Research Article

Treatments perceived to be helpful for neuropathic pain after traumatic spinal cord injury: A multicenter cross-sectional survey study

Thomas N. Bryce[1], Chung-Ying Tsai[1], Andrew D. Delgado[1], Sara J. Mulroy[2], Abigail Welch[3], Diana D. Cardenas[5], Heather B. Taylor[4], Elizabeth R. Felix[5]

[1]Department of Rehabilitation and Human Performance, Icahn School of Medicine at Mount Sinai, New York, New York, USA, [2]Pathokinesiology Laboratory, Rancho Los Amigo National Rehabilitation Center, Downey, California, USA, [3]Craig Hospital, Englewood, Colorado, USA, [4]Department of Physical Medicine & Rehabilitation, The University of Texas Health Science Center at Houston, Houston, Texas, USA, [5]Department of Physical Medicine and Rehabilitation, University of Miami, Miami, Florida, USA

Design: Cross-sectional survey.
Objective: To evaluate the perceived helpfulness of pharmacological and non-pharmacological interventions and their combinations for neuropathic pain (NeuP) and subcategories of NeuP after spinal cord injury (SCI).
Setting: Six Spinal Cord Injury Model System Centers.
Methods: Three hundred ninety one individuals at least one year post traumatic SCI were enrolled. A telephone survey was conducted to determine the pharmacologic and non-pharmacologic treatments used in the last 12 months for each participant's three worst pains, whether these treatments were "helpful", and if currently used, each treatments' effectiveness.
Results: Two hundred twenty participants (56%) reported 354 distinct NeuPs. Pharmacological treatments rated helpful for NeuP were non-tramadol opioids (opioids were helpful for 86% of opioid treated NeuPs), cannabinoids (83%), and anti-epileptics (79%). Non-pharmacological treatments rated helpful for NeuP were massage (76%), body position adjustment (74%), and relaxation therapy (70%). Those who used both opioids and exercise reported greater NeuP treatment helpfulness compared to participants using opioids without exercise ($P = 0.03$).
Conclusions: Opioids, cannabinoids, and massage were reported more commonly as helpful than treatments recommended as first-line therapies by current clinical practice guidelines (CPGs) for NeuP after SCI (antiepileptics and antidepressants). Individuals with SCI likely value the modulating effects of pharmacological and non-pharmacological treatments on the affective components of pain in addition to the sensory components of pain when appraising treatment helpfulness.

Keywords: Neuropathic pain, Spinal cord injury, Pharmacological treatment, Non-pharmacological treatment, Opioids

Introduction

Neuropathic pain (NeuP) is common after spinal cord injury (SCI) with approximately one-half of individuals reporting ongoing pain of this type.[1–4] Of those with ongoing pain, over half feel the pain impacts their quality of life and interferes with their activities of daily living, including work.[5]

According to the International Spinal Cord Injury Pain Classification, NeuP can be divided into three subtypes: at-level SCI pain, below-level SCI pain, and other NeuP; the latter being NeuP not directly related to the SCI (*e.g.* pain from a peripheral neuropathy).[6] At- and

Correspondence to: Thomas N. Bryce. Email: thomas.bryce@mountsinai.org

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/yscm.

DOI 10.1080/10790268.2022.2108665

below-level NeuP are thought to be distinct entities each with a different pathophysiology manifesting with a different evolving time course and different characteristics.[2,6] At-level SCI pain is perceived at or within the three dermatomes below the neurological level of injury (NLI) but not greater than three dermatomes below. This type of pain is reported by approximately one-third of individuals and has a relatively consistent prevalence at all time points post injury.[1–4] This is in contrast to below-level SCI pain which is perceived to be in a region more than three dermatomes below the NLI. Below-level SCI pain is relatively uncommon soon after injury but increases in prevalence over the first year with approximately one-fourth of individuals with SCI reporting this type of ongoing pain by one year post injury.[1–4]

Ongoing reports of pain long after injury suggest that available treatments may not be effective for everyone. Unfortunately, despite the range of options, few treatments of NeuP have been evaluated in individuals with SCI using high quality randomized clinical trials. Predictably, treatments falling outside the recommendations made in clinical practice guidelines (CPGs) have little empirical evidence supporting them.[7–9] The 2016 SCI CanPain CPG[9] for instance recommends only ten different interventions for NeuP after SCI with varying levels of evidence and strengths of recommendation: four medications of unique classes (two gabapentinoids, one tricyclic antidepressant, and lamotrigine), two opioids, and four non-pharmacological interventions (transcutaneous direct current stimulation with and without visualization, transcutaneous electrical nerve stimulation [TENS], and the dorsal root entry zone [DREZ] procedure).

Administration of large-scale surveys gives a unique opportunity for individuals with SCI to self-report the treatments they have tried and whether they were helpful in managing pain. However, to date published survey results only refer to treatment of pain after SCI in general as the surveys were administered at a time when there was no accepted method of differentiating types of pain by major category (NeuP versus non-NeuP), nor an accepted standardized list of potential pain treatments. Cardenas and Widerström-Noga both conducted pain surveys in the early 2000s, finding in their respective studies that opioids, massage, and cannabis,[10] and physical therapy, opioids, and sedatives[11] provided the most relief. Another survey from the Netherlands detailed that acupuncture/magnetism, cannabis/alcohol, physiotherapy and exercise, and massage or relaxation were rated as the most effective pain treatments.[12] In a survey of exclusively non-pharmacological pain therapies, people with SCI reported massage and heat provided the best pain relief.[13] Comparing these studies, there were common findings. Regardless of which treatment was rated highest, anticonvulsants were consistently rated as less effective across surveys than other treatments. Despite this finding, gabapentinoids, prototypical anticonvulsants, were identified as the most widely used pharmacological treatments and, along with tricyclic antidepressants, are the first line treatments recommended by all the CPGs that address neuropathic pain.[7–9] This suggests a discrepancy between the treatments that are most frequently prescribed versus what individuals with SCI actually find to be effective.

The purpose of this investigation was to detail the types of treatments people with traumatic SCI use specifically for NeuP, to assess whether these treatments were perceived to be "helpful", and if currently used, to assess each treatments' helpfulness. "Helpful" was the term used in the survey as it was thought to be more lay friendly than the term "effective". This study built on the prior research by distinguishing between NeuP and non-NeuP and expanding the survey cohort to include individuals from across the US (representing six Spinal Cord Injury Model Systems [SCIMS]). Moreover, the survey assessed a more comprehensive range of pharmacological and non-pharmacological interventions than previous studies, developed by experts in the field with decades of collective experience in treatment of SCI-related NeuP.[14] The aims of the analyses presented here were to: (1) Identify the treatments that are perceived as helpful for NeuP by individuals with SCI; (2) Assess differences between at- and below-level NeuPs with regard to treatments that are perceived as helpful; and (3) Explore whether combinations of treatments could further enhance treatment helpfulness.

Methods

This was a cross-sectional survey study of a subset of participants in the SCIMS program.[15] Participants aged 18 years or older, at least one-year post SCI, and enrolled in the SCIMS (for detailed inclusion/exclusion criteria, please refer to the review of the SCIMS program[15]), were recruited from six SCIMS Centers between March 2017 and July 2019 to complete a survey about their pain and pain treatment. The local institutional review boards of each of the participating centers approved the survey and this project. If participants had pain during the last 7 days prior to interview, interviewers used the International Spinal Cord Injury Pain Basic Data Set (Version 2.0)[16] to assess

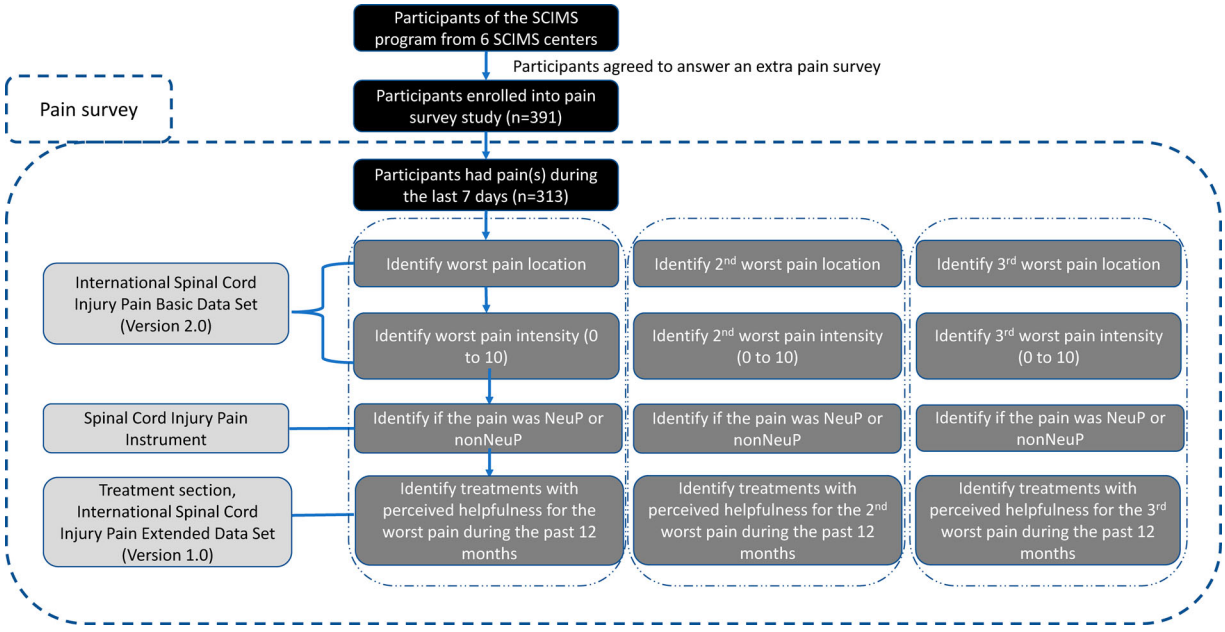

Figure 1 Flow chart of survey administration.

participants' pain locations (up to 3 worst pain sites) and intensity (0 – 'no pain' to 10 – 'pain as bad as you can imagine') over those last seven days (Figure 1). The Spinal Cord Injury Pain Instrument (SCIPI) was used to differentiate NeuP (SCIPI score ≥ 2) from non-NeuP.[17,18] Participants' NeuPs were categorized into at-level, below-level, and other NeuP subgroups based on their level of injury and their reported locations of pain (Figure 1).

Interviewers then queried the use and helpfulness over the prior 12 months of all treatments listed in the 'treatments' section of the International Spinal Cord Injury Pain Extended Data Set Version 1.0.[14] The treatment section of the survey included specific pharmacological and non-pharmacological interventions as well as an "other" section under each for unlisted treatments to be described. The pharmacological treatments listed in the survey were: antidepressants, antiepileptics, tramadol, non-tramadol opioids, cannabinoids, acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs)/aspirin, benzodiazepines, anti-spasticity drugs, topical anesthetics, and topical capsaicin. As tramadol is not a pure opioid and also impacts both the noradrenergic and serotoninergic systems, it was differentiated from other pure opioids. The non-pharmacological treatments listed in the survey were: physiotherapy (aerobic exercise, passive exercise, resistance exercise, position adjustment, joint mobilization/manipulation), passive and stimulation therapies (massage, acupressure, TENS, ultrasound, laser, heat therapy), relaxation and psychotherapy (biofeedback, relaxation, meditation), procedural interventions [trigger point injection, acupuncture, joint injections, intrathecal pumps, spinal cord stimulator, transcranial brain stimulation (transcranial direct current stimulation or repetitive transcranial magnetic stimulation), percutaneous peripheral nerve stimulation], and surgical interventions [DREZ lesioning, spinal surgery, and deep brain stimulation (implanted brain electrodes)]. For every treatment the participant reported as having used in the past 12 months, the participant was asked whether the treatment was helpful ('yes,' 'no,' or 'uncertain'). Separate ratings were collected for each pain condition identified by the participant for up to the three "worst" pains (Figure 1). In addition, for treatments that were currently being used, participants were asked to rate on a seven-point Likert scale the effect of the treatment on (a) pain and (b) global well-being (1 – 'very much improved', 2 – 'much improved', 3 – 'minimally improved', 4 – 'no change', 5 – 'minimally worse', 6 – 'much worse', and 7 – 'very much worse').

Statistical analysis

Treatments were rank ordered based on the percentage of individuals who received that treatment during the past 12 months and answered yes to the question "Was the treatment helpful for your pain?" Because a wide variety of treatments were listed in the survey, we only reported the treatments used by more than 20% of participants with NeuP(s) (commonly used

treatments) and more than 50% of these participants thought the treatments were helpful for their NeuP(s).

Wilcoxon signed-rank tests were used to compare the same participants' ratings of treatment effect on pain and global well-being (using a 7-point Likert scale) between two specific currently used treatments to see if one treatment had a better perceived effect than the other. Reported ratings of pain improvement were analyzed by Mann–Whitney U tests to compare the effects of a combination of pharmacological and non-pharmacological treatments with the use of a specific pharmacological treatment alone to explore if the combination of treatments enhanced reported helpfulness. Due to the multiple comparisons used in the analysis, the Benjamini-Hochberg Procedure (B-H Procedure) with a false discovery rate of 20% were used to control for Type I error inflation.[19,20] Statistical significance was identified based on the comparisons between original P-values that were less than 0.05 and the critical values generated from B-H Procedure. All statistical analyses were performed using SPSS 22.0 software (IBM Corporation, Armonk, New York, USA).

Table 1 Demographic and clinical characteristics of participants with NeuP.

Characteristics		N (percent) or mean (SD)
Participants with NeuP – N		220
NeuP sites – N		354
Mean age [years] (SD)		49.8 (13.0)
Mean time since injury [years] (SD)		18.2 (13.9)
Sex – N (%)		Male: 173 (79%) Female: 47 (21%)
Average pain intensity [0–10 numerical rating scale[a]] (SD)	Worst pain	7.1 (1.9)
	2nd worst pain	6.4 (2.3)
	3rd worst pain	5.9 (2.2)
Neurological level of injury – N (%)	Cervical	80 (36%)
	Thoracic	104 (47%)
	Lumbar and sacral	15 (7%)
	Missing	21 (10%)
ASIA impairment scale – N (%)	A	98 (45%)
	B	31 (14%)
	C	36 (16%)
	D	33 (15%)
	Missing	22 (10%)

[a]Average pain intensity was rated using integers from 0 to 10 (0 = "no pain"; 10 = "pain as bad as you can imagine").
Abbreviations: NeuP, neuropathic pain; ASIA, American Spinal Injury Association; N, number; SD, standard deviation.

Results

Participant demographics

Of the total 391 participants enrolled in the study, 220 (56%) participants reported having experienced at least one NeuP during the previous 7 days. A total of 652 differentiated pain problems were reported across all participants, with 354 (54%) of the pains being classified as NeuP (Table 1). Approximately 80% of the participants with NeuP were male, 54% had paraplegia, and 45% had a complete SCI (10% of participants were missing NLI and injury completeness data). The average pain intensity rating of NeuPs identified as participants' "worst pain" was 7.1 (±1.9), rated on a scale of 0–10.

Pain types

Among all the participants who reported NeuP, 119 reported experiencing one NeuP (30% of total participants), 68 reported two NeuPs (17%), and 33 reported three NeuPs (8%). Because 21 participants with 32 different NeuPs were missing NLI data, 322 different NeuPs were classified into the subtypes of at-level, below-level, and other NeuP (Table 2). Below-level SCI pain was the most common subtype of NeuP. More than half of the NeuPs (53%) were identified as the "worst pain" by participants (Table 2).

Pharmacological treatments

The most common pharmacological treatments (all used by at least 20% of participants) in descending order of the number of pain sites treated during the previous year were non-tramadol opioids (164 pain sites were treated with non-tramadol opioids), antiepileptics (141 pain sites), NSAIDs/aspirin (134 pain sites), cannabinoids (104 pain sites), anti-spasticity medications (92 pain sites), acetaminophen (92 pain sites),

Table 2 The number (%) of below-level, at-level, and other NeuP.

	Subtype of NeuP experienced			Subtype of NeuP that is experienced as the Worst pain		
	B-L	At-L	other	B-L	At-L	other
N (%)	158 (49%)	112 (35%)	52 (16%)	77 (24%)	63 (20%)	30 (9%)
Total N (%)	322 NeuPs were classified			170 (53%)		

Abbreviations: NeuP, neuropathic pain; N, number; B-L, Below-level; At-L, At-level.
Note: %, percentage of total NeuP that were classified (322).

Table 3 The number of pain sites for which specific interventions were thought to be helpful, the number of specific distinct pains treated with each of these interventions, and (the percent helpful) for each NeuP subtype.

	All NeuP	Below-level NeuP	At-level NeuP	Other NeuP
Pharmacologic treatments				
N of sites Non-Tramadol Opioids were helpful/N of sites treated with Non-Tramadol Opioids (%)	141/164 (86%)	54/66 (82%)	42/48 (88%)	28/31 (90%)
N of sites Cannabinoids were helpful/N of sites treated with Cannabinoids (%)	86/104 (83%)	32/39 (82%)	23/29 (79%)	12/16 (75%)
N of sites Antiepileptics were helpful/N of sites treated with Antiepileptics (%)	112/141 (79%)	46/59 (78%)	37/49 (76%)	14/15 (93%)
N of sites Tramadol was helpful/N of sites treated with Tramadol (%)	33/47 (70%)	17/22 (77%)	7/10 (70%)	5/7 (71%)
N of sites Acetaminophen was helpful/N of sites treated with Acetaminophen (%)	61/92 (66%)	25/39 (64%)	20/26 (77%)	11/16 (69%)
N of sites NSAIDs/Aspirin were/was helpful/N of sites treated with NSAIDs/Aspirin (%)	81/134 (60%)	26/51 (51%)	31/49 (63%)	18/24 (75%)
N of sites Antispastic medication was helpful/N of sites treated with Antispastic medication (%)	55/92 (60%)	27/50 (54%)	12/20 (60%)	11/17 (65%)
N of sites Antidepressants medication was helpful/N of sites treated with Antidepressants medication (%)	28/53 (53%)	16/28 (57%)	5/9 (56%)	7/8 (88%)
Non-pharmacologic treatments				
N of sites Massage was helpful/N of sites treated with Massage (%)	85/112 (76%)	35/45 (78%)	27/35 (77%)	11/18 (61%)
N of sites Body position adjustment was helpful/N of sites treated with Body position adjustment (%)	153/208 (74%)	62/87 (71%)	47/61 (77%)	26/39 (67%)
N of sites Relaxation therapy was helpful/N of sites treated with Relaxation therapy (%)	39/56 (70%)	17/24 (71%)	10/12 (83%)	8/10 (80%)
N of sites Heat therapy was helpful/N of sites treated with Heat therapy (%)	63/93 (68%)	21/36 (58%)	16/24 (67%)	13/17 (76%)
N of sites Passive exercise was helpful/N of sites treated with Passive exercise (%)	143/216 (66%)	53/83 (64%)	46/69 (67%)	28/40 (70%)
N of sites Aerobic exercise was helpful/N of sites treated with Aerobic exercise (%)	45/71 (63%)	19/30 (63%)	18/25 (72%)	3/8 (38%)
N of sites Resistance exercise was helpful/N of sites treated with Resistance exercise (%)	54/95 (57%)	23/42 (55%)	14/30 (47%)	11/16 (69%)

Abbreviations: N, number; NeuP, neuropathic pain; NSAIDs, non-steroidal anti-inflammatory drugs.

antidepressants (53 pain sites), and tramadol (47 pain sites) (Table 3). Of these pharmacological treatments, those perceived most helpful for NeuP listed in descending order of perceived helpfulness were non-tramadol (non-tramadol opioids were helpful for 86% of non-tramadol opioids treated NeuPs), cannabinoids (83%), antiepileptics (79%), tramadol (70%), and acetaminophen (66%) (Table 3).

Of these pharmacological treatments, those perceived most helpful for below-level and at-level NeuP, when evaluated separately, were the same as for overall combined NeuP (Table 3).

Non-pharmacological treatments

The most common non-pharmacological treatments in descending order of the number of pain sites treated during the previous year were passive exercise (216 pain sites were treated with passive exercise), body position adjustment (208 pain sites), massage (112 pain sites), resistance exercise (95 pain sites), heat therapy (93 pain sites), and aerobic exercise (71 pain sites) (Table 3). Of these non-pharmacological treatments, those perceived most helpful for NeuP overall listed in descending order of perceived helpfulness were massage (massage was helpful for 76% of massage treated NeuPs), body position adjustment (74%), relaxation therapy (70%), heat therapy (68%), and passive exercise (66%) (Table 3). Results varied slightly for the subtypes of at-level or below-level NeuP where aerobic exercise replaced heat therapy within the group of the top five non-pharmacological treatments perceived most helpful.

Combinations of pharmacological and non-pharmacological treatments

Analyses included an exploration of whether the combinations of two of the three most helpful pharmacological treatments (opioids, cannabinoids, or antiepileptics) together or the combination of one of these pharmacological treatments with one of the three most helpful non-pharmacological treatments (massage, exercise, or relaxation) is more helpful than using a single

Table 4 Helpfulness rating of pharmacologic interventions (non-tramadol opioids, antiepileptics, or cannabinoids) in combination with massage, relaxation therapy, active exercise, or with each other for NeuP and global well-being.

Intervention(s)	N	Mean helpfulness rating for pain (SD)[a]	P value (Effect size, r)	Mean helpfulness rating for global wellbeing (SD)[a]	P value (Effect size, r)
Non-Tramadol Opioids (with concurrent Massage)	21	2.0 (1.0)	0.33 (0.11)	2.6 (1.4)	0.84 (0.02)
Non-Tramadol Opioids (without concurrent Massage)	57	2.2 (0.8)		2.6 (1.0)	
Non-Tramadol Opioids (with concurrent Exercise)	23	1.8 (0.7)	0.03[b] (0.24)	2.5 (1.3)	0.6 (0.06)
Non-Tramadol Opioids (without concurrent Exercise)	55	2.3 (0.9)		2.6 (1.1)	
Non-Tramadol Opioids (with concurrent Relaxation)	9	1.9 (0.8)	0.33 (0.11)	2.9 (1.5)	0.54 (0.07)
Non-Tramadol Opioids (without concurrent Relaxation)	69	2.2 (0.9)		2.5 (1.1)	
Non-Tramadol Opioids (with concurrent Cannabinoids)	20	2.3 (1.0)	0.58 (0.06)	2.5 (1.1)	0.74 (0.04)
Non-Tramadol Opioids (without concurrent Cannabinoids)	55	2.2 (0.8)		2.7 (1.2)	
Non-Tramadol Opioids (with concurrent Antiepileptics)	39	2.1 (0.9)	0.37 (0.10)	2.7 (1.2)	0.43 (0.09)
Non-Tramadol Opioids (without concurrent Antiepileptics)	38	2.3 (0.9)		2.5 (1.1)	
Antiepileptics (with concurrent Massage)	24	2.5 (0.9)	0.98 (0.00)	3.29 (1.08)	0.02[b] (0.26)
Antiepileptics (without concurrent Massage)	60	2.5 (0.9)		2.65 (0.99)	
Antiepileptics (with concurrent Exercise)	31	2.6 (0.8)	0.53 (0.07)	2.9 (1.1)	0.74 (0.04)
Antiepileptics (without concurrent Exercise)	53	2.5 (1.0)		2.8 (1.0)	
Antiepileptics (with concurrent Relaxation)	10	2.8 (0.8)	0.41 (0.09)	3.1 (1.5)	0.94 (0.01)
Antiepileptics (without concurrent Relaxation)	74	2.5 (0.9)		2.8 (1.0)	
Antiepileptics (with concurrent Non-Tramadol Opioids)	39	2.7 (0.9)	0.08 (0.20)	3.1 (1.1)	0.06 (0.21)
Antiepileptics (without concurrent Non-Tramadol Opioids)	39	2.4 (1.0)		2.6 (1.0)	
Cannabinoids (with concurrent Massage)	19	2.37 (0.90)	0.26 (0.16)	1.84 (0.90)	0.23 (0.17)
Cannabinoids (without concurrent Massage)	33	2.06 (0.86)		2.21 (1.05)	
Cannabinoids (with concurrent Exercise)	19	2.0 (0.9)	0.27 (0.15)	1.7 (0.7)	0.1 (0.23)
Cannabinoids (without concurrent Exercise)	33	2.3 (0.8)		2.3 (1.1)	
Cannabinoids (with concurrent Relaxation)	11	2.2 (0.6)	0.92 (0.01)	2.4 (1.0)	0.27 (0.15)
Cannabinoids (without concurrent Relaxation)	41	2.2 (0.9)		2.0 (1.0)	
Cannabinoids (with concurrent Non-Tramadol Opioids)	20	2.3 (0.9)	0.62 (0.07)	2.1 (0.9)	0.97 (0.01)
Cannabinoids (without concurrent Non-Tramadol Opioids)	26	2.2 (0.9)		2.2 (1.1)	

Abbreviations: NeuP, neuropathic pain; N, number of participants; Exercise (resistance or aerobic exercise); Relaxation, relaxation therapy.
Note: Statistical method: Mann-Whitney U test.
[a]Effectiveness rating (1 – very much improved, 2 – much improved, 3 – minimally improved, 4 – no change, 5 – minimally worse, 6 – much worse, and 7 – very much worse).
[b]Statistically significant difference after the Benjamini-Hochberg Procedure.

pharmacological treatment alone (*e.g.* opioids + antiepileptics versus opioids alone or opioids + massage versus opioids alone). Mann–Whitney U tests were used to compare the groups (see Table 4). For people using antiepileptics or cannabinoids, there were no significant differences in the treatment helpfulness for

NeuP when taken alone as compared to being taken in combination with another of the two pharmacological or three non-pharmacological treatments (P ranges from 0.08 to 0.98, see Table 4). However, the rating of the helpfulness of pharmacological treatment on participants' NeuP was significantly greater in the group using non-tramadol opioids and exercise compared to the group using non-tramadol opioids without exercise (P = 0.03, significant result after the B-H procedure, Table 4).

Discussion

The purpose of this study was to detail the types of treatments people with traumatic SCI use specifically for NeuP, to assess whether these treatments were perceived to be "helpful", and if currently used, to assess each treatments' helpfulness. It was found, as has been shown previously for pain after SCI in general,[10,11] that non-tramadol opioids, cannabinoids, and massage seem to be helpful for a greater percentage of users than the CPG recommended antiepileptics and antidepressants specifically for NeuP.[7–9] The treatments that were most frequently reported as helpful for at-level and below-level NeuP(s) were the same for both subtypes. Furthermore, the degree of helpfulness of opioids for the treatment of pain seemed to be greater when they were combined with exercise rather than being used alone.

It is interesting to note that in this study that there were not major differences in the degree of helpfulness of various treatments for the different subtypes of pain. The reason for this is not clear, however one contributing factor may be common underlying mechanisms of the associated affective aspects of the pain experience of which many of these interventions treat indirectly.

In clinical trials, the primary and most commonly evaluated, accepted, and reported outcome is a reduction in pain intensity. As such, antiepileptics and antidepressants seem to be effective in some individuals in decreasing pain intensity.[7–9] However, this is not the sole determinant of effectiveness for pain in individuals with SCI when they are appraising the benefit of a treatment. The experience of pain is not just dependent on the intensity of the pain but also on its unpleasantness, its complex affective aspects, and its interference with sleep, mood, and activity. Other effects of drugs and non-pharmacological treatments, especially those thought to be most helpful by this study's population, would seem to make pain more tolerable by perhaps affecting these other aspects of pain (as opposed to just being less intense as may be assessed in a clinical trial). Therefore, there are treatments that respondents reported as being helpful in this survey that might be unexpected based only on treatment outcomes commonly reported in clinical trials (*e.g.* pain intensity). There is a gap in knowledge however about the effect of various treatments on other aspects of the pain interference that merits further study.

Similar results can be found in other studies, although caution needs to be taken in comparing the following referenced studies as the present study did not explore reasons for using cannabis other than for pain. In one study, therapeutic cannabinoid users reported that, after relieving pain, the most common reasons for use included relieving insomnia (43%) and stress (42%).[21] In another, relieving distress caused by pain (73%), improving sleep (63%), general relaxation (64%), improving mood (50%), intoxication (12%), and habit (18%) were the most common reasons for cannabis use after relieving pain (82%).[22] It has been demonstrated repeatedly that insomnia commonly is experienced by those with chronic pain and the relationship between lack of sleep and pain is thought to be bidirectional, with lack of sleep exacerbating pain and pain interrupting sleep.[23–25] Similarly, psychological stress is a known predictor of chronic pain while at the same time pain can worsen stress. It is not unreasonable that addressing these other factors with pharmacological and non-pharmacological interventions may impact pain as well.

Previous studies have indicated that massage can promote relaxation and positive psychological effects. A meta-analysis study, albeit including only one study of persons with SCI, showed that massage can positively affect anxiety and depression.[26] Several randomized controlled and crossover trials in different populations including persons with SCI also report that massage can significantly reduce fatigue and heart rate variability, improve sleep quality, and provide a sense of relaxation.[27] In this present study, massage was rated as one of the most helpful treatments potentially supporting the idea that relaxation and a reduction psychological stress can impact SCI related NeuP.

Limitations of this study are several. The assignment of broad pain type, NeuP and non-NeuP, was defined by the SCIPI, a measure which is not completely sensitive and specific.[17,18] In addition, the differentiation of at-level and below-level NeuP subtypes is also not completely specific as subtype assignment was dependent upon combining the location of pain on the body and the NLI from an International Standards for the Neurological Classification of SCI examination,[28] which was performed several years earlier for a large

number of participants in this study. Individuals may not have accurately recalled some treatments received or have been biased toward underreporting treatments that were not helpful. In addition, as data about treatments was limited to those treatments used during the previous year, there is missing information on treatments tried and discontinued previous to the preceding year of interview. A participant trying a particular intervention and finding it of no value or very helpful two years prior to the study would not have that information counted. Conversely, if they had been treated in the past with a specific treatment and that pain was no longer present at the time of interview, the treatment helpfulness and effectiveness of that particular intervention would not be captured. This creates a selection bias which likely influences the reported helpfulness and effectiveness of all treatments at least to some degree. Individuals also might have been reluctant to accurately report their cannabinoid use depending on the legality of its use where they live. Similarly, reports of opioid use may have been under-reported given the current stigma of this intervention.[29] As most participants used more than one treatment for their NeuP, the combination of different treatments may have interaction effects which could influence the results of statistical analyses. Therefore, in this current study we primarily used descriptive statistics to indicate the subjective survey results. Finally, as individuals may have had more than one NeuP and each pain was rated separately with regard to an intervention being helpful, the number of times a particular treatment is thought to be helpful may have been overcounted. It should also be noted that the proportion of those with paraplegia and complete SCI in this study were higher than the aggregate proportion of individuals in the SCIMS database with paraplegia (41%) and complete SCI (32%) and therefore this sample is not necessarily representative of all people with SCI.[30]

Conclusion

The results of this study support the concept that using interventions based solely on their ability to reduce ratings of pain intensity may not lead to patient-perceived successful treatment of pain after SCI. The pain experience, the definition of which recently has been updated by the International Association for the Study of Pain (IASP) to be "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" alludes to this by giving equal emphasis not only to the sensory but also to emotional components of pain.[31] In the absence of treatments which would seem to abolish NeuP completely, the practitioner needs to consider affective components such as depression, anxiety, and the interference of pain on sleep and daily activities. Although some complementary or non-pharmacological treatments such as massage or repositioning, heat, or passive exercise, may not have strong evidence for decreasing pain intensity, it should be acknowledged that this may be partly due to the difficulty of studying these interventions using a conventional randomized and blinded clinical trial. These interventions likely do provide relief for some individuals in terms of addressing the other aspects of the pain experience and help to ameliorate pain after SCI. Future studies should address the recurring differences between what types of pain treatments patients, clinicians, and researchers perceive as helpful. It also should be noted that even though opioids and cannabinoids are thought by users to be helpful interventions, there are very significant risks of opioid and cannabinoid use which must be considered before they are recommended for management of chronic NeuP.[32]

List of abbreviations

B-H	Benjamini-Hochberg
CPG	clinical practice guideline
DREZ	dorsal root entry zone
NeuP	neuropathic pain
NLI	neurological level of injury
non-NeuP	non-neuropathic pain
NSAIDs	non-steroidal anti-inflammatory drugs
SCI	spinal cord injury
SCIMS	SCI Model Systems
SCIPI	spinal cord injury pain instrument
TENS	transcutaneous electrical nerve stimulation

Acknowledgements

Susie Charlifue, PhD, Jeff Berliner, DO, and Lisa Spielman, PhD critically reviewed the manuscript and Laiba Afzal helped with the data analysis.

Disclaimer statements

Contributors TNB was responsible for designing the work that led to the submission, interpreting results, and drafting and revising the manuscript. CYT was responsible for designing the work that led to the submission, acquiring and analyzing the data, interpreting results, and drafting and revising the manuscript. ADD was responsible for designing the work that led to the submission, screening/recruiting eligible participants,

and acquiring and analyzing the data. AW, SJM, and HT were responsible for designing the work that led to the submission, interpreting results, and revising the manuscript. DC and ERF were responsible for designing the work that led to the submission, coordinating data collection and quality control across participating centers interpreting the results, and revising the manuscript.

Funding The contents of this manuscript were developed under grants from the National Institute on Disability, Independent Living, and Rehabilitation Research [NIDILRR grant numbers 90SI5017, 90SI5027, 90SI5023, 90SI5018, 90SI5015, 90SI5019, 90DP0083]. NIDILRR is a Institute within the Administration for Community Living (ACL), Department of Health and Human Services (HHS). The contents of this manuscript do not necessarily represent the policy of NIDILRR, ACL, HHS, and you should not assume endorsement by the Federal Government.

Conflicts of interest Thomas N. Bryce, Chung-Ying Tsai, Andrew D. Delgado, Sara J. Mulroy, Abigail Welch, Diana D. Cardenas, Heather B. Taylor, and Elizabeth R. Felix, declare no proprietary, financial, professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of, the manuscript entitled, "Treatments perceived to be helpful for neuropathic pain after traumatic spinal cord injury: A multicenter cross-sectional survey study".

Data archiving The data generated and analyzed during the current study are available through the Spinal Cord Injury Model Systems upon request.

Statement of ethics Institutional Review Board approval (HSM# 11-01603) was obtained prior to conducting any study related procedures, and informed consent was obtained from each participant. We certify that all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

References

1 Finnerup NB, Jensen MP, Norrbrink C, Trok K, Johannesen IL, Jensen TS, *et al*. A prospective study of pain and psychological functioning following traumatic spinal cord injury. Spinal Cord 2016;**54**:816–821.
2 Finnerup NB, Norrbrink C, Trok K, Piehl F, Johannesen IL, Sorensen JC, *et al*. Phenotypes and predictors of pain following traumatic spinal cord injury: a prospective study. J Pain Off J Am Pain Soc 2014;**15**:40–48.
3 Siddall PJ, McClelland JM, Rutkowski SB, Cousins MJ. A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury. Pain 2003;**103**:249–257.
4 Warner FM, Cragg JJ, Jutzeler CR, Finnerup NB, Werhagen L, Weidner N, *et al*. Progression of neuropathic pain after acute spinal cord injury: a meta-analysis and framework for clinical trials. J Neurotrauma 2019;**36**:1461–1468.
5 Cardenas DD, Bryce TN, Shem K, Richards JS, Elhefni H. Gender and minority differences in the pain experience of people with spinal cord injury. Arch Phys Med Rehabil 2004;**85**:1774–1781.
6 Bryce TN, Biering-Sørensen F, Finnerup NB, Cardenas DD, Defrin R, Lundeberg T, *et al*. International spinal cord injury pain classification: part I. Background and description. March 6–7, 2009. Spinal Cord 2012;**50**:413–417.
7 Attal N, Cruccu G, Baron R, Haanpää M, Hansson P, Jensen TS, *et al*. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol 2010;**17**:1113–1e88.
8 Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, *et al*. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. The Lancet 2015;**14**:162–173.
9 Guy SD, Mehta S, Casalino A, Côté I, Kras-Dupuis A, Moulin DE, *et al*. The CanPain SCI clinical practice guidelines for rehabilitation management of neuropathic pain after spinal cord: recommendations for treatment. Spinal Cord 2016;54(Suppl. 1): S14–S23.
10 Cardenas DD, Jensen MP. Treatments for chronic pain in persons with spinal cord injury: a survey study. J Spinal Cord Med 2006;**29**:109–117.
11 Widerström-Noga EG, Turk DC. Types and effectiveness of treatments used by people with chronic pain associated with spinal cord injuries: influence of pain and psychosocial characteristics. Spinal Cord 2003;**41**:600–609.
12 Heutink M, Post MW, Wollaars MM, van Asbeck FW. Chronic spinal cord injury pain: pharmacological and non-pharmacological treatments and treatment effectiveness. Disabil Rehabil 2011;**33**:433–440.
13 Norrbrink Budh C, Lundeberg T. Non-pharmacological pain-relieving therapies in individuals with spinal cord injury: a patient perspective. Complement Ther Med 2004;**12**:189–197.
14 Widerström-Noga E, Biering-Sørensen F, Bryce TN, Cardenas DD, Finnerup NB, Jensen MP, *et al*. The international spinal cord injury pain extended data Set (version 1.0). Spinal Cord 2016;**54**:1036–1046.
15 Chen Y, DeVivo MJ, Richards JS, SanAgustin TB. Spinal cord injury model systems: review of program and national database from 1970 to 2015. Arch Phys Med Rehabil 2016;**97**: 1797–1804.
16 Widerstrom-Noga E, Biering-Sorensen F, Bryce TN, Cardenas DD, Finnerup NB, Jensen MP, *et al*. The international spinal cord injury pain basic data set (version 2.0). Spinal Cord 2014;**52**:282–286.
17 Bryce TN, Richards JS, Bombardier CH, Dijkers MP, Fann JR, Brooks L, *et al*. Screening for neuropathic pain after spinal cord injury with the spinal cord injury pain instrument (SCIPI): a preliminary validation study. Spinal Cord 2014;**52**:407–412.
18 Franz S, Schuld C, Wilder-Smith EP, Heutehaus L, Lang S, Gantz S, *et al*. Spinal cord injury pain instrument and painDETECT questionnaire: convergent construct validity in individuals with spinal cord injury. Eur J Pain Lond Engl 2017;**21**:1642–1656.
19 Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Ser B Methodol 1995;**57**:289–300.
20 McDonald J. Handbook of biological statistics. Baltimore: Sparky House Publishing; 2014.
21 Lake S, Walsh Z, Kerr T, Cooper ZD, Buxton J, Wood E, *et al*. Frequency of cannabis and illicit opioid use among people who use drugs and report chronic pain: a longitudinal analysis. PLoS Med 2019;**16**; doi:10.1371/journal.pmed.1002967.
22 Campbell G, Hall WD, Peacock A, Lintzeris N, Bruno R, Larance B, *et al*. Cannabis use, pain and prescription opioid use in people living with chronic non-cancer pain: findings from a four-year prospective cohort. Lancet Public Health 2018;**3**:e341–e350.
23 Hah JM, Sturgeon JA, Zocca J, Sharifzadeh Y, Mackey SC. Factors associated with prescription opioid misuse in a cross-

sectional cohort of patients with chronic non-cancer pain. J Pain Res 2017;**10**:979–987.
24 Kundermann B, Krieg J-C, Schreiber W, Lautenbacher S. The effect of sleep deprivation on pain. Pain Res Manag 2004;**9**:25–32.
25 Smith MT, Haythornthwaite JA. How do sleep disturbance and chronic pain inter-relate? Insights from the longitudinal and cognitive-behavioral clinical trials literature. Sleep Med Rev 2004;**8**: 119–132.
26 Moyer CA, Rounds J, Hannum JW. A meta-analysis of massage therapy research. Psychol Bull 2004;**130**:3–18.
27 Lovas J, Tran Y, Middleton J, Bartrop R, Moore N, Craig A. Managing pain and fatigue in people with spinal cord injury: a randomized controlled trial feasibility study examining the efficacy of massage therapy. Spinal Cord 2017;**55**: 162–166.
28 Kirshblum SC, Burns SP, Biering-Sorensen F, Donovan W, Graves DE, Jha A, *et al*. International standards for neurological classification of spinal cord injury (revised 2011). J Spinal Cord Med 2011;**34**:535–546.
29 Nichols VP, Toye F, Eldabe S, Sandhu HK, Underwood M, Seers K. Experiences of people taking opioid medication for chronic non-malignant pain: a qualitative evidence synthesis using meta-ethnography. BMJ Open 2020;**10**:e032988.
30 Spinal Cord Injury Facts and Figures at a Glance 2018 SCI Data Sheet. University of Alabama at Birmingham National Spinal Cord Injury Statistical Center website. https://www.nscisc.uab.edu/Public/Facts%20and%20Figures%20-%202018.pdf. Accessed January 6, 2019.
31 Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, *et al*. The revised international association for the study of pain definition of pain: concepts, challenges, and compromises. Pain 2020. doi:10.1097/j.pain.0000000000001939
32 Bryce TN. Opioids should not be prescribed for chronic pain after spinal cord injury. Spinal Cord Ser Cases 2018;**4**:66.