males=18, females=6; Level of injury: paraplegia, tetraplegia; Time since	1. Analysis of treatment on PC-WUSPI scores using ANOVA showed a significant effect of time for both

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
PEDro=7 N=24	injury=5-33 yr; Length of shoulder pain=4 mo-22 yr. Type of pain=nociceptive. **Treatment:** Subjects received either acupuncture treatments (sessions lasted 20-30 min) or Tager Psychophysical Integration (approx. 45 min). Consisted of both table work and mental gymnastic exercises. **Outcome Measures:** Intake questionnaire (demographics and medical history), Weekly log, Wheelchair User's Shoulder Pain Index (WUSPI), Numeric rating scale, Verbal rating scale, range of motion.	treatments (Acupuncture p<0.001 and Trager p=0.001). 2. Overall a reduction of the PC-WUSPI could be seen when looking at the data from the beginning of treatment to the end for both groups (p<0.05). 3. Looking at the effect of treatment on the numeric rating scores, the ANOVA showed a significant effect of time for both acupuncture and Trager groups for average pain and most severe pain (p<0.01, p<0.001 respectively), for the least severe pain the acupuncture group showed a significant reduction (p<0.01) compared to the Trager group. 4. There was a statistically significant effect for both groups on verbal pain rating (p=0.001).
Norrbrink &Lundeberg 2011 Sweden Prospective Controlled Trial N=30	**Population:** Age=47.1 yr. Mean time since injury was 11.9 yr. Type of pain=neuropathic. **Intervention:** Participants were placed in one of two groups to receive acupuncture or massage therapy. Both groups received treatment 2x/wk for 6 wk. **Outcome Measures:** VAS	1. Worst pain intensity and pain unpleasantness improved significantly in the acupuncture group compared to the massage group. 2. However, no significant differences were seen in pain intensity between the two groups.
Rapson et al. 2003 Canada Pre-Post N=36	**Population:** Age=17-75 yr; Gender: males=23, females=13; Level of injury: cervical to lumbar; Length of pain=1 mo->15yr. Type of pain=neuropathic and musculoskeletal. **Treatment:** SCI patients were given acupuncture treatments. **Outcome measures:** Pain.	1. 24 participants improved in response to electro-acupuncture while 12 showed no improvement. 2. Bilateral pain (n=21) more likely to respond to electro-acupuncture than those with unilateral pain (n=3, p=0.014). 3. Those with symmetric pain had a higher response to treatment than those who asymmetric pain (p=0.26). 4. It was also noted that those with burning pain that was bilateral and symmetric (p=0.006) was more likely to improve after electroacupuncture. 5. Similar findings were noted for those who experienced bilateral symmetric constant burning pain (p=0.005).
Nayak et al. 2001 USA Pre-post Initial N=31; Final N=22	**Population:** Mean age=43.14 yr; Gender: males=15, females=7; Level of injury: C1-L3; Severity of injury: AIS: A, C, D; Time since injury=8.49 yr; Length of pain=8.46 yr. Type of pain=neuropathic and musculoskeletal. **Treatment:** 15 acupuncture treatments were administered over a 7.5-week period using a specific set of acupuncture points with additional points being selected by subjects based on	1. Pain intensity decreased over time: worst pain (p<0.05), average pain, (p<0.01), and present pain (p<0.01). 2. Post-treatment decline in pain intensity was maintained at 3 mo follow-up (pre-treatment vs. follow-up: p<0.01). 3. A difference in the ratings of pain intensity between pre- and post-treatment (p<0.001) was noted and this was maintained 3 mo after the

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	individual history and clinical examination. **Outcome measures:** Pain intensity: numeric rating scale, general health: individualized symptom rating scale, pain impact and interference: activity scale, mood, psychological well-being-general well-being schedule and expectations.	end of treatment (pre-treatment vs. follow-up: p<0.01). 4. Those that did report pain relief at 3 mo follow up reported only moderate levels of pain intensity on the NRS at the beginning of the study (7.83±0.75) compared to those who did not report pain relief (9.67±0.58, p<0.01). 5. Pain interference: a decrease in pain interference with ADLs was also noted (p<0.05). Respondents showed a reduction in interference with ADLs at post-treatment (p<0.01).

Discussion

Evidence from the studies above suggests acupuncture results in significant decrease in pain intensity over time compared to control (Estores et al. 2017). However, no group differences were found between acupuncture and sham treatment (Dyson-Hudson 2007) or Tager Psychophysical Integration (Dyson-Hudson 2001) or massage (Norrbrink & Lundeberg 2011). True acupoint was significantly more effective in reducing pain intensity compared to sham or no acupoint (Yeh et al. 2010). Electroacupunture was also shown to improve symmetric bilateral burning pain post intervention (Rapson et al. 2003).

Conclusion

There is level 1a evidence (from two randomized controlled trials; Dyson-Hudson et al. 2001, 2007) that in general acupuncture is no more effective than Trager therapy or sham acupuncture in reducing nociceptive musculoskeletal shoulder pain post SCI.

There is level 1b evidence (from one randomized controlled trial; Yeh et al. 2010) that electroacupuncture reduces neuropathic pain of patients with SCI.

There is level 2 evidence (Norrbrink & Lundeberg 2011) that acupuncture is as effective as massage in reducing pain post SCI

Acupuncture may not reduce post-SCI neuropathic and musculoskeletal pain.

Electrostimulation acupuncture is effective in improving neuropathic pain in SCI pain.

Acupuncture is as effective as massage at reducing pain post SCI.

10.4 Physical Activity for Post-SCI Pain

Exercise has been shown to improve subjective well-being for individuals with chronic disease and disability. Specifically, a study found high amounts of heavy intensity and mild intensity physical activity correlated with lower levels of pain among individuals with SCI who use a manual wheelchair as their primary mode of mobility (Tawashy et al. 2009).

Table 9 Physical Activity for Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Exercise		
Middaugh et al. 2013 USA RCT PEDro=5 N=15	**Population:** Mean age=38yr; Gender: males=12, females=3; Level of injury: paraplegia=13, quadriplegia=2; Mean time post injury=16yr; Type of pain: musculoskeletal. **Treatment:** Individuals using wheelchairs were randomized to an exercise program alone (control, n=7) or with EMG biofeedback (treatment, n=8). Exercise programs were taught in two 90min sessions and were to be performed at home (1x/d, 5d/wk, 10wk). EMG biofeedback training was provided in 4 sessions (90min). Outcomes were assessed at baseline, 10wk, and 6mo. **Outcome Measures:** Wheelchair User Shoulder Pain Index (WUSPI).	1. The treatment group had a significant reduction in WUSPI score at 10wk (Δ=64%, p=0.02) while the control group did not (Δ=27%, p=0.42). 2. There were significant reductions in WUSPI score at 6mo in both the control group (Δ=63%, p=0.03) and treatment group (Δ=82%, p=0.004).
Ginis et al. 2003 Canada RCT PEDro=6 N=34	**Population:** SCI: Mean age=38.6 yr; Gender: males=23, females=11; Severity of injury: complete=14, incomplete=13. Type of pain=neuropathic and musculoskeletal. **Treatment:** Participants in the non-exercise group were asked to continue their usual activities but they were asked not to exercise regularly. Those in the exercise group participated in 5 min of stretching, 15-30 min of aerobic arm ergometry exercise and 45-60 min of resistance exercise. These subjects trained 2x/wk in small groups. **Outcome Measures:** Pain perception (two items from the Short form-36 Health Survey), symptom self-efficacy and perceived control (two core items from the Beliefs scale and a modified version of the arthritis belief scale), stress was measured using the perceived stress scale.	1. After 3 mo, changes in potential mediators were seen in: • The treatment group showed a significant decrease in stress (p=0.01) and pain (p=0.03) than the control group. • The two groups for QoL (p=0.007); satisfaction with physical function (p<0.01); satisfaction with physical appearance (p=0.007); depression (p=0.02). 2. Stress and pain (mediators of QoL): • Once baseline pain and stress were controlled for, the 3 mo scores for pain was (R2=.15, p<0.01) and for stress it was (R2=0.12,p<0.01). • These were significant predictors of baseline adjusted 3 mo QoL. 3. Stress and pain as mediators of depression: • Changes in pain but not stress explained significant variance in baseline adjusted depression scores (R2=0.19 and 0.04). • Adjusted pain scores showed variance in the adjusted 3 mo

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
		depression scores (R2=0.19 and <0.01).
Curtis et al. 1999 USA RCT PEDro=5 N=42	**Population:** Mean age=35 yr; Gender: males=35, females=7; Level of injury=cervical to lumbar; Duration of wheelchair use=24 yr. Type of pain=nociceptive. **Treatment:** The experimental group attended a 60 min educational session where they were instructed in five shoulder exercises. **Outcome Measures:** Self-report questionnaire (demographic and medical info), Wheelchair User's Shoulder Pain Index (WUSPI), and Visual Analogue Scale (VAS) used to rate intensity of pain.	1. When looking at the effect of exercise intervention on performance corrected (PC) WUSPI, a two factor repeated measures ANOVA showed a significant effect of time only (p=0.048). 2. There were no significant differences between control and experimental group in age, years of wheelchair use or activity levels although the control group had much lower pain scores at baseline.
Nawoczenski et al. 2006 USA Prospective Controlled Trial N=41	**Population:** Exercise group: Mean age=47.1 yr; Gender: males=15, females=6, Level of injury: C=3, T2-T7=7, T8-T12=7, L=4; Severity of injury: incomplete=13, complete=8; Control group: Mean age=38.1 yr; Gender: males=13, females=7, Level of injury: T2-T7=7, T8-T12=12, L=1; Severity of injury: incomplete=6, complete=14; Type of pain=musculoskeletal. **Treatment:** Those in the experimental group (n=21) were given an 8 wk home exercise program consisting of stretching and strengthening exercises. This program was augmented at 4 wk (or sooner). Changes included increasing elastic band resistance, increasing repetitions, or both. The asymptomatic control group (n=20) was not given any exercises. **Outcome Measures:** Wheelchair User's Shoulder Pain Index (WUSPI); Shoulder Rating Questionnaire (SRQ)	1. SRQ and WUSPI scores significantly improved in the experimental group, pre- to post-test (p<0.001 and p=0.002, respectively). 2. Over time, satisfaction scores in the intervention group significantly improved (p<0.001).
Crane et al. 2017 USA Pre-Post N_{start}=89 N_{finish}=45	**Population:** Mean age=43.8±15.3 yr; Gender: males=34, females=11; Time since injury=1.0-21.0 yr; Severity of injury: AIS A/B=23, C/D=22; Type of pain=undifferentiated. **Intervention:** Participants engaged in a physical therapy group exercise class twice/wk for 3 mo. **Outcome Measures:** Exercise frequency and intensity, perceived health (EuroQOL), pain (bodily pain sub scale from short form-36), mood (PHQ-2 depression rating), sleep and television watching habits.	1. Significant increase in days per week of strenuous and moderate exercise (p=0.01) along with a significant improvement in state of health (p=0.05) from baseline to post-intervention. 2. No significant difference between baseline and post-intervention for days per week of mild exercise (p=0.08), hours of TV watching per week (p=0.10), PHQ-2 score (p=0.19) or bodily pain sub scale (p=0.24).
Serra-Ano et al. 2012 Spain Pre-Post	**Population:** Age=26-70yr; Gender: males=15; Severity of injury=complete. Type of pain=nociceptive.	1. Significant decrease in pain intensity was reported post treatment (p<0.05).

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
N=15	**Treatment:** SCI individuals with chronic shoulder pain participated in an 8 week resistance training program with 3 sessions per week. **Outcome Measures:** Wheelchair User's Shoulder Pain Index (WUSPI)	2. Upper limb functionality including rotation, flexion and extension improved significantly post treatment ($p<0.05$).
Finley & Rodgers 2007 USA Pre-Post N=17	**Population:** Mean age=46 yr; Gender: males=9, females=8; Mean duration of wheelchair use=15 yr; Type of disability: SCI=9, spina bifida=1, ataxia=1, postpolio syndrome=1, spinal stenosis=1, stroke=1, rheumatoid arthritis=1; Type of pain=musculoskeletal. **Treatment:** 4 wk baseline phase where patients used personal wheelchairs (no intervention), followed by a 5 mo phase where patients used the intervention wheelchair (MAGICWheels 2-gear wheel). There was a 4 wk retention period in which patients used their personal wheels again. Once a day patients were instructed to navigate in uneven terrain or on a hill. **Outcome Measures:** Wheelchair User's Shoulder Pain Index (WUSPI), WUFA, self-reported activities (Activities Log), and timed hill climb test with Rating of Perceived Exertion (RPE).	1. Shoulder ROM, upper-extremity strength, or the occurrence of specific shoulder diagnoses did not differ after use of MAGICWheels ($p<0.05$). 2. Shoulder pain was significantly decreased following the treatment at wk 2 ($p=0.004$) through wk 16 ($p=0.015$). 3. At wk 20, one patient reported increased pain from unrelated factor. 4. During the 4 wk retention phase, the WUSPI scores indicated a trend toward increasing shoulder pain. However, no significant increase was found compared to the last week of using the MAGICWheels ($p<0.05$). 5. During the MAGICWheels phase, patients encounter significantly more carpeted ($p<0.01$) and grass ($p<0.001$) surfaces in comparison to the baseline phase. 6. During the retention phase patients encountered significantly more hills ($p=0.009$) and gravel ($p=0.03$) surfaces in comparison to the baseline phase. 7. No difference was found in WUFA following the use of the 2-gear wheel ($p=0.06$). 8. There was significantly longer hill time during the use of the 2-gear wheel ($p=0.01$), however no difference was found in the RPE ($p=0.013$).
Nash et al. 2007 Netherlands Pre-Post N=7	**Population:** Age=39-58 yr; Level of injury=T5-T12; Severity of injury=complete; Type of pain=musculoskeletal. **Treatment:** Seven participants volunteered to undergo 16 weeks of circuit resistance training (CRT), 3 times weekly on non-consecutive days, each session lasting 45 min. Included were: circuit resistance training, low-intensity endurance activities, military press, horizontal rows, pectoralis (horizontal row), preacher curls, wide-grip latissimus pull-downs, and seated dips.	1. Participants reported a reduction in pain. WUPSI scores decreased from 31.8±23.5 to 5.0±7.7 ($p=0.008$). 3/7 participants reported near-complete resolution of shoulder pain following treatment. 2. All completed training, with peak Vo_2 values increasing from 1.64±0.45 to 1.81±0.54L/min ($p=0.01$). 3. Anaerobic power increased significantly as a result of training; peak power increased by 6% and

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	Outcome Measures: Wheelchair User's Shoulder Pain Index (WUSPI).	average power by 8.6% (p=0.005 and p=0.001, respectively).
Ditor et al. 2003 Canada Pre-post N=7	**Population:** SCI: Mean age=43.3 yr; Gender: males=5, females=2; Level of injury: C5-T12; Severity of injury: AIS A, B; Time since injury=3-23 yr; Type of pain=neuropathic. **Treatment:** Patients previously part of a 9 mo exercise training, given for 3 mo, 2x/wk of continued supervised exercise training in a laboratory setting. **Outcome Measures:** Exercise adherence (% of available sessions that were attended [max. 2x/wk]), Perceived Quality of Life Scale (PQOL), Pain (2 pain items from the Short form-36 Health Survey), Perceived Stress Scale ([PSS).	1. There was a significant decrease in exercise adherence over the 3 mo follow-up period in comparison to the 9-month adherence rate (42.7% vs. 80.65%, respectively; p<0.01). 2. At 3 mo follow-up, there was a significant decrease in PQOL (p<0.05). 3. Also, a trend was found for increased pain (p=0.07) and stress (p=0.12). 4. There was a significant negative correlation between pain scores at the completion of the 9-month study and adherence during the 3-month follow-up (R=-0.91; p<0.01).
Exoskeleton		
Baunsgaard et al. 2018 Denmark Pre-Post N=52	**Population:** Mean age=35.8 yr; Gender: males=36, females=16; Time since injury: recently injured (≤1 yr)=25, chronically injured (>1 yr)=27; Level of injury: motor complete tetraplegia=3, motor incomplete tetraplegia=11, motor complete paraplegia=22, motor incomplete paraplegia=16; Severity of injury: AIS A/B=36, C/D=16; Type of pain=neuropathic and nociceptive. **Intervention:** Participants engaged in gait training three times/wk for eight wks via an Ekso GT robotic exoskeleton (Ekso Bionics). **Outcome Measures:** Pain (International SCI Pain Basic Data Set (ISCI-PBDS), spasticity (modified ashworth scale (MAS), range of motion (ROM) (goniometry), spinal cord independence measure (SCIM III) and bowel, lower urinary tract function and quality of life (QOL) (ISCI-basic data set).	1. 40% of the participants experienced pain at all assessment time points, 29% reported pain at 1, 2 or 3 time points and 31% reported no pain at all. 2. No significant difference in either group from baseline to wk 8 regarding pain during day-to-day activities, overall mood, ability to get a good night's sleep or number of pain problems experienced the previous week (p>0.05). 3. 7 participants reported neuropathic pain, 15 reported nociceptive pain, and 4 reported they experienced both. 4. Areas where nociceptive pain was reported were the lower back, upper back, shoulder, and knee, whereas neuropathic pain was reported at the thought and lower extremity as well as the lower back and hip. 5. No difference in ROM detected from baseline to wk 8 or to follow-up (p>0.05). 6. SCIM III scores improved significantly in the recently injured and chronically injured groups (p<0.05 for both). 7. Improvements seen within the ISCIBDS awareness of the need to defecate for 6 of 25 participants in the recently injured group, and none in the chronically injured group. 8. No significant change in QOL for the recently injured group, but significant

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
		improvements for QOL in the chronically injured group from baseline to wk 8 (p=0.03) and follow-up (p=0.01).
Stampacchia et al. 2016 Italy Pre-Post N=21	**Population:** Mean age=48.1±12.3 yr; Gender: males=17, females=4; Time since injury=122.7±104.8 mo; Level of injury: C=4, T(D)=13, L=4; Severity of injury: AIS A=12, B=2, C=0, D=7; Type of pain=neuropathic. **Intervention:** Participants engaged in a powered robotic exoskeleton walking session. **Outcome Measures:** Standing time, walking time, number of steps, numeric rating scale (NRS), modified Ashworth scale (MAS) and Penn spasm frequency scale (PSFS) for muscle spasticity, NRS for pain, patient's global Impression of change (PGIC) scores and PGIC visual analog scores (VAS) and positive and negative sensations questionnaire.	1. Standing time was positively correlated with walking time (p<0.002) and number of steps (p<0.0001). 2. Spasticity scores were significantly reduced for NRS (p<0.001), MAS (p<0.001), and PSFS (p<0.001). 3. Average pain scores across all participants did not change significantly (p=0.094), but the effect size was low. 4. Across only patients that reported pain before the robot-assisted session (n=12) there was a significant pain reduction (p=0.002), with no significant change in pain scores for those who did not report pain before the session (n=9) (p=0.25). 5. Reduction of pain was not correlated with reductions in spasticity (p>0.05). 6. PGIC scores and PGIC VAS scores indicated that patients did experience a moderate change. 7. Significant negative correlation between the two subscales of the questionnaire was observed (p<0.0001), showing high positive sensation scores and low negative sensation scores.
Yoga		
Curtis et al. 2017 Canada RCT Crossover PEDro=6 N=22	**Population:** Yoga group (n=10): Mean age=47.9±19.5 yr; Gender: Not reported; Level of injury: paraplegia=6, tetraplegia=0, ambulatory/unspecified=4; Severity of injury: complete=2, incomplete/disease-related=8. Control group (n=12): Mean age=54.8±10.1 yr; Gender: Not reported; Level of injury: paraplegia=4, tetraplegia=4, ambulatory/unspecified=4; Severity of injury: complete=5, incomplete/disease-related=7; Type pf pain=neuropathic and nociceptive. **Intervention:** Participants were randomized to a 6 wk, twice wkly Iyengar yoga group or a 6 wk wait-listed control group, then after the first yoga group completed their sessions, the wait-list control group engaged in the yoga protocol. **Outcome Measures:** Pain (brief pain inventory (BPI), pain catastrophizing	1. Yoga group had significantly lower scores for the HADS (p<0.05) and significantly higher scores for the SCS (p<0.05) at post-intervention than at baseline. 2. Fixed-factor models showed significantly lower HADS scores postintervention compared to preintervention (p<0.05) with time being the main predictor of HADS scores (p<0.05). 3. There was a trend noticed for FFMQ scores from preintervention to postintervention for total scores (p=0.09) and observing scores (p=0.06). 4. Postintervention scores for the SCS and FFMQ were both significantly higher than at preintervention (p>0.05).

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	scale (PCS)), psychological (acceptance and action questionnaire (AAQ), hospital anxiety and depression scale (HADS), general self-efficacy scale (GSES), posttraumatic growth inventory (PTGI-SF), Connor-Davidson resilience scale (CD-RISC), self-compassionate scale (SCS)) and mindfulness (five-facet mindfulness questionnaire (FFMQ) measures taken 1-2 wks before and after the program.	

Discussion

Exercise programs which included resistance and strength training were shown to significantly improve pain post SCI (Ginis et al. 2003; Nawoczenski eta l. 2006; Serra-Ano eta l. 2012; Finley & Rogers 2007; Nash et al. 2007). There is conflicting evidence for the use of exoskeleton walking to reduce SCI related pain (Stampacchia et al. 2016; Baunsgaard et al. 2018).

Conclusion

There is level 1b evidence (from one randomized controlled trial; Ginis et al. 2003) that a resistance training based exercise program significantly reduces post-SCI neuropathic and musculoskeletal pain.

There is level 2 evidence (Middagh et al. 2013) that exercise combined with biofeedback improves musculoskeletal pain post SCI.

There is conflicting evidence from two level 4 pre-post studies (Stampacchia et al. 2016; Baunsgaard et al. 2018) for the use of exoskeleton for reducing pain post SCI.

Resistance training based exercise reduces post-SCI neuropathic and musculoskeletal pain.

Exercise combined with biofeedback reduces musculoskeletal pain post SCI

Exoskeleton may not reduce pain post SCI

10.5 Behavioural Management of Pain Post SCI

10.5.1 Visual Illusion

Visual illusion therapy is a cognitive technique which uses guided images to alter perceptions and modify behaviour. It has been used in various studies to alleviate pain responses by changing feelings of perceived discomfort (Kazdin 2001; Korn 2002; Kwekkeboom 2001). It is based on a cortical model of pathological pain (Harris, 1999). This model states that the injury

causes a mismatch between motor output and sensory feedback which in turn contributes to the pain. Studies have found normalization of the cortical proprioception representation results in recovery from pain (Floor et al. 2000; Maihofner et al. 2004; Pleger et al. 2005).

Table 10 Visual Illusion

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Richardson et al. 2019 USA RCT PEDro=8 N=59	**Population:** Mean age=44.8±10.8 yr; Gender: males=47, females=12; Time since injury=14.9±11.0 yr; Level of injury: paraplegia=34, tetraplegia=25; Severity of injury: complete=38, incomplete=21; Type of pain=neuropathic. **Intervention:** Participants were randomly assigned to a 20 min virtual reality (VR) walking treatment group, or a 20 min VR wheeling control group. **Outcome Measures:** Pain (numeric rating scale (NRS), neuropathic pain scale (NPS)) and personality factors (absorption scale of the multidimensional personality questionnaire-brief form (MPQ-BF) and Tellegen Absorption Scale (TAS)).	1. No significant interaction between treatment and pain type on change in pain level (p=0.48) and no significant difference in mean pain changes between treatment groups (p=0.30). 2. Significant pre-post pain reduction in the VR walking condition (p<0.01) but not in the VR wheeling condition (p=0.07). 3. When correction factors were applied for Type-1 error for multiple (simultaneous) testing of pain reduction across treatments and pain subtype, pain reduction was revealed to be significant for neuropathic pain (NP) (p=0.0037), musculoskeletal (MS) (p=0.0035) and complex neuropathic or mixed pain (cNP) (p=0.0025). 4. Other significant predictors of pain reduction were duration of injury (p=0.049) and anticonvulsant (p=0.013). 5. The odds of a given pain site of an individual attaining clinical reduction in pain following the VR walking condition was increased by a factor of 3.69 compared with those in the VR wheeling group (p=0.04), and those with an education longer than 12 years also had higher odds of attaining significant responses. 6. Significant reduction in pain unpleasantness, but not intensity, in the VR walking group compared to the VR wheeling group (p<0.01 and p=0.27 respectively). 7. Reduction in NP pain unpleasantness, as assessed by NPS, was significantly greater in the VR walking group as opposed to the VR wheeling group when adjusted for age and duration of injury (p<0.01). 8. Higher abbreviated TAS scores were associated with greater reductions in NP intensity in the walking condition compared to the wheeling condition. 9. Odds of attaining a clinical reduction (30% or more reduction) in the VR walking condition were increased by

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
		a factor of 13.06 compared to the wheeling condition (p=0.01). 10. Other significant predictors of achieving clinical reduction were age (p=0.02) and time since injury (p<0.01). 11. For every year higher than the sample mean age, and every year increase in duration of injury, the odds of attaining clinically significant reduction increase by a factor of 12% and 22% respectively (p<0.01). 12. Significant reductions in the VR walking group compared to the VR wheeling group in cold pain (p=0.04), deep pain (p=0.02) and sensitivity in the skin (p=0.04), whereas changes in sharp pain (p=0.31), hot pain (p=0.90), dull pain (p=0.10), itchy pain (p=0.18) and surface pain (p=0.37) were all non-significant between groups. 13. After Type-1 error corrections for simultaneous testing was complete, participants in the VR walking group still experiences a significant reduction in NP experienced as sharp (p<0.0005), hot (p<0.0001), dull (p<0.0001), sensitivity (p<0.0001), deep (p<0.0001), and more surface-like (p<0.0001) from pre- to posttreatment. 14. Surface pain was the only factor that was significantly reduced following VR wheeling (p=0.0015).
Lovas et al. 2017 Australia RCT PEDro=4 N=40	**Population:** Mean age=46.0±11.6 yr; Gender: males=34, females=6; Time since injury=18.4±12.1 yr; Level of injury: paraplegia=30, tetraplegia=9; Severity of injury: complete=20, incomplete=19; Type of pain=neuropathic and musculoskeletal. **Intervention:** Participants were randomized to either a Swedish upper body massage group (MT) or n active concurrent control guided imagery (GI) relaxation group for 5 wks with one session per wk. **Outcome Measures:** Short-form McGill pain questionnaire (MPQ) and Chalder's fatigue scale (CFS).	1. No significant differences between groups for pain severity scores (p>0.05). 2. Pain scores reduced significantly over time from pre-treatment to post-treatment in both groups (p<0.01). 3. No significant interaction effect between groups and intervention over time (p<0.05). 4. No significant between-group differences in overall CFS scores (p>0.05). 5. Fatigue scores reduced significantly over time (p<0.01). 7. No significant interaction effect between groups and intervention over time (p>0.05).
Ozkul et al. 2015 Turkey RCT Crossover	**Population:** Mean age=32.33; Gender: males=18, females=6; Level of injury: paraplegia=6, quadriplegia=18; Severity	1. There was a reduction in VAS-PI immediately after VI (p=0.07) and

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
PEDro=5 N=24	of injury: incomplete=7, complete=17; Mean time post injury=12.46mo; Type of pain=neuropathic. **Treatment:** Participants received transcutaneous electrical nerve stimulation (TENS) and visual illusion (VI) in a randomized sequence. Each treatment was delivered for 2wk with a 1wk washout period in between. Outcomes were assessed pre and post each treatment period. **Outcome Measures:** Visual Analogue Scale - Pain Intensity (VAS-PI), Neuropathic Pain Scale (NPS), Brief Pain Inventory (BPI).	TENS (p=0.08), but there was no statistically significant group effect. 2. There was a significant reduction in pain 2wk post TENS (p=0.04) but not 2wk post VI (p>0.05). 3. On NPS, VI significantly decreased the following pain types: hot (p=0.047), sharp (p=0.02), unpleasant (p=0.03), and deep (p=0.047); TENS did not show any significant effects. 4. On BPI, VI significantly decreased the negative effect of pain on moving ability (p=0.04) and TENS significantly decreased the negative effect of pain on mood (p=0.03), relationships (p=0.04), and sleep (p=0.04).
Soler et al. 2010 Spain RCT PEDro=8 N=40	**Population:** Age=21-66 yr, Severity of injury: AIS A=32, B=8. Type of pain=neuropathic **Intervention:** Patients were randomly divided into four groups: transcranial DCS and visual illusion group received direct current stimulation over C3 or 4 at a constant 2 mA intensity for 20 min and after 5 min of transcranial DCS video with someone walking was shown and the legs of person for 15 min with a vertical mirror so patients could see themselves walking; transcranial DCS group with control visual illusion received the above mentioned transcranial DCS however for the visual illusion only received a video of faces or landscapes, visual illusion group and sham transcranial DCS had electrodes placed on the same area as the treatment group however the stimulator was turned off after 30 s of stimulation and placebo group consisted of both the control visual illusion and the sham transcranial DCS. **Outcome Measures:** Numeric Rating Scale (NRS)	1. The most significant reduction in NRS of pain perception was seen in the combined transcranial DCS and visual illusion group compared to the visual illusion group (p=0.008) or the placebo group (p=0.004). 2. Pain reduction was also greatest in the transcranial DCS and visual illusion group than the other three groups at first and last follow up; however, no difference was seen at second follow-up. 3. Visual illusion group was shown to have significant improvement in neuropathic pain intensity at last day of treatment (p=0.02); however, this effect was not maintained over the long-term period. 4. Combined transcranial DCS and visual illusion group also showed significant improvement in ability to work, perform daily tasks, enjoyment, interference of pain in sleep (p<0.05). 5. Transcranial DCS sessions were found to be safe, with minor side effects including mild headache.
Pozeg et al. 2017 Switzerland PCT N_{SCI}=20 $N_{healthy}$=20	**Population:** SCI (treatment) group: Mean age=47.3±12.0 yr; Gender: males=18, females=2; Time since injury=17.1±18.1 yr; Level of injury: C=0, T=20, L=0; Severity of injury: AIS A=15, B=3, C=2, D=0; Type of pain=neuropathic. Healthy Control (HC) group: Mean age=43.0±11.8 yr; Gender: males=18, females=2; Type of pain=neuropathic.	1. Synchronous visuotactile stimulation allowed for significantly stronger experience of ownership over the virtual legs (p=0.037) and significantly stronger referred touch (p<0.001) without significantly effecting ratings of control items (p=0.112).

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	Intervention: Participants were familiarized and tested on a virtual leg illusion (VLI) device and had asynchronous and synchronous visuotactile stimulation to the participant's back immediately above the lesion or at the shoulders, which displayed virtual legs. **Outcome Measures:** Illusory leg ownership with illusory global body ownership (induced in the full body illusion (FBI)), Cambridge depersonalization scale (CDS) and anomalous body experience (ABE).	2. Significant main effect of group on the ratings of illusory ownership (p=0.028) showing SCI patients felt less ownership over the illusory legs than HC group. 3. No significant group differences found in ratings of illusory touch, referred touch, or control items (p≥0.153 for all). 4. No significant effect of back location or interaction effects (p≥0.063). 5. No significant differences observed with regards to illusion or control ratings between the patients with SCI with and without preserved tactile leg sensations (p≥0.096), between the participants with SCI with or without neuropathic pain (p≥0.075), or between participants with SCI with complete and incomplete lesions (p≥0.103). 6. Exponentially decaying relationship between duration of SCI and magnitude of illusory leg ownership was found to be significant (p=0.016) as well s between duration of SCI and the magnitude of illusory referred touch (p=0.036), but only in the synchronous condition, all other conditions not significant (p≥0.081). 7. No significant correlations found between the illusory ratings and the level of SCI (all p≥0.125). 8. No significant main effects of synchrony, back location or interactions on the pain change ratings between post-illusion and baseline ratings (all p≥0.147), but significant pain reduction when lower back was stimulated synchronously with the virtual legs when pain change was compared against zero and only in this condition (0.04); this comparison was found to be insignificant via multiple comparison testing. 9. Significant main effects of synchrony on full body illusion where synchronous visuotactile stimulation induced stronger illusory body ownership (p<0.001) and stronger illusory touch (p<0.001) compared to asynchronous stimulation, but no significant modulation of the ratings of control items (p=0.823). 10. Contrasting the VLI, no significant main effects or group (all p≥o.558) or

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
		interaction effects (all p≥0.146) on any of the FBI questionnaire items. 11. No differences in illusion or control ratings found between participants with SCI with and without preserved tactile leg sensations (all p≥0.481), between participants with SCI with and without neuropathic pain (all p≥0.332) or between participants with SCI with complete and incomplete lesions (p≥0.173). 12. No significant correlations found between ratings on body ownership and illusory touch with SCI duration or with SCI level (all p≥0.052). 13. Synchrony of visuotactile stimulation did not modulate the pain change via the pain ratings (p=0.92), but the FBI significantly reduced the pain compared to baseline measures in both the synchronous (p=0.02) and asynchronous (p=0.02) conditions. 14. No significant differences vetween SCI and HC groups for the total CDS or ABE subscale scores (all p≥0.26), but participants with SCI rated significantly higher on, “parts of my body feel as if they didn’t belong to me” (p=0.028) and “I have to touch myself to make sure I have a body or a real existence” (p=0.009).
Jordan et al. 2016 USA Cohort N=35	**Population:** Age:47.5 yr; Type of pain=neuropathic. **Intervention:** Participants received illusory therapy through a 20 min first person view video of an actor walking along a path. Participants were asked to imagine either walking or wheeling depending on their group allocation. **Outcome Measures:** Change in painful sensation on a 11-point numeric rating scale.	1. Significant decrease in pain was seen among those in the virtual walking vs. virtual wheeling condition (p=.03). 2. A decrease in at-level pain was seen pre-post among those in the virtual walking group (p=.08).
Kumru et al. 2013 Spain Cohort N=52	**Population:** Age25-69yrs; Sex: male=34, female=18. Type of pain neuropathic and musculoskeletal, with a subanalysis of neuropathic. **Treatment:** Three cohorts of individuals (group 1(N=18)=SCI neuropathic pain; group 2(N=20)=SCI non-neuropathic pain; group 3(N=14)=healthy matched) underwent daily transcranial direct current stimulation along with visual illusion therapy for 2 weeks The visual illusion involved the participant seated viewing a video of the matching gender walking on a treadmill.	1. SCI individuals with neuropathic pain had a 37.4% improvement in pain intensity post treatment. 2. 13 of 18 individuals in the neuropathic group reported 50% decrease in pain intensity post treatment. 3. Evoked pain perception was significantly lower in the neuropathic pain group compared to SCI nonneuropathic and healthy controls.

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	Outcome Measures: Numeric Rating Scale (NRS)	4. Pain threshold was significantly higher in the neuropathic pain group compared to the other two groups.
Villiger et al. 2013 Switzerland Pre-Post N=14	**Population:** Age:52.7yr; Severity of injury: AIS C=2, D=12; Type of pain=neuropathic and mixed. **Intervention:** Intense virtual reality training was provided to patients with chronic incomplete SCI. Participants were asked to complete four tasks designed to work lower limbs through virtual controlled movement sensors for 45 mins for 16 to 20 sessions over a 4-wk period. **Outcome Measures:** Neuropathic Pain Scale (NPS)	1. Decrease in pain intensity and unpleasantness was found post treatment and follow-up ($p<0.05$). 2. Of those with neuropathic pain, 5 out of 9 participants reached MCID post treatment and retained improvement at follow up.
Gustin et al. 2008 Australia Pre-Post N=15	**Population:** SCI, Type of pain=neuropathic. **Intervention:** All participants were trained in movement imagery for seven days. Each participant was asked imagine right ankle plantarflexion and dorsiflexion for 8 min. **Outcome Measures:** McGill Pain Questionnaire **(**MPQ), Visual Analogue Scale (VAS)	1. Individuals with neuropathic pain reported a significant increase in pain intensity during movement imagery, $p<0.01$. 2. Individuals without neuropathic pain reported a significant increase in non-pain intensity during movement imagery, $p<0.01$.
Moseley 2007 UK Pre-Post N=5	**Population:** Mean age=32.2yr; Level of injury: T=1, L=4; Type of pain=neuropathic. **Treatment:** Individuals with SCI (n=5) engaged in: (1) virtual walking exercise; (2) guided imagery with a psychologist who took them through a scene in which they were pain free and doing something they liked; (3) watching an animated film. During the second part of the study, participants performed 10 min of virtual walking on 15 consecutive weekdays. **Outcome Measures:** McGill Pain Questionnaire **(**MPQ); Visual Analogue Scale (VAS)	1. Pain decreased by approximately 65% with virtual walking; less so for guided visual imagery and film viewing. 2. The amount of time to return to pre-task pain VAS after virtual walking was 34.9 min; after guided imagery 13.9 min; and after watching a film 16.3 min. 3. The decrease in perceived foreignness of the legs was 43mm during virtual walking, 4mm during guided imagery, and 3mm while watching the film. 4. Change in foreignness was related to change in pain during virtual walking ($p=0.04$). 5. During the 3-week trial of virtual walking, overall pre-task pain gradually decreased; and pain relief gradually increased; these effects persisted at 3 months follow-up.

Discussion

Two studies examined the effect of visual illusion in combination with transcranial direct current stimulation (tDCS; Soler et al. 2010; Kumru et al. 2012). Soler et al. (2010) examined the effectiveness of visual imagery for neuropathic pain post SCI. The authors found the greatest improvement in pain perception, pain reduction, ability to work, perform daily tasks, enjoyment, interference of sleep in the combined tDCS and visual illusion group ($p<0.05$). Thirty percent of participants in this combined group also reported a 30% or more improvement in pain intensity. The visual illusion group reported significant improvement in neuropathic pain intensity on the last day of treatment ($p=0.02$); however, the effect was not maintained over 12 weeks. One cohort study (Kumru et al. 2012) found that combined transcranial direct current stimulation and visual imagery may improve pain intensity among individuals with neuropathic pain post SCI.

Two studies examined virtual walking in improving neuropathic pain post SCI (Moseley et al. 2007; Jordan et al. 2016). Moseley (2007) reported on five individuals with both a T12-L3 paraplegia (AIS B) and neuropathic pain who engaged in a virtual activity, where they were led through a guided walking exercise, visualizing that they were walking pain free. Of the four subjects who completed the trial (one patient withdrew from the study earlier due to distress), there was a mean 42 mm reduction in neuropathic pain following individual treatments, and 53 and 42 mm reductions immediately and three months following virtual walking daily for three weeks based on a 100 mm visual analog scale. Control treatments were visual imagery alone, and watching a movie, both of which resulted in less dramatic pain reduction; however, no statistical comparisons were done. Jordan et al. (2016) compared virtual walking with virtual wheeling. The study found that those in the virtual walking group had a significant decrease in their neuropathic pain symptoms.

Viliger et al. (2013) provided virtual reality training in which participants were asked to complete four lower limb movement tasks. The study found significant decrease in pain intensity post treatment. Gustin et al. (2008) involved the participants to imagine right ankle plantarflexion and dorsiflexion for eight minutes. In contrast to the studies above, a significant increase in neuropathic pain intensity post guided visual imagery, ($p<0.01$).

Conclusion

There is level 1 (Soler et al. 2010) that visual illusion combined with tDCS results in improvement of post SCI pain. There is level 2 (Jordan et al. 2016) evidence that virtual walking reduced post SCI neuropathic pain. There is level 4 (Viliger et al. 2013) evidence that virtual reality related lower limb tasks may reduce pain post SCI. There is level 4 evidence (Gustin et al. 2008) that visual imagery of ankle movements is not sufficient to reduce pain post SCI.

Visual illusion combined with tDCS results in improvement of pain post SCI

Virtual reality lower limb training may reduce pain post SCI

Virtual walking reduces neuropathic pain post SCI

Visual imagery of ankle movements does not reduce pain post SCI

10.5.2 Hypnotic Suggestions

Hypnosis has been used to reduce pain in a number of painful clinical conditions as well as experimental pain (Jensen et al. 2000). Hypnosis is appealing as a potential treatment because it is non-pharmacological although its use is controversial given the variability in hypnotic responsiveness.

Table 11 Hypnotic Suggestion Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Jensen et al. 2009 USA RCT PEDro=5 N=37	**Population:** Mean Age=49.6yrs; Sex: males=28, females=9. Type of pain=neuropathic. **Intervention:** Participants were randomized to receive either hypnosis or biofeedback. Individuals receiving hypnosis underwent 10 sessions of training daily or weekly. While the biofeedback group received 10 sessions of Electromyography biofeedback. **Outcome Measures:** Numeric Rating Scale (NRS)	1. Individuals with neuropathic pain a significant decrease in daily pain intensity was seen in the hypnosis group post-session ($p<0.01$) but not the biofeedback group. 2. Neither treatment was effective in reducing pain for individuals without neuropathic pain.
Jensen et al. 2000 USA Pre-post N=22	**Population:** Age=24-76 yr; Gender: males=64%, females=36%; Time since injury=1.75-42.33 yr; Duration of pain=13.88 yr. Type of pain=neuropathic and musculoskeletal. **Treatment:** Hypnotic suggestions for pain relief were given to each subject. **Outcome Measures:** Pain intensity and unpleasantness and hypnotic responsiveness (modified version of the Stanford Hypnotic Clinical scale).	1. 86% reported decrease in pain intensity and unpleasantness from pre-induction to just after induction. 2. A significant time effect emerged for both pain intensity ($p<0.001$) and pain unpleasantness ($p<0.001$). 3. Significant effect for analgesic suggestion on pain intensity over and above the effects of the induction alone, with a significant decrease occurring in reported pain intensity before and after the analgesic suggestion ($p<0.05$). 4. Pre-induction, post-induction, and post-analgesia suggestion pain intensity ratings were all significantly lower than average pain during the previous 6 months ($p<0.01$, $p<0.0001$, $p<0.0001$ respectively). 5. Statistical significance was noted for two of the associations: Effect of pain plus analgesia suggestion on pain intensity ($p<0.01$) and effect of induction alone relative to least pain ($p<0.05$).

Discussion

Jensen et al. (2009) randomly allocated participants into hypnosis or the biofeedback treatment group. Participants in the hypnosis group reported a significant decrease in neuropathic pain intensity compared to those in the biofeedback group ($p<0.01$). However, no such effect was seen between the two groups in individuals without neuropathic pain. Jensen et al. (2000), in a

before and after study, examined the impact of hypnosis on pain post-SCI. Eighty-six percent of the SCI patients reported a decrease in pain intensity and unpleasantness after hypnosis, although there was no control group.

Conclusion

There is level 2 and level 4 evidence (from one randomized controlled trial and one pre-post study; Jensen et al. 2009, 2000) that hypnosis reduces neuropathic and musculoskeletal pain intensity post SCI.

Hypnosis may reduce neuropathic and musculoskeletal pain intensity post SCI.

10.5.3 Biofeedback

Biofeedback involves training individuals to gain control over brain states through electroencephalography (EEG) in order to help improve pain intensity. Biofeedback has been previously been shown to improve pain intensity in individuals with fibromyalgia and migraines (Jensen et al. 2013).

Table 12 Biofeedback Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Middaugh et al. 2013 USA RCT PEDro=5 N=15	**Population:** Mean age=38yr; Gender: males=12, females=3; Level of injury: paraplegia=13, quadriplegia=2; Mean time post injury=16yr; Type of pain: musculoskeletal (cervical and shoulder). **Treatment:** Individuals using wheelchairs were randomized to an exercise program alone (control, n=7) or with EMG biofeedback (treatment, n=8). Exercise programs were taught in two 90min sessions and were to be performed at home (1x/d, 5d/wk, 10wk). EMG biofeedback training was provided in 4 sessions (90min). Outcomes were assessed at baseline, 10wk, and 6mo. **Outcome Measures:** Wheelchair User Shoulder Pain Index (WUSPI).	1. The treatment group had a significant reduction in WUSPI score at 10wk (Δ=64%, p=0.02) while the control group did not (Δ=27%, p=0.42). 2. There were significant reductions in WUSPI score at 6mo in both the control group (Δ=63%, p=0.03) and treatment group (Δ=82%, p=0.004).
Jensen et al. 2009 USA RCT PEDro=5 N=37	**Population:** Mean Age=49.6yrs; Sex: males=28, females=9. Type of pain=neuropathic **Intervention:** Participants were randomized to receive either hypnosis or biofeedback. Individuals receiving hypnosis underwent 10 sessions of training daily or weekly. While the biofeedback group received 10 sessions of Electromyography biofeedback. **Outcome Measures:** Numeric Rating Scale (NRS)	1. Individuals with neuropathic pain a significant decrease in daily pain intensity was seen in the hypnosis group post-session (p<0.01) but not the biofeedback group. 2. Neither treatment was effective in reducing pain for individuals without neuropathic pain.

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Jensen et al. 2013 USA Pre-Post N=10	**Population:** Mean Age=46.1yrs; Sex: males=7, females=3; Time since injury=12.3yrs Type of pain=neuropathic and musculoskeletal. **Intervention:** SCI individuals with chronic pain were provided with 4 sessions of electroencephalography (EEG) Biofeedback for pain management. **Outcome Measures:** Numeric Rating Scale (NRS)	1. Significant improvement in worst pain intensity (p=0.01) and pain unpleasantness (p=0.026) was seen post treatment and at 3 month follow up. 2. No significant improvement in average pain intensity or sleep was seen.

Discussion

A pre-post study (Jensen et al. 2013) found biofeedback improved worst pain intensity but not average pain intensity among individuals with SCI pain. Jensen et al. (2009) randomly allocated participants into hypnosis or the biofeedback treatment group. Participants in the hypnosis group reported a significant decrease in neuropathic pain intensity compared to those in the biofeedback group ($p<0.01$). However, no such effect was seen between the two groups in individuals without neuropathic pain. Middaugh et al. (2013) found that exercise and EMG biofeedback training resulted in significant reduction in WUSPI scores post intervention and at 6 month follow up.

Conclusion

There is level 4 evidence (from one pre-post study; Jensen et al. 2013) that biofeedback may reduce worst pain intensity post SCI but not average pain intensity.

There is level 1b evidence (from 1 RCT; Middaugh et al. 2013) that combined EMG biofeedback and exercise may reduce pain post SCI.

There is level 1b evidence (from 1 RCT; Jensen et al. 2009) that biofeedback is not as effective as hypnosis in reducing neuropathic pain post SCI.

Biofeedback may reduce neuropathic and musculoskeletal pain intensity post SCI.

10.5.4 Cognitive Behavioural Therapy

Cognitive behavioural therapy (CBT) is a commonly used psychological intervention for chronic pain. Often used as a part of a more comprehensive pain management program, it attempts to modify beliefs and coping skills, particularly when these beliefs and coping skills are dysfunctional.

Table 12 Cognitive Behavioural Therapy

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Burke et al. 2019 Ireland RCT PEDro=7 N=69	**Population:** Mean age=51.0±13.0 yr; Gender: males= 52, females=17; Time since injury=16.0±21,1 yr; Level of injury: C=17, T=30, L=14; Severity of injury: AIS A=4, B=2, C=3, D=5, Not reported=55; Type of pain=neuropathic and nociceptive. **Intervention:** Participants were randomized to a control group or a spinal cord injury (SCI) cognitive behavioural therapy pain management program (CBT-PMP) delivered once a wk for 3 mo. **Outcome Measures:** Quality of life (world health organization quality of life bref (WHOQOL-BREF)), QOL (international spinal cord injury quality of life basic data set (ISCI-QOLBDS)), pain profile (international spinal cord injury pain basic data set with numeric rating scale (NRS) (ISCIPBDS)), pain presentation (douleur neuropathique en 4 questions (DN4)), pain acceptance (the chronic pain acceptance questionnaire-8 (CPAQ-8)), pain interference (brief pain inventory (BPI), mood (hospital anxiety and depression scale (HADS)), sleep (sleep quality index (PSQI)), global impression of change PGIC), adverse events.	1. No significant difference between intervention and control groups for WHOQOL-BREF and ISCI-QOLBDS (p>0.05). 2. Significant group X time interaction showing that pain levels differed over time between groups by NRS (p=0.016). 3. Worst pain scores showed similar group X time interaction with differed pain levels over time between groups (p=0.0004). 4. BPI showed a significant group X time effect (p=0.031) but not interaction. 5. No significant group X time interaction for the HADS questionnaire, PSQI for sleep or CPAQ for pain acceptance (p>0.05 for all). 6. Post-intervention there was a moderate linear relationship observed between number of module where users engaged with 80% or more of the content and reductions in measures of NRS (p=0.05), ISCIPBDS (p=0.08), LSF domain (p=0.04), BPI (p=0.10) and HADS depression subscale (p=0.10). 7. 3 mo follow-up revealed a moderate linear relationship between module engagement and improvements in sleep quality (p=0.06), AMS subcategory of ISCIPBDS (p=0.0), and the depression (p=0.03) and anxiety (p=0.05) subscales of HADS. 8. Immediately post-intervention 2 participants reported being very much improved, 8 reported being much improved, 9 reported minimal improved, and 10 reported no change. 9. At the 3 mo follow-upm 27 of the participants answered and 3 reported very much improved, 10 said much improved, 7 reported minimal improvement and 7 reported no change. 10. Two minor adverse events, one shoulder problem and one reported an increase in leg spasms following stretches.

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Heutink et al. 2012 Netherlands RCT PEDro=6 N=61	**Population:** Mean age=58.8 yr; Gender: males=39, females=22; Duration of pain=5.4 yrs; Type of pain=neuropathic. **Treatment:** SCI Individuals with chronic neuropathic pain were randomly assigned to receive interdisciplinary pain management which included Cognitive behavioural therapy (CBT) and education or wait list control group. The intervention consisted of 10 sessions over 10 week period with a comeback session 3 weeks after the 10^{th} session. **Outcome Measures:** Chronic Pain Grade Questionnaire; Hospital Anxiety and Depression Scale (HADS).	1. Pain intensity decreased over time among the two group, p<0.01. 2. Significant difference in pain intensity was seen between the two groups post intervention. However, no group difference between the two group were seen in pain intensity at 3 month follow-up. 3. No significant difference in HADS depression was seen between the two groups or over time. 4. Individuals in the CBT group found significant improvement in anxiety (p<0.027)and participation in activities (p<0.008) compared to the control group.
Perry et al. 2010 Australia PCT N=36	**Population:** Mean age=43.8 yr; Gender: males=28, females=8; Level of injury: tetraplegia=13, paraplegia=20, Severity of injury: complete=13, incomplete=23; Duration of pain=60.5 mo; Type of pain=neuropathic and musculoskeletal. **Treatment:** SCI patients with chronic pain were placed in either the multidisciplinary cognitive behavioural pain management program (PMPs) group (N=19) which involved a pharmacological treatment plan and individual and group based cognitive behavioural therapy for pain; or the usual care group (N=17). **Outcome Measures:** Pain response self-statement scale; Pain self-efficacy questionnaire; Multidimensional Pain Inventory (MPI); Hospital Anxiety and Depression Scale (HADS); SF-12 Mental Component Scale	1. At baseline, the PMP group had significantly worse usual pain intensity scores than the usual care group. 2. A significant improvement was seen in MPI and SF-12 MCS scores in the PMP group compared to the control group post treatment (p=0.026, p=0.015). 3. Mean scores of participants in the PMP group moved from moderate to mild disability. 4. A trend towards improvement on the usual pain intensity and HADS depression score was seen in the PMP group at 1 mo post treatment; however, the HADS depression scores returned to pre-treatment levels at 9 mo follow-up.
Norrbrink et al. 2006 Sweden PCT N=38	**Population:** SCI: Treatment: Mean age=53.2 yr; Gender: males=9, females=18; Control: Mean age=49.9 yr; Gender: males=5, females=6; Severity of injury: AIS A-E. Type of pain=neuropathic. **Treatment:** SCI individuals were provided standard treatment of interdisciplinary pain management. The individuals in the interdisciplinary pain management participated in a 10 wk, 2x/wk treatment program which included four elements: 1) education (1.5 hr); 2.) behavioural therapy (1.5 hr); 3) relaxation techniques and stretching/light exercise (1 hr); and 4) body awareness training (1hr). **Outcome Measures:** Pain Chart and pain rating was completed, pain intensity and unpleasantness was assessed with the	1. From baseline to 12 mo evaluation period, the treatment group experienced decrease in: • Anxiety and depression. • Sleep. 2. No change was seen over time in: • Pain intensities and unpleasantness. • Health-related quality of life. • Life satisfaction. 3. A significant improvement was noted for the Emotional Reaction subscale only (p<0.01). 4. The two groups showed significant differences on the depression and SOC scores. 5. A significant decrease in the number of visits between baseline and the 12

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	Borg CR10 scale, Quality of sleep (survey), Nottingham Health Profile (Quality of life) was completed, Mood (Hospital Anxiety and Depression) was assessed, Coherence and use of the healthcare system were also assessed.	mo assessment period was noted for the treatment group (from 15 to 5; p<0.03), along with the median number of visits to physicians (from 3 to 1; p<0.03).
Dear et al. 2018 Australia Pre-Post N=68	**Population:** Mean age=48.0±13.0 yr; Gender: males=34, females=34; Time since injury=8.0±10.0 yr; Level of injury: paraplegia=43, tetraplegia=16, undiagnosed=9; Severity of injury: complete=15, incomplete=44, undiagnosed=9; Type of pain=neuropathic. **Intervention:** Participants enrolled in a pain management program where they completed five online lessons and homework that was systematically released over an 8-wk period. **Outcome Measures:** Pain disability index (PDI), patient health questionnaire 9-item (PHQ-9), Wisconsin brief pain questionnaire (WBPQ), generalized anxiety disorder scale 7-item (GAD-7), pain self-efficacy questionnaire (PSEQ), pain catastrophizing questionnaire (PCS), satisfaction with life scale (SWLS).	1. Significant overall effect observed for pain-related disability (p<0.001), depression (p<0.001), and anxiety (p<0.001). 2. Significant improvements in disability, depression and anxiety levels after treatment (p<0.001) and 3-mo follow-up (p<0.015). 3. Significant improvements in average pain levels from baseline to post-treatment (p<0.001). 4. Significant overall time effects observed for PSEQ (p=0.002), PCS (p<0.001) and SWLS (p<0.001) as well as a significant increase in PCS and SWLS (p<0.001). 5. SWLS continued to increase from post-treatment to 3-mo follow-up (p=0.006) but PCS did not (p=0.062). 6. No significant improvements in PSEQ from baseline to post-treatment (p=0.631) but significant improvements were observed from post-treatment to 3-mo follow-up (p=0.018).
Burns et al. 2013 Canada Pre-Post N=17	**Population:** Mean age=48 yr; Gender: males=11, females=6; Level of injury: tetraplegia=8, paraplegia=9, Severity of injury: complete=3, incomplete=14; Duration of pain>6 mo; Type of pain=neuropathic and musculoskeletal. **Treatment:** SCI Individuals with chronic pain were provided group based interdisciplinary pain management which included Cognitive behavioural therapy (CBT) self-management, and exercise biweekly for 10 weeks. **Outcome Measures:** Multidimensional Pain Inventory (MPI)	1. No significant improvement in pain severity subscale of MPI was seen post intervention or at 12 months. 2. Significant improvement in life interference and life control subscales was seen (p<0.01) up to the 12 month follow up.

Discussion

Two studies examined the effect of internet delivered CBT on pain intensity post SCI (Burke et al. 2019; Dear et al. 2018). Burke et al. (2019) found significant improvement compared to control. In a pre-post trial, Dear et al. (2018) found improvement in pain intensity post intervention. Four studies examined the effectiveness of interdisciplinary pain management on chronic pain post SCI. Perry et al. (2010) placed SCI individuals with chronic pain into a multidisciplinary cognitive behavioural pain management program, involving pharmacological and CBT treatment, or in a usual care control group. This was the only study to find significant

improvement in both the MPI and SF-12 MCS scores in the treatment group compared to the control group post treatment. A trend towards improved pain intensity and HADS score was also seen in the treatment group post treatment; however, scores returned to pre-treatment scores by nine month follow-up. Norrbrink et al. (2006), Burns et al. (2013), and Heutink et al. (2012) found no improvement in pain intensity among individuals receiving treatment. However, both studies found significant improvement in related psychosocial factors post treatments. Norrbrink et al. (2006) found significant improvement in anxiety, depression and sleep interference post treatment. Burns et al. (2013) found change in life interference and locus of control. Significant improvement in anxiety and participation in activities was seen in Heutink et al. (2012) among individuals that received CBT.

Conclusions

There is level 1b evidence (from one randomized controlled trial; Heutink et al. 2012) that cognitive-behavioural therapy improves pain intensity post-SCI in the short-term.

There is level 1b evidence (Burke et al. 2019) that internet delivered CBT may improve pain intensity compared to control.

There is level 2 evidence (from one prospective controlled trial; Perry et al. 2010) that a cognitive behavioural pain management program with pharmacological treatment may improve secondary outcomes among SCI individuals with chronic pain post SCI.

Cognitive behavioral therapy combined with pharmacological treatment may result in improvement in secondary outcomes among SCI individuals with chronic pain.

Cognitive-behavioral pain management programs (internet delivered and face to face) may reduce post-SCI pain.

10.5.5 Mindfulness

Table 13 Mindfulness Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Hearn et al. 2018 United Kingdom RCT PEDro=7 N_{start}=67 N_{finish}=	**Population:** Mean age=44.4±10.4 yr; Gender: males=31, females=36; Time since injury (yr): 1-2=11, 2-4=18, 4-8=19, 8-12=6, 12-15=7, 15+=6; Level of injury: C=25, T=37, L=5; Severity of injury: AIS A=9, B=17, C=19, D=22; Type of pain=neuropathic. **Intervention:** Participants were randomized to either an 8-wk online mindfulness intervention or an 8-wk internet delivered psychoeducation. **Outcome Measures:** Depression symptom severity and anxiety (hospital anxiety and depression scale (HADS)), quality of life (QoL)(world health	1. HADS scores for depression were much higher for those that discontinued the psychoeducation intervention than those who completed it (p=0.051) with no other significant differences between those who completed the intervention and those who did not. 2. Significant differences post-intervention between groups for mindfulness facets of acting with awareness, describing and non-reactivity to inner experience (p<0.05) as well as total FFMQ score (p<0.05).

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	organization quality of life (WHOQOL-BREF) , pain perception (numeric rating scale), pain catastrophizing scale (PCS) and mindfulness (five facet mindfulness questionnaire (FFMQ).	3. No significant differences between groups for any QoL, pain intensity and mindfulness facets of observing and non-judging post-intervention ($p>0.05$). 4. Significant between group difference in severity of depression and pain catastrophizing at 3-mo follow-up ($p<0.050$).

Discussion

In an RCT, Hearn and colleagues (2018) found that online mindfulness was effective in improving level of depression and pain catastrophizing compared to psychoeducation control group. However, no difference in average pain intensity was seen between the two groups.

Conclusion

There is level 1b evidence that mindfulness is no more effective than psychoeducation for improving post SCI pain.

Mindfulness is not effective at improving post SCI pain.

10.6 Transcranial Direct Current Stimulation Post SCI Pain

Transcranial Direct Current Stimulation (tDCS) ability to relieve pain has been studied previously; However, it's mechanism is still not completely understood. It is believed to play a role through its modulatory affect on the central pathways targeted by antidepressants (Knechtel et al. 2013).

Table 14 Transcranial Direct Current Stimulation Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Choi et al. 2019 Korea RCT Crossover PEDro=8 N=10	**Population:** Mean age=40.7±11.6 yr; Gender: males=7, females=3; Time since injury=8.9±7.1 yr; Level of injury: C=10, T/L=0; Severity of injury: AIS A=6, B=4, C/D=0; Type of pain=neuropathic. **Intervention:** Participants were randomized to transcutaneous spinal direct current stimulation (tsDCS) or a sham tsDCS, underwent a washout period after the first set and were then give the other condition.	1. Pain reduction was statistically significant from pre- to post-session in the sham tsDCS condition only ($p=0.0102$). 2. Significant change in pain intensity immediately after stimulation and at 1 h after treatment ($p<0.05$ for both). 3. No significant differences between active and sham tsDCS for NRS or for PGA, and no significant decrease in NRS for the active tsDCS group ($p>0.05$ for both).

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	Outcome Measures: Subjective pain perception via numeric rating scale (NRS), patient global assessment (PGA), present pain intensity (PPI) and adverse events.	4. Sham treatment reduced the PPI scores, but PPI distributions immediately after stimulation, 1h after and 2h after were significantly different in the sham tsDCS condition only (p=0.0452). 5. No adverse events reported.
Li et al. 2018 USA RCT Crossover PEDro=6 N=12	**Population:** Mean age=43.4±11.7 yr; Gender: males=7, females=5; Time since injury=15.5±12.3 yr; Level of injury: C=10, T=2, L=0; Severity of injury: all incomplete; Type of pain=neuropathic. **Intervention:** Participants completed both the real and sham transcranial direct cranial stimulation (tDCS) followed by active breathing-controlled electrical stimulation/conventional electrical stimulation (BreEStim and EStim respectively) and were randomized to which they would complete in the first session and three days later in the second session. **Outcome Measures:** Visual analog scores (VAS) for pain and analgesic effects.	1. 10 of the 12 participants completed both conditions because of timing conflicts. 2. Positive analgesic effects were seen in active tDCS, but only in 4 of 10 participants in the sham tDCS and in BreEStim all but one participant saw positive analgesic effects. 3. No difference in active and sham tDCS seen at the group level. 4. VAS decreased from 5.7-5.1 after active tDCS and from 6.0-5.4 after the sham tDCS. 5. Significant decrease in VAS after BreEStim in the active and sham tDCS group (p<0.00001 for both). 6. All 12 participants completed the active tDCS and BreEStim and a main effect of time was observed to be significant (p<0.00001). 7. No significant change of VAS observed after active tDCS, but a significant change was seen after active BeEStim (p<0.05).
Thibault et al. 2017 (Phase I) USA RCT PEDro=8 N=33	**Population:** Mean age=51.2±12.5 yr; Gender: males=24, females=9; Time since injury=5.2±2.0 yr; Type of pain=neuropathic. **Intervention:** Participants were randomized to either an active transcutaneous direct current stimulation (tDCS) group or a sham tDCS group for 5 sessions over 5 days with assessments at baseline, post-intervention, 1-wk and 3-mo follow-up. **Outcome Measures:** Visual analog scores (VAS) for pain, patient health questionnaire (PHQ-9) and satisfaction with life scale (SWLS).	1. Linear regression models revealed that group status was associated with significant changes in VAS scores at 1-wk follow-up average (p=0.0003) and least pain (p=0.043). 2. No significant changes in PHQ-9 scores or SWLS scores at any time points (p>0.05 for all).
Thibault et al. 2017 (Phase 2) USA RCT PEDro=8 N=9	**Population:** Mean age=49.0±14.4 yr; Gender: males=7, females=2; Time since injury=6.3±8.1 yr; Type of pain=neuropathic. **Intervention:** Participants were randomized to either an active transcutaneous direct current stimulation (tDCS) group or a sham tDCS group for 10 sessions of tDCS, once a day during weekdays for 2 wks with assessments	1. Linear regression models showed that group status was associated with significant changes in VAS average at 4-wk follow-up (p=0.016). 2. No significant changes identified for any other outcomes at any other timepoints (VAS, PHQ-9 and SWLS).

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	taken after 5 and 10 sessions and 2-, 4- and 8-wk follow-up. **Outcome Measures:** Visual analog scores (VAS) for pain, patient health questionnaire (PHQ-9) and satisfaction with life scale (SWLS).	
Ngernyam et al. 2015 Thailand RCT Crossover PEDro=8 N=20	**Population:** Mean age=44.5yr; Gender: males=15, females=5; Level of injury: paraplegia=13, quadriplegia=7; Severity of injury: incomplete=11, complete=9; Mean time post injury=54.65mo; Type of pain=neuropathic. **Treatment:** Participants received active and sham anodal transcranial direct current stimulation (tDCS) over the left primary motor area (M1) in a randomized sequence. tDCS was delivered in separate 20min sessions with a 1wk washout period in between. Outcomes were assessed pre and post each session. **Outcome Measures:** Numerical Rating Scale - Pain Intensity (NRS-PI), Peak theta-alpha frequency (PTAF).	1. For pain intensity, there was a significant main effect for time ($p<0.001$) and significant time x condition interaction ($p=0.031$). 2. Active tDCS showed a significant reduction in pain intensity after treatment ($p<0.001$) while sham tDCS did not ($p=0.096$). 3. Active tDCS showed significantly greater reduction in pain intensity immediately ($p=0.043$) and 24hr ($p=0.041$) after treatment than sham tDCS. 4. Active tDCS showed a significantly greater association between decreased pain intensity and increased PTAF than sham tDCS ($p=0.003$). 5. There was no significant association between change in pain intensity and duration of injury or pain for either condition.
Wrigley et al. 2013 Australia RCT PEDro=9 N=10	**Population:** Mean age=56.1yr; Duration of pain=15.8yr; Type of pain=neuropathic. **Treatment:** Participants were randomized to tDCS or sham. One 20 min treatment session was delivered each day for 5 consecutive days. A 4 week washout period took place before crossover to sham or treatment. **Outcome Measures:** Numeric rating scale	1. No significant effect of tDCS on pain intensity or pain unpleasantness
Soler et al. 2010 Spain RCT PEDro=8 N=40	**Population:** Age=21-66yr, Severity of injury: AIS A=32, B=8; Type of pain=neuropathic. **Intervention:** Patients were randomly divided into four groups: transcranial DCS and visual illusion group received direct current stimulation over C3 or C4 at a constant 2 mA intensity for 20 min and after 5 min of transcranial DCS video with someone walking was shown and the legs of person for 15 min with a vertical mirror so patients could see themselves walking; transcranial DCS group with control visual illusion received the above mentioned transcranial DCS; however, for the visual illusion only received a video of faces or landscapes, visual illusion group and sham transcranial DCS had electrodes placed on the same area as the treatment	1. The most significant reduction in NRS of pain perception was seen in the combined transcranial DCS and visual illusion group compared to the visual illusion group ($p=0.008$) or the placebo group ($p=0.004$). 2. Pain reduction was also greatest in the transcranial DCS and visual illusion group than the other three groups at first and last follow up; however, no difference was seen at second follow-up. 3. Visual illusion group was shown to have significant improvement in neuropathic pain intensity at last day of treatment ($p=0.02$); however, this

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	group however the stimulator was turned off after 30 sec of stimulation and placebo group consisted of both the control visual illusion and the sham transcranial DCS. **Outcome Measures:** Numeric Rating Scale (NRS)	effect was not maintained over the long-term period. 4. Combined transcranial DCS and visual illusion group also showed significant improvement in ability to work, perform daily tasks, enjoyment, interference of pain in sleep ($p<0.05$). 5. Transcranial DCS sessions were found to be safe, with minor side effects including mild headache.
Fregni et al. 2006 USA RCT PEDro=9 N=17	**Population:** Type of pain=neuropathic. **Treatment:** Subjects received either sham (10 sec of stimulation with same procedure but then turned off) or active tDCS (2 mA, 20 min for 5 days). **Outcome Measures:** VAS	1. Treatment produced significant decrease in pain scores over time ($p<0.0001$). 2. The largest pain reduction was noted after session five; effect decreased during follow-up, though pain scores remained lower than baseline scores. 3. There was no significant effect of treatment on either anxiety or depression scores in either group. 4. Effects on cognitive function similar for tDCS and sham.
Yoon et al. 2014 Korea PCT N=16	**Population:** Mean =44.1yr; Gender: male=12, female=4; Time since injury>6months; Type of pain=neuropathic. **Treatment:** SCI individuals with chronic neuropathic pain received either active or sham transcranial direct current stimulation for 20 minutes, 2 times a day for 10 days. **Outcome Measures:** Numeric Rating Scale (NRS); Patient Global Impression of Change (PGIC)	1. Individuals in the active group had significant reduction in pain intensity post treatment ($p=0.016$). 2. 2 individuals in the treatment group experienced reduction in pain intensity of greater than 30%, with the group average of 22.9% reduction. 3. No significant difference was seen between the two groups in PGIC.
Kumru et al. 2013 Spain Cohort N=52	**Population:** Age=25-69yrs; Gender: male=34, female=18. Type of pain=neuropathic and musculoskeletal, with a subanalysis of neuropathic. **Treatment:** Three cohorts of individuals (group 1(N=18)=SCI neuropathic pain; group 2(N=20)=SCI non-neuropathic pain; group 3(N=14)=healthy matched) underwent daily transcranial direct current stimulation along with visual illusion therapy for 2 weeks The visual illusion involved the participant seated viewing a video of the matching gender walking on a treadmill. **Outcome Measures:** Numeric Rating Scale (NRS)	1. SCI individuals with neuropathic pain had a 37.4% improvement in pain intensity post treatment. 2. 13 of 18 individuals in the neuropathic group reported 50% decrease in pain intensity post treatment. 3. Evoked pain perception was significantly lower in the neuropathic pain group compared to SCI nonneuropathic and healthy controls. 4. Pain threshold was significantly higher in the neuropathic pain group compared to the other two groups.

Discussion

There is conflicting evidence for the effectiveness of tDCS in reducing pain post SCI. Three RCTs found treatment of tDCS did not reduce pain intensity compared to sham treatment (Choi et al. 2019; Li et al. 2018; Wrigley et al. 2013). While, four RCTs found a significant reducing in pain intensity post intervention and at follow up compared to sham treatment (Fregni et al. 2006; Ngernyam et al. 2015; Thibault et al. 2017a; Thibault et al. 2017b). Evaluating of optimal frequency and dosage of treatment is warranted.

Soler and colleagues (2010) found that combined tDCS and visual illusion treatment resulted in significant reduction in pain compared to either treatment alone or placebo control. Secondary outcomes of quality of life, return to work, and sleep were also improved in the combined group.

Conclusion

There is level 1a evidence (from randomized controlled trials; Fregni et al. 2006; Ngernyan et al. 2015; Soler et al. 2010; Thibault et al. 2017a; Thibault et al. 2017b; Choi et al. 2019) for the benefits of transcranial direct current stimulation in reducing post-SCI pain.

There is level 1b evidence (Soler et al. 2010) for combined tDCS and visual illusion in improving post SCI pain.

Transcranial direct current stimulation may be effective in reducing post SCI neuropathic pain.

10.7 Transcranial Electrical Stimulation Post SCI Pain

Transcranial Electrical Stimulation (TCES) treatment involves applying electrodes to an individual's scalp to allow electrical current to be applied and presumably stimulate the underlying cerebrum (Tan et al. 2006).

Table 15 Transcranial Electrical Stimulation Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Tan et al. 2006 USA RCT PEDro=10 N=38	**Population:** Type of pain=neuropathic and musculoskeletal. **Treatment:** Subjects received 1 hr Transcranial Electrical Stimulation (TCES) or sham TCES for 21 days to treat neuropathic or musculoskeletal pain. Following this, the control group was offered the opportunity to participate in an open-label TCES study. **Outcome Measures:** Brief Pain Inventory (BPI)	1. No significant difference between TCES and sham groups for BPI. However, several individual interference items were significantly reduced, from pre to post intervention, in the TCES group only. 2. For active TCES, average daily pain intensity from pre to post assessment decreased significantly (p=0.03) compared to the sham (control) group. 3. Significant reduction in daily pain intensity noted in treatment group

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
		(pre-post) (p=0.02) but not in control group (p=0.34). 4. During open label trial, a reduction in pain was noted after TCES treatment (p=0.003)
Capel et al.2003 Canada RCT PEDro=8 N=30	**Population:** Type of pain=neuropathic and musculoskeletal. **Treatment:** SCI subjects randomly assigned to one of two groups. Treatment group received transcranial electrostimulation (TCES) twice daily for 4 days, while controls received sham treatment. After an 8 wk washout period, treatments were reversed for sham treatment group only; thus, during the second half of the observation period, all received active treatment. Three subjects left the study early, two because of interactions between TCES and medications. **Outcome Measures:** Short form McGill Pain Questionnaire (SF-MPQ); State Trait Anxiety Inventory (STAI); Beck Depression Inventory (BDI)	1. During first part of the study, those on TCES reported less severe pain vs. baseline (p=0.0016); controls reported no change. 2. During phase two of study, control group (now receiving TCES) also reported significantly less pain (p<0.005). 3. Treatment group used fewer medications (analgesics and antidepressants) while receiving TCES (p<0.05). 4. Groups did not differ in pre-morbid psychological states (i.e., STAI, BDI) nor was treatment effect associated with mood in either group.

Discussion

Two RCTs found TCES was effective in reducing average pain intensity compared to sham control (Capel et al. 2003; Tan et al. 2006). Additionally, Capel and colleagues (2003) found significant reducing in use of medications among those in the TCES group compared to control.

Conclusion

There is evidence level 1a evidence (from two randomized controlled trials; Capel et al. 2003; Tan et al. 2006) for the benefits of transcranial electrical stimulation in reducing neuropathic and musculoskeletal post-SCI pain.

Transcranial electrical stimulation is effective in reducing post SCI pain.

10.8 Static Magnetic Field Therapy Post SCI Pain

Table 16 Static Magnetic Field Therapy Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Panagos et al. 2004 USA Pre-Post	**Population:** Type of pain=nociceptive musculoskeletal shoulder pain.	1. On SF-MPQ, pain intensity decreased (p<0.01). 2. Significant decreases also were

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
N=8	**Treatment:** A concentric field type magnet (500 gauss) was placed over one shoulder for 1 hr. **Outcome Measures:** Short form McGill Pain Questionnaire (SF-MPQ); Visual Analogue Scale (VAS)	noted in severity of sharp and stabbing pain, and degree of tenderness (p=0.033, p=0.02, and p=0.021, respectively). 3. Pain intensity on VAS and in response to pressure did not change significantly with magnet application.

Discussion

Static Magnetic Field (SMF) therapy has been studied as a treatment for pain post SCI. Panagos et al. (2004) in a pre-post study involving eight individuals, on average 12 years post injury, found that placing a static field magnet of 500 gauss over a self-identified 'trigger point' resulted in patients reporting less stabbing, sharp and tender pain ($p<0.05$); however, there was no significant change noted on a VAS pain severity scale. These results are severely limited by the uncontrolled study design and relatively few study participants.

Conclusion

There is level 4 evidence (from one pre-post study; Panagos et al. 2004) that using a static field magnet helps to reduce reports of sharp, stabbing nociceptive shoulder pain but does not significantly reduce the VAS score of pain in individuals with a SCI.

Static field magnet may reduce nociceptive shoulder pain post SCI.

10.9 Transcutaneous Electrical Nerve Stimulation for Pain Post SCI

Transcutaneous Electrical Nerve Stimulation (TENS) is commonly used as an electroanalgesic and has been shown to be efficacious in the treatment of chronic musculoskeletal pain (Johnson et al. 2007). TENS is believed to preferentially stimulate large alpha sensory nerves and reduce pain at the presynaptic level in the dorsal horn of the spinal cord through nociceptive inhibition (Cheing et al. 1999).

Table 17 Transcutaneous Electrical Nerve Stimulation for Pain Post SCI

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Bi et al. 2015 China RCT PEDro=7 N_{start}=52 N_{end}=48	**Population:** TENS group: Mean age=35.5±9.0 yr; Gender: males=17, females=7; Time since injury=7.0±4.1 mo; Level of injury: tetraplegia=10, paraplegia=16; Severity of injury: complete=15, incomplete=11; Type of pain=neuropathic. Control group: Mean age=33.6±8.5 yr; Gender: males=15, females=9; Time since injury=6.8±3.1 mo; Level of injury: tetraplegia=7, paraplegia=19; Severity of	1. Significant difference between the TENS and control group in VAS pain severity scores ($p<0.05$). 2. Significant difference between the TENS and control group in MPQ pain severity scores ($p<0.05$).

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	injury: complete=18, incomplete=8; Type of pain=neuropathic. **Intervention:** Participants were randomized to either a TENS group and treated with TENS or a control group and treated with sham TENS for 20 min, 3 times/wk for 12 wks. **Outcome Measures:** Pain (visual analog scale (VAS) and the McGill Pain Questionnaire (MPQ)). Transcutaneous electrical nerve stimulation (TENS)	
Ozkul et al. 2015 Turkey RCT Crossover PEDro=5 N=24	**Population:** Mean age=32.33; Gender: males=18, females=6; Level of injury: paraplegia=6, quadriplegia=18; Severity of injury: incomplete=7, complete=17; Mean time post injury=12.46mo; Type of pain=neuropathic. **Treatment:** Participants received transcutaneous electrical nerve stimulation (TENS) and visual illusion (VI) in a randomized sequence. Each treatment was delivered for 2wk with a 1wk washout period in between. Outcomes were assessed pre and post each treatment period. **Outcome Measures:** Visual Analogue Scale - Pain Intensity (VAS-PI), Neuropathic Pain Scale (NPS), Brief Pain Inventory (BPI).	1. There was a reduction in VAS-PI immediately after VI (p=0.07) and TENS (p=0.08), but there was no statistically significant group effect. 2. There was a significant reduction in pain 2wk post TENS (p=0.04) but not 2wk post VI (p>0.05). 3. On NPS, VI significantly decreased the following pain types: hot (p=0.047), sharp (p=0.02), unpleasant (p=0.03), and deep (p=0.047); TENS did not show any significant effects. 4. On BPI, VI significantly decreased the negative effect of pain on moving ability (p=0.04) and TENS significantly decreased the negative effect of pain on mood (p=0.03), relationships (p=0.04), and sleep (p=0.04).
Norrbrink 2009 Sweden PCT N=24	**Population:** Age=47.2yr; Gender: males=20, females=4; Level of injury: C=13, T=8, L=3. Type of pain=neuropathic and musculoskeletal **Intervention:** Patients were provided with either low frequency (2Hz) or high frequency (80Hz) transcutaneous electrical nerve stimulation (TENS) stimulation for 30-40 min 3x/day for 2 wk followed by a 2 wk washout period and switched stimulation frequency. **Outcome Measures:** Numeric Rating Scale (NRS)	1. No significant difference was found between the two modes of stimulation. 2. 21% reported reduction of greater than or equal to 2 units of general pain intensity (more than 1.8 considered significant clinical reduction), 29% in worst pain intensity and 33% in pain unpleasantness. 3. 29% reported a favorable effect on the global pain relief scale from HF and 38% from LF stimulation.
Zeb et al. 2018 Pakistan Pre-Post N=60	**Population:** Mean age=52.6±0.5; Gender: males=45, females=15; Severity of injury: all incomplete; Type of pain=neuropathic. **Intervention:** Participants engaged in high frequency (80 Hz) transcutaneous electrical nerve stimulation (TENS) for 45 min/day, 4 days/wk for 8wks with assessments at baseline and post-intervention. **Outcome Measures:** Pain intensity (visual analog score (VAS)).	1. Mean pain intensity decreased in a linear fashion and showed a significant difference from pre- to post-intervention (p<0.05).

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Davis & Lentini 1975 USA Case Series N=31	**Population:** Type of pain=neuropathic **Treatment:** Patients were tested with transcutaneous nerve stimulation. **Outcome Measures:** Subjective patient report.	1. Those with a cervical injury (n=4) were not successfully treated with TENS. About 1/3 of patients (n=11) felt that the treatment was a success, with those experiencing at-injury site pain most effectively treated.

Discussion

In an RCT, TENS was found to significantly reduce pain severity compared to a sham group over a 12 week intervention (Bi et al. 2015). Ozkul and colleagues (2015) found TENS was effective in reducing pain intensity, mood, and sleep interference compared to VI overall. However, VI resulted in significant reduction in hot, sharp, unpleasant, and deep pain types while TENS was not. In terms of low vs. high frequency TENS, Norrbring (2009) found no significant difference between the two frequencies in reducing pain post SCI.

Conclusion

There is level 1b evidence (Bi et al. 2-15) that transcutaneous electrical nerve stimulation reduced pain post SCI.

Transcutaneous electrical nerve stimulation may reduce pain post SCI.

10.10 Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a non-invasive and relatively safe technology where electromagnetic currents in a coil produces magnetic pulses which crosses the cranium and induces neuron depolarization (Defrin et al. 2007). Magnetic stimulation of the motor cortex has been shown to attenuate post-stroke pain (Migita et al. 1995).

Table 18 Transcranial Magnetic Stimulation

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Nardone et al. 2017 Italy RCT PEDro=9 N=12	**Population:** Mean age=43.1±13.2 yr; Gender: males=9, females=3; Time since injury=10.3±5.0 yr; Level of injury: C=8, T=4, L=0; Severity of injury: A=2, B=5, C=2, D=3; Type of pain=neuropathic. **Intervention:** Patients were randomized to either an active repetitive transcranial magnetic stimulation (rTMS) (1250 pulses at 10 Hz or a sham treatment for 10 sessions over 2 wks.	1. Sum score of pain showed a significant main effect for group ($p=0.02$) and time ($p<0.001$). 2. Significant interaction between group and time ($p<0.001$). 3. RTE scores were observed to be lower in the treatment group versus the sham group. 4. Post hoc tests revealed a significant difference between groups for RTE

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	Outcome Measures: Visual analog scale (VAS and McGill pain questionnaire (MPQ) for pain, relative treatment effect (RTE), Hamilton rating scale for depression (HAM-D) and Hamilton rating scale for anxiety (HAM-A).	after the 2 wks of treatment ($p<0.001$). 5. A significant main effect for time was shown for HAM-D scores ($p<0.001$). 6. Significant interaction between group and time for HAM-D scores in the treatment group ($p<0.001$). 7. Variance-type tests for HAM-A revealed no significant effects.
Yilmaz et al. 2014 Turkey RCT PEDro=7 $N_{Initial}=17$; $N_{Final}=16$	**Population:** Mean age=38.6yr; Gender: males; Level of injury: paraplegia; Severity of injury: incomplete=6, complete=10; Mean time post injury=134yr; Type of pain=neuropathic. **Treatment:** Participants were randomized to receive active (treatment, n=9) or sham (control, n=7) repetitive transcranial magnetic stimulation (rTMS, 1x/d, 10d). Outcomes were assessed pre and post treatment, and at 6wk and 6mo follow-up. **Outcome Measures:** Visual Analogue Scale – Pain Intensity (VAS-PI).	1. There was a significant reduction in VAS-PI score in the treatment group at 10d and 6wk ($p=0.004$) and in the control group at 10d ($p=0.02$). 2. There was no significant difference in VAS-PI score between groups at baseline, 10d, 6wk, or 6mo ($p>0.05$).
Jette et al. 2013 Canada RCT PEDro=7 N=16	**Population:** SCI: Mean age=50yr; Gender: males=11, females=5; Level of injury: quadriplegia=4, paraplegia=12. Type of pain=neuropathic. **Treatment:** SCI individuals with chronic neuropathic pain were randomly assigned to receive 3 sessions of active or sham rTMS over hand or leg area. Participants were then crossed over to receive the alternative treatment. **Outcome Measure:** Numeric Rating Scale (NRS)	1. Significant reduction in pain was seen in both hand ($p=0.003$) and leg ($p=0.047$) conditions 20 minutes post treatment; while no significant difference was seen in control group. 2. Pain improvement lasted up to 48 hours in both the hand ($p=0.021$) and leg (0=0.008). 3. Those with incomplete injury in the hand condition had greater reduction than those with complete ($p=0.018$).
Kang et al. 2009 South Korea RCT PEDro=9 N=13	**Population:** SCI: Mean age=54.8yr; Gender: males=11, females=5; Level of injury: quadriplegia=5, paraplegia=6. Type of pain=neuropathic. **Treatment:** SCI individuals with chronic neuropathic pain were randomized to receive 5 sessions of rTMS or sham rTMS. Participants were then crossed over to receive the alternative treatment after a 12 week washout period. **Outcome Measure:** Numeric Rating Scale (NRS); Brief Pain Inventory (BPI)	1. No significant effect of time or group was seen for rTMS on NRS scores post treatment and at 3 week follow up. 2. Significantly lower NRS scores for worst pain were seen 1 week post rTMS period compared to those with sham rTMS, $p=0.028$. 3. No significant effect of time or group was seen on the BPI
Defrin et al. 2007 Israel RCT PEDro=10 N=12	**Population:** SCI: Mean age=54 yr; Gender: males=7, females=4. Type of pain=neuropathic. **Treatment:** Patients were randomly placed into two groups: real or sham 10 daily motor TMS treatments (500 trains at 5 Hz for 10 sec; total of 5000 pulses at intensity of 115% of motor threshold) over a 2 wk period, using figure-of-8 coil over the vertex.	1. The real and sham TMS stimulated similar, significant decreases in VAS scores ($p<0.001$) following all of the 10 treatment sessions, and in VAS and MPQ scores following the final treatment series. 2. The reduction in MPQ scores in the real TMS group continued during the follow-up period.

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	Outcome Measure: Chronic pain intensity (visual analog scale [VAS]) Chronic pain experience (McGill Pain Questionnaire [MPQ]), pain threshold, and level of depression (Beck Depression Inventory [BDI]).	3. There was no significance between group differences in the magnitude of pain reduction. 4. At follow-up, patients in the TMS group reported a 30% reduction in chronic pain intensity, compared to a 10% pain reduction reported by patients in the sham TMS group. 5. A significant increase in heat-pain threshold was found only for patients in the real TMS group (4°C, $p<0.05$) at the end of the series. 6. There was a significant difference in the magnitude of change in pain threshold between the real and sham TMS groups ($p<0.05$). 7. Real and sham TMS groups showed a significant decrease in BDI values following the treatment period in comparison to pre-treatment BDI values ($p<0.01$). 8. This reduction was maintained by both groups at follow-up ($p<0.01$). 9. Only patients in the TMS treatment group exhibited a decreased level of depression during follow-up in comparison to the values at the end of treatment ($p<0.05$).

Discussion

There is conflicting evidence for the effectiveness of rTMS in reducing pain post SCI. Three RCTs found no significant difference between rTMS and sham groups in pain intensity post intervention (Defrin et al. 2017; Kange et al. 2009; Ylimaz et al. 2014). Two RCTs found rTMS significantly reduced pain intensity compared to a sham control treatment (Jette et al. 2013; Nardone et al. 2017). Jette et al. (2013) found that reduction in pain intensity was greater among those incomplete injury compared to complete. Evaluation of potential subgroups that may benefit from rTMS treatment is warranted.

Conclusion

There is level 1a evidence (from four randomized controlled trials; Jette et al. 2013; Defrin et al. 2007;) that rTMS may not significantly reduce average pain intensity post-SCI.

There is level 1b evidence (from one RCT Kang et al. 2009) that rTMS significantly reduces worst pain compared to sham rTMS.

Transcranial magnetic stimulation may not reduce post-SCI average pain intensity.

Transcranial magnetic stimulation may reduce post-SCI worst pain intensity.

10.11 Neuromuscular electrical stimulation

Neuromuscular electrical stimulation (NMES) has been reported to improve several pain conditions, such as back pain, shoulder pain, wrist pain, knee pain.

Table 19 NMES Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Chen et al. 2018 China PCT N=54	**Population:** NMES+carbamazepine group: Mean age=41.8±12.6 yr; Gender: males=25, females=2; Time since injury=31.2±11.5 mo; Level of injury: C=12, T=13, L=2; Severity of injury: AIS A=16, B=3, C=5, D=3; Type of pain=neuropathic. Carbamazepine group: Mean age=43.5±13.7 yr; Gender: males=23, females=4; Time since injury=29.7±10.8 mo; Level of injury: C=14, T=10, L=3; Severity of injury: AIS A=18, B=2, C=3, D=4; Type of pain=neuropathic. **Intervention:** Participants were assigned to either an NMES + carbamazepine group or a carbamazepine only group for 3 mo of treatment with outcomes measures at baseline and post-intervention. **Outcome Measures:** Pain intensity numerical rating scale (NRS), quality of life (QOL) sort form 36 (SF-36) scale, and adverse events. *Neuromuscular electrical stimulation (NMES), neuropathic pain (NPP)	1. No significant difference in NRS for NPP or the QOL in SF-36 in the NMES group (p>0.05). 2. No serious adverse events in either group.

Discussion

In an RCT, Chen and colleagues (2018) found that combined NMES and carbamazepine was equally as effective at reducing pain intensity compared to carbamazepine alone.

Conclusion

There is level 2 evidence (Chen et al. 2018) that NMES combined with carbamazepine is no more effective than carbamazepine alone in improving pain post SCI

Combined NMES and carbamazepine is no more effective than carbamazepine alone for SCI pain.

10.12 FES

Table 20 FES Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Wilbanks et al. 2016 USA Pre-Post N=10	**Population:** Mean age=47.0±12.0 yr; Gender: males=8, females=2; Time since injury=18.0±14.0 yr; Level of injury: all T; Severity of injury: AIS A=5, B=2, C=3, D=0; Type of pain=musculoskeletal. **Intervention:** Participants engaged in 30 min of functional electrical stimulation (FES) rowing 3 days/wk for 6 wks for a total of 18 sessions. **Outcome Measures:** VO_2peak (FES-rowing and UBE conditions), distance rowed, arm power output, wheelchair user shoulder pain index (WUSPI), body composition, body weight, thigh lean mass, upper extremity strength, muscle activity, quality of life (QOL-SCI), participation (LIFE-H), and qualitative exit interview.	1. Significantly reduced WUSPI scores (p=0.002).

Discussion

One pre-post trial found 30 minutes of FES rowing over 6 weeks resulted in significant reduction shoulder related pain post SCI.

Conclusion

There is limited level 4 evidence (Wilbanks et al. 2016) that FES improves shoulder pain post SCI.

FES may improve musculoskeletal shoulder pain post SCI.

10.13 Breathing controlled electrical Stimulation

Table 21 BreEstim Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Karri et al. 2018 USA RCT PEDro= N=21	**Population:** SCI+NP (n=10): Mean age=48.2 yr; Gender: males=10, females=0; Time since injury=13.3; Level of injury: C=7, T=0, L=3; Severity of injury: AIS A=2, B=1, C=4, D=3.	1. Significant difference in VAS scores across time for the active treatment (p<0.01) but not for the null treatment group (p>0.01).

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	SCI-NP (n=11): Mean age=38.6 yr; Gender: males=8, females=3; Time since injury=11.4 yr; Level of injury= C=4, T=7, L=0; Severity of injury: AIS A=3, B=2, C=5, D=1; Type of pain=neuropathic. **Intervention:** SCI+NP patients received a breathing-controlled electrical stimulation (BreEStim) or a fake BreEStim randomly on separate days with at least a 3 day break between, both SCI-NP and SCI+NP participants had their visual analog scale pain scores and heart rate variability taken for comparison. Note that only the SCI+NP group had the BreEStim (active and null). **Outcome Measures:** VAS scores and HRV.	2. At baseline both the HRV time domain (p=0.01) and the HRV frequency domain (p<0.05) were significantly lower in the SCI+NP group than in the SCI-NP group. 3. Significant interaction between effects of time and treatment and HRV for both time parameters (p=0.04). 4. Parasympathetic tone profoundly increased across time only for the active intervention (p<0.05). 5. Significant increase across time with active treatment for both time parameters (p=0.02) but no differences for the null treatment (p>0.05). 6. Frequency parameters showed o significant differences across time for the null or active treatments (p>0.05).
Li et al. 2018 USA RCT Crossover PEDro=6 N=12	**Population:** Mean age=43.4±11.7 yr; Gender: males=7, females=5; Time since injury=15.5±12.3 yr; Level of injury: C=10, T=2, L=0; Severity of injury: all incomplete; Type of pain=neuropathic. **Intervention:** Participants completed both the real and sham transcranial direct cranial stimulation (tDCS) followed by active breathing-controlled electrical stimulation/conventional electrical stimulation (BreEStim and EStim respectively) and were randomized to which they would complete in the first session and three days later in the second session. **Outcome Measures:** Visual analog scores (VAS) for pain and analgesic effects.	1. 10 of the 12 participants completed both conditions because of timing conflicts. 2. Positive analgesic effects were seen in active tDCS, but only in 4 of 10 participants in the sham tDCS and in BreEStim all but one participant saw positive analgesic effects. 3. No difference in active and sham tDCS seen at the group level. 4. VAS decreased from 5.7-5.1 after active tDCS and from 6.0-5.4 after the sham tDCS. 5. Significant decrease in VAS after BreEStim in the active and sham tDCS group (p<0.00001 for both). 6. All 12 participants completed the active tDCS and BreEStim and a main effect of time was observed to be significant (p<0.00001). 7. No significant change of VAS observed after active tDCS, but a significant change was seen after active BeEStim (p<0.05).
Li et al. 2016 (1) USA Pre-Post N=13	**Population:** Mean age=48.5±12.3 yr; Gender: males=6, females=7; Time since injury=58.2±45.8 mo; Level of injury: C=7, T=4, L=2; Severity of injury: AIS A=2, B=6, C=1, D=4; Type of pain=neuropathic. **Intervention:** In the first of two experiments in this study, each of the 13	1. VAS average scores decreased from 6.3-3.7 after BreEStim120 and from 5.2-4.4 after EStim120. 2. Significant main effect of intervention (p<0.001) with no main effect if stim. 3. Significant interaction between intervention and stim observed (p<0.001).

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	participants received both breathing-controlled electrical stimulation (BreEStim) and conventional electrical stimulation (EStim) with at least 3 days between bouts and 120 electrical stimuli each. **Outcome Measures:** Visual analog score (VAS) for pain and analgesic effects.	4. Significantly greater reduction in VAS score after BreEStim120 than after EStim120 ($p<0.001$) and the duration of the analgesic effect was significantly longer after BreEStim120 compared to EStim120 ($p=0.04$). 5. Significantly greater intensity of electrical current during EStim120 compared to BreEStim120 ($p=0.0189$).

Discussion

Three studies examined the effectiveness of BreEstim on reducing pain post SCI. Karri et al. (2018) found BreEstim significantly reduced pain compared to sham treatment. Li and colleagues (2018) found participants receiving BreEStim demonstrated reduction in pain intensity regardless of recuiving active or sham tDCS. In a pre-post trial, participants were provided both a BreEStim and a conventional eStim device. The study found that participants experienced a reduction in pain intensity when using the BreEStim compared to conventional stimulation.

Conclusion

There is Level 1b evidence from one RCT (Karri et al. 2018) that breathing-controlled electrical stimulation may improve pain post SCI

Breathing-controlled electrical stimulation may improve post SCI pain.

10.14 Diet

Table 21 Diet Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Allison et al. 2016 Canada RCT PEDro=8 N=20	**Population:** 48.7±14.0 yr; Gender: males=10, females=10; Time since injury=13.1±10.8 yr; Level of injury: C=12, T=6, L=2; Severity of injury: AIS A=7, B=2, C=3, D=8; Type of pain=neuropathic. **Intervention:** Participants were randomized to either a control group or an anti-inflammatory diet group for 12 wks. **Outcome Measures:** Center for epidemiological studies depression scale (CES-D), self-report neuropathic pain	1. Significant group X time interaction for CES-D score ($p=0.01$) and significant reduction in CES-D score from baseline to 3 mo ($p<0.01$). 2. Significant group X time interaction for sensory component of self-report neuropathic pain scores ($p<0.01$). 3. Significant reduction in pain sensory scores from baseline to 3 mo in the treatment group ($p<0.01$). 4. Significant increase in pain sensory scores from baseline to 1 mo in

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	questionnaire (NPQ), change in inflammatory mediators (IL-2, IL-6, IL-1β, TNF-α and IFN-y) and relationship between pain and inflammatory mediators.	control group (p=0.04) but not from baseline to 3 mo (p=0.21). 5. No significant group X interaction for the affective component of the self-report neuropathic pain scores (p=0.17). 6. Change scores of sensitivity pain found not to be significantly different between treatment and control groups (p=0.35) and no significant changes within the group for sensitivity pain scores (treatment: p=0.19; control: p=0.96). 7. Proinflammatory composite score (average of IL-2, IL-6, IL-1β, TNF-α and IFN-y) was significantly different between the control and treatment groups (p=0.01) and there was a significant reduction found in the treatment group from baseline to 3 mo (p=0.02) but no significant change in the control group (p=0.07). 8. Mann-Whitney test indicated significantly different change scores between the treatment group and the control group for IFN-y (p=0.01), IL-1β (p=0.01), and IL-2 (p=0.01) and a trend for CRP (p = 0.10). 9. Friedman test showed a statistically significant reduction in IFN-y (p=0.01), IL-1β (p<0.01), IL-6 (p<0.05), and a trend for CRP (p=0.10) in the treatment group and no significant changes in the control group (p>0.05). 10. Wilcoxon signed-rank test indicated a significant reduction in IFN-y (p=0.01) and IL-1β (p<0.01) as well as a trend for IL-6 (p=0.08) in the treatment group with no significant changes in control group (p>0.05). 11. Significant positive correlation between reduced pain score and PGE2 (p=0.01). 12. Significant positive correlation between change in sensitivity score and proinflammatory cytokines IL-1β and IL-2 and eicosanoid PGE2 (p=0.008).
Allison and Ditor, 2018 Canada Secondary Analysis of RCT (Allison et al. 2016) N=5	**Population:** Mean age=51.5±15.3 yr; Gender: males=1, females=4; Time since injury=12.8±11.3 yr; Level of injury: C=2, T=3, L=0; Severity of injury: AIS A=2, B/C=0, D=3; Type of pain=neuropathic. **Intervention:** Original study - Participants were randomized to either a control group	1. Dietary compliance significantly varied between end of the study and the 1 yr follow-up (p<0.01) and a significant reduction in compliance scores from 3 mo to 1 yr (p<0.01) as they were no longer significantly different from baseline (p=0.18).

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	or an anti-inflammatory diet group for 12 wks. This study – Taking a look at 5 of the original participants 1 yr later and making assessments. **Outcome Measures:** Dietary compliance and center for epidemiological studies depression scale (CES-D), neuropathic pain questionnaire (NPQ).	2. CES-D showed a trend toward an increase from 3 mo to 1 yr follow-up (p=0.10) as they were no longer significantly different from baseline (p=0.74). 3. No significant difference in NPQ sensory scores from 3 mo to follow-up (p=0.42), and scores remained significantly different from baseline (p=0.02). 4. Significant increase in NPQ affective scores from 3 mo to follow-up (p=0.05) as they were not longer significantly different from baseline (p=0.24). 5. No significant difference in NPQ sensitivity scores from 3 mo to follow-up (p=0.34) but follow-up scores were also not significantly different from baseline (p=0.15).

Conclusion

There is level 1b evidence that inflammatory diet results in significant reduction in neuropathic pain post SCI.

Inflammatory diet may improve neuropathic pain post SCI.

11.0 Pharmacological Management of Post-SCI Pain

Pharmacological interventions are the standard treatment for SCI pain. The limited effectiveness of non-pharmacological treatments has contributed to increasing use of pharmacological interventions to deal with what is often very severe and disabling pain.

11.1 Pharmacological Measures Overall

Table 22 Pharmacological Interventions and Post-SCI Pain

Author Year; Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Widerström-Noga & Turk 2003 USA Case control N=120	**Population:** Mean age=40.6 yr; Gender: males=94, females=26; Level of injury=cervical, non-cervical; Time since injury=9.8 yr; Type of pain=neuropathic and nociceptive. **Treatment:** Individuals with SCI related pain filled out a questionnaire; data from	1. Overall 59.2% of participants used pharmacological or non-pharmacological treatments to control pain. 40.8% indicated they had not used nor had they been prescribed any medication for pain.

Author Year; Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	the questionnaire was analysed by dividing individuals into two groups: those that received pain treatment and those that did not. **Outcome Measures:** Sociodemographic data and characteristics of injury, intensity of pain, location of pain, quality of pain, allodynia (pain in response to a stimulus that would not provoke pain), Multidimensional Pain Inventory (MPI) (designed to assess the impact of pain and adaptation to chronic pain), difficulty in dealing with pain and pain treatments.	2. Pain Severity: Pain severity was found to be higher for those who had received pain medications (PM) (3.9±1.3, p=0.001) compared to those who had not used any pain treatment. The intensity of pain was higher for those on PM than for those not on PM (p=0.022). 3. Pain Locations: Those using PM reported more painful areas than those not using PM (p=0.001) with frontal/genital pain reported more often (p<0.000). 4. Quality of Pain: Those on PM used more descriptive adjectives to describe their pain compared to those not using PM (p=0.031). 5. Difficulty in Dealing with Pain: Those using PM reported having more difficulty dealing with pain than those not using PM (p<0.000). 6. Pain impact: Those using PM had higher scores for the pain severity scale and the life interference scale compared to the group not using PM (p<0.002).

Discussion

Widerström-Noga and Turk (2003), not unexpectedly, found that SCI patients with more severe pain, in more locations, those with allodynia or hyperalgesia, and those in whom the pain was more likely to interfere with activities were more likely to use pain medications.

Trials of simple non-narcotic analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen or non-narcotic “muscle relaxants” are common clinical practice in SCI pain. Unfortunately, these medications are often ineffective in complete SCI neuropathic pain relief and have potential risks such as gastric ulceration with prolonged use.

For neuropathic or “central” pain seen following SCI, psychotropic drugs such as antidepressants and anticonvulsants are reportedly the most effective (Donovan et al. 1982). Despite increasing popularity, few drugs (with the exception of Gabapentin and pregabalin) have regulatory approval for use in neuropathic pain and selection for individual patients is largely based on anecdotal evidence, of off-labelled use.

11.2 Anticonvulsants in SCI Pain

Anticonvulsant medications are often utilized in treating neurogenic or deafferent pain following SCI based on the theory that these drugs alter sodium conduction in uncontrolled hyperactive neurons (“convulsive environment”) in the spinal cord. Carbamazepine has been reported as being somewhat effective in the paroxysmal, sharp, shooting pain of trigeminal neuralgia (Swerdlow 1984). Gibson and White (1971) described relief resulting from carbamazepine treatment in two cases of L2 and T8 SCI with intractable pain below the level of SCI. A similar effect of Carbamazepine (200 mg 2x daily in combination with Amitriptyline 50 mg 3x daily) was

reported in a complete C8 patient with dysesthesia below the level of the injury (Sandford et al. 1992). Again, controlled studies utilizing these drugs in SCI pain are lacking with the exception of gabapentin and pregabalin.

Gabapentin and pregabalin are now regarded as first-line treatments of neuropathic pain (Ahn et al. 2003; Moulin et al. 2007). Gabapentin and pregabalin have been recommended as first line treatments for neuropathic pain in Canadian and international guidelines (Gajraj 2007). The mechanism of action for Pregabalin and Gabapentin is through binding the alpha-2 delta receptors in the central nervous system. These receptors are present on the presynaptic nerve terminals. When bound by gabapentin or pregabalin they decrease the influx of calcium into the presynaptic terminal there by decreasing the release of excitatory neurotransmitters. Gabapentin and pregabalin appear to potentiate GABA effects centrally through enhancement of GABA synthesis and release. Levendoglu et al. (2004) noted that neuropathic pain is ultimately generated by excessive firing of pain-mediating nerve cells, insufficiently controlled by segmental and non-sequential inhibitory circuits. Gabapentin and pregabalin work by increasing GABA and reducing the release of glutamate thereby suppressing the sensitivity of N-methyl-D-asparate (NMDA) receptor. This has been shown to reduce neuronal hyper-excitability recorded at the spinal dorsal horn near the level of injury (Ahn et al. 2003). Gabapentin and pregabalin are relatively well tolerated with only a few transient side effects, lack of organ toxicity, and no evidence of significant interaction with other medications (Levendoghu et al. 2004; Gajraj 2007).

Table 23 Anticonvulsants for SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Gabapentin		
Kaydok et al. 2014 Turkey RCT PEDro=7 N=28	**Population:** Age=42.8yrs' Time since SCI=35.3 mons; Duration of pain=29.3 mons; Type of pain=neuropathic. **Treatment:** Participants were randomly allocated to the gabapentin or pregabalin group. Those in the gapapentin group received an initial dose of 300 mg/day which was titrated to a max dose of 3600 mg/day by the 4th week. Those in the pregabalin group received an initial dose of 150mg/day which was titrated to a max of 600mg/day by the 4th week. These dosages were maintained for 8 weeks. Patients then underwent a 2 week washout period and were crossed over to the alternative group. **Outcome Measure**s: VAS	1. No significant difference in VAS between gabapentin and pregabalin.
Rintala et al. 2007 USA RCT PEDro=10 N=38	**Population:** SCI: Mean age=42.6 yr; Gender: males=20, females=2; Level of injury: paraplegia=7, tetraplegia=12; Severity of injury: AIS A-C=19, D=3; Time since injury=12.6 yr; Duration of pain=7.3 yr. Type of pain=neuropathic. **Treatment:** Patients were randomized into one of six groups: 1) gabapentin-amitripyline-diphenhydramine (GAD;	1. No significant difference was seen at 8 weeks in subjects with high (≥ 10) baseline CESD-SF scores in : • Effectiveness of amitriptyline over gabapentin (p=0.061). • Effectiveness of gabapentin over diphenhydramine (p=0.97). 2. Subjects with low (<10) baseline CESD-SF scores showed no

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	n=7); 2) GDA (n=6); 3) AGD (n=6); 4) ADG (n=6); 5) DGA (n=7); 6) DAG (n=6). Each drug was administered for 9 wk with one washout week before and after each drug treatment, for a total of 31 wk. The maximum doses were 50mg 3x/day for amitriptyline, 1200mg 3x/day for gabapentin, and 25mg 3x/day for diphenhydramine (control). **Outcome Measures:** Center of Epidemiologic Studies Depression Scale-Short Form (CESD-SF)	significant difference among the medications.
Levendoglu et al. 2004 Turkey RCT PEDro=9 N=20	**Population:** Age=23-62 yr; Gender: males=13, females=7; Onset of pain post injury=1-8 mo; Duration of pain=6-45 mo. Type of pain=neuropathic. **Treatment:** Subjects were randomized to gabapentin or placebo for a 4 wk titration period. Following this 4 wk period subjects continued to receive max tolerated doses. After a 2 wk washout period the treatments were switched in a crossover design. **Outcome Measures**: Neuropathic pain scale, VAS, and Lattinen test were used to assess pain and quality of sleep.	1. Both placebo and the gabapentin improved pain scores for the following: pain intensity ($p<0.000$), shape ($p<0.000$), hot ($p<0.001$), unpleasantness ($p<0.000$), deep and surface pain ($p<0.001$), at week 4 and 8 of administration. 2. Intensity of pain decreased significantly for the gabapentin groups during treatment $p<0.001$) and the intensity of pain differed between the two groups at all time periods ($p<0.001$). 3. VAS scores indicated that there was significant pain relief, which began at week 2 and continued until week 6 ($p<0.05$) and pain relief between the two groups at the end of the stable dosing periods was significantly different ($p<0.000$). 4. More experienced side effects in the treatment group then in the placebo group ($p<0.05$).
Tai et al. 2002 USA RCT PEDro=6 N=7	**Population:** Age=27-47 yr; Gender: males=6, females=1; Level of injury=C2-T7; Time since injury=1 mo-20 yr. Type of pain=neuropathic. **Treatment:** Subjects with neuropathic pain were treated with gabapentin or placebo. **Outcome Measure**s: Neuropathic Pain Scale, which has 10 categories of pain types.	1. Significant reduction of "unpleasant feeling" with gabapentin vs. placebo ($p=0.028$). 2. Trends of reductions with gabapentin vs. placebo for "pain intensity" ($p=0.094$) and "burning feeling" ($p=0.065$). 3. No other differences for any other pain descriptors including "sharp," "dull," "cold," "sensitive," "itchy," "deep," and "surface."
Ahn et al. 2003 Korea Pre-post N=31	**Population:** Mean age=45 yr; Gender: males=19, females=12; Level of injury: paraplegia, tetraplegia; Severity of injury: complete, incomplete; Duration of pain=10 yr. Type of pain=neuropathic. **Treatment**: Subjects were started on 300 mg of gabapentin, which was increased over 18 days to 1500 mg, followed by a 5 wk maintenance period. If pain score did not decrease during this time period, meds were increased to	1. At the end of the study, both groups showed they had lower mean scores for pain and sleep interference score ($p<0.05$). 2. Mean pain score for Group 1 decreased more than it did for Group 2 ($p<0.05$). 3. This score decreased more for Group 1 during wk 2-8 than it did for Group 2 ($p<0.05$).

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	2400 mg/day and 3600 mg/day. Group 1 had <6 mo of pain and group 2 >6 mo. **Outcome Measures**: Pain and sleep interference scores of the two groups were compared.	4. Mean sleep interference score for Group 1 decreased more than it did for Group 2 ($p<0.05$).
To et al. 2002 Australia Case Series N=44	**Population:** Age=15-75 yr; Gender: males=28, females=10; Level of injury: paraplegia, tetraplegia. Type of pain=neuropathic. **Treatment:** Neuropathic pain was treated with gabapentin. **Outcome Measures:** Level of pain experienced by subjects.	1. 76% of subjects reported some improvement in pain after taking gabapentin. 2. Visual Analogue Scores decreased from 8.86 pre-treatment to 4.13 post-treatment (6 mo later) ($p<0.001$), with a significant curvilinear trend ($p=0.001$).
Pregabalin		
Min et al. 2016 South Korea RCT Crossover PEDro=6 N=55	**Population:** Mean age=51.7yr; Gender: males=44, females=11; Level of injury: paraplegia=29, quadriplegia=26; Severity of injury: incomplete=45, complete=10; Mean time post injury=2458d; Type of pain=neuropathic. **Treatment:** Participants received pregabalin (300mg/d) and oxcarbazepine (300mg, 2x/d), each for 1-2wk, provided in a randomized sequence. Participants were divided according presence or absence of evoked pain. Outcomes were assessed before and after each trial. **Outcome Measures:** Visual Analogue Scale - Pain Intensity (electrical pain, burning pain, pricking pain, numbness, allodynia, hyperalgesia).	1. Overall, both pregabalin and oxcarbazepine were effective in relieving all types of pain ($p<0.05$), and there were no significant differences between medications in effectiveness. 2. Oxacarbazepine was significantly more effective in relieving electrical, burning, and numbness pain in those without evoked pain than those with it ($p<0.05$). 3. Pregabalin was significantly more effective in relieving burning pain in those without evoked pain than those with it ($p<0.05$). 4. In those with evoked pain present, pregabalin was significantly more effective than oxcarbazepine in relieving allodynia and hyperalgesia than pregabalin ($p<0.001$). 5. In those with evoked pain absent, there was no significant difference between medications in effectiveness.
Kaydok et al. 2014 Turkey RCT PEDro=7 N=28	**Population:** Age=42.8yrs' Time since SCI=35.3 mons; Duration of pain=29.3 mons; Type of pain=neuropathic. **Treatment:** Participants were randomly allocated to the gabapentin or pregabalin group. Those in the gapapentin group received an initial dose of 300 mg/day which was titrated to a max dose of 3600 mg/day by the 4th week. Those in the pregabalin group received an initial dose of 150mg/day which was titrated to a max of 600mg/day by the 4th week. These dosages were maintained for 8 weeks. Patients then underwent a 2 week washout period and were crossed over to the alternative group. **Outcome Measure**s: Visual analog pain scale (VAS), neuropathic pain scale	1. No significant difference in VAS between gabapentin and pregabalin.

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	(NPS), Lattinen test (LT) and Beck depression inventory (BDI) pain diary.	
Cardenas et al. 2013 USA RCT PEDro=10 N=219	**Population:** Mean age=45.7yrs; Gender: Male=176; Female=43; Type of pain=neuropathic. **Treatment:** SCI individuals with neuropathic below level pain for greater than 3 months were randomized to a twice daily pregabalin group (up to 600mg/d) or placebo for 12 weeks. **Outcome Measures:** Duration-adjusted average change in pain,	1. Significant improvement in pain was seen in the treatment group compared to placebo, p=0.0003. 2. Significant improvement in pain related sleep interference scores were seen post treatment in the pregabalin group compared to placebo, p<0.05.
Arienti et al. 2011 Italy RCT PEDro=6 N=47	**Population:** Severity of injury: AIS A=33; B, C and D=14. Level of injury: paraplegia=19, tetraplegia=7. Type of pain=neuropathic. **Intervention:** Patients were randomly placed into three groups: pharmacological group received 600 mg per day of pregabalin. The pharmacological and osteopathic group received 600mg per day of pregabalin and osteopathical treatment once a week for the first month, once every fortnight for the second month, once during the third month all for 45 min each by an osteopathic physician. The osteopathic group received on the osteopathic treatment described above. **Outcome Measures:** Verbal numeric scale (VNS)	1. Rates of improvement based on the VNS scores were similar across the two treatments (p=0.26). 2. The highest pain relief was seen in the combined pharmacological and osteopathic group compared to the pharmacological alone (p=0.05) and the osteopathic alone (p=0.001).
Vranken et al. 2008 Netherlands RCT PEDro=9 N=40	**Population:** Treatment group: Mean age=54.2 yr; Gender: males=11, females=9; Control group: Mean age=54.7 yr; males=10, females=10. Type of pain=neuropathic. **Treatment:** Those in treatment group received escalating doses of pregabalin (150 mg, 300 mg, or 600 mg daily), while the control group received placebo. **Outcome Measures:** Visual Analogue Scale (VAS)	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 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.
Sidall et al. 2006 Australia RCT PEDro=9 N=137	**Population:** Mean age=45 yr; Gender: males=19, females=12; Level of injury: paraplegia, tetraplegia; Severity of injury: complete, incomplete; Duration of pain=10 yr. Type of pain=neuropathic. **Treatment:** Patients were randomized to either flexible-dose pregabalin 150 to 600 mg/day (n=70) or placebo (n=67), administered BID **Outcome Measures:** Pain scores, sleep interference and anxiety scores of the two groups were compared.	1. The mean baseline pain score was 6.54 in the pregabalin group and 6.73 in the placebo group. 2. The mean endpoint pain score was lower in the pregabalin group (4.62) than the placebo group (6.27; p<0.001). 3. Efficacy observed as early as wk 1 and maintained for the duration of the study.

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
		4. The average pregabalin dose after the 3 wk stabilization phase was 460 mg/day. 5. Pregabalin was associated with improvements in disturbed sleep ($p<0.001$) and anxiety ($p<0.05$) 6. Mild or moderate, typically transient, somnolence and dizziness were the most common adverse events.
Carbamazepine		
Min et al. 2016 South Korea RCT Crossover PEDro=6 N=55	**Population:** Mean age=51.7yr; Gender: males=44, females=11; Level of injury: paraplegia=29, quadriplegia=26; Severity of injury: incomplete=45, complete=10; Mean time post injury=2458d; Type of pain=neuropathic. **Treatment:** Participants received pregabalin (300mg/d) and oxcarbazepine (300mg, 2x/d), each for 1-2wk, provided in a randomized sequence. Participants were divided according presence or absence of evoked pain. Outcomes were assessed before and after each trial. **Outcome Measures:** Visual Analogue Scale - Pain Intensity (electrical pain, burning pain, pricking pain, numbness, allodynia, hyperalgesia).	1. Overall, both pregabalin and oxcarbazepine were effective in relieving all types of pain ($p<0.05$), and there were no significant differences between medications in effectiveness. 2. Oxacarbazepine was significantly more effective in relieving electrical, burning, and numbness pain in those without evoked pain than those with it ($p<0.05$). 3. Pregabalin was significantly more effective in relieving burning pain in those without evoked pain than those with it ($p<0.05$). 4. In those with evoked pain present, pregabalin was significantly more effective than oxcarbazepine in relieving allodynia and hyperalgesia than pregabalin ($p<0.001$). 5. In those with evoked pain absent, there was no significant difference between medications in effectiveness.
Salinas et al. 2012 Colombia RCT PEDro=9 $N_{Initial}=46$; $N_{Final}=44$	**Population:** Mean age=36yr; Gender: males=42, females=4; Level of injury: paraplegia=28, quadriplegia=18; Severity of injury: incomplete=13, complete=33; Time post injury <2wk; Type of pain=neuropathic. **Treatment:** Individuals without neuropathic pain were randomized to receive carbamazepine (600mg/d, n=24) or placebo (control, n=22) for 1mo. Outcomes were assessed pre and post treatment, and at 3 and 6mo follow-up. **Outcome Measures:** Visual Analogue Scale - Pain Intensity (VAS-PI), Short Form 36 Scale (SF-36).	1. At 1mo, significantly less of the treatment group reported moderate/intense pain (VAS-PI$\geq$4) than the control group (2 vs 8, $p=0.024$). 2. At 3mo, more of the treatment group reported moderate/intense pain than the control group, but the difference was not significant (8 vs 6, $p=0.498$). 3. At 6mo, less of the treatment group reported moderate/intense pain than the control group, but the difference was not significant (6 vs 8, $p=0.298$). 4. There was no significant difference between groups in SF-36 scores.
Chen et al. 2018 China PCT	**Population:** NMES+carbamazepine group: Mean age=41.8±12.6 yr; Gender: males=25, females=2; Time since	1. No significant difference in NRS for NPP or the QOL in SF-36 in the NMES group ($p>0.05$).

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
N=54	injury=31.2±11.5 mo; Level of injury: C=12, T=13, L=2; Severity of injury: AIS A=16, B=3, C=5, D=3; Type of pain=neuropathic. Carbamazepine group: Mean age=43.5±13.7 yr; Gender: males=23, females=4; Time since injury=29.7±10.8 mo; Level of injury: C=14, T=10, L=3; Severity of injury: AIS A=18, B=2, C=3, D=4; Type of pain=neuropathic. **Intervention:** Participants were assigned to either an NMES + carbamazepine group or a carbamazepine only group for 3 mo of treatment with outcomes measures at baseline and post-intervention. **Outcome Measures:** Pain intensity numerical rating scale (NRS), quality of life (QOL) sort form 36 (SF-36) scale, and adverse events. *Neuromuscular electrical stimulation (NMES), neuropathic pain (NPP)	2. No serious adverse events in either group.
Lamotrigine		
Agarwal & Joshi, 2017 India RCT PEDro=6 N=147	**Population:** Age=18+ yr; Gender: males=136, females=11; Level of injury: paraplegia=64, tetraplegia=83; Severity of injury: AIS A=112. B/C/D=35; Type of pain=neuropathic. **Intervention:** Participants with neuropathic pain (NP) were randomized to either amitriptyline or lamotrigine for 3 wk trials to compare the effects of pain suppression. **Outcome Measures:** Short-form MC Gill Pain Questionnaire (SFMPQ2) score on pain, adverse events and withdrawn patients.	1. No significant differences between reduction of pain scores between the amitriptyline and lamotrigine groups (p>0.05). 2. Only notable adverse events were dry mouth and drowsiness, and patients reported exceeding the 50 mg dose recommendation in the amitriptyline group with no adverse events in the lamotrigine group. 3. 140 of the 147 subjects completed the study, 5 dropped out and two passed away.
Finnerup et al. 2002 Denmark RCT PEDro=10 N=30	**Population:** SCI patients with pain at or below the level of injury. Type of pain=neuropathic. **Treatment:** A 1 wk baseline period was followed by two treatment periods of 9 wk. Lamotrigine slowly increased to a maximum of 400 mg or placebo separated by a 2 wk washout period. **Outcome Measures:** The primary outcome measure was the change in median pain score from baseline week to the last week of treatment. Secondary outcome measures included thresholds to standardized sensory stimuli using quantitative sensory testing.	1. Twenty-two patients completed the trial. 2. No statistically significant effect of lamotrigine as evaluated in the total sample 3. In patients with incomplete SCI, lamotrigine significantly reduced pain at or below SCI level. 4. Patients with brush evoked allodynia and wind-up-like pain in the area of maximal pain were more likely to have a positive effect to lamotrigine than patients without these evoked pains.
Levetiracetam		
Finnerup et al. 2009 Denmark RCT PEDro=7	**Population:** Mean age=52.8 yr; Gender: males=29, females=7; Level of injury: C=13, T=19, L=4; Severity of injury: AIS A=13, B=2, C=3, D=18; Type of pain: at	1. Levitiracetam treatment showed no significant improvement in median pain intensity compared to placebo treatment (p=0.46).

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
N=36	level=17, below level=31; Type of pain=neuropathic. **Treatment:** Patients were randomized into two 5 week treatment groups receiving either levetiracetam or placebo tablets. After a 1 wk washout period, individuals were crossed over to the 2nd group. Patients received 500 mg x2 for the first week, 1000mg x2 in the second week, and 1500 mg x2 in wk 3-5. Patients were assessed at baseline, end of each treatment and 6 mo follow-up. **Outcome Measures:** Neuropathic pain symptom inventory	2. No difference was seen in pain relief between the patients treated with levitiracetam alone and those with concomitant main medication. 3. Side effects due to levetiracetam included incoordination, dizziness, somnolence, constipation and confusion; however, these effects were not statistically different from those in the placebo group.
Valproate		
Drewes et al.1994 Denmark RCT PEDro=5 N=20	**Population:** Mean age=32.5 yr; Gender: males=15, females=5; Level of injury: paraplegia=16, tetraplegia=4; Type of pain=neuropathic. **Treatment:** Subjects were administered 600 mg of valproate or placebo 2x 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 wk, followed by a 2 wk washout period, followed by 3 wk of cross-over treatment. **Outcome Measures:** McGill Pain Questionnaire **(**MPQ)	1. A trend toward improvement was noted among those in the valproate group; however, differences between the two groups were not significant.

Discussion

Gabapentin

Three studies found that gabapentin was no better than placebo in improving pain intensity post SCI (Rintala et al. 2007; Kaydok et al. 2014; Tai et al. 2002). While, Levendoglu et al. (2004) found gabapentin significantly reduced post SCI neuropathic pain compared to placebo. Three pre-post studies found gabapentin had a time effect in reducing pain post SCI (To et al. 2002; Ahn et al. 2003; Putzke et al. 2002).

Pregabalin

Six studies examined the efficacy of pregabalin on pain post SCI. Min et al. (2016) found pregabalin and oxcarbazepine were equally effective in relieving pain overall. However, was more effective in relieving burning pain, allodynia, and hyperalgesia. Kaydok et al. (2014) found no significant difference in pain reducing between gabapentin and pregabalin. Siddall et al. (2006) published the results of a double blind randomized control trial evaluating the use of flexible dose pregabalin in the treatment of neuropathic pain in spinal cord injury. A total of 137 subjects with central neuropathic pain post spinal cord injury participated. The primary outcome was the VAS pain scale and secondary outcomes included sleep interference and anxiety scales. Seventy patients were randomized to receive pregabalin and 67 patients received placebo. At the end of the trial the pregabalin treated patients had significantly more pain relief.

The pregabalin treated subjects also reported significantly improved sleep and anxiety. Side effects were mild and transient and included dizziness, drowsiness and edema (similar to gabapentin).

Arienti et al. (2011) compared treatment of pain in three groups: 1) pregabalin only group; 2) pregabalin and osteopathy group; 3) osteopathy group. The study found significant improvement in pain perception and pain relief in the combined pregabalin and osteopathy group compared to the other two groups ($p<0.01$). Further, relief of pain was faster in the combined group compared to the pregabalin and osteopathy only groups.

In a RCT conducted by Vranken et al. (2008) 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.

Cardenas et al. (2013) studied 220 patients with neuropathic pain post SCI they were randomized to 150-600mg of pregabalin (108 patients) vs Placebo (112) patients. The patients in the treatment group experienced significant improvements in all primary and key secondary outcomes including duration adjusted average change in pain, change in mean pain scores,percentage of patients with greater that 30% reduction in pain and reduction in pain related sleep interference scores compared to placebo. The improvements were seen as early as one week after initiation of treatment and lasted for the duration of the 17 week study. As with previous studies the medication was generally well tolerated, somnolence and dizziness were the most common side effects. This study provided class 1 evidence for the effectiveness of pregabalin 150mg to 600mg in the treatment of neuropathic pain post spinal cord injury.

Lamotrigine

Two studies evaluated the effectiveness of lamotrigine in reducing pain post SCI. Agarwal and Joshi (2017) found lamotrigine resulted in similar reduction in pain compared to amitriptyline. Finnerup et al. (2002) studied the effects of lamotrigine on post SCI pain. Although the overall result showed no difference between placebo and lamotrigine, there was a significant reduction in pain in the incomplete spinal cord group.

Levetiracetam

Finnerup et al. (2009) conducted a randomized, double blind, crossover trial of levetiracetam in SCI individuals with pain. Participants were placed in either the levetiracetam or placebo group for five weeks and then crossed over after a one week washout period. This study found no significant difference between the levetiracetam and the placebo treatment group in improving pain intensity ($p=0.46$).

Valproate

In a double-blind cross-over study (n=20), Drewes et al. (1994) examined the effects of a three 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.

Table 24 Summary of Anticonvulsant Pain Treatment Post SCI

Study	Study Type	N	Intervention	Outcome
Rintala et al. 2007	RCT	22	Gabapentin	-
Levendoglu et al. 2004	RCT	20	Gabapentin	+
Tai et al. 2002	RCT	7	Gabapentin	+
To et al. 2002	Non-RCT	44	Gabapentin	+
Ahn et al. 2003	Non-RCT	31	Gabapentin	+
Putzke et al. 2002	Non-RCT	21	Gabapentin	+
Cardenas et al. 2013	RCT	219	Pregabalin	+
Siddall et al. 2006	RCT	137	Pregabalin	+
Vranken et al. 2008	RCT	40	Pregabalin	+
Finnerup et al. 2002	RCT	30	Lamotrigine	+*
Finnerup et al. 2009	RCT	36	Levetiracetam	-
Drewes et al. 1994	RCT	20	Valproate	-

Note: *=in individuals with incomplete SCI

Conclusion

There is level 1b evidence (Levendoglu et al. 2004) that the gabapentin improves neuropathic pain post SCI compared to placebo.

There is level 1b evidence (Rintala et al. 2007) that gabapentin is no more effective as an active placebo in improving neuropathic pain post SCI.

There is level 1b evidence (Kaydok et al. 2014) that gabapentin and pregabalin are equally effective at reducing neuropathic pain post SCI.

There is level 1b evidence (from one randomized controlled trial; Arienti et al. 2011) that combined pregabalin and osteopathy treatment improves pain post SCI.

There is level 4 evidence (from one pre-post study; Ahn et al. 2003) that the anticonvulsant Gabapentin is more effective when SCI pain is<6 months than >6 months.

There is level 1b evidence (from one randomized controlled trial; Finnerup et al. 2002) that lamotrigine improves neuropathic pain in incomplete spinal cord injury

There is level 1b evidence (from one randomized controlled trial; Finnerup et al. 2009) that Levetiracetam is not effective in reducing neuropathic pain post SCI.

There is level 2 evidence (from one randomized controlled trial; Drewes et al. 1994) that valproic acid does not significantly relieve neuropathic pain post SCI.

Gabapentin and pregabalin improve neuropathic pain post SCI.

Combined osteopathy and pregabalin may improve pain post SCI.

Lamotrigine may improve neuropathic pain in incomplete spinal cord injury

Levetiracetam is not effective in reducing neuropathic pain post SCI.

Valproic acid does not reduce neuropathic pain post SCI.

11.3 Tricyclic Antidepressants in Post-SCI pain

Tricyclic antidepressant drugs are thought to modulate pain by inhibiting the uptake of norepinephrine and serotonin in the CNS. Sandford et al. (1992) have suggested that the tricyclic antidepressants exert an analgesic effect by making more serotonin available in the CNS, thereby potentiating the inhibitory action of the dorsal horn of the spinal cord. Unfortunately, these medications are often sedating and produce a variety of anticholinergic side effects.

The partial effectiveness of tricyclic antidepressants (TCA) in some SCI patients with dysesthetic pain suggests that this drug is simply affecting the pain by treating the depression. Sandford et al. (1992) noted that pain and depression maybe chemically linked. Depression can lower pain thresholds or pain tolerances thereby increasing the patient's experience of pain. However, Max et al. (1987) were able to show that TCA had analgesic properties despite low doses or short treatment cycles with analgesic activity occurring independent of mood changes.

Davidoff et al. (1987b) reported trazodone's lack of effectiveness in relieving pain in 19 SCI patients with chronic dysesthetic pain, using a double-blind placebo controlled trial. Trazodone reportedly selectively inhibits serotonin and norepinephrine uptake in a ratio of 25:1, and is thought to produce greater analgesia and less anticholinergic side-effects compared to non-selective agents such as amitriptyline.

Table 25 Tricyclic Antidepressants in Post-SCI Pain

Author Year; Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Amitriptyline		
Agarwal & Joshi, 2017 India RCT PEDro=6 N=147	**Population:** Age=18+ yr; Gender: males=136, females=11; Level of injury: paraplegia=64, tetraplegia=83; Severity of injury: AIS A=112. B/C/D=35; Type of pain=neuropathic. **Intervention:** Participants with neuropathic pain (NP) were randomized to either amitriptyline or lamotrigine for 3 wk trials to compare the effects of pain suppression. **Outcome Measures:** Short-form MC Gill Pain Questionnaire (SFMPQ2) score on	1. No significant differences between reduction of pain scores between the amitriptyline and lamotrigine groups ($p>0.05$). 2. Only notable adverse events were dry mouth and drowsiness, and patients reported exceeding the 50 mg dose recommendation in the amitriptyline group with no adverse events in the lamotrigine group.

Author Year; Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	pain, adverse events and withdrawn patients.	3. 140 of the 147 subjects completed the study, 5 dropped out and two passed away.
Rintala et al. 2007 USA RCT PEDro=10 N=38	**Population:** SCI: Mean age=42.6 yr; Gender: males=20, females=2; Level of injury: paraplegia=7, tetraplegia=12; Severity of injury: AIS A-C=19, D=3; Time since injury=12.6 yr; Duration of pain=7.3 yr. Type of pain=neuropathic. **Treatment:** Patients were randomized into one of six groups: 1) gabapentin-amitripyline-diphenhydramine (GAD; n=7); 2) GDA (n=6); 3) AGD (n=6); 4) ADG (n=6); 5) DGA (n=7); 6) DAG (n=6). Each drug was administered for 9 wk with one washout week before and after each drug treatment, for a total of 31 wk. The maximum doses were 50mg 3x/day for amitriptyline, 1200mg 3x/day for gabapentin, and 25mg 3x/day for diphenhydramine (control). **Outcome Measures:** Center of Epidemiologic Studies Depression Scale-Short Form (CESD-SF)	1. Amitriptyline was significantly more effective than diphenhydramine at 8 weeks, in subjects with high (≥ 10) baseline CESD-SF scores (p=0.035). 2. No significant difference was seen at 8 weeks in subjects with high (≥ 10) baseline CESD-SF scores in : • Effectiveness of amitriptyline over gabapentin (p=0.061). • Effectiveness of gabapentin over diphenhydramine (p=0.97). 3. Subjects with low (<10) baseline CESD-SF scores showed no significant difference among the medications.
Cardenas et al. 2002 USA RCT PEDro=9 N=84	**Population:** Mean age=41 yr; Gender: males=80%, females=20%; Level of injury: cervical, lumbar; Severity of injury: AIS: A-D; Time since injury=169 mo. Type of pain=.europathic and musculoskeletal. **Treatment:** Subjects with chronic pain randomized to a 6 wk course of amitriptyline or placebo 1-2 hr before bedtime. **Outcome Measures**: Average pain measure (scale 0-10), Short form McGill Pain Questionnaire (SF-MPQ), Brief Pain Inventory (BPI), Center of Epidemiologic Studies Depression Scale (CESD) , Functional Independence Measure (FIM).	1. There were no significant differences between the two groups at baseline and at the 6 wk time period for any of the measures except satisfaction with life which showed higher scores for those in the placebo group (p=0.004). 2. For those who remained on the two medications, it was noted that those in the amitriptyline group had significantly higher severity ratings for increased spasticity (p=0.005) than those in the control group.
Duloxetine		
Vranken et al. 2011 Netherlands RCT PEDro=9 N=48	**Population:** Age=53 yr; Type of pain=neuropathic. **Intervention:** Participants were randomized to one of two groups: flexible dose placebo who received 1-2 capsules a day or placebo. **Outcome Measures:** Visual Analogue Scale (VAS)	1. A two-point reduction on VAS in pain intensity was seen in the duloxetine group after 8 wk of treatment. 2. A decrease in pain was seen in the duloxetine group compared to the control group (p=0.05). 3. No significant between group differences were seen in SF-36.
Venlafaxine		
Richards et al. 2015 USA RCT PEDro=9	**Population:** Mean age=40yr; Gender: males=99, females=34; Time since injury=10.9yr. Type of pain=neuropathic, nociceptive, or mixed.	1. No significant improvement in pain related outcomes were seen among those with neuropathic or mixed pain. 2. Individuals with nociceptive pain

Author Year; Country PEDro Score Research Design Total Sample Size	Methods	Outcome
N=123	**Treatment:** Participants were randomized to receive either venlafaxine or placebo. The treatment group received a starting dose of 37.5mg/d which was titrated up to a max of 225mg/d by week 6 if tolerated. Doses could be increased by another 300mg at week 10 if needed to treat depression. **Outcome Measures**: Numeric Rating Scale (NRS)	reported significant improvement in outcomes including: pain intensity (p=0.018) and pain interference subscales general activity (p=0.018), mood (p=0.048), mobility (p=0.005), normal work (p<0.001), relations with other people (p=0.021), sleep (p=0.014), and enjoyment of life (p=0.017).
Trazodone		
Davidoff et al. 1987b USA RCT PEDro=6 Initial N=19; Final N=18	**Population:** Mean age=39 yr; Gender: males=16, females=2; Time since injury=49 mo. Type of pain=neuropathic. **Treatment:** Subjects underwent a 2 wk placebo lead-in period with a 6 wk randomization to 150 mg trazodone per day or placebo. **Outcome Measures**: McGill Pain Questionnaire **(**MPQ), Sternbach Pain Intensity (SPI), Zung Pain and Distress Index (PAD)	1. No significant differences were noted between the groups on MPQ, SPI, or PAD. 2. More subjects reported side effects in the experimental group (p<0.05). 3. More subjects in the placebo group completed the 8 wk study (p<0.01).

Discussion

Tricyclic antidepressants are often recommended for the treatment of neuropathic pain following non-SCI causes. Therefore, it is important to study the use of tricyclic antidepressants in the treatment of post-SCI pain. Agarwal and Joshi (2017) found no significant difference in pain reduction between amitriptyline or lamotrigine. Cardenas et al. (2002) reported no significant difference in randomized spinal cord injury patients receiving either amitriptyline or placebo given 1-2 hours before bedtime for a period of six weeks. Heilporn (1978) using combinations of melitracin and TENS reported relief of pain in eight of eleven SCI patients with dysesthetic pain. Vranken et al. (2011) found individuals receiving duloxetine reported clinically significant (>2 units on VAS) improvement on pain compared to those in a placebo control group. In an interesting study by Rintala et al. (2007), amitripyline was no better than gabapentin in depressed and non-depressed subjects but was better than diphenhydramine for depressed subjects only.

Davidoff et al. (1987b), in a six week double-blind placebo-controlled trial, found that trazodone was ineffective at relieving pain in 18 SCI patients with chronic neuropathic pain.

Conclusion

There is level 1b evidence (from one randomized controlled trial; Rintala et al. 2007) that amitriptyline is effective in the treatment of post-SCI neuropathic pain in individuals only when there is concomitant depression.

There is level 1b evidence (Agarwal & Joshi 2017) that amitriptyline is no more effective as lamotrigine in improving pain post SCI.

There is level 1b evidence (from one randomized controlled trial; Vranken et al. 2011) that duloxetine may improve neuropathic pain post SCI.

There is level 1b evidence (from one randomized controlled trial; Davidoff et al. 1987b) that trazodone does not reduce post-SCI neuropathic pain.

Amitriptyline is effective in reducing neuropathic pain in depressed SCI individuals.

Amitriptyline is no more effective as lamotrigine in improving pain post SCI

Duloxetine may improve neuropathic pain post SCI

Trazodone does not reduce post-SCI neuropathic pain.

11.4 Anaesthetic Medications

Anaesthetic medication such as lidocaine and ketamine are sodium channel blockers and can be delivered by a number of routes. Ketamine is a non-competitive NMDA receptor antagonist that can be administered epidurally, intrathecally, and orally to treat neuropathic pain syndromes (Hocking & Cousins 2003).

Table 26 Anaesthetic Medications for Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Lidocaine		
Finnerup et al. 2005 Denmark RCT PEDro=10 N=24	**Population:** Type of pain=neuropathic. **Treatment:** Subjects were 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. **Outcome Measures:** McGill Pain Questionnaire (MPQ)	1. In the total sample of patients, lidocaine reduced pain vs. placebo ($p<0.01$). 2. Assessing those with and without evoked pain, lidocaine still superior to placebo at reducing pain ($p<0.01$ and $p<0.048$, respectively). 3. More patients reported pain relief with at level and below-level pain while receiving lidocaine vs. placebo.
Kvarnstrom et al. 2004 Sweden RCT PEDro=10 N=10	**Population:** Type of pain=neuropathic. **Treatment:** SCI patients were recruited for participation. Ketamine (0.4 mg/kg) vs. lidocaine (2.5 mg/kg) vs. saline placebo administered intravenously over 40 min. **Outcome Measures:** Visual Analogue Scale (VAS)	1. VAS scores were significantly reduced in ketamine vs. the placebo group ($p<0.01$). 2. Comparing lidocaine and placebo group, no significant difference noted ($p=0.60$). 3. Pain relief was not linked to altered temperature thresholds or other changes in sensory function.
Attal et al. 2000 France RCT PEDro=10	**Population:** Type of pain=neuropathic. **Treatment:** Patients participated, six with stroke and ten with SCI. Subjects given 5mg of lidocaine or saline over a 30 min	1. Effects of lidocaine on pain were greater than effects of placebo, starting at end of injection, and

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
N=16	period. Treatments given in separate sessions, 3 wk apart. Order of sessions was randomized. **Outcome Measures:** Visual Analogue Scale (VAS), McGill Pain Questionnaire (MPQ)	lasting for up to 45 min post injection ($p<0.05$). 2. More people received pain relief with lidocaine than with placebo; however, relief waned by 60 min post injection. 3. Lidocaine reduced pain in 11 patients; and, in 6 of 12 patients, burning pain totally or partially relieved. 4. 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 min post injection.
Loubser & Donovan 1991 USA RCT PEDro=8 N=21	**Population:** Age=18-58 yr; Gender: males=15, females=6; Level of injury: cervical, lumbar; Duration of chronic pain=>6 mo; Type of pain=nociceptive. **Treatment:** Subjects had a lumbar subarachnoid catheter inserted. Subjects recorded their pain intensity at baseline. This was followed by two separate injections (placebo and 5% lidocaine in dextrose). A decrease in pain was considered a positive response to the treatment. **Outcome Measures:** Pain.	1. All 21 patients tolerated the injection (anaesthetics and placebo) well. 2. 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. 3. The decrease in pain reduction following lidocaine was significant ($p<0.01$) for the treatment group only.
Mexiletine		
Chiou-Tan et al. 1996 USA RCT PEDro=8 Initial N=15; Final N=11	**Population:** Mean age=44 yr; Gender: males=11, females=2; Severity of injury: AIS: A-E; Time since injury=7 yr.; neuropathic. **Treatment:** Following a 1 wk washout period subjects were given either 150 mg of mexiletine or placebo (150 mg 3x/day) followed by another 1 wk washout period then subjects placed in opposite group. **Outcome Measures:** McGill pain score.	1. Visual analogue showed no significant differences for average pain levels over the past week and pain at time of test regardless of which medication (drug or placebo) subject was taking. 2. Results of the McGill Pain score also showed no significant differences between the groups. 3. No change in level of function for either group at any time of the study.
Ketamine		
Amr 2010 Egypt RCT PEDro=6 N=40	**Population:** Age=48.6yr; Gender: males=33, females=7; Type of pain=neuropathic. **Treatment:** Participants were randomly assigned to treatment or control group. Participants in the treatment received 80mg intravenous ketamine over a 5 hours period daily for 1 week and 300mg gabapentin 3 times daily. The placebo group received placebo infusion and 300 mg of gabapentin 3 times daily. **Pain Scale:** Visual Analogue Scale (VAS)	1. Significant reduction in pain intensity was seen among individuals receiving ketamine infusion combined with gabapentin compared to those in the placebo group. The reduction remained significant up till 2 weeks post infusion ($p<0.05$).

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Kvarnstrom et al. 2004 Sweden RCT PEDro=10 N=10	**Population:** Type of pain=neuropathic. **Treatment:** SCI patients were recruited for participation. Ketamine (0.4 mg/kg) vs. lidocaine (2.5 mg/kg) vs. saline placebo administered intravenously over 40 min. **Pain Scale:** Visual Analogue Scale (VAS)	1. VAS scores were significantly reduced in ketamine vs. the placebo group (p<0.01). 2. Comparing lidocaine and placebo group, no significant difference noted (p=0.60). 3. Pain relief was not linked to altered temperature thresholds or other changes in sensory function.
Eide et al. 1995 Norway RCT PEDro=7 N=9	**Population:** Age=25-72 yr; Gender: males=8, females=1; Level of injury: cervical, thoracic; Severity of injury: AIS: A-D; Onset of pain: <6 mo post injury, Length of pain: 14-94 mo. Type of pain=neuropathic. **Treatment:** Ketamine hydrochloride, alfentanil or a placebo was given as combination of bolus and continuous intravenous infusions. The bolus dose was administered for 60 secs and the continuous intravenous infusion started simultaneously and was delivered by IVAC syringe pump. This lasted 17-21 min while the testing was performed. **Outcome Measures:** Visual Analogue Scale (VAS).	1. Freidmann's two-way analysis by ranks showed differences between the various treatments (p=0.005). 2. The effect of alfentanil and ketamine was also significant (p<0.01 and p<0.04 respectively). 3. No significant differences were noted between the actions of ketamine and alfentanil (Wilcoxon p=0.19). 4. Significant differences were noted between the treatment groups (p=0.008). It was also noted that allodynia was not more changed by ketamine than by alfentanil (Wilcoxon p=0.93). 5. Alfentanil reduced wind-up-like pain (p=0.014) compared to the placebo group. The effect of ketamine on wind-up-like pain was not significantly reduced (p=0.07). 6. A high correlation between the serum concentration of ketamine and the reduction of continuous pain (r=0.78, p<0.002) and the reduction of wind-up-like pain (r=0.83, p<0.002) was noted.

Table 27 Summary of Anaesthetic Treatments Post SCI Pain

Study	Study Type	N	Intervention	Outcome
Finnerup et al. 2005	RCT	24	Lidocaine	+
Attal et al. 2000	RCT	16	Lidocaine	+
Kvarnstrom et al. 2004	RCT	10	Lidocaine	-
Loubser & Donovan 1991	RCT	21	Lidocaine	+
Chiou-Tan et al. 1996	RCT	15	Mexiletine	_
Kvarnstrom et al. 2004	RCT	10	Ketamine	+
Eide et al. 1995	RCT	9	Ketamine	+

Discussion

Lidocaine

Given the severity of post-SCI pain, treatments such as lumbar epidural and subarachnoid infusions or anaesthetics are sometimes utilized and there is some evidence for these treatments. Loubser and Donovan (1991) conducted an RCT of 21 patients who were provided two separate lumbar subarachnoid injections of placebo and 5% lidocaine in dextrose. Following the lidocaine injection (n=13) there was a significant mean reduction in pain ($p<0.01$) for an average of two hours despite the fact that eight patients showed no changes. However, this treatment provided short-term relief of pain only. The authors regarded the value of this treatment as more a diagnostic procedure than a therapeutic one.

Attal et al. (2000) 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. (2005) those patients who received lidocaine intravenously (n=24) in two treatment sessions six days apart reported significantly less pain than those who did not receive intravenous lidocaine.

Kvarnstrom et al. (2004) found no evidence for the effectiveness of intravenous lidocaine in reducing neuropathic pain when compared to placebo.

Mexilitine

Chiou-Tan et al. (1996) provided 15 SCI individuals with either oral mexiletine (an orally administered derivative of lidocaine) or placebo (150mg 3x 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

Three RCTs found ketamine was successful in reducing neuropathic pain post SCI (Amr 2010; Kvanrnstrom et al. 2004; Eide et al. 1995). Eide et al. (1995) in an RCT of intravenous ketamine hydrochloride (NMDA receptor antagonist), alfentanil (μ-opioid receptor agonist) or placebo were provided as combination of bolus and continuous intravenous infusions. There was a significant benefit to ketamine or alfentanil vs. placebo for allodynia. Alfentanil reduced wind-up pain compared to placebo but not ketamine overall; however, there was a high correlation between the serum concentration of ketamine and the reduction in continuous pain and wind-up pain. The effects of ketamine and alfentanil were significant when compared to placebo.

Conclusion

There is level 1b evidence (from one randomized controlled trial; Loubser & Donovan 1991) that Lidocaine delivered through a subarachnoid lumbar catheter provides short-term relief of pain greater than placebo.

There is level 1a evidence (from two randomized controlled trials; Kvarnstrom et al. 2004; Eide et al. 1995) that intravenous Ketamine significantly reduces allodynia when compared to placebo.

There is level 1b evidence (from one randomized controlled trial; Chiou-Tan et al. 1996) that mexilitene (a derivative of lidocaine) does not improve SCI dysesthetic pain when compared to placebo.

Lidocaine through a subarachnoid lumbar catheter and intravenous Ketamine improve post-SCI neuropathic pain short term.

Mexilitene does not improve SCI dysesthetic pain.

11.5 Antispasticity Medications

Herman et al. (1992) note that baclofen, an α-aminobutyric acid $(GABA)_B$ receptor agonist,acts to suppress spasticity in SCI patients centrally within the spinal cord itself. GABA is known to be involved in several analgesics pathways (Sawynok 1987) and experimentally induced allodynia has been shown to be suppressed by baclofen (Henry 1982). However, baclofen, by treating spasticity, may reduce the musculoskeletal pain associated with spasticity. Continuous intrathecal infusion of baclofen can be effective, when oral baclofen is ineffective, in further reducing post-SCI spasticity and/or pain (dysesthetic, musculoskeletal, neurogenic; Boviatsis et al. 2005; Herman & D'Luzansky 1991; Penn & Kroin 1987; Plassat et al. 2004). For an in-depth discussion of intrathecal baclofen and its effects on spasticity in SCI, please refer to the Spasticity chapter.

Table 28 Antispastic Medications for Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Baclofen		
Loubser & Akman1996 USA Pre-post N=16	**Population:** Age=21-63 yr; Gender: males=15, females=1; Severity of injury: Frankel classification: A-C; Type of pain: neurogenic=6, musculoskeletal=6, Type of pain=neuropathic and musculoskeletal. **Treatment:** Intrathecal Baclofen pump implantation. **Outcome Measures:** Visual Analogue Scale **(**VAS).	1. The majority (75%) of patients reported chronic pain prior to the procedure. 2. No significant differences were noted on VAS at 6 mo and 12 mo following pump implantation. 3. For those with neurogenic pain symptoms, ANOVA revealed a non-significant effect of intrathecal baclofen on pain at both 6 and 12 mo. (F2, 16), adjusted 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 the Baclofen infusion while neurogenic pain did not.
Boviatsis et al. 2005 Greece Case Series Initial N=22; Final N=21	**Population:** MS, SCI (N=7): Level of injury: C4 to T11; Type of pain=undifferentiated; Results were presented by etiology. **Treatment:** Subjects were implanted with an intrathecal baclofen infusion pump delivering a continuous flow at a fixed rate of bolus intrathecal Baclofen.	1. The self-assessment pain scale revealed a limited improvement in pain (p=0.0941).

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	Outcome Measures: Barthel index scale, Ashworth scale and Penn spasm scale, self-assessment pain scale.	
Plassat et al. 2004 France Case Series Initial N=41;Final N=37	**Population:** SCI (N=17), MS and cerebral spasticity - spasticity of spinal cord origin, N=33); Type of pain=neuropathic and nociceptive. **Treatment:** Intrathecal Baclofen pump implantation. Those suffering from neuropathic pain received co-administration of morphine or clonidine. **Outcome Measures: Visual Analogue Scale (**VAS), Satisfaction Score for locomotion, pain, sleep, and Ashworth Scale.	1. Of the 25/40 patients suffering pain before ITB (Intrathecal Baclofen), 80% noted 25% improvement in pain and 40% noted 30-50% improvement. Twenty percent reported no change.
Motor Point Phenol Block		
Uchikawa et al. 2009 Japan Case Series N=7	**Population:** Mean age=55.8 yr; Gender: males=6, females=1; Level of injury: C; Severity of injury: AIS A=2, C=1, D=4; Type of pain=undifferentiated. **Treatment:** A teflon coated needle and a weak electric stimulation was used to localize a motor point on the anterior surface of the scapula. Phenol was injected into the point where the strongest muscle contraction was observed. Assessments were made before and 24 hr post injection. **Outcome Measures:** Visual Analogue Scale (VAS), Ashworth Scale, flexion, abduction, rotation.	1. Significant improvement was observed in passive ROM of shoulder flexion, abduction and external rotation and shoulder pain - VAS ($p<0.05$). 2. No significant improvement was seen in the modified Ashworth scale ratings and the manual muscle test ratings for flexion, abduction and external rotation.
Botulinum Toxin		
Han et al. 2016 Korea RCT PEDro=9 N=40	**Population:** SCI: Mean age=48 yr; Severity of injury: AIS A=5, B-D=23; Cause of injury: traumatic=3, falls=8, gunshot wounds=1, diving=3, knife wound=1, blunt trauma=1; Type of pain=neuropathic. **Treatment:** Patients with neuropathic pain post SCI were randomly divided into botulinum toxin (BTX) type A injection group or a placebo group. Treatment group received 200U of BTX-A while the placebo group received saline. **Outcome Measures:** VAS, WHOQOL-BREF. Outcomes were assessed at 4 and 8 weeks post injection.	1. Significant reduction in VAS score was seen at 4 weeks (p=.003) and 8 weeks (p=.005) post injection compared to the placebo group. 2. 30% or greater pain relief was experienced by 30% of patients at 4 and 8 weeks in the treatment group; while, only 5% and 10% of the placebo group experienced greater than 30% relief at 4 and 8 weeks in the placebo group.. 3. No significant improvements on quality of life was seen.
Marciniak et al. 2008 USA Case Series N=28	**Population:** SCI: Mean age: BTX=53.1yrs; Placebo=48.9yrs; Type of pain=undifferentiated. **Treatment:** Botulinum toxin (BTX) type A injection for focal spasticity control. **Outcome Measures:** Improvement in ambulation, positioning, upper-extremity function, hygiene, pain.	1. Improvement was seen post-injection in ambulation (56%), positioning (71%), upper-extremity function (78%), hygiene (66.6%), and pain (83.3%). 2. The effectiveness of BTX injections was not influenced by early use of BTX injections (less than a year after onset of symptoms) vs. late use.

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
		3. Improvement in those with upper arm compared to lower arm injections was similar. 4. SCI completeness did not affect improvement.

Discussion

Baclofen

Boviatsis et al. (2005) and Plassat et al (2004) presented case series data that reflected improvements in self-reported pain ratings after intrathecal baclofen administration. Herman et al. (1992) in a RCT found that intrathecal baclofen significantly suppressed the dysesthetic (burning) pain among six of the seven subjects ($p<0.001$). Only one of the placebo patients noted the dysesthetic pain was abolished. Intrathecal baclofen did not have a significant impact on pinch induced pain. Therefore, in this study, intrathecal baclofen appeared to have an impact on post-SCI dysesthetic pain in addition to treating the spasticity. Loubser and Akman (1996) performed a before and after study of implanted Baclofen infusion pumps provided for spasticity. Twelve of sixteen patients described pre-existing chronic pain but there was no significant difference in the VAS neurogenic pain symptoms at 6 and 12 months ($p=0.26$) while musculoskeletal pain symptoms and pain severity decreased in conjunction with control of spasticity in 5 of 6 patients. In this study, it appeared musculoskeletal pain was reduced more with intrathecal baclofen, presumably by reducing spasticity.

Hence, it would appear that intrathecal baclofen improves chronic post-SCI pain but the actual mechanism has not been adequately established. There is evidence that baclofen infusion pumps may be helpful for both neuropathic and musculoskeletal pain after SCI (Loubser & Akman 1996). However, studies have shown that intrathecal baclofen only reduces SCI pain when pain is related to muscle spasms (Coffey et al. 1993; Meythaler et al. 1992). Suppression of central pain through baclofen antagonism of substance P has been postulated (Herman et al. 1992).

Motor Point Phenol Block

In a case series, Uchikawa et al. (2009) followed seven spinal cord injury individuals with spastic shoulder pain underwent a motor point phenol block procedure. A significant improvement in VAS shoulder pain was seen post injection ($p<0.05$).

Botulinum Toxin

In a double blind placebo study, Han et al. (2016) found BTX-A significantly improved post SCI neuropathic pain based on average pain ratings on the VAS at 4 and 8 weeks. The study found no significant improvements in quality of life. Marciniak et al. (2008) treated 29 SCI patients with Botulinum toxin type A injections to treat focal spasticity. Pain was improved by 83.3%.

Conclusion

There is conflicting level 4 evidence (from two case series studies and one pre-post study; Boviatsis et al. 2005; Plassat et al. 2004; Loubser & Akman 1996) that intrathecal baclofen reduces dysesthetic pain post-SCI.

There is level 4 evidence (from one pre-post study; Loubser & Akman 1996) that intrathecal baclofen reduces musculoskeletal pain post-SCI in conjunction with spasticity reduction.

There is level 4 evidence (from one case series study; Uchikawa et al. 2009) that motor point phenol block is effective in reducing short term spastic shoulder pain post SCI.

There is level 1 evidence (from one RCT; Han et al. 2016) that local botulinum toxin injections may reduce neuropathic pain post SCI.

Intrathecal Baclofen improves musculoskeletal pain post SCI and may help dysethetic pain related to spasticity.

Motor point phenol block reduces spastic shoulder pain.

Botulinum toxin injections reduce neuropathic pain.

11.6 Opioids for Post-SCI Pain

To date there are few research studies examining opioids in the treatment of SCI pain. There is a substantial body of research investigating the benefits of opioid analgesics in the treatment of non-cancer chronic pain and some of those studies examined the impact of opioids on neuropathic pain. There are no studies employing opioid analgesics in post-SCI pain. Furlan et al. (2006) conducted a meta-analysis of effectiveness and side-effects of opioid analgesics for chronic non-cancer pain. Their meta-analysis found that opioids reduced pain and improved functional outcomes when compared to placebo for both nociceptive and neuropathic pain syndromes. Strong opioids (oxydone and morphine) were significantly superior to naproxen and nortriptyline for pain relief but not functional outcomes. Weak opioids (propylene, tramadol and codeine) did not significantly do better than NSAIDS or tricyclic anti-depressants for either pain relief or functional outcomes (Furlan et al. 2006). The authors found that clinically, only constipation and nausea were significantly more common with opioids. The big concern with opioids is of course addiction or opioid abuse. Unfortunately, as Furlan et al. (2006) notes in their meta-analysis, the existing randomized trials were not designed to evaluate addiction.

Table 29 Opioids for Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Norrbrink & Lundeberg 2009 Sweden RCT PEDro=8 N=35	**Population:** Mean age=51.3 yr; Gender: males=28, females=7; Level of injury: tetraplegia=16, paraplegia=19; Type of pain=neuropathic. **Treatment:** Patients were randomized in a 2:1 ratio (tramadol/placebo) and treatment was administered for 4 wk. Both patients and staff were blind to the treatments. Each patient was given 50 mg tramadol or placebo 3x/day. The daily	1. Significant differences were seen in between group pain ratings ($p<0.05$). 2. Patient Global Impression of Change rating was significantly higher in the tramadol group than the control group. 3. Significant improvements were seen in ratings of anxiety, global life satisfaction and sleep quality ($p<0.05$).

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	dose was increased by one tab for 5 5 days to a maximum dose of 8 tab. **Outcome Measures:** Patient Global Impression of Change; Multidimensional Pain Inventory	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.
Attal et al. 2002 France RCT PEDro=10 N=15	**Population:** SCI: Mean age=54.9 yr; Gender: males=6, females=9; Mean duration of pain=5 yr; Type of pain=neuropathic and nociceptive. **Treatment:** Initially, patients received intravenous morphine titrated up to the maximal tolerated dosage using successive bolus injections of 2 mg morphine every 10 minutes. Double blind phase began 3 wk after titration phase. **Outcome Measures:** Spontaneous pain, tactile allodynia, psychophysical measurements, mechanical detection and pain thresholds, thermal detection and pain.	1. Spontaneous pain scores decreased immediately after the end of the infusion of morphine and placebo for up to 120 min in both groups. 2. The effects of the morphine did not differ significantly from those who were given the placebo post injection. 3. Those who reported pain relief from the treatment was higher (3x) after the morphine than after the placebo was given from 15-60 min post injection. 4. Burning pain was weakened by the morphine in seven patients and by placebo in four patients. 5. 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. 6. Morphine only significantly reduced dynamic mechanical allodynia ($p<0.01$).
Eide et al. 1995 Norway RCT PEDro=7 N=9	**Population:** Age=25-72 yr; Gender: males=8, females=1; Level of injury: cervical, thoracic; Severity of injury: AIS: A-D; Onset of pain: <6 mo post injury, Length of pain: 14-94 mo; Type of pain=neuropathic. **Treatment:** Ketamine hydrochloride, alfentanil or a placebo was given as combination of bolus and continuous intravenous infusions. The bolus dose was administered for 60 sec and the continuous intravenous infusion started simultaneously and was delivered by IVAC syringe pump. This lasted 17-21 min while the testing was performed. **Outcome Measures:** Visual Analogue Scale (VAS).	1. Freidmann's two-way analysis by ranks showed differences between the various treatments ($p=0.005$). 2. The effect of alfentanil and ketamine was also significant ($p<0.01$ and $p<0.04$ respectively). 3. No significant differences were noted between the actions of ketamine and alfentanil (Wilcoxon $p=0.19$). 4. Significant differences were noted between the treatment groups ($p=0.008$). It was also noted that allodynia was not more changed by ketamine than by alfentanil (Wilcoxon $p=0.93$). 5. Alfentanil reduced wind-up-like pain ($p=0.014$) compared to the placebo group. The effect of ketamine on wind-up-like pain was not significantly reduced ($p=0.07$). 5. A high correlation between the serum concentration of ketamine and the reduction of continuous pain ($r=0.78$, $p<0.002$) and the reduction of wind-up-like pain ($r=0.83$, $p<0.002$) was noted.

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Barrera-Chacón et al. 2011 Spain Pre-Post N_{start}=57 N_{end}=54	**Population:** Age: 46.4 yr, Severity of injury: AIS A=27, B=1, C=10; Type of pain=neuropathic. **Intervention:** Participants were provided with oxycodone treatment for neuropathic pain. **Outcome Measures:** Visual Analogue Scale (VAS)	1. Pain intensity significantly decreased after 3 mo of oxycodone treatment, p<0.001. 2. Improvement in sleep and physical activity levels was also seen. 3. 83% of individuals were taking adjunct anticonvulsant treatment. 4. The most common side effect included constipation (33%).

Discussion

Attal et al. (2002) found the intravenous morphine titrated to maximal tolerated dosage, significantly reduced dynamic mechanical allodynia but not necessarily spontaneous or burning pains. Oral opioids remain untested in this population.

Norrbrink and Lundeberg (2009) 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 individuals with post SCI pain ($p<0.05$). However, no significant improvement was seen in pain unpleasantness and depression levels.

Eide et al. (1995) randomly assigned individuals with chronic SCI pain into three groups receiving ketamine hydrochloride, alfentanil (μ-opioid receptor agonist) or placebo treatment. The study found alfentanil and ketamine effectively reduced SCI pain compared to placebo treatment ($p<0.04$, $p<0.01$); however no difference was seen between the two treatments in overall pain. Alfentanil significantly reduced wind up like pain while ketamine did not.

In a pre-post study, Barrera-Chacón et al. (2010) found oxycodone significantly decreased pain intensity and improved sleep ($p<0.001$) among individuals experiencing neuropathic pain post SCI. These effects were seen mostly in combination with anticonvulsant treatment.

Conclusion

There is level 1b evidence (from one randomized controlled trial; Attal et al. 2002) that intravenous morphine significantly reduces mechanical allodynia more than placebo.

There is level 1b evidence (from one randomized controlled trial; Norrbrink & Lundeberg 2009) that tramadol is effective in reducing neuropathic pain post SCI.

There is level 1b evidence (from one randomized controlled trial; Eide et al. 1995) that alfentanil reduces overall post SCI pain.

There is level 1b evidence (from one randomized controlled trial; Eide et al. 1995) that alfentanil is more effective at reducing wind up like pain than ketamine.

There is level 4 evidence (from one pre-post study; Barrera-Chacon et al. 2010) that oxycodone and anticonvulsants may be effective in improving SCI neuropathic pain.

Intravenous morphine reduces mechanical allodynia.

Tramadol reduces neuropathic pain.

Alfentanil reduces chronic pain post SCI.

Alfentanil is more effective in reducing wind up like pain post SCI than ketamine.

Oxycodone and anticonvuslants may improve neuropathic SCI pain.

11.7 Cannabinoids in Post-SCI Pain

Wade et al. (2003) note that delta-9-tetra hydrocannabinol (THC) and other cannabinoids have been shown to improve both tremor and spasticity in animal models of multiple sclerosis supported by anecdotal reports that cannabis relieves some of the troublesome symptoms of multiple sclerosis and spinal cord injury (Baker et al. 2000; Consroe et al. 1997; Dunn & Davis 1974; Martyn et al. 1995; Meinck et al. 1989; Petro & Ellenberger 1981; Ungerleider et al.1987). There is a clinical impression that marijuana smoking is very common among patients post-SCI; however, there are social and legal implication to its use and medical concerns about smoking as a delivery system.

Table 30 Cannabinoids and Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Wilsey et al. 2016 USA RCT Crossover PEDro=8 N=42	**Population:** Mean age=46.4±13.6 yr; Gender: males=29, females=13; Level of injury: C=22, T=14, L=6; Severity of injury; Type of pain=neuropathic. **Intervention:** Participants completed all conditions over the course of 3 8 hr sessions, during which were given either a placebo cannabis vapor, 2.9%, or 6.7% delta-9 THC with assessments taken at time of administration and hourly after for 7 hrs. Crossover design was used so each session they were given a different treatment condition. **Outcome Measures:** Pain intensity numeric rating scale (NRS), pain relief (patient global impression of change (PGIC)), neuropathic pain scale (NPS), allodynia visual analog scale (VAS), heat-pain threshold, drug effect VAS, spasticity NRS and PGIC, modified Ashworth scale	1. Significant dose effect on pain intensity was observed after controlling for baseline pain ($p<0.0001$) and a significant stairstep effect between conditions was observed where significantly less pain was felt at the 2.9% delta 9-THC dose compared to baseline, and significantly less pain was felt at the 6.7% dose compared to baseline and the 2.7% dose. 2. Pain intensity was observed to be significantly lower for both dosages of delta 9-THC compared to baseline ($p<0.05$), but only the 6.7% dose showed significance over the following 2 hrs ($p<0.01$). 3. Four sided effects (“bad drug effect,” “nauseous,” “changes perceiving time,” and “difficulty remembering

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	(MAS) for spasticity, vital signs (heart rate (HR), blood pressure (BP)), neurocognitive assessments (attention and concentration, fine motor speed processing speed and learning and memory (Wechsler adult intelligence scale digit symbol test (DST), (trail marking test (TMT), grooved pegboard test (GBT), paced auditory serial addition test (PASAT), Hopkins verbal learning test revised (HVLT)).	things") showed no significant effect on pain, but others did (p ranged from <0.0001 to p=0.02), but main effect for delta 9-THC treatment remained significant above all effects of psychomimetic measures (p<0.0004). 4. 18 participants achieved a 30% pain reduction (clinically important while using placebo, while 26 and 35 reached 30% for the lower and higher dosages respectively. 5. Significantly more pain relief with active cannabis compared to placebo (p<0.0001) and the effect was observed immediately after vaporization (p<0.005) and 1 hr (p<0.04), but not 2 hrs later (p>0.2). 6. For second vaporization, but active cannabis doses provided greater pain relief than placebo immediately (p<0.001) and one hour later (p<0.05), but only one dose remained effective in reducing pain significantly compared to placebo (2.9% at time 360, p=0.03; 6.7% at time 420, p=0.03) with no time showing a significant difference in pain relief between active delta 9-THC doses. 7. Across all timepoints, measurements of NPS showed that vaporized cannabis positively and significantly affected all measured multidimensional pain descriptors associated with neuropathic pain, even after controlling for baseline levels (p<0.0001 except for itching: p=0.04).
Andresen et al. 2016 Denmark RCT PEDro= N=73	**Population:** Mean age=56.3±11.6 yr; Gender: males=54, females=19; Time since injury=10.3±11.7 yr; Level of injury: tetraplegia=32, paraplegia=41; Severity of injury: AIS A=24, B=3, C=15, D=31; Type of pain=neuropathic. **Intervention:** Participants were randomized to a ultramicronized (Normast) group or a placebo group taking dosages 2 times daily with 12 h between dosages, for 12 wks. **Outcome Measures:** Change in neuropathic pain intensity from baseline wk to wk 12 and analysis and effects on spasticity, evoked pain, sleep problems, anxiety, depression and global impression of change.	1. No significant difference between change in neuropathic pain intensity observed between the Normast and placebo groups (p=0.46). 2. No significant difference over time between the two groups when using covariates (p=0.82). 3. Normast group had a significant reduction in their use of resuce medication compared to the placebo group (p=0.02). 4. Normast group showed a significant increase in intensity of spasticity observed in the pain diary recordings compared to a decrease in the placebo group (p=0.013). 5. No significant differences observed in any of the other outcome measures (p>0.05).

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Rintala et al. 2010 USA RCT PEDro=5 N=7	**Population:** Mean age: 50.1 yr. Severity of injury: AIS A=4, B=1, D=2. Level of injury: paraplegia=4, tetraplegia=3. Mean time since injury was 21.9 yr. Type of pain=neuropathic, **Treatment:** Participants were randomized into two groups: 1) 5 mg dronabinol titrated every third day (max 20 mg/day) ; 2) 25 mg diphenhydramine day one then titrated up to 75 mg/day. Participants remained in a seven day stabilization phase once titration was complete and then a 28 day maintainence phase. Next participants completed a nine day weaning-off phase followed by a seven day washout period. Each participant then crossed over to the other group. **Outcome Measures:** Brief Pain Inventory (BPI)	1. Pain intensity was not significantly different between the dronabinol and diphenhydramine groups. 2. No significant difference was seen in side effects between the groups. 3. Most common side effects included dry mouth, constipation, fatigue and drowsiness.
Hagenbach et al. 2007 Switzerland Phase 1-2 Non-RCT N=25 Phase 3 RCT PEDro=4 N=13	**Population:** SCI (N=15): Age=29-66 yr; Gender: males=11, females=2; Level of injury: C4-T11; Severity of injury: AIS: A,B,C,D Type of pain=neuropathic. **Treatment:** Phase 1-2: Patients received 10 mg oral tetra hydrocannabinol (THC) on day one. Dose titration began on day two until the maximum tolerated dose or treatment aim was achieved and maintained for 6 wk. Phase 3: 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. Significant improvement in pain was seen on day one compared to baseline measures (p=0.047). 2. No significant improvement in pain post SCI was seen compared to placebo on day 8 and 43. 3. Individuals in the oral THC group showed no significant difference in mood or attention compared to the placebo group or to baseline.

Discussion

Wilsey et al. (2016) found cannabis vapor significantly reduced pain post SCI compared to placebo vapor. Rintala et al. (2010) examined the effect of dronabinol versus an active control (diphenhydramine) on pain post SCI. The study found no significant difference on pain intensity between the two treatments.

Hagenbach et al. (2007) conducted a study examining primarily 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 the pain of SCI individuals 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. (2007) found individuals in the treatment group had no significant pain reduction compared to those in the placebo group.

Given that marijuana has anecdotally been thought to have benefits for post-SCI pain, Wade et al. (2003) conducted an RCT of sublingual 2.5 mg THC and/or cannabidiol and found that it helped to reduce pain, muscle spasm, spasticity and sleep in a group of largely multiple sclerosis patients with neuropathic pain. It is of note that only a small percentage of the patients in this study had spinal cord injuries hence did not meet inclusion criteria. Cannabinoids are a promising treatment, which would benefit from other studies.

Conclusion

There is level 1b evidence (Wilsey et al. 2016) that cannabis vapour improves pain post SCI

There is conflicting level 2 evidence (from one randomized controlled trial; Hagenbach et al. 2007) for the use of delta-9-tetra hydrocannabinol in reducing spastic pain in SCI individuals.

There is level 2 evidence ((from one randomized controlled trial; Rintala et al. 2010) that dronabinol is not effective in reducing pain intensity post SCI.

Cannabinoids are a potential new treatment for post-SCI pain in need of further study.

Dronabinal is not effective in reducing pain post SCI.

11.8 Clonidine for Post-SCI Pain

Clonidine is an alpha-2 adrenoceptor agonist which has been shown to activate spinal receptors that reduce responses to painful stimuli (Yaksh 1985). Ackerman et al. (2003) note that clonidine inhibits nociceptive impulses by activating alpha-2 adrenoceptors in the dorsal horn of the spinal cord (Rainov et al. 2001). 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 (Osenbach & Harvey 2001) and possibly by inhibition of substance P release (Ackerman et al. 2003; Hassenbusch et al. 1999). Ackerman et al. (2003) noted selective alpha-2 adrenergic antagonists (e.g. Yohimbine) have been shown to reverse clonidine-induced analgesia (Osenbach & Harvey 2001). Teasell and Arnold (2004) were able to show that venous alpha-adrenoceptor hyper-responsiveness was present in patients with RSD, in diabetic peripheral neuropathy (Arnold et al. 1993) and below the level of lesion in quadriplegics (Arnold et al. 1995). They speculated that this alpha-adrenoceptor hyper-responsiveness was in fact due to alpha-2 adrenoceptor dysfunction leading to overstimulation of the post-synaptic alpha-1 adrenoceptor peripherally. This would fit with the observation that clonidine reduces pain post-SCI below the level of the lesion, presumably through its alpha-2 adrenoceptor agonist function.

Ackerman et al. (2003) noted that clonidine may be useful for patients who are non-responsive to opioids. Clonidine appears to work synergistically with opioids to provide pain relief (Osenbach & Harvey 2001; Plummer et al. 1992; Siddall et al. 2000; Tallarida et al. 1999).

Table 31 Clonidine for Treatment of SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Siddall et al. 2000 Australia RCT PEDro=8 N=15	**Population:** Age=26-78 yr; Type of pain=neuropathic: 13 had below level neuropathic pain, 4 at level of neuropathic pain, 3 had both neuropathic and nociceptive pain. **Treatment:** Placebo, morphine or Clonidine was delivered via catheter into lumbar intrathecal space. The subjects were first given either: 2, 1 mg morphine, 50-100 mcg of Clonidine or placebo. Dosage was increased if the subject had no side effects and no pain relief. Subjects could receive up to 1.5 times the initial drug dosage if necessary. Once the subject received satisfactory pain relief or side effects from the drug they were on they were given a mixture of morphine and Clonidine. **Outcome Measures:** Numerical pain rating scale, numerical pain relief score, a verbal pain rating and a nausea scale and sedation scores were recorded.	1. The administration of morphine or clonidine resulted in a mean reduction in pain levels but this was not statistically significant compared to the effect of placebo. 2. When the mixture of morphine and clonidine was administered there was a significant reduction in pain when compared to those on placebo (p=0.0084).
Uhle et al. 2000 Germany PCT N=10	**Population:** Age=34-77 yr; Gender males=4, females=6; Time since injury=1-10 yr; Type of pain=neuropathic. **Treatment:** Subjects, once implanted with a medical pump, were originally given 3 mL of saline followed by 1 mL of morphine, this was followed by a second dose of morphine (0.02 mg) provided no side effects or benefits were noted. This was followed by Clonidine (30 ug in 1 mL) and then depending on side effects a final dose of Clonidine (50 ug in 1 mL). After each drug administration the catheter was flushed with saline. **Outcomes Measures:** Not specified.	1. Subjects reported a good to excellent pain reduction following the administration of Clonidine administration. 2. After Clonidine bolus subjects experienced an optimum pain reduction. Average dose of Clonidine was initially 53 ug/day and this decreased (or stabilized) to 44 ug/day.

Discussion

Siddall et al. (2000) in a cross-over RCT of 20 subjects with post-SCI neuropathic pain received intrathecal morphine, clonidine or placebo at the lumbar level. Once the subjects received satisfactory pain relief or drug side effects they were given a mixture of clonidine and morphine. Morphine or clonidine showed a trend in pain reduction, which was not statistically significant but when the combination of morphine and clonidine was administered there, was a significant reduction in pain. Siddall et al. (2000) did postulate that by administering half the effective minimum dose of clonidine and morphine together resulted in a synergistic addictive effect above the simple summing up of each drug in isolation. In a study by Uhle et al. (2000) 10 patients were given morphine followed by clonidine via a medical pump. Patients given clonidine experienced a good to excellent reduction in their pain.

Conclusion

There is level 1b evidence (from one randomized controlled trial; Siddall et al. 2000) that intrathecal clonidine alone does not provide pain relief greater than placebo.

There is level 2 evidence (from one prospective controlled trial; Uhle et al. 2000) that the combination of intrathecal morphine and clonidine provides pain relief greater than placebo.

Intrathecal Clonidine alone does not appear to provide pain relief although it may be helpful in combination with Intrathecal Morphine.

11.9 Topical Capsaicin

Capsaicin is an active alkaloid in hot peppers. It has been successfully used to reduce pain in herpes zoster, diabetic neuropathy and post-mastectomy pain syndrome (Sandford & Benes 2000). It works as an inhibitor of substance P.

Table 32 Topical Capsaicin in Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Sandford & Benes 2000 USA Case Series N=8	**Population:** SCI: Age=18-66 yr; Gender: males=6, females=2; Level of injury: C6-L5; Severity of injury: complete=4, incomplete=4; Cause of injury: MVA=3, GSW=3, fall=1, aneurysm repair=1; Type of pain=nociceptive (radicular). **Treatment:** Patients who underwent topical capsaicin therapy to reduce pain were retrospectively reviewed. **Outcome Measures:** Reduction in pain.	1. Patients showed improvement in pain in 1-2 wk of topical capsaicin therapy. 2. Two patients showed long-term efficacy for over 2 yr.

Discussion

Topical capsaicin was used to treat radicular post-SCI pain for 1-2 weeks (Sandford & Benes 2000). Patients showed improvement in pain and 2 of the 8 patients were still improved for over two years.

Conclusion

There is level 4 evidence (from one case series study; Sandford & Benes 2000) that topical capsaicin reduces post-SCI radicular pain.

Topical capsaicin reduces post-SCI radicular pain.

11.10 Lithium Carbonate

Lithium carbonate may have the potential to be a neuroregenerative agent for spinal cord injury (Yang et al. 2012).

Table 33 Lithium Carbonate for Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Yang et al. 2012 China RCT PEDro=8 $N_{Initial}$=40; N_{Final}=36	**Population:** Mean age=40yr; Gender: males=35, females=1; Severity of injury: incomplete=7, complete=29; Time post injury >1yr; Type of pain=neuropathic. **Treatment:** Participants were randomized to receive oral lithium carbonate (0.6-1.2mmol/L, treatment, n=18) or placebo (control, n=18) for 6wk. Outcomes were assessed pre and post treatment and at 6mo follow-up. **Outcome Measures:** Visual Analogue Scale - Pain Intensity (VAS-PI), Modified Ashworth Scale (MAS), Sensory scores (touch and pinprick).	1. VAS-PI scores were significantly lower in the treatment group than in controls at 6wk (p=0.014), which lasted up to 4.5mo post treatment (p=0.041). 2. Sensory and MAS scores did not change significantly from baseline to 6wk or to 6mo in either group; the difference between groups was not significant at either time point.

Discussion

In a double blind placebo controlled randomized trial, Yang et al. (2012) found that individuals that received lithium carbonate had markedly reduced VAS scores over a 6 week period and at 6 month follow-up compared to the placebo group.

Conclusion

There is level 1b evidence (from one RCT; Yang et al. 2012) that lithium carbonate may reduce neuropathic pain post SCI

Lithium carbonate may reduce neuropathic pain post SCI

11.11 Transdermal Nitroglycerine

Berrazueta and colleageus (1996) first used transdermal nitroglycerine has been previously used for treating shoulder tendinopathy. In muscle cells of blood vessels, nitroglycerine (NT) transforms into nitric oxide. Nitric oxide has been shown to play a role in tendon repair by enhancing fibroblast regeneration and vasodilation (Murrell 2007).

Table 34 Transdermal Nitroglycerine for Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Giner-Pascual et al. 2011 Spain PCT N=45	**Population:** SCI: all subjects with tendinopathy of the shoulder; Type of pain=musculoskeletal. **Treatment:** Patients were divided into a treatment and placebo group. The treatment group received a quarter of a 1.25mg NT patch over the shoulder and were followed for 6-months. The placebo group received a placebo patch. **Outcome Measures:** SCIM; WUSPI; VAS.	1. Significant improvement was seen in the primary outcome measures including SCIM, WUSPI, and VAS at 6 month follow-up. 2. Those in the treatment group reported a number of side effects including headaches, facial reddening, dizziness, and tachycardia.

Discussion

One prospective controlled trial found transdermal NT patch was effective in improving pain intensity and functional movements among people with shoulder tendinopathy post SCI. Safety of the treatment is yet to be assessed.

Conclusion

There is level 2 evidence (from one prospective controlled trial; Giner-Pascual et al. 2011) that Transdermal Nitroglycerine reduces post-SCI shoulder tendinopathy pain.

Transdermal Nitroglycerine may reduce post-SCI should tendinopathy pain.

12.0 Surgical Interventions

12.1 Spinal Cord Stimulation

Spinal cord stimulation has been used to try to treat intractable pain. The procedure is both expensive and invasive.

Table 35 Spinal Cord Stimulation Post SCI

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Meier et al. (2015) Denmark RCT PEDro=8 N=14	**Population:** Median age=53yr; Gender: males=5, feamles=9; Mean time post injury=79mo; Type of pain: complex regional pain syndrome=5, peripheral neuropathic=9. **Treatment:** Individuals were examined during activated and deactivated spinal cord stimulation (SCS), provided in a randomized sequence, via quantitative sensory testing (QST).	1. For mechanical (tactile, pressure, and vibration) thresholds, there was no significant difference between conditions for detection and pain. Both tactile and pressure thresholds were lower on the affected side than the control side, while vibration threshold was the same on both sides.

	Outcome Measures: Pain thresholds (mechanical, thermal, and wind-up-like); Pain intensity; Pain areas.	2. For thermal (hot and cold) thresholds, there was no significant difference between conditions for detection. However, the heat pain threshold was slightly but significantly different between sides during SES activation (p=0.01). 3. For wind-up-like pain, there was no significant difference between conditions for detection and tolerance. 4. Areas of brush allodynia were significantly smaller (p=0.037) during the activated condition (225cm^2) than the deactivated condition (310cm^2). 5. There were no significant differences between conditions for areas of spontaneous pain or pinprick hyperalgesia. 6. There was no significant difference between conditions for present or recent pain intensity. 7. Overall, 93% of patients were able to identify SES activation.
Cioni et al. 1995 Italy Case Series N=25	**Population:** Age=33-76 yr; Gender: males=19, females=6; Time since injury=1-39 yr. Type of pain=neuropathic and musculoskeletal. **Treatment:** An epidural electrode was inserted percutaneously over the posterior columns of the spinal cord. Spinal cord stimulation was performed with the following parameters: 85 cycles/sec, duration of 210 msec and varied intensity for comfortable parasthesias 30 min every 3 hr during the day. Mean follow-up was 37.3 mo. **Outcome Measures:** Pain relief.	1. During stimulation, 22 patients reported paresthesia overlapping the painful area. 2. 9 patients enjoyed 50% pain relief at the end of the test period. No pain relief was found in 3 of the patients. No statistical results reported.

Discussion

Meier et al. (2015) evaluated the effectiveness of activated SCS and deactivated SCS. The study found activated SCS resulted in smaller areas of brush allodynia compared to deactivated. No difference was seen in wind-up like pain. Cioni et al. (1995) reported inserting epidural electrodes over the posterior columns of the spinal cord to allow for spinal cord stimulation. During spinal cord stimulation, 22 patients reported paraesthesia overlapping the painful area. Nine patients reported 50% pain relief and three patients experienced no pain relief.

Conclusion

There is level 1b evidence (Meier et al. 2015) that spinal cord stimulation map improve allodynia related pain post SCI.

There is level 4 evidence (from one case series study; Ciono et al. 1995) that spinal cord stimulation improves post-SCI pain.

Spinal cord stimulation may improve post-SCI allodynia pain.

12.2 Dorsal Longitudinal T-Myelotomy for Pain Management Post-SCI

Table 36 Dorsal Longitudinal T-Myelotomy Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Livshits et al. 2002 Germany/Israel Case Control N=40	**Population:** Type of pain=neuropathic. **Treatment:** Individuals with SCI underwent one of two different surgical procedures: longitudinal T-myelotomy using the Bishof II technique (n=20), or longitudinal myelotomy en croix (Pourpre procedure) (n=20). **Outcome Measures:** Short form McGill Pain Questionnaire (SF-MPQ); Visual Analgoue Scale (VAS)	1. All individuals (regardless of surgical procedure) reported some pain relief. 2. The Pourpre procedure appeared better than the Bischof II procedure at relieving pain, as measured by VAS and SF-MPQ (in the immediate and long term). 3. By yr 5 and yr 10, individuals in both groups reported a return of motor spasticity.

Discussion

Livshits et al. (2002) conducted a case control study comparing two approaches of dorsal longitudinal T-myelotomy (i.e., Pourpre vs. Bischof II) with respect to their effectiveness in reducing pain and spasticity in people with SCI, initially refractory to more conservative approaches (N=40). Systematic follow-up assessments at six months, five and ten years were conducted. In this study, significant pain reduction was obtained with either of these surgical techniques, as measured using scores obtained from the Short Form – McGill Pain Questionnaire (Short form McGill Pain Questionnaire), the Present Pain Intensity scale, and a visual analog scale, but this appeared to be more notable with the Pourpre versus the Bischof II procedure.

Conclusion

There is level 3 evidence (from one case control study; Livshits et al. 2002) to support the use of dorsal longitudinal T-myelotomy procedures, in particular Pourpre's technique, to reduce spastic pain post SCI.

Dorsal longitudinal T-myelotomy procedures reduce pain post SCI.

12.3 Dorsal Rhizotomy

Dorsal rhizotomy is a procedure where the sensory roots are divided either intradurally or extradurally. According to Nashold (1991) a single one or two level root rhizotomy may be appropriate when the pain is localized as in those patients with paraparesis and single root pain. Moreover, Nashold (1991) reported the Dorsal Root Entry Zone (DREZ) procedure was more likely to be successful in these patients.

Table 37 Dorsal Root Entry Zone Procedure Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Falci et al. 2002 USA PCT N=41	**Population:** Type of pain=neuropathic. **Intervention:** The first nine patients were placed in group 1 and the next 32 in group 2. Individuals in group 1 underwent Dorsal Root Entry Zone (DREZ) microcoagulation using recorded spontaneous neuroelectrical hyperactivity in DREZ as a guide. While the second group underwent DREZ microcoagulation using the above recorded spontaneous nuroelectrical hyperactivity in the DREZ as well as recorded evoked hyperactivity during TCS of the DREZ. **Outcome Measures:** Visual Analogue Scale (VAS)	1. Seven patients in the first group achieved at least 50% pain relief post treatment while five patients achieved 100%. 2. In the second group, 84% of patients reported 100% pain relief post treatment; while 88% reported at least 50%. 3. In patients in the second group that experienced below level pain, 81% of patients reported 100% pain relief; while 19% that experienced above level pain all achieved 100% pain relief. 4. The intervention did not result in any deaths. 5. 82% of patients lost partial or complete pinprick sensation in the corresponding DREZ. 6. 68% experienced partial or complete loss of light touch sensation.
Chun et al. 2011 Korea Pre-post N=38	**Population:** Age: 49 yr, Level of injury: T=5, Conus Medullaris=33. Severity of Injury: AIS A=27; B11; Type of pain=neuropathic. **Treatment:** MDT was performed according to Sindou's technique **Outcome Measures:** Visual Analogue Scale (VAS)	1. Overall patients achieved good (79.0%), fair (10.5%) and poor (10.5%) poor pain relief. 2. Good pain relief was achieved in 82.5% of those with mechanical pain and 100% with combined pain, vs. 20% with thermal pain 3. Good pain relief was achieved in those with diffuse pain (73.3%) and segmental pain (82.6%). 4. Good pain relief was achieved in those with intermittent pain (78.2%) and continuous pain (80.0%)
Spaic et al. 2002 Yugoslavia (Serbia) Case series N=26	**Population:** Type of pain=neuropathic. **Treatment:** Dorsal Root Entry Zone (DREZ) surgical treatment **Outcome Measures:** Visual Analogue Scale (VAS)	1. DREZ surgical treatment was found to be effective at reducing pain in the majority of patients, more so for those with mechanical and combined vs. thermal pain. 2. Long-term pain relief was achieved in 90% of those with mechanical pain and 25% of those with combined pain.
Sindou et al. 2001 France/Egypt Case series N=44	**Population:** Type of pain=neuropathic and musculoskeletal. **Treatment:** Patients underwent Dorsal Root Entry Zone (DREZ) procedure to reduce pain. **Outcome Measures:** Visual Analogue Scale (VAS)	1. By 10 days, 70% of patients had experienced good pain relief, 18.5% fair pain relief, and 11.5% poor pain relief. 2. 3 months later, 66% reported continued good pain relief. 3. Better pain relief was seen in those with segmental vs. below-lesion pain and in those with conus medullaris vs. higher injuries.
Spaic et al. 1999 Yugoslavia (Serbia)	**Population:** Type of pain=neuropathic.	1. 4/6 patients reported complete pain relief; 2/6 reported 80% pain relief.

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Case series N=6	**Treatment:** DREZotomy surgical procedure. **Outcome Measures:** Self-reported pain relief.	2. Two patients who had been using pain medication reported no longer needing them.
Rath et al. 1997 Germany Case series N=23	**Population:** Type of pain=neuropathic **Treatment:** Patients underwent Dorsal Root Entry Zone (DREZ) procedure. **Outcome Measures:** Patients were asked to judge postoperative pain relative to preoperative pain (%).	1. Of the 23 patients who underwent the procedure, 11 were judged to have experienced good pain relief; the remaining 12 were said to have had a fair or poor result. 2. Better results were seen for those with 'end-zone' vs. diffuse pain.
Sampson et al. 1995 USA Case series N=39	**Population:** Type of pain=neuropathic and musculoskeletal. **Treatment:** Patients received Dorsal Root Entry Zone (DREZ) procedures from 1978 to 1992. **Outcome Measures:** Pain relief, as indicated by subsequent treatment and activity levels.	1. 21 of the 39 reported good results, while the remaining 18 reported fair results at a mean of 3 yr. 2. 30/39 had no post-operative complications.
Nashold et al. 1990 USA Case series N=18	**Population:** Type of pain=neuropathic and musculoskeletal. **Treatment:** Patients who had a SCI and Dorsal Root Entry Zone (DREZ) procedures and drainage to remove cysts that had developed <1 post injury. **Outcome Measures:** Pain relief, as indicated by subsequent treatment and activity levels.	1. 14/18 patients reported good pain relief with combined cyst drainage. Good pain relief was defined as not requiring any analgesics and activities not limited because of pain.
Friedman & Nashold 1986 USA Case series N=56	**Population:** Type of pain=not stated. **Treatment:** Patients underwent Dorsal Root Entry Zone (DREZ) procedure. **Outcome Measures:** Pain relief, as indicated by subsequent productivity levels.	1. 50% of patients reported good pain relief, 9% fair, 4% poor following DREZ procedure. 2. Better results were obtained for those with segmental vs. diffuse pain.

Discussion

In the Falci et al. (2002) study, individuals were divided into two treatment groups: the first nine patients underwent DREZ micro-coagulation using recorded spontaneous neuro-electrical hyperactivity in as a guide; while the second group underwent DREZ micro-coagulation using both the recorded spontaneous and evoked hyperactivity as a guide. Individuals were followed up to six years post-surgery and pain was measured using the VAS. The study found that more participants (50% vs. >80%) in the second group reported 100% pain relief than those in the first group.

Chun et al. (2011) reported on 38 individuals treated with the procedure, between 2003 and 2008. These individuals suffered from various types of neuropathic pain including segmental versus diffuse, mechanical versus thermal or a combination of both, and intermittent versus continuous pain. Previous management with medication had proven unsuccessful. After surgery, individuals were followed for a period ranging between 19 and 84 months (average of 42 months) to measure the degree of pain relief. At follow-up, individuals were asked to rate the intensity of their pain using the VAS. Pain relief was considered by the authors to be "good" if pain was reduced by more than 75%, "fair" if it was reduced by 25-75% and "poor" if pain was

reduced less than 25%. Individuals with intermittent pain and continuous pain achieved high rates of good pain relief (78% and 80%, respectively).[9]

Notably, Nashold et al. (1990) reported 14 of 18 individuals (77%) with paraplegia who underwent cyst drainage and the DREZ surgical procedure reported pain relief following surgery. In general, approximately 50% or more of the patients across these case series achieved greater than 50% pain relief or experienced no pain-related activity limitations and no need for narcotics following the surgery (Friedman & Nashold 1986; Nashold et al. 1990; Rath et al. 1997; Sampson et al. 1995; Sindou et al. 2001; Spaic et al. 1999; Spaic et al. 2002). However, all of these were retrospective, uncontrolled reports with obvious methodological limitations, such as ill-defined eligibility criteria (i.e., potential selection bias) and inadequate outcome measurement which limits the generalizability of the results.

Conclusion

There is level 2 evidence (from one prospective controlled trial, one pre-post study, and seven case series studies; Falci et al. 2002; Chun et al. 2011; Sindou et al. 2001; Spaic et al. 1999, 2002; Rath et al. 1997; Sampson et al. 1995; Bashold et al. 1990; Friedman & Nashold 1986) to support the use of the DREZ surgical procedure to reduce pain post SCI. It may be that some populations (segmental pain) are more likely to benefit from this procedure.

DREZ surgical procedure reduces pain post SCI.

12.4 Mesenchymal stromal cells

Table 38 Mesenchymal stromal cells for Post-SCI Pain

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
Vaquero et al. 2018 Spain Pre-Post N=10	**Population:** Mean age=45.1±10.6 yr; Gender: males=9, females=1; Time since injury=18.1±16.7 yr; Level of injury: C=5, T=2, L=3; Severity of injury: AIS A=3, B=2, C=3, D=2; Type pf pain=neuropathic. **Intervention:** Participants received intrathecal administrations of 100 million mesenchymal stromal cells (MSCs) into their subarachnoid space via lumbar puncture in mo 1, 4, and 7 of the study for a total of 300 million MSCs, with follow-up at 4, 7 and 10 mo. **Outcome Measures:** Neuropathic pain scores (NP).	1. Over the follow-up period there is a clear significant reduction in NP scores for all but 1 patient. 2. Significant improvement from baseline to mo 4 for NP score, and this was maintained throughout the entire follow-up period (p=0.003).
Vaquero et al. 2018 Spain Pre-Post Extended Follow-Up N=11	**Population:** Mean age=44.9±10.2 yr; Gender: males=7, females=4; Time since injury=13.7±14.8 yr; Level of injury: C=4, T=4,L=3; Severity of injury: AIS A=3, B=4, C=3, D=1; Type pf pain=neuropathic.	1. 4 of 11 participants in the safety analysis group experienced mild adverse events (AE) to the extent of transitory sciatic pain, headaches and pain in area of lumbar puncture,

Author Year Country PEDro Score Research Design Total Sample Size	Methods	Outcome
	Intervention: Participants had 3 administrations of 100 million mesenchymal stromal cells (MSCs) into their subarachoid space via lumbar puncture over 3 mo, and were followed for 10 mo. **Outcome Measures:** Efficacy analysis in 9 of the participants and safety analysis in 11, VAS	with one serious AE unrelated to treatment. 2. 8 participants had NP shown via VAS scores, but at follow-up all scores either decreased or became 0 (p=0.012), except for one participant whose NP was not modified.

Discussion

Two pre-post studies evaluated the effectiveness of intrathecal administrations of mesenchymal stromal cells into the subarachnoid space in improving neuropathic pain among those with SCI. The preliminary evidence from the studies suggest that the transplantation is safe, with mild adverse events. Reduction in neuropathic pain were seen in most patients at follow-up. Evidence regarding it's use is still limited and warrants further examination.

Conclusion

There is level 4 evidence that mesenchymal stromal cells may improve pain post SCI

Mesenchymal stromal cells may improve post-SCI pain.

12.5 Sympathectomy

Sympathectomy is not recommended for pain following SCI (Nashold 1991). As mentioned previously, sympathetic blockade and sympathectomy have reportedly failed to relieve the central pain of SCI (Friedman & Nashold 1986; Melzack & Loeser 1978; White 1969).

12.6 Lateral Spinothalamic Tractotomy

Hazouri and Mueller (1950) described three selected cases of patients with intractable root pain, subsequent to severe trauma to the cauda equina which resulted in paraplegia (L2-4 lesions). All three patients demonstrated a distinct increase in the threshold for perception of pain and "an even more remarkable increase in the threshold for reaction to pain." Lateral spinothalamic tractotomy in all three of these patients resulted in complete relief from pain. Threshold studies subsequent to the tractotomy "revealed a striking return of perception and reaction thresholds to a normal range."

12.7 Spinal Cordotomy

This procedure can be performed openly or percutaneously. Anterior spinothalamic tracts subserving pain and temperature function are sectioned, often requiring a bilateral approach. Spinal cordotomy is an option but is rarely employed and there is little evidence that it works.

13.0 Summary

Pain following SCI is quite common. The most common type of pain post SCI is central or neuropathic in nature characterized by a dysesthetic, burning pain below the level of SCI. Borderzone or segmental pain is much less common; occurring along the border between normal and absent sensation. The precise etiology of central/neuropathic or borderzone segmental pain is not known. There is some evidence suggesting an association may exist between the central or neuropathic dysesthetic burning pain and abnormalities of the sympathetic nervous system. Musculoskeletal pain, either secondary to the original trauma or to overuse is both common and well understood. Unfortunately, the management of central or neuropathic pain remains difficult and largely ineffective.
For many SCI patients, pain has a significant impact on quality of life.

Over 50% of SCI patients develop chronic pain. Severe pain is more common the lower down the lesion in the spinal cord. Pain post SCI most often begins within the first 6-12 months post-SCI.

The most common types of pain post SCI are: 1) a burning pain (likely neuropathic) usually localized to the front of torso, buttock or legs or 2) an aching pain (likely musculoskeletal) usually localized to the neck, shoulders and back.

There is level 2 evidence (from one randomized controlled trial and one prospective controlled trial; Chase et al. 2012; Norrbrink & Lundeberg 2011) that massage therapy may not improve neuropathic and musculoskeletal pain intensity post SCI.

There is level 1b evidence (from one randomized controlled trial; Arienti et al. 2011) that osteopathy alone is not effective in improving neuropathic pain post SCI.

There is level 1a evidence (from two randomized controlled trials; Dyson-Hudson et al. 2001, 2007) that in general acupuncture is no more effective than Trager therapy or sham acupuncture in reducing nociceptive musculoskeletal shoulder pain post SCI.

There is level 1b evidence (from one randomized controlled trial; Yeh et al. 2010) that acupuncture and electroacupuncture reduces neuropathic pain of patients with SCI.

There is level 1b evidence (from one randomized controlled trial; Ginis et al. 2003) that a regular exercise program significantly reduces post-SCI neuropathic and musculoskeletal pain.

There is level 2 evidence (from one prospective controlled trial and one pre-post study; Nawoczenski et al. 2006; Serra-Ano et al. 2012) that a shoulder exercise protocol reduces the intensity of nociceptive shoulder pain post-SCI.

There is level 4 evidence (from one pre-post study; Finley & Rodgers 2007) that the MAGIC wheels 2-gear wheelchair results in less nociceptive shoulder pain.

There is level 2 and level 4 evidence (from one randomized controlled trial and one pre-post study; Jensen et al. 2009, 2000) that hypnosis reduces neuropathic and musculoskeletal pain intensity post SCI.

There is level 4 evidence (from one pre-post study; Jensen et al. 2013) that biofeedback may reduce neuropathic and musculoskeletal pain intensity post SCI.

There is level 2 evidence (from one prospective controlled trial; Perry et al. 2010) that a cognitive behavioural pain management program with pharmacological treatment may improve secondary outcomes among SCI individuals with chronic pain post SCI.

There is level 1b evidence (from one randomized controlled trial one prospective controlled trial, and one pre-post study; Heutink et al. 2012; Norrbrink et al. 2006; Burns et al. 2013) that cognitive-behavioural therapy alone does not change post-SCI pain intensity.

There is conflicting level 1b evidence (from one randomized controlled trial, a chohort study and two pre-post studies; Soler et al. 2010; Kumru et al. 2013; Gustin et al. 2008; Moseley 2007) that visual imagery may reduce at level neuropathic pain post SCI for a short period.

There is strong evidence level 1a evidence (from four randomized controlled trials; Capel et al. 2003; Fregni et al. 2006; Soler et al. 2010; Tan et al. 2006) for the benefits of transcranial electrical stimulation in reducing neuropathic and neuropathic and musculoskeletal post-SCI pain.

There is level 4 evidence (from one pre-post study; Panagos et al. 2004) that using a static field magnet helps to reduce reports of sharp, stabbing nociceptive shoulder pain but does not significantly reduce the VAS score of pain in individuals with a SCI.

There is level 4 evidence (from one case series study; Davis & Lentini 1975) that transcutaneous electrical nerve stimulation reduced at-the-injury site pain in only a minority of patients with thoracic or cauda equina SCI, but not those with cervical SCI.

There is level 1a evidence (from two randomized controlled trials; Jette et al. 2013; Defrin et al. 2007) that transcranial magnetic stimulation significantly reduced post-SCI neuropathic pain significantly over the long-term.

There is level 1a evidence (from two randomized controlled trials, and one case series, pre-post, and observational study; Levendoglu et al. 2004; Tai et al. 2002; To et al. 2002; Ahn et al. 2003; Putzke et al. 2002) that the Gabapentin and pregabalin improve neuropathic pain post SCI.

There is level 1b evidence (from one randomized controlled trial; Arienti et al. 2011) that combined pregabalin and osteopathy treatment improves pain post SCI.

There is level 4 evidence (from one pre-post study; Ahn et al. 2003) that the anticonvulsant Gabapentin is more effective when SCI pain is<6 months than >6 months.

There is level 1b evidence (from one randomized controlled trial; Finnerup et al. 2002) that lamotrigine improves neuropathic pain in incomplete spinal cord injury

There is level 1b evidence (from one randomized controlled trial; Finnerup et al. 2009) that Levetiracetam is not effective in reducing neuropathic pain post SCI.

There is level 2 evidence (from one randomized controlled trial; Drewes et al. 1994) that valproic acid does not significantly relieve neuropathic pain post SCI.

There is level 1b evidence (from one randomized controlled trial; Rintala et al. 2007) that amitriptyline is effective in the treatment of post-SCI neuropathic pain in individuals only when there is concomitent depression.

There is level 1b evidence (from one randomized controlled trial; Vranken et al. 2011) that duloxetine may improve neuropathic pain post SCI.

There is level 1b evidence (from one randomized controlled trial; Davidoff et al. 1987b) that trazodone does not reduce post-SCI neuropathic pain.

There is level 1b evidence (from one randomized controlled trial; Loubser & Donovan 1991) that Lidocaine delivered through a subarachnoid lumbar catheter provides short-term relief of pain greater than placebo.

There is level 1a evidence (from two randomized controlled trials; Kvarnstrom et al. 2004; Eide et al. 1995) that intravenous Ketamine significantly reduces allodynia when compared to placebo.

There is level 1b evidence (from one randomized controlled trial; Chiou-Tan et al. 1996) that mexilitene (a derivative of lidocaine) does not improve SCI dysesthetic pain when compared to placebo.

There is conflicting level 4 evidence (from two case series studies and one pre-post study; Boviatsis et al. 2005; Plassat et al. 2004; Loubser & Akman 1996) that intrathecal baclofen reduces dysesthetic pain post-SCI.

There is level 4 evidence (from one pre-post study; Loubser & Akman 1996) that intrathecal baclofen reduces musculoskeletal pain post-SCI in conjunction with spasticity reduction.

There is level 4 evidence (from one case series study; Uchikawa et al. 2009) that motor point phenol block is effective in reducing short term spastic shoulder pain post SCI.

There is level 4 evidence (from one case series study; Marciniak et al. 2008) that local botulinum toxin injections to treat focal spasticity reduces pain.

There is level 1b evidence (from one randomized controlled trial; Attal et al. 2002) that intravenous morphine significantly reduces mechanical allodynia more than placebo.

There is level 1b evidence (from one randomized controlled trial; Norrbrink & Lundeberg 2009) that tramadol is effective in reducing neuropathic pain post SCI.

There is level 1b evidence (from one randomized controlled trial; Eide et al. 1995) that alfentanil reduces overall post SCI pain.

There is level 1b evidence (from one randomized controlled trial; Eide et al. 1995) that alfentanil is more effective at reducing wind up like pain than ketamine.

There is level 4 evidence (from one pre-post study; Barrera-Chacon et al. 2010) that oxycodone and anticonvulsants may be effective in improving SCI neuropathic pain.

There is conflicting level 2 evidence (from one randomized controlled trial; Hagenbach et al. 2007) for the use of delta-9-tetra hydrocannabinol in reducing spastic pain in SCI individuals.

There is level 2 evidence ((from one randomized controlled trial; Rintala et al. 2010) that dronabinol is not effective in reducing pain intensity post SCI.

There is level 1b evidence (from one randomized controlled trial; Siddall et al. 2000) that intrathecal clonidine alone does not provide pain relief greater than placebo.

There is level 2 evidence (from one prospective controlled trial; Uhle et al. 2000) that the combination of intrathecal morphine and clonidine provides pain relief greater than placebo.

There is level 4 evidence (from one case series study; Sandford & Benes 2000) that topical capsaicin reduces post-SCI radicular pain.

There is level 4 evidence (from one case series study; Ciono et al. 1995) that spinal cord stimulation improves post-SCI pain.

There is level 3 evidence (from one case control study; Livshits et al. 2002) to support the use of dorsal longitudinal T-myelotomy procedures, in particular Pourpre's technique, to reduce spastic pain post SCI.

There is level 2 evidence (from one prospective controlled trial, one pre-post study, and seven case series studies; Falci et al. 2002; Chun et al. 2011; Sindou et al. 2001; Spaic et al. 1999, 2002; Rath et al. 1997; Sampson et al. 1995; Bashold et al. 1990; Friedman & Nashold 1986) to support the use of the DREZ surgical procedure to reduce pain post SCI. It may be that some populations (segmental pain) are more likely to benefit from this procedure.

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Abbreviations

AISA	ASIA Impairment Scale
BCM	Broad Compression Massage
BDI	Beck Depression Inventory
BPI	Brief Pain Inventory
BTX	Botulinum Toxin
CBT	Cognitive Behavioural Therapy
CDP	Central Dysesthetic Pain
CESD-SF	Center of Epidemiologic Studies Depression Scale-Short Form
CRT	Circuit Resistance Training
CSQ	Coping Strategies Questionnaire
DAAC	Duration-adjusted average change
DREZ	Dorsal Root Entry Zone
EEG	Electroencephalography
EMG	Electromyography
FIM	Functional Independence Measure
GABA	Gamma-Aminobutyric Acid
GAD	Gabapentin Amitripyline Diphenhydramime
HADS	Hospital Anxiety and Depression Scale
ISCIP	International Spinal Cord Injury Pain
ITB	Intrathecal Baclofen
LCT	Light Contact Touch
MMPI	Minnesota Multiphasic Personality Inventory
MPI	Multidimensional Pain Inventory
MPQ	McGill Pain Questionnaire
NMDA	N-methyl D Aspartate
NRS	Numeric Rating Scale
NSAIDS	Non-steroidal Anti-inflammatory Drugs
PAD	Zung Pain and Distress
PC	Performance Corrected
PGIC	Patient Global Impression of Change
PM	Pain Medications
PMP	Pain Management Program
PQOL	Perceived Quality of Life
PSS	Perceived Stress Scale
QI	Energy Flow
QOL	Quality of Life
ROM	Range of Motion
RPE	Rating of Perceived Exertion
SCI	Spinal Cord Injury
SF-36	Short Form-36
SF-MPQ	Short Form- McGill Pain Questionnaire
SHCS	Stanford Hypnotic Clinical Scale
SPI	Sternbach Pain Intensity
SRQ	Shoulder Rating Questionnaire
STAI	State Trait Anxiety Inventory
TCA	Tricyclic Antidepressants
TCES	Transcranial Electrical Stimulation
tDCS	Transcranial Direct Current Stimulation
TENS	Transcutaneous Electrical Nerve Stimulation

THC	delta-9-tetra hydrocannabinol
TMS	Transcranial Magnetic Stimulation
VAS	Visual Analogue Scale
VNS	Verbal Numeric Scale
WHYMPI	West Haven Yale Multidimensional Pain Inventory
WUFA	Wheelchair Users Functional Assessment
WUSPI	Wheelchair Users Shoulder Pain Index