Neuropathic pain after spinal ord injury: A systematic review and meta-analysis

Burke D, Fullen BM, Stokes D, Lennon O

Abstract

Background and Objective: Following spinal cord injury (SCI) chronic pain is a common secondary complication, with neuropathic pain (NP) cited as one of the most distressing and debilitating conditions leading to poor quality of life, depression and sleep disturbances. Neuropathic pain presenting at or below the level of injury, is largely refractory to current pharmacological and physical treatments. No consensus on the prevalence of NP post SCI currently exists, hence this systematic review was undertaken.

Databases: The review comprised three phases: a methodological assessment of databases (Pubmed, EMBASE, Web of Knowledge, CINAHL, Cochrane Library and PEDro) identifying potential papers and screening for inclusion criteria by two independent reviewers; data extraction; and finally rating of internal validity and strength of the evidence, using a published valid and reliable scale. Meta-analysis estimated pooled point prevalence rates using a random effects model.

Results: In total 17 studies involving 2,529 patients were included in the review. Overall point prevalence rates for NP were established at 53% (38.58-67.47); 19% (13.26-26.39) for at-level NP and 27% (19.89-34.61) for below-level NP, with high heterogeneity noted (I^2 =84-93%).

Conclusions: Prevalence rates for NP following SCI are high. Future studies should include established definitions, classifications systems and assessment tools for NP at defined time points post SCI to follow the trajectory of this problem across the lifespan and include indices of sleep, mood and interference to allow for appropriate, optimal and timely NP management for each patient.

Introduction

Chronic pain is a common secondary complications post spinal cord injury (SCI), with estimated prevalence of 61% reported (1). Pain can have an all-encompassing, detrimental effect, resulting in reduced quality of life (2, 3), depression (4, 5) and sleep disturbances (6). Neuropathic pain (NP) presents at or below the level of injury (7) and is cited as the most 'severe pain' post SCI (8). It is largely refractory to current treatment approaches dominated by pharmacotherapy, of which pregabalin has shown the most effectiveness from randomised controlled trials (9, 10). Patients frequently experiment with non-pharmacological treatments (11) yet to date there is a significant lack of research for behavioural and physical approaches for SCI NP (12).

Following SCI NP is associated with a significant increase in utilisation of health care resources. Visits to physicians, emergency departments, required surgical procedures and prescription utilisation when compared to individuals with SCIs who do not have NP incur an incremental cost implication of $17,369 per annum (13). A lack of clarity exists in the literature regarding the profile of NP post SCI. Two published systematic reviews previously reported the prevalence of general chronic pain post injury (1, 14). One review included traumatic SCIs only (14) and the second one excluded studies reporting NP (1). A published review of determinants and chronicity of NP post SCI reported NP prevalence at 40% (15). Limitations of that review included that NP did not require a definition or classification and it failed to employ statistical meta-analysis.

To date, the presentation of NP in relation to SCI or demographic characteristics remain undefined. Some studies report that NP is more prevalent in paraplegia (16, 17), incomplete lesions and traumatic SCIs (16-18), in females (19) and in older patients (20, 21), but others report contradictory findings (15, 22-24). To date, no review has proposed meta-analysis of NP prevalence in the SCI sub-populations, an area where conflict in the literature exists. Furthermore reports indicate that NP either intensifies (25) or remains at stable levels post injury (15, 26-28).

This study aims to systematically review the literature addressing NP from studies which include an adequate definition and assessment of NP post SCI. Where possible meta-analysis will be undertaken to estimate pooled point prevalence rates of NP in the total population, in sub-groups of the population defined by SCI and demographic characteristics and at specific time points post injury.

Methods

Study Selection

As no established guideline for systematic reviews of prevalence studies exists, the conduct and reporting of this review was informed by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (29) where applicable.

Phase 1 Database Search

Guided by a medical liaison librarian, an inclusive search strategy was developed to identify studies reporting the prevalence of NP following SCI. Medical Subject Headings (MESH) or Controlled Vocabulary, appropriate to each database, in addition to free text were employed. Limits of human studies and English language were applied where databases allowed.

Two search strings included a variety of terms used to describe SCI and NP, the singular and plural of each and American and English spelling versions combined using the Boolean operator OR. Each search string (SCI and NP) was combined with the Boolean operator AND. No restrictions in study designs were applied in the initial search. Six electronic databases were searched from inception up to March 31st 2015: PubMed, Embase, Web of Knowledge, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, and Physiotherapy Evidence Database (PEDro). To identify additional studies, references from reviews and included articles were cross-checked.

Inclusion and Exclusion Criteria

Studies comprising individuals ≥ 18 years of age with traumatic or non-traumatic SCI where NP prevalence was reported were included. To ensure accuracy in NP reports within studies, each study was required to provide evidence of either i) a definition of NP (an IASP definition or a definition that closely mapped to same) or ii) reference to a classification system for NP after SCI (the International Spinal Cord Injury Pain (ISCIP) consensus on classification of pain after SCI (7) or a classification system that closely mapped to same and included a number of ISCIP descriptors such as: 'hot-burning', 'tingling', 'pricking', 'pins and needles', 'sharp', 'shooting', 'squeezing', 'painful cold' and 'electric shock-like'). Studies were analysed for inclusion by the two independent reviewers (D.B., O.L.) based on the criteria outlined. Where disagreement arose regarding the definition or classification of NP cited, studies were discussed with a third party (B.M.F.) and a resolution was reached.

Exclusion criteria included studies where all subjects were selected on the basis of reported pain, intervention studies where the recruited sample was not representative of the SCI population as a whole, review articles (after references were cross-checked) and conference abstracts.

Phase 2 Data Extraction

Results from all search engines were imported to EndNote desktop (version 7.2) and duplicates were removed. Results were screened by title by one reviewer (D.B) and after irrelevant studies were excluded, studies were independently screened by abstract by two reviewers (D.B., O.L.) and reasons for exclusion of studies were recorded. Remaining citations (n=69) were obtained in full-text format and again were independently double-reviewed against inclusion criteria (D.B., O.L.). Reasons for exclusion of studies were again documented. Where disagreement arose, studies were discussed with a third party (B.M.F.) and a resolution was reached (n=11).

Information from included studies was summarised in tabular format under the following headings; study design, sample size, response rate, sample selection methodology, inclusion criteria, study population characteristics, time points from SCI to assessments, definition of NP employed, assessment tool used to identify NP, recall periods for NP report, NP prevalence including at and below-level NP and overall NP and descriptions of non-responders.

Phase 3 Quality Assessment

The quality of studies was assessed independently by two reviewers (D.B., O.L.) based on established criteria recommended by Leboef-Yde and Lauritsen (30) and Walker (31). The original recommendations were created for low back pain prevalence studies and altered specifically for SCI (1). Each study was scored from a maximum 18 points. Fulfilment of 75% of criteria is indicative of a good quality study (30, 31). Any discrepancy in scoring was discussed with a third party (B.M.F.) and consensus reached.

Meta-analysis

Proposed meta-analysis included pooled point prevalence of NP, including at and below-level NP and at defined time points post SCI using R software (version 3.1.3) (32).

Proposed sub-analysis, where data permitted, included pooled point prevalence of NP in tetraplegia versus paraplegia, complete versus incomplete SCI, traumatic versus non-traumatic SCIs, in males versus females, in older versus younger patients and at different timelines post injury. Acute, subacute and intermediate phase of SCI were collapsed into one variable and defined as acute SCI, this included any study providing data up to six months post SCI, remaining studies which recorded NP at greater than six months post SCI were defined as chronic SCI (33). A random effects model was proposed for sub-analysis due to the expected heterogeneity across studies (34). Where data were presented on the same population at different time points in two or more manuscripts, to

avoid duplication of data, the largest group available was taken for inclusion in overall analysis. Where group sizes were unchanged across assessments, the most recent assessment was used in overall analysis. The number of cases of NP and total sample size were entered for individual studies and pooled point prevalence was calculated and displayed in forest plots.

Results

From an initial total of 3,075 studies, 17 studies were included in the review; 8 prospective studies (8, 22, 35-40), six cross-sectional studies (19, 41-45), and three retrospective studies (24, 46, 47). A PRISMA flow diagram (29) of the selection process is summarised in Figure 2.

Characteristics of studies

The characteristics of included studies is summarised in Table 2.1. A total of 2,529 individuals with SCIs were analysed, with study sizes ranging from 24 to 456 participants. Between 44% (39) and 92% (37) of respondents were male. Overall participants age ranged from 31 (42) to 56 years (47). Ten studies (8, 22, 24, 36, 38, 39, 42, 43, 45, 47) included only patients with traumatic SCIs. One study focussed solely on non-traumatic SCIs (46). The remaining six studies included both, with traumatic SCIs frequency ranging from 64% (44) to 84% (41).

Ten studies were conducted in European countries (19, 22, 24, 35, 36, 42, 44-47), four in Australia (8, 37, 38, 40, 41) and the remainder were based in the United States (43), Israel (40) and China (39). Response rates, defined in studies as the number of subjects who participated from those invited, and in surveys as those who responded from those who were contacted, were 90% or higher in 7 studies (19, 36-38, 40, 43, 45), above 70% in four studies (8, 39, 41, 47), below 70% in three studies

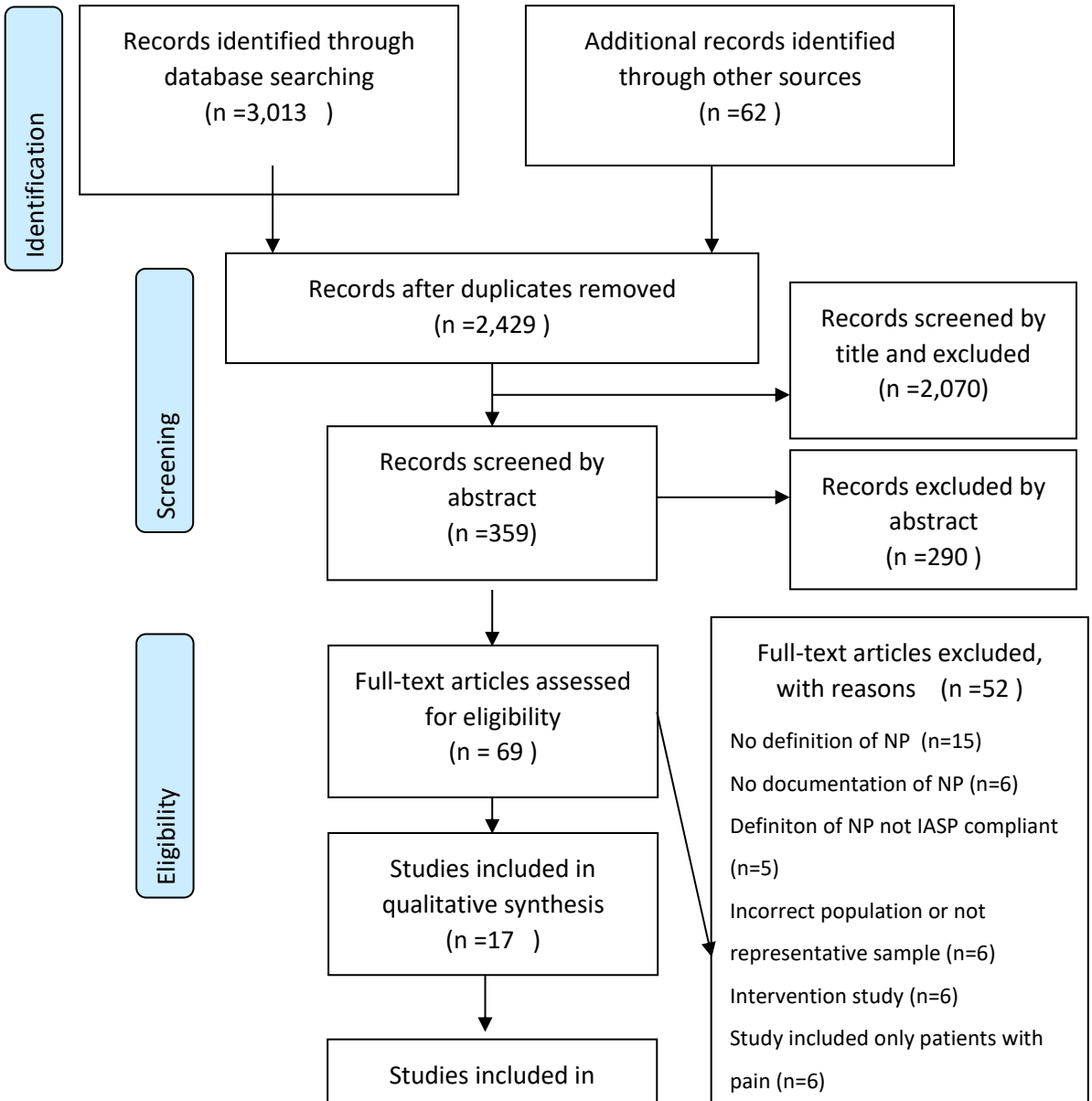
(22, 35, 44), not disclosed in one study (42), and not applicable in two retrospective studies (24, 46). Only two studies (22, 39) used validated NP screening tools for assessment.

Data from three manuscripts (8, 19, 45) were excluded from meta-analysis as the patient cohort was reported in other papers (24, 38) included in the current review. In one study (47), data from two different countries were reported. Here, only the Swedish cohort was excluded due to overlap with another study (24). Authors from five studies (22, 36, 37, 42, 48), where data were displayed in figures and bar-charts, were contacted for exact numeric data. Four authors responded (22, 36, 37, 42) and provided study results, the fifth was excluded when no response to correspondence was received (48).

Quality Assessment

Quality assessment of each included study is summarised in (Table 3). The overall mean quality score achieved 14.5 ± 2.7 was above the minimum threshold score of 13.5 for a good quality study classification (30, 31). Four studies (40, 42-44) were classified as poorer quality (<13.5). Where feasible, in the planned meta-analyses, these studies were removed in subsequent sensitivity analysis.

Figure 2. PRISMA Flow Diagram



Included

Table 1 Characteristics of Included Studies

Author, Country and Study Design	Study Designed to Record Pain	Sample Selection Method & Number	Sample size, Response rate	Inclusion/Exclusion	Age , Gender, Age at SCI, Cause of SCI	SCI Level/ AIS or ASIA &/or Completeness	Traumatic SCI %	Description of non-responders
Adriaansen (2013) Netherlands **Pro**	No	Recruited from 8 rehab centres through project focused on restoring WC mobility. N=139	SS: NR, pts at start n=224. RR: n=156 (1 yr) n=99 (2yr), n=146 (5yrs).	Incl: recent SCI, aged 18-65, AIS A-D, Dutch language, wheelchair dependent ≥ long distance.	Age: mean (SD): 1yr= 40 (14), 2yr= 41 (14), 5yr= 44 (13) Gender: (n + % male): 1yr n=112 (72%), 2yr n=74 (75%), 5yr n=106 (73%). Age at SCI: NR. Cause of SCI: NR	SCI Level (% Tetraplegia): 1yr 33%, 2yr 31%, 5yr 34%. AIS: NR Completeness (%complete): 1yr 53%, 2yr 54%, 5yr 58%.	1yr 77% 2yr 81% 5yr 78%	NR.
Aito (2007) Italy **Pro & Retro**	No	Pts admitted for acute care (1996-2006). N=82	SS: n=87 RR: n=5 excl.	Incl: traumatic central cord syndrome (TCCS). Excl: died before follow-up, missing data, unable to be Ax due to mental illness or orthopaedic impairment.	Age: mean 52 (range 16-82). Gender: male, n=72 (88%), female, n=10 (12%). Age at SCI mean (range) (y): Falls n=58 (27–82), RTA n=50 (19–71), Sports n=23 (16–44). Cause of SCI (%): RTA n=47 (57%), Falls n=30 (36%), Sport n=5 (7%).	SCI Level: NR AIS: Asia A Discharge (DC) n = 0 Follow-up (FU) n= 0. Asia B DC n= 0 FU n= 0. Asia C DC n= 11 (13 %) FU n=11 (14%). Asia D DC n=70 (86%) FU n= 62 (76%) Asia E DC n=1 (1%) FU n= 9 (11%).	100%	NR.
Barrett (2003) Australia **C/S**	Yes	Every pt. admitted to SCI unit over 6 months. N=88	SS: n=110 admitted, RR: excl. based on criteria n=8, declined n=2, DC before interview n=12.	Incl: > 6 months post SCI. Excl: communication difficulties, psychiatric disorder, consent refused, aged <18yrs, dementia, delirium, acute change in chronic SCI because of ongoing pathologic process, DC before interview.	Age ± SD (y): 48.4 ± 13. Gender: (male: female) 5.5:1. Age at SCI: NR. Cause of SCI: RTA n=20 (23%), Motorcycle Accident n=9 (9%), Diving/water sports n=21 (24%), Fall n=17 (19%), Non-traumatic n=14 (16%), Horse n=3 (3%) Other n=5 (6%).	SCI Level (%): Cervical 60% , Thoracic 32% , Lumbosacral 8%. Completeness: NR AIS: NR	84% (74/88)	No significant differencs between study group and excl. group.
Budh (2003) Sweden	Yes	Pts with SCI registered to Spinalis SCI Unit	SS: n=603 pts RR: n= 456	Nil pts excluded.	Age (mean): 47.04 yrs Age (range): 11-84 yrs.	SCI Level Cervical: n=200 (44%)	75% (340/456)	NA.

C/S		offered yearly health exam. N=456			Gender: female n=120(26%), male n=336(74%). Age at SCI: NR. Cause of SCI: NR.	Thoracic: n=161 (35%) Lumbar/Sacral: n=77 (17%), Unknown n=18 (4%). AIS: A n=144 (32%), B n=38 (8%), C 3 n=9 (9%), D n=185 (41%), E n=46 (10%), Unknown n=4 (1%).		
Celik (2013) Turkey **C/S**	Yes	Pts admitted for rehab to inpatient clinic. N=90	SS: NR RR: n=90	Incl: TSCI, attended inpatient rehab. Excl: atraumatic SCI and/or brain injury, pain prior to SCI.	Age (mean) yrs: 30.81 ±11.68. Age (range) yrs: 14-64. Gender: Male n=73 (81%), Female n=17 (19%). Age at SCI: NR. Cause of SCI: RTA n=30 (33%), Fall n=38 (42%), Gunshot n=14 (16%), Other n=8 (9%).	SCI Level: C1-4 n= 9 (10%), C5-8= 17 (19%), T1-5= 13 (14%), T6-12= 42 (47%), L 1-2= 4 (4%), Cauda Equina Syndrome n=5 (6%). Completeness: Complete n=52 (58%) Incomplete n=38 (42%). AIS: NR.	100%	NA.
Finnerup (2014) Denmark **Pro**	Yes	Pts admitted to neurosurgery in Denmark & Sweden. N=88	SS: n=163 RR: n=90 (n=1 died, n=1 moved).	Incl: TSCI, aged ≥18 yrs Excl: alcohol/substance abuse, psychiatric disease, brain damage, language problems, dementia.	Age (mean) ± SD yrs: 48.9 ± 15.9. Age (range) yrs: 18-77. Gender: male n=79 (88%), female n=11 (12%), Age at SCI: NR. Cause of SCI: Transport n=33 (37%), Fall n=42 (47%), Sports n=8 (9%), Other n=7 (8%).	SCI Level: Cervical 52 (58%), Thoracic 28 (31%), Lumbosacral 10 (11%). Completeness: NR. AIS: A n=38 (42%), B n=8 (9%), C n=20 (22%), D n=23 (26%), E n=1(1%).	100%	NR.
Frisbie (1990) America **C/S**	Yes	Pts assigned to SCI service for long term care. N=66	SS: n=73 in total RR: n=66 qualified for interview.	Incl: Pts with TSCI and memory of events <3 months post TSCI.	Age (median) yrs: 55. Age (range) yrs: 33-89. Gender: NR Age at SCI: NR Cause of SCI: NR	SCI Level: NR Completeness: NR AIS:NR	100%	NR.

Heutink (2011) Netherlands **C/S**	Yes	SCI pts treated in Rehab Centre (1990-2005) N=279	SS: n=575 RR: n=279 n=215 with chronic SCI pain incl in analysis.	Incl: SCI pts treated from1990-2005, aged ≥18 yrs, living in the community.	Age (mean ± SD): 51.3 ±14.0. Gender: male n=133 (62%), female n=81 (38%) NR n=1 (0%). Age at SCI: NR. Cause of SCI: NR.	SCI level: paraplegia n=127 (59%), tetraplegia n=80 (37%), NR n=8(4%). Completeness: Complete SCI n=92 (43%), Incomplete SCI n=120 (56%), NR n=3 (1%). AIS: NR.	64.2% (138/215)	NR
Levi (1995) Sweden **C/S**	No	Files checked from hospitals, organisations, private rehab facilities (1975-now) for pts with TSCI in the area of Stockholm SCI Centre. N=353	SS: n=400 RR: n=374 (n=21 excl.)	Incl: TSCI living in area of centre. Excl: Diagnosis other than TSCI.	Age (mean) ± SD: 42 ± 14 yrs. Age (range): 11-78 yrs. Age (median) 41 yrs. Gender: male n=286 (81%), female n=67 (18%). Cause of SCI: Transport n=161 (46%), Fall n=131 (37%), Other accident n=28 (8%) Sequelae of external causes of morbidity and mortality n=1 (0%), Self-harm n= 14 (4%), assault n=11 (3%), Unknown n=4 (1%), War= 3 (1%).	SCI level: Cervical n=147 (42%), Thoracic n=127 (36%), Lumbar n=52 (15%), Sacral n=5 (1%), No level n=22 (6 %). Completeness: Complete SCI: n=139 (39%), Incomplete SCI: n=210 (60%), No information: n=4 (1%). AIS: NR.	100%	NR.
New (1997) Australia **Pro**	Yes	All pts entering active rehab after acute SCI. N=24	SS:NR RR:24	Incl: pts entering rehab post-acute SCI. Excl: NR	Age (mean) yrs: 41.2 (range 15-76). Gender: male n=22 (92%), female n= 2 (8%). Age at injury: NR Cause of SCI: NR	SCI Level: Tetraplegia n=13 (54%), Cauda Equina Lesion n=8(34%). Completeness: Incomplete SCI: n=15 (63%), Complete SCI: n=9 (37%). AIS:NR	79% (19/24)	NR.
Siddall (1999) Australia **Pro**	Yes	Pts with acute TSCI admitted to Spinal Unit. N=100	SS: n=197 RR: n=94 excl, n=3 declined, All pts not available for each Ax	Incl: pts admitted to Unit < 3 months post TSCI. Excl: no deficit on DC, communication	Age (mean): 38 (SD±17) range 18-78. Gender: male n=83 (83%) female n=17 (17%). Age at injury: NR (acute population) Cause: Motor accident n=42 (42%), Fall n=24 (24%), Sports n=18 (18%), Bicycle	SCI Level: Cervical n=51 (51%), Thoracic n=25 (25%), Lumbar n=23 (23%), Sacral n=1 (1%). Completeness:	100%	No significant differences between pts in each Ax + pts with

			(2 wk n=70, 4 wk n=89, 8 wk n=85, 13 wk n=75, 26 wk n=58) n=2 pts died.	difficulty, > 3 months post SCI, atraumatic SCI, Brain injury, Aged <18 yrs, Psychiatric disorder, Ventilated, No consent, Lost to follow up, Deceased.	n=5 (5%), Crush injury n=6 (6%), Miscellaneous n=5 (5%).	Complete SCI n=36 (36%), Incomplete SCI: n=64 (64%). AIS: NR.		complete data.
Siddall (2003) **Australia** **Pro**	Yes	All pts incl in Siddall (1999) N=73	SS: n=100 RR: n=13 unable to contact, n=7 died, n=7 declined.	Incl: participants from Siddall (1999). Excl: NA	Age mean (range): 40 (21-81). Sex: male n=60 (82%) female n=13 (18%). Age at SCI: NR. Cause of SCI: NR.	SCI Level: Tetraplegia n=36 (49%). Completeness: Complete SCI n=28 (38%), Incomplete n=45 (62%). AIS: NR.	100%	No significant differences with previous study population.
Wen (2013) **China** **Pro**	Yes	Pts treated in Mianzhu Hospital for SCI caused by an earthquake. N=26	SS: n=26 RR: n=2 pts lost to follow up, n=1 pt died by Ax 3.	Incl: Traumatic SCI. Excl: None	Pts Ax in 2012: Age yrs mean (SD): 53.5 (16.7) Gender: female n= 13 (57%), male n=10 (44%). Age at SCI: NR. Cause of SCI: Earthquake.	SCI Level: Cervical n=3 (13%), Thoracic n=14 (61%), Lumbar n=5 (22%), Sacral n=1 (4%). Completeness of SCI: Incomplete SCI n=20 (77%), Complete n=6 (23%). AIS: A n=5 (22%), B n=2 (9%), C n=7 (30%), D n=4 (17%), E n=3 (13%).	100%	2 pts lost to follow up + one pt died.
Werhagen (2004) **Sweden** **Retro**	No	All pts who visited SCI clinic for the first time (1995-2000) N=402	SS: 402 RR: NA	Incl: TSCI. Excl: non-traumatic SCI.	Age N(%) yrs: 0-19 n=91 (23%), 20-29 n=126 (31%), 30-39 n=76 (19%), 40-49 n=61 (15%), ≥50 n= 48 (12%). Gender: male n=319 (79%) female n=83 (21%). Age at SCI: NR. Cause of SCI: NR.	SCI Level: Paraplegia n=234 (58%), Tetraplegia n=168 (42%). AIS: A n=157 (39%), B-E n=245 (61%). SCI Level + AIS: Tetraplegia/AIS A n= 54 (13%), Paraplegia/AIS A n=103 (26%),	100%	NA.

						Tetraplegia/AIS B-E n= 114 (28%), Paraplegia/AIS B-E n= 131 (33%).		
Werhagen (2007) **Sweden** **Retro**	Yes	All pts who visited SCI clinic for the first time (1995-2000). N=95	SS: 95 RR: NA	Incl: non-traumatic SCI. Excl: TSCI, spinal tumours from primary neoplasms elsewhere in body, multiple sclerosis, primary syringomyelia, spina bifida.	Age: 0-19 n= 11 (12%) 20-29 n= 16 (17%) 30-39 n=18 (19%) 40-49 n=15 (16%) ≥50 n= 35 (37%). Gender: male n=60 (63%) female n=35 (37%). Age at SCI by cause of SCI mean (range) yrs: Vascular diseases 53.7 (16-79), Spinal stenosis 46.0 (23-84), Infection 43.0 (11-75), Benign tumour 36.9 (17-82), Malignant tumour 16.3 (0-84). Cause of SCI: vascular myelopathies n=16 (17%), spinal stenosis n=25 (26%), infection n=30 (32%), benign tumours n=13 (14%), malignant tumours n=11 (12%).	SCI Level: Paraplegia n=68 (72%), Tetraplegia n=27 (28%), AIS: A n=11 (12%), AIS B-E n=84 (88%). SCI Level + AIS: Tetraplegia/AIS A n=2 (2%), Tetraplegia/AIS B-E n=26 (27%), Paraplegia/AIS A n=9 (10%), Paraplegia/AIS B-E n=58 (61%).	0%	NA.
Werhagen (2012) **Sweden & Italy** **Retro**	No	Pts registered to databases of SCI centres. N=140	Florence SS: n=86 RR: n=18 no contact, n=2 refused, n=66 Incl. Sweden SS: n=80 RR: n=6 refused, n=74 incl.	Incl: TSCI ≥ 25yrs with AIS A-C at follow up. Excl: NR	**Italian pts:** Age mean (range) yrs: 56 (31-82). Gender: male n=48 (73%) female n=18 (27%). Age at SCI mean (range) yrs: 23 (4-53). Cause of SCI: Fall n=23 (35%), RTA n=31 (47%), Sports n=1 (2%), Diving n=7 (11%), Other n=4 (5%). **Swedish pts:** Age mean (range) yrs: 52 (33-80). Gender: male n=58 (78%), female n=16 (22%). Age at SCI mean (range) yrs: 21 (0-45). Cause of SCI: Fall n=11 (15%), RTA n=44 (59%), Sports n=5 (7%), Diving n=9 (12%), Other 5(7%).	**Italian pts**: SCI Level: Paraplegia n=39 (59%), Tetraplegia n=7 (41%), AIS: A n=49 (74%), B n=13 (20%), C n=4 (6%). **Swedish pts**: SCI Level: Paraplegia n=49 (66%), Tetraplegia n=25 (34%). AIS: A n=56 (76%), B n=10 (14%), C n=8 (10%).	100%	NR.

Zeilig (2012) Israel **Pro**	No	Pts recruited from rehab medical centre. N=28	SS: NR RR: n=30, n=1 died, n=1 lost contact.	Incl: SCI >T10, incomplete, < 3 weeks. Excl: acute/chronic pain at/ below SCI, cerebral damage, neurological disorders, medical problems, diseases causing potential neural damage, skin lesions in testing sites, psychiatric/ cognitive issues.	Age mean (range) yrs: 33.4 (18-58). Gender: male n=21 (75%), female n=7 (25%). Age at injury: NR. Cause of SCI: RTA n=13 (46%), Surgery n=7 (25%), Fall n=5 (18%), Stabbing n=2 (7%), Contusion n=1 (4%).	SCI Level: Cervical n=9 (32%), Thoracic n=19 (68%). AIS: A n=0, B n=8 (29%), C n=14 (50%), D n=6 (21%), E n=0.	71.4 (20/28)	NR.

AIS, American Spinal Injury Association Impairment Scale (AIS); ASIA, American spinal Injury Association Impairment Scale; C/S, cros-sectional study; DC, discharge, excl, excluded; FU follow-up; Incl, included; NA, not applicable, NR, not reported; N, number; NR, not reported, pt, patient; rehab, Pro, prospective study; rehabilitation; Retro, retrospective study; RR, response rate; RTA, road traffic accident; SS, sample size; SCI, spinal cord injury; SD, standard deviation; TSCI, traumatic spinal cord injury, yr, year.

Assessment of Neuropathic Pain

Table 2.3 outlines assessment methods and NP prevalence rates in each study. The presence of NP was examined from within two weeks (38, 40) to 25 years or more (47) post SCI. Prevalence rates were recorded using a range of methodologies: over the phone, n=2 (8, 39), a self-reported questionnaire, n=1 (35), a postal survey, n=1 (44), examination by a neurologist, n=5 (36, 37, 43, 45, 47), a standardised pain interview, n=3 (19, 41, 42), and sensory testing and pain interview, n=5 (22, 24, 38, 40, 46).

Four studies defined NP according to the IASP definition of NP, two studies (8, 38) cited the older definition (49) and the remaining two studies (22, 39) used the updated version (50). Nine studies used classifications systems for SCI pain, two studies were guided by the ISCIP classification (22, 39), seven studies (8, 24, 38, 41, 42, 46, 47) quoted the classification devised by Siddall et al. (1997, 2000) (51, 52) and one study (35) cited work from Burchiel and Hsu (2001) (53). The remaining studies quoted other literature (19, 37, 40, 44) or used a self-developed definition and classification of NP (36, 43, 45) which were deemed to be suitable for inclusion by the two independent reviewers (D.B, O.L).

Neuropathic Pain Prevalence

A number of meta-analyses were undertaken to determine NP pooled prevalence rates. Overall point prevalence rates of NP for all studies and for acute and chronic SCI were determined. Point prevalence of NP at and below-level for all studies were determined and for acute and chronic SCI. Furthermore sub-analysis of NP prevalence in paraplegia versus tetraplegia presentations, in traumatic SCIs, in older patients versus younger patients and at one year post SCI was conducted.

Table 2 Quality Assessment of Included Studies

Study (Year)	Source population, a random selected sample or a sample which represents the target population (2 points).	Either the reasons for nonresponses (to study invitation), the non-responders, a comparison of responders and non-responders, or the sample and a representative population are described. (2 points).	Response rate ≥ 90% (2 points) or between 70% and 90% (1 point).	Were the data from a pain prevalence study (2 points) or from a study not specifically designed for that purpose (1 point).	Data were collected on an identical fashion for all subjects (2 points) Otherwise (1 point).	Data were collected by means of a validated (3 points), or non-validated questionnaire/interview (2 points), or retrospectively by proxies or medical records (1 point).	A description was given of the target population and the setting the sample was drawn from (2 points).	Description of the injury (etiology, level, completeness, and timing), and patient (age, and gender) (>3 items = 1point).	Final sample size stated (1 point).	Prevalence recall period should be stated (1 point).	Total ([a] low quality study).
Adriaansen (2013)	2/2	2/2	0/2	1/2	2/2	2/3	2/2	1/1	1/1	1/1	14
Aito (2007)	2/2	2/2	2/2	1/2	2/2	2/3	2/2	1/1	1/1	0/1	15
Barrett (2003)	2/2	2/2	1/2	2/2	1/2	2/3	2/2	1/1	1/1	1/1	15
Budh (2003)	2/2	2/2	2/2	2/2	2/2	2/3	2/2	1/1	1/1	1/1	17
Celik (2012)	0/2	0/2	0/2	2/2	2/2	2/3	2/2	1/1	1/1	0/1	10[a]
Finnerup (2013)	2/2	2/2	0/2	2/2	1/2	3/3	2/2	1/1	1/1	1/1	15
Frisbie (1990)	2/2	0/2	2/2	2/2	2/2	2/3	0/2	0/1	1/1	1/1	12 [a]
Heutink (2011)	2/2	0/2	0/2	2/2	2/2	2/3	2/2	1/1	1/1	1/1	13 [a]
Levi (1995)	2/2	2/2	2/2	1/2	2/2	2/3	2/2	1/1	1/1	0/1	15
New (1997)	2/2	0/2	2/2	2/2	2/2	2/3	2/2	1/1	1/1	1/1	15
Siddall (1999)	2/2	2/2	2/2	2/2	2/2	2/3	2/2	1/1	1/1	0/1	16
Siddall (2003)	2/2	2/2	1/2	2/2	2/2	2/3	2/2	1/1	1/1	0/1	15
Wen (2008)	2/2	0/2	1/2	2/2	2/2	3/3	2/2	1/1	1/1	1/1	15
Werhagen (2004)	2/2	2/2	N/A 2/2	1/2	2/2	2/3	2/2	1/1	1/1	0/1	16
Werhagen (2007)	2/2	2/2	N/A 2/2	2/2	2/2	2/3	2/2	1/1	1/1	0/1	16
Werhagen (2012)	2/2	2/2	1/2	1/2	2/2	2/3	2/2	1/1	1/1	0/1	14
Zeilig (2012)	2/2	0/2	2/2	1/2	2/2	2/3	2/2	1/1	1/1	0/1	13 [a]

Table.3. Assessment and Prevalence of Neuropathic Pain of Included Studies.

Author, Year, Country	Time points from SCI for Assessment	Definition or Classification of Neuropathic Pain	Assessment of Neuropathic Pain	Pain Recall Period	Prevalence of Neuropathic Pain
Adriaansen (2013) Netherlands	Ax 1 yr, 2 yr, 5yr post DC from inpatient rehabilitation.	Burchiel and Hsu (2001): AL or BL pain originating from syringomyelia, spinal cord ischaemia or trauma.	Ax by interview at 1yr and 5yr and Ax by phone at 2yr. Recorded presence and severity of 8 NP characteristics. Rated on a 5 point scale "not severe"-"very severe". Score / 40. Severe NP = ≥1/8 as severe/very severe.	Pain in last yr.	TNP: 1yr 143/156 (92%) 2yr n=83/99 (84%), 5yr n=127/146 (87%).
Aito (2007) Italy	Ax ≥18 months post DC from hospital - mean 33 months.	Own definition: symptoms of burning/shooting into the area with sensory disturbances to pinprick and touch without relation to movements or signs of inflammation. Pain could be spontaneous/ provoked by touch/ cold, continuous, and/or paroxysmal components.	Ax by experienced SCI doctors in SCI + from electronic database.	NR.	TNP: n=39/82 (48%) NP by age (y): 0-30 n=2/9 (22%), 31-50 n=11/26 (42%), 51-65 n= 13/25 (52%), 65-over n= 13/22 (59%).
Barrett (2003) Australia	Time since SCI ± SD (y): 16.68 ± 12.6 (Ax at least once≥ 6 months post SCI).	Siddall et al. (1997): At-level neuropathic pain was defined as having a burning, stabbing, electrical quality, & located in the dermatomes above/ below level of injury. Below-level neuropathic pain defined as burning, stabbing, shooting pain located diffusely below the level of injury.	Interview with standardised pain questionnaire (location, description, onset and evoking stimuli), pain type placed into 5 categories (MSK, at, above or below NP, visceral and allodynia).	NRS + VRS for the past wk.	TNP: NR AL NP: n=10/88 (11%). BL NP: n=21/88 (24%).
Budh (2003) Sweden	Time since SCI n (%): 0-2 yr 44 (10%) 3-4 yr 87(19%) 5-10 yr 100 (22%) 11-20yr 102 (22%) >20 yr 120 (26%) NR 3 (1%)	Levi and Ertzgaard (1998): Neurogenic pain is pain triggered by injury to the nervous system and is referred to an area with altered or diminished sensibility. Pain is burning, stabbing, pricking. Exam to rule out tissue damage outside the nervous system, or make such a cause for pain unlikely.	Assessed in clinic using questionnaire investigating pain (location, quality, onset, number of painful body regions, influencing factors and intensity using VAS). Pain classified as nociceptive, neurogenic or mixed pain.	Pain present at least for the last 2 wks or recurrent during at least 4 x 2-wk periods in the last year.	TNP: n=208/456 (46%) NP alone n=133/456 (29%), Mixed NP +other n=75 (16%).

Celik (2013) Turkey	Time since SCI (mean): 7.12 ± 7.34 months (longest 36 months)	Siddall and Loser (2001): pain originates from a lesion or disease that affects the nervous system. Expressed as burning, sharp, electric, and/or shooting pain.	Ax in clinic with the Mc Gill Pain Questionnaire.	NR.	TNP n=61/90 (68%). TNP Para n=42/64 (66%), TNP Tetra n=19/26 (73%).
Finnerup (2014) Denmark	Ax < 1 month post SCI if condition allowed (otherwise Ax by 3 months), Ax again at 6 + 12 months post SCI.	Treede et al. (2008) *IASP definition of NP*. Byrce et al. (2012): *International Spinal Cord Injury Pain (ISCIP) Classification.*	Interview using Mc Gill Pain Questionnaire, ISCIP Basic Data Set, Brief pain inventory, pain treatment recorded from records and patient, bedside sensory testing (pinprick, brush, cold and warm stimuli).	Pain in the last wk.	1 month (90), 6 months (78), 12 months (88). TNP: n=34/90 (34%), n= 41/78 (53%), n=52/88 (59%). AL NP: n=22/90 (24%), n=28/78 (36%), n=28/88 (32%). BL NP: n=9/90 (10%), n=17/78(22%), n=28/88 (32%).
Frisbie (1990) America	Time since SCI (median) yrs: 16 range 3-45.	Own definition: burning, stabbing, needles and pins or numbness, above, at or below the level of paralysis.	Interview to diagnose pain, NP confirmed once coinciding structural pathology not found.	Pain lasting longer than 3 weeks was chronic pain.	TNP: n=24/66 (36%).
Heutink (2011) Netherlands	Time since SCI (mean) ± SD yrs: 11.6 ± 10.7.	Bockenek et al. (2002): burning, shooting, stabbing, or tingling, above, at, or below SCI level.	Postal/online survey. Patients indicated their type of pain from descriptions of pain types provided.	Pain in past 6 months.	TNP 149/279 (54%), Above level NP 11/279 (4%), AL NP 82/279 (29%), BL NP 111/279 (40%).
Levi (1995) Sweden	Age at injury (mean): 31yrs. Age at contact (mean): 42yrs.	Own definition: pain of a burning, stabbing or sharp-shooting quality at, or below the neurological level of lesion.	Classified by physician after detailed pain history.	NR.	TNP n=167/353 (47%), NP alone n=107/353 (30%), NP + non-NP n=60/353 (17%).
New (1997) Australia	Average stay in acute ward 31 days. Pts Ax < 48 hrs on rehab ward, Ax weekly to DC, Ax for any new pain/increase in pain, Ax 1,3,6,12 months post DC, Ax over phone 13-16 months post DC.	Frisbie and Aguilera (1990): burning, stabbing, needles and pins or numbness, above, at or below the level of paralysis.	Ax by principal author, diagnosed based on NP definition.	Pain in last wk at 13-16 month Ax.	TNP Admission n=15/24 (63%), DC n=13/24 (54%), 1 Yr n=15/22 (68%).
Siddall (1999) Australia	2, 4, 8, 13, 26 wk post TSCI.	Merskey and Bogduk (1997) *IASP definition of NP.* Siddall et al. (1997)*:* sharp, shooting, stabbing, electric or burning pain in the dermatomes at, above, or below the level of injury.	Interview to classify pain according to description and apparent origin. Sensory testing included Ax of pin prick and light touch.	NR.	2 wk (70);6 month (58) TNP: NR AL NP: n=27 (38%); n=21 (36%) BL NP n=10 (14%); n=11 (19%)
Siddall (2003)	> 5 yrs post SCI.	Merskey and Bogduk (1997) *IASP definition of NP.*	Phone interviews to classify pain according to location, description	NR.	TNP: NR NP AL n=30/73 (41%),

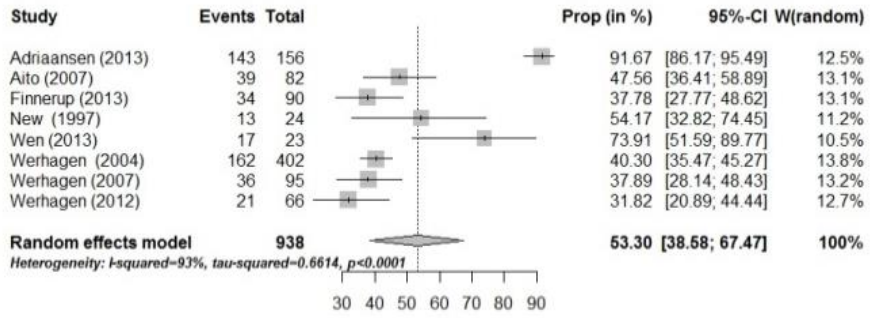
Australia		Siddall et al. (1997)*:* sharp, shooting, stabbing, electric or burning pain in the dermatomes at, above, or below the level of injury.	and apparent origin. Pain intensity recorded with NRS + VAS.		NP BL n=25/73 (34%).
Wen (2013) China	Earthquake May 2008, Baseline Ax: May-August 2009 Follow-up Ax: August - November 2010, July 2012 , October 2012.	Treede et al. (2008) IASP definition of NP. Byrce et al. (2012): *International Spinal Cord Injury Pain (ISCIP) Classification.*	Ax 1-3 in person, Ax 4 by phone. Questioned on pain (severity, timing, location, pattern, quality and aggravating and alleviating factors) and Identification (ID) pain questionnaire.	Pain in the last wk.	TNP n=17/23 (74%), AL NP 5/23 (22%). BL NP 12/23 (52%),
Werhagen (2004) Sweden	Time since SCI (median): 6 yrs (range) 2 months - 46 yrs.	Siddall et al. (2000): neuropathic pain, pain without primary relation to movements or signs of inflammation, & sensory disturbances to pin prick and touch within a painful territory corresponding to the SCI. Pain could be spontaneous, or provoked by touch/cold, continuous, and/or with paroxysmal. Classified as above-level pain, AL or BL NP.	NP diagnosed by neurologist when it met the criteria of Siddall et al (2000). Pain without primary relation to movements or sign of inflammation, sensory disturbances to pin prick and touch within the painful territory, corresponding to the spinal cord lesion.	NR.	TNP n=162/402 (40%), NP AL n=52/402 (13%), NP BL n=110/402 (27%) NP above-level n=2/402 (1%), NP + ASIA: A n=66/157, (42%) ASIA B-E n=96/245 (39%). NP + Level: Para n=91/234 (40%), Tetra n=71/168 (42%). NP + Age: 0-19 n=23/91 (26%), 20-29 n=45/126 (36%), 30-39 n=37/76 (49%), 40-49 n=28/61 (46%), ≥50 n= 29/48 (60%).
Werhagen (2007) Sweden	Ax 1 year after SCI N (%): 55 (58%). Time since SCI mean (range) yrs: 9.6 (2-38).	Siddall et al. (2000): as above in Werhagen (2004).	As above in Werhagen (2004)	NR.	TNP: n=36/95 (38%), AL NP: n=14/95 (15%), BL NP: n=22/95 (23%), above level NP: 0. NP +ASIA: A n=4/11 (36%), B-E n=32/84 (38%). NP + SCI: Para n=24/68 (35%), Tetra n=12/27 (44%). NP + ASIA + SCI level: Tetra/ASIA A n=0, Tetra/ASIA B-E n=12/26 (46%), Para/ASIA A n=3/9 (33%), Para/ASIA B-E n=21/58 (36%). NP + Age: 0-19 n= 4/11 (36%), 20-29 n= 5/16 (31%), 30-39 n= 7/18 (39%), 40-49 n= 8/15(53%), ≥50 n= 12/35 (34%).

Werhagen (2012) Sweden & Italy	Time since injury mean (range) yrs: Italian pts:33 (25-60). Swedish pts: 31 (25-54).	Siddall et al. (2000): as above in Werhagen (2004).	Pts interviewed by questionnaire about medical complications included the presence of NP and underwent a neurological and general examination by a neurologist.	NR.	Italian pts: TNP n=21/66 (32%), AL NP n=7/66 (11%), BL NP n=14/66 (21%). Swedish pts: TNP n=24/74 (32%), AL NP n=8/74 (11%), BL NP n=16/74 (22%).
Zeilig (2012) Israel	Ax 2-4 wks, 1-2.5 months, 2.5-6 months post SCI / until NP developed.	Widerstrom-Noga et al. (2008): spontaneous and/or evoked burning, stabbing, shooting pain at or below the level of spinal lesion.	NP diagnosed using neurological exam, x-ray and electromyography according to the definition and characteristics of central pain. Additional quantitative sensory testing of warm, cold, heat-pain and touch thresholds as well as graphaesthesia, allodynia, hyperpathia and wind-up pain.	NR.	TNP: n=17/28 (61%), AL NP n=4/28 (14%), BL NP n=13/28 (46%). Onset of BL NP post SCI mean (SD) range (months): 3.8± 2 (1-8).

AL, at-level of spinal lesion; Ax, assessed; BL, below level of spinal lesion; IASP, International Association for the Study of Pain, ISCIP, International Spinal Cord Injury Pain, MSK, musculoskeletal; NP, neuropathic pain; NR, not reported; NRS,numeric rating scale; Para, paraplegia; SCI, spinal cord injury; Tetra, tetraplegia; TNP, total neuropathic pain; VRS, verbal rating scale; VAS, visual analogue scale; wk, week; yr, year,

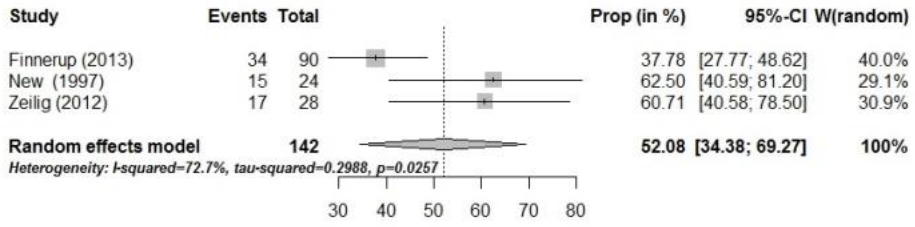
Overall Neuropathic Pain Point Prevalence: From a total of twelve studies with 1,401 patients, pooled prevalence for NP was 53% (95% CI= 43.33-63.38; I^2=91%). Sensitivity analysis, where low quality studies were removed, resulted in no reduction in pooled prevalence 53% (95% CI=38.58-67.47) established from a total of 938 patients (Figure 3). High heterogeneity I^2=93% remained. Insufficient data (n=2 studies) were presented to allow calculation of overall NP prevalence from strict IASP definition of NP. Prevalence rates in the two studies ranged from 34-74%.

Figure 3 Overall NP Point Prevalence Sensitivity Analysis.



Overall NP Point Prevalence in <u>Acute SCI:</u> From a total of three studies with 142 subjects, pooled prevalence was 52% (95% CI=34.38-69.27, I^2=73%) (Figure 4). Further sensitivity analysis was not possible due to the lower number of included studies.

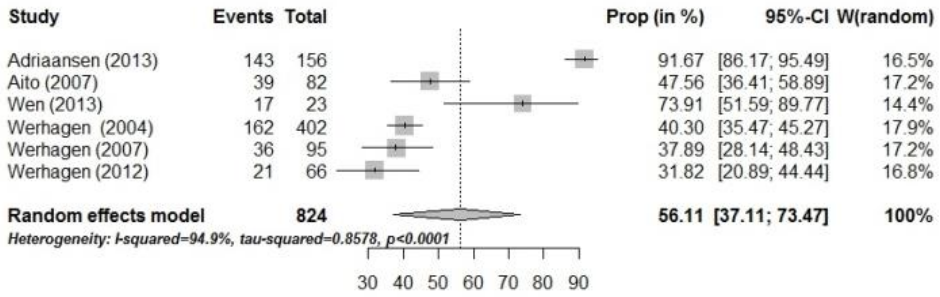
Figure 4 Overall NP Point Prevalence in Acute SCI (≤ 6 months) Sensitivity Analysis.



Overall <u>NP</u> Point Prevalence in <u>Chronic SCI:</u> From a total of nine studies with 1259 subjects, pooled prevalence was 55% (95% CI=42.35-66.42, I^2=93%) (Appendix 5) increasing to 56% (95% CI=37.11-

73.47, I^2=95%) during sensitivity analysis (Figure 2.5). After one year post injury from a total of seven studies with 1013 subjects, pooled prevalence was 44% (95% CI=36.82-51.66, I^2=78%) (Appendix 5) decreasing to 43% (95% CI=34.79-51.55, I^2=69%) during sensitivity analysis (Appendix 5).

Figure 5 Overall NP Point Prevalence in Chronic SCI (>6 months) Sensitivity Analysis.



***NP Point Prevalence <u>at-level</u>*:** From a total of nine studies with 1141 subjects, overall pooled at-level NP prevalence was 19% (95% CI=13.26-26.39, I^2=84.5%) (Appendix 5). From a total of three studies in acute SCI of 188 subjects, pooled at-level prevalence was 27% (95% CI=15.93-41.12, I^2=70%) (Figure 6). Further sensitivity analysis was not possible due to the lower number of included studies. From a total of six studies in chronic SCI of 953 pooled at-level prevalence was 16% (95% CI=10.19-24.47, I^2=86%) (Appendix 5) decreasing to 13% (95% CI=10.80-15.95, I^2=0%) during sensitivity analysis (Figure 7). From a total of three studies with 183 subjects who adhered to strict IASP definition of NP, pooled at-level NP prevalence was 29% (95% CI=19.65-40.85, I^2=55%).

Figure 6 NP Point Prevalence At-level in Acute SCI (≤ 6 months).

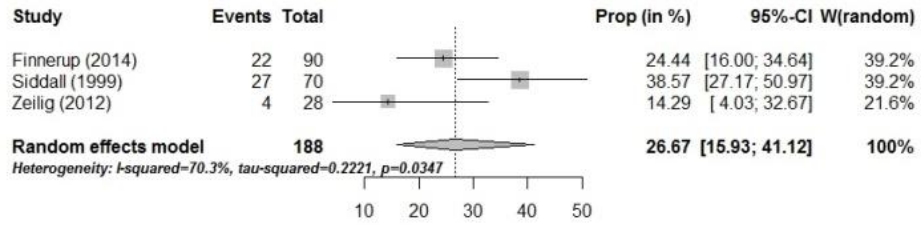
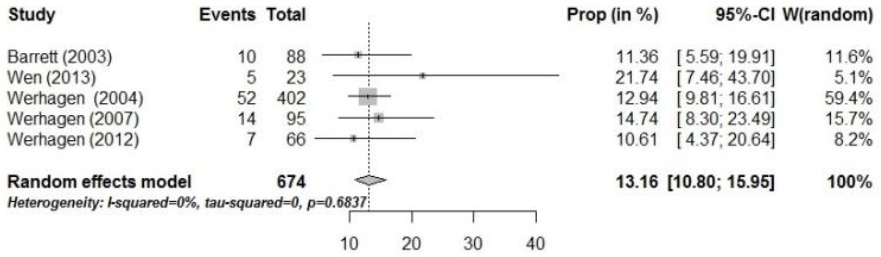


Figure 7 NP Point Prevalence At-level in Chronic SCI (> 6 months) Sensitivity Analysis.



***NP Point Prevalence <u>below-level</u>*:** From a total of nine studies with 1141 subjects, overall pooled below-level NP prevalence was 27% (95% CI=19.89-34.61, I^2=84%). From a total of three studies in acute SCI of 188 subjects, pooled below-level prevalence was 20% (95% CI=7.06-45.18, I^2=89%) (Figure 2.8). Further sensitivity analysis was not possible due to the low number of included studies. From a total of six studies in chronic SCI of 953 pooled below-level prevalence was 30% (95% CI=22.83-37.68, I^2=80%) decreasing to 27% (95% CI=21.18-33.50, I^2=55%) during sensitivity analysis (Figure 2.9). From a total of three studies with 183 subjects who adhered to strict IASP definition of NP, pooled below-level NP prevalence was 21% (95% CI=6.86-49.23, I^2=90%).

Figure 8 NP Point Prevalence Below-level in Acute SCI (≤ 6 months).

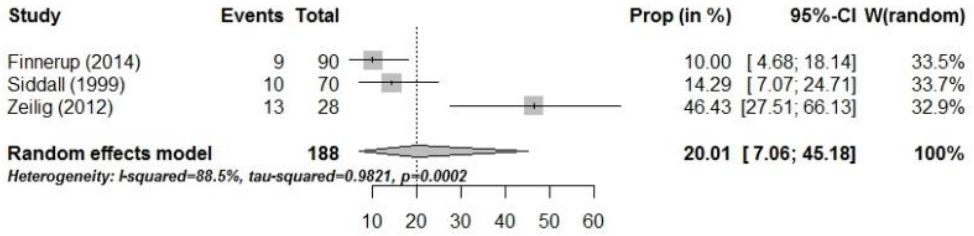
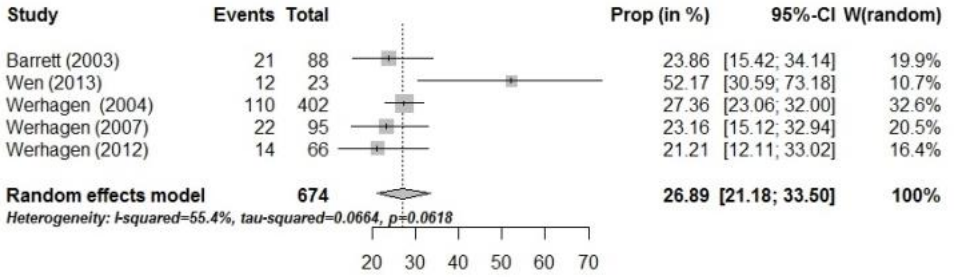


Figure 9 NP Point Prevalence Below-level in Chronic SCI (>6 months) Sensitivity Analysis.



NP prevalence in Complete SCI versus Incomplete SCI lesions

Insufficient data were presented to allow comparison in NP prevalence by completeness of injury.

NP prevalence in Paraplegia and Tetraplegia presentations

From a total of three studies with 366 subjects, pooled NP prevalence in paraplegia was 46% (95% CI=30.32-62.78, I^2=87%). From the same three studies with 221 subjects with tetraplegia pooled NP prevalence was 52% (95% CI=34.38-68.95, I^2=75%). One study was of low quality (42), however, further sensitivity analysis was not possible due to the low number of included studies.

NP prevalence in Traumatic and Non-Traumatic SCI

From a total of seven studies with 819 subjects with traumatic SCIs pooled NP point prevalence was 47% (95% CI=36.94-56.37, I^2=83%) (Appendix 2.5) decreasing to 43% (95% CI=34.75-51.62, I^2=69%) on sensitivity analysis. Only one study exclusively included 95 participants with non-traumatic SCIs (46) which reported overall NP rates of 38%, with 15% reporting at-level NP and 23% with below-level NP. Neither pooled prevalence calculation nor comparison between groups in this population was possible.

Age Related NP prevalence post SCI

Three studies categorised NP by age allowing pooled prevalence rates of NP to be dichotomised to <50 or ≥50 years of age in accordance with the categories reported. For those <50 years of age (n=449), the overall pooled point prevalence was 38% (95% CI=33.49-42.44) with low heterogeneity (I^2=0%). Those aged 50 or older (n=130) had a higher prevalence rate of 51% (95% CI=35.93-65.18, I^2=65%).

Gender Related NP prevalence post SCI

Insufficient data were presented to allow comparison in NP prevalence by gender.

Neuropathic Pain Prevalence at Specific Time Points post SCI

Only three studies reported overall point prevalence rates at a common specific time point post SCI of one year. From 266 subjects the point prevalence of NP was 76% (95% CI=44.98-92.83, I^2=94%) at this time.

Discussion

This is the first systematic review and meta-analysis to consider the pooled point prevalence of NP post SCI. Rates of NP were found to be higher, at 53%, than the 40% rate previously reported (15, 54). At-level (19%) and below-level (27%) NP pooled point prevalence rates were estimated for the first time in this current review. Neuropathic pain appears to be more prevalent after 6 months of injury compared with acute SCI. At-level NP develops more commonly in the acute stage post SCI and below-level NP begins to increase after 1 year. It was beyond the scope of this current review to provide an overview of the trajectory of NP post injury. The literature synthesised only reported NP at one common time point of 1 year post injury which had a high point prevalence of 74%. Neuropathic pain was found to present more frequently in participants with tetraplegia and older patients. Clinically these populations should be prioritised when screening for NP. This review serves to highlight NP as a common problem post SCI that warrants further attention and effective management strategies (26, 27).

Less strict pain definitions previously led to over-estimation of general chronic pain in SCI (1). In the current review, only meta-analyses where strict IASP definitions of NP were employed were possible for at-level and below-level NP (8, 22, 38, 39). Less strict definitions when compared with IASP adherent studies were found to underestimate (-10%) at-level and overestimate (+6%) below-level NP respectively. At-level and below-level NP pooled prevalence rates when summed (19% and 27% respectively), do not equal the total NP prevalence rate (53%). Given that subjects may present with both pain types simultaneously, this may be suggestive of an overestimation of overall NP prevalence or may be due to not all studies providing a breakdown of at and below-level NP. Furthermore below-level NP could be underreported by the inclusion of subjects with cauda equina lesions in analysis, only two studies (35, 47) excluded this cohort from study participation and no study reported excluding patients with this level of SCI from analysis. From this current review, one

cannot definitively conclude whether less strict pain definitions led to over-estimation of prevalence rates of NP after SCI.

A lack of consensus in research studies on the assessment of NP post SCI has previously been identified as an issue (7). The IASP Neuropathic Pain Special Interest Group (NeuPSIG) guidelines advise that screening questionnaires are appropriate to identify patients who may have NP and a further clinical examination with sensory testing should form the basis of a NP diagnosis (55). The majority of included studies in the current review did not adhere to these guidelines with only two studies using validated NP questionnaires (22, 39) and only five studies (22, 24, 38, 40, 46) including physical examination and sensory testing. The Neuropathic Pain Special Interest Group (NeuPSIG) guidelines also state however that a definite diagnosis of NP is attained if the patient has a diagnostic test confirming a lesion of the somatosensory system and negative or positive sensory signs, within the innervation territory of the lesion. A probable diagnosis of NP is recorded if one of these criteria is satisfied. In the case of SCI NP, the lesion to the somatosensory system, the SCI, is confirmed routinely by MRI making any NP symptoms in an around the SCI lesion probable NP. In addition, all of the studies in this review recorded sensory descriptors of NP which strengthens the probable diagnosis of NP in each study. To allow for standardisation across future research in this area, studies should appropriately define NP using the IASP definition (50), include the ISCIP classification of SCI NP (7) and use a validated NP screening tool, followed by a clinical examination including sensory testing when indicated. The Douleur Neuropathique en 4 (DN4) (56) is an example of one such tool to record NP in SCI patients with proven, high diagnostic accuracy (57, 58) and includes the pre-requisite sensory testing.

In the current review 59% of included studies (n=10) addressed traumatic SCI solely and 6% (n=1) looked at non-traumatic SCI only. This indicates a bias in NP research towards SCI of traumatic origin. Current demographic trends of an anticipated increase in cancer-related SCIs with an ageing

population (59), a characteristic previously linked with increased NP prevalence (20, 48), suggest that non-traumatic SCI will become more prevalent in the near future. It has been reported that traumatic SCIs (16, 17) have increased levels of reported NP. In the current review the pooled prevalence of NP for traumatic SCI (N=5) was lower than overall NP rates at 43%. Only one study enabled the prevalence rate in non-traumatic SCI to be identified at the lower rate of 38% (46). Further studies in non-traumatic SCI are required to redress this imbalance in the literature and establish pooled NP prevalence in this population.

Similar to reports of musculoskeletal pain (60) and NP (61) in the general population, the current review supports an association between increased age and NP prevalence in SCI with 13% more NP prevalence noted in those over 50 when compared with their younger counterparts. However, other studies included in the review did not provide data by age and therefore prohibited their inclusion in the meta-analysis. Conflicting results exist in these studies with one study reporting increased below-level NP in younger patients (22) and one study finding overall NP to be more common in older patients (19). The finding that increasing age is associated with more NP may be indicative of either a direct age effect on NP, or may reflect an increased prevalence because of time post injury. In the absence of data relating to NP prevalence at discreet time periods post injury, this cannot be elucidated further here.

Potential mechanisms for NP development post SCI described in detail in the literature (25, 26, 28) are now considered briefly within the context of the current findings. Peripheral mechanisms suggest that at the site of spinal cord trauma, surrounding nerve cells can exhibit inflammatory and neurochemical changes leading to augmented responsiveness to peripheral stimulation or neuronal hyper excitability which may give rise to at-level NP (25, 26, 62). This is supported by the findings in this review that at-level NP was more common in acute SCI. In addition to neuronal hyper excitability, activation of residual spinothalamic pathways (26, 28, 38) by inflamed damaged axons in

the tract (63), may cause below-level NP. This process has a longer time of onset explaining why below-level NP develops later within the first year post injury which was also upheld by findings of this review. Due to insufficient data presented it could not be determined whether at or below-level NP was more common in incomplete or complete lesions. Further research is warranted given the conflicting findings reported in the literature to date, (8, 22, 24).

Finally, the results of this current review must be considered with the following limitations. Only studies in English were included and the high heterogeneity noted in much of the pooled analyses must be considered in the overall interpretation of the results. Standardisation across future studies with respect to definition and classification of neuropathic pain is required to reduce this finding.

In conclusion this is the first systematic review and meta-analysis to provide pooled prevalence rates of NP post SCI. Prevalence rates for NP of over 50% post SCI highlight the significance of this problem which is largely refractory to current treatment approaches and has a poor prognosis for recovery. Neuropathic pain is found to be more prevalent 1 year post injury, below lesion level, in older people and tetraplegics. Whilst identified economic costs of this issue are measurable, the emotional and physical suffering for the individual is never fully captured. Future studies should include established definitions, classification systems and assessment tools for NP at clear time points post SCI to follow the trajectory of this problem across the lifespan and include indices of sleep, mood and interference to allow for appropriate, optimal and timely pain management for each patient.

Acknowledgments

The authors thank Dr Keith Smart and Dr Amanda Carty for their expert advice on pain and SCI aspects of this study. An unrestricted educational grant from Pfizer Healthcare Ireland supported the study. The authors declare no conflict of interest with relation to this manuscript.

References

1. van Gorp S, Kessels AG, Joosten EA, van Kleef M, Patijn J. Pain prevalence and its determinants after spinal cord injury: a systematic review. Eur J Pain. 2015;19(1):5-14.

2. Westgren N, Levi R. Quality of life and traumatic spinal cord injury. Arch Phys Med Rehabil. 1998;79(11):1433-9.

3. Vall J, Batista-Braga VA, Almeida PC. Central neuropathic pain and its relation to the quality of life of a person with a traumatic spinal cord injury. Rev Neurol. 2006;42(9):525-9.

4. Cairns DM, Adkins RH, Scott MD. Pain and depression in acute traumatic spinal cord injury: origins of chronic problematic pain? Arch Phys Med Rehabil. 1996;77(4):329-35.

5. Kishi Y, Robinson RG, Forrester AW. Comparison between acute and delayed onset major depression after spinal cord injury. J Nerv Ment Dis. 1995;183(5):286-92.

6. Budh CN, Hultling C, Lundeberg T. Quality of sleep in individuals with spinal cord injury: a comparison between patients with and without pain. Spinal Cord. 2005;43(2):85-95.

7. 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. Spinal Cord. 2012;50(6):413-7.

8. 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(3):249-57.

9. Cardenas DD, Nieshoff EC, Suda K, Goto S, Sanin L, Kaneko T, et al. A randomized trial of pregabalin in patients with neuropathic pain due to spinal cord injury. Neurology. 2013;80(6):533-9.

10. Siddall PJ, Cousins MJ, Otte A, Griesing T, Chambers R, Murphy TK. Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. Neurology. 2006;67(10):1792-800.

11. Budh CN, Lundeberg T. Non-pharmacological pain-relieving therapies in individuals with spinal cord injury: a patient perspective. Complement Ther Med. 2004;12(4):189-97.

12. Mehta S, Orenczuk K, McIntyre A, Willems G, Wolfe DL, Hsieh JT, et al. Neuropathic pain post spinal cord injury part 1: systematic review of physical and behavioral treatment. Top Spinal Cord Inj Rehabil. 2013;19(1):61-77.

13. Margolis JM, Juneau P, Sadosky A, Cappelleri JC, Bryce TN, Nieshoff EC. Health care resource utilization and medical costs of spinal cord injury with neuropathic pain in a commercially insured population in the United States. Arch Phys Med Rehabil. 2014;95(12):2279-87.

14. Dijkers M, Bryce T, Zanca J. Prevalence of chronic pain after traumatic spinal cord injury: a systematic review. J Rehabil Res Dev. 2009;46(1):13-29.

15. Margot-Duclot A, Tournebise H, Ventura M, Fattal C. What are the risk factors of occurence and chronicity of neuropathic pain in spinal cord injury patients? Ann Phys Rehabil Med. 2009;52(2):111-23.

16. Davidoff G, Roth E, Guarracini M, Sliwa J, Yarkony G. Function-limiting dysesthetic pain syndrome among traumatic spinal cord injury patients: a cross-sectional study. Pain. 1987;29(1):39-48.

17. Vall J, Costa CM, Santos Tde J, Costa SB. Neuropathic pain characteristics in patients from Curitiba (Brazil) with spinal cord injury. Arq Neuropsiquiatr. 2011;69(1):64-8.

18. Teixeira MJ, Paiva WS, Assis MS, Fonoff ET, Bor-Seng-Shu E, Cecon AD. Neuropathic pain in patients with spinal cord injury: report of 213 patients. Arq Neuropsiquiatr. 2013;71(9a):600-3.

19. Budh CN, Lund I, Ertzgaard P, Holtz A, Hultling C, Levi R, et al. Pain in a Swedish spinal cord injury population. Clinical rehabilitation. 2003;17(6):685-90.

20. Stormer S, Gerner HJ, Gruninger W, Metzmacher K, Follinger S, Wienke C, et al. Chronic pain/dysaesthesiae in spinal cord injury patients: results of a multicentre study. Spinal Cord. 1997;35(7):446-55.

21. Anke AG, Stenehjem AE, Stanghelle JK. Pain and life quality within 2 years of spinal cord injury. Paraplegia. 1995;33(10):555-9.

22. 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. 2014;15(1):40-8.

23. Nakipoglu-Yuzer GF, Atci N, Ozgirgin N. Neuropathic pain in spinal cord injury. Pain Physician. 2013;16(3):259-64.

24. Werhagen L, Budh CN, Hultling C, Molander C. Neuropathic pain after traumatic spinal cord injury--relations to gender, spinal level, completeness, and age at the time of injury. Spinal Cord. 2004;42(12):665-73.

25. Siddall PJ. Management of neuropathic pain following spinal cord injury: now and in the future. Spinal Cord. 2009;47(5):352-9.

26. Finnerup NB, Baastrup C. Spinal cord injury pain: mechanisms and management. Curr Pain Headache Rep. 2012;16(3):207-16.

27. Felix ER. Chronic neuropathic pain in SCI: evaluation and treatment. Phys Med Rehabil Clin N Am. 2014;25(3):545-71, viii.

28. D'Angelo R, Morreale A, Donadio V, Boriani S, Maraldi N, Plazzi G, et al. Neuropathic pain following spinal cord injury: what we know about mechanisms, assessment and management. Eur Rev Med Pharmacol Sci. 2013;17(23):3257-61.

29. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264-9, w64.

30. Leboeuf-Yde C, Lauritsen JM. The Prevalence of Low Back Pain in the Literature A Structured Review of 26 Nordic Studies From 1954 to 1993. Spine. 1995;20(19):2112-8.

31. Walker BF. The prevalence of low back pain: a systematic review of the literature from 1966 to 1998. J Spinal Disord. 2000;13(3):205-17.

32. R T. R: A language and environment for statistical computing Vienna, Austria.: R Foundation for Statistical Computing; 2015. Available from: http://www.R-project.org/.

33. Rowland JW, Hawryluk GW, Kwon B, Fehlings MG. Current status of acute spinal cord injury pathophysiology and emerging therapies: promise on the horizon. Neurosurg Focus. 2008;25(5):E2.

34. Higgins JPT GS. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration. 2011.

35. Adriaansen JJ, Post MW, de Groot S, van Asbeck FW, Stolwijk-Swüste JM, Tepper M, et al. Secondary health conditions in persons with spinal cord injury: a longitudinal study from one to five years post-discharge. Disabil Rehabil. 2013;45(10):1016-22.

36. Aito S, D'Andrea M, Werhagen L, Farsetti L, Cappelli S, Bandini B, et al. Neurological and functional outcome in traumatic central cord syndrome. Spinal Cord. 2007;45(4):292-7.

37. New PW, Lim TC, Hill ST, Brown DJ. A survey of pain during rehabilitation after acute spinal cord injury. Spinal Cord. 1997;35(10):658-63.

38. Siddall PJ, Taylor DA, McClelland JM, Rutkowski SB, Cousins MJ. Pain report and the relationship of pain to physical factors in the first 6 months following spinal cord injury. Pain. 1999;81(1-2):187-97.

39. Wen H, Reinhardt JD, Gosney JE, Baumberger M, Zhang X, Li J. Spinal cord injury-related chronic pain in victims of the 2008 Sichuan earthquake: A prospective cohort study. Spinal Cord. 2013;51(11):857-62.

40. Zeilig G, Enosh S, Rubin-Asher D, Lehr B, Defrin R. The nature and course of sensory changes following spinal cord injury: predictive properties and implications on the mechanism of central pain. Brain. 2012;135(Pt 2):418-30.

41. Barrett H, McClelland JM, Rutkowski SB, Siddall PJ. Pain characteristics in patients admitted to hospital with complications after spinal cord injury. Arch Phys Med Rehabil. 2003;84(6):789-95.

42. Celik C, Boyaci S, Ucan H. Pain in patients with traumatic spinal cord injury. Journal of Musculoskeletal Pain. 2013;21(1):53-7.

43. Frisbie JH, Aguilera EJ. Chronic pain after spinal cord injury: an expedient diagnostic approach. Paraplegia. 1990;28(7):460-5.

44. 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(5):433-40.

45. Levi R, Hultling C, Nash MS, Seiger A. The Stockholm spinal cord injury study: 1. Medical problems in a regional SCI population. Paraplegia. 1995;33(6):308-15.

46. Werhagen L, Hultling C, Molander C. The prevalence of neuropathic pain after non-traumatic spinal cord lesion. Spinal Cord. 2007;45(9):609-15.

47. Werhagen L, Aito S, Tucci L, Strayer J, Hultling C. 25 years or more after spinal cord injury: clinical conditions of individuals in the Florence and Stockholm areas. Spinal Cord. 2012;50(3):243-6.

48. Demirel G, Yllmaz H, Gencosmanoglu B, Kesiktas N. Pain following spinal cord injury. Spinal Cord. 1998;36(1):25-8.

49. Merskey H. Descriptions of chronic pain syndromes and definitions of pain terms. Classification of chronic pain. Pain. 1994;Suppl 3:226.

50. Treede RD, Jensen TS, Campbell JN, Cruccu G, Dostrovsky JO, Griffin JW, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology. 2008;70(18):1630-5.

51. Siddall PJ, Taylor DA, Cousins MJ. Classification of pain following spinal cord injury. Spinal Cord. 1997;35(2):69-75.

52. Siddall PJ YR, Loeser JD. Pain following spinal cord injury: Clinical features, prevalence, and taxonomy. IASP Newsletter. 2000;3(3):3-7.

53. Burchiel KJ, Hsu FP. Pain and spasticity after spinal cord injury: mechanisms and treatment. Spine. 2001;26:146-60.

54. Finnerup NB, Jensen TS. Spinal cord injury pain--mechanisms and treatment. Eur J Neurol. 2004;11(2):73-82.

55. Haanpää M, Attal N, Backonja M, Baron R, Bennett M, Bouhassira D, et al. NeuPSIG guidelines on neuropathic pain assessment. PAIN®. 2011;152(1):14-27.

56. Bouhassira D, Attal N, Alchaar H, Boureau F, Brochet B, Bruxelle J, et al. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). Pain. 2005;114(1-2):29-36.

57. Hallstrom H, Norrbrink C. Screening tools for neuropathic pain: can they be of use in individuals with spinal cord injury? Pain. 2011;152(4):772-9.

58. Calmels P, Mick G, Perrouin-Verbe B, Ventura M. Neuropathic pain in spinal cord injury: identification, classification, evaluation. Ann Phys Rehabil Med. 2009;52(2):83-102.

59. Guilcher SJT, Munce SEP, Couris CM, Fung K, Craven BC, Verrier M, et al. Health care utilization in non-traumatic and traumatic spinal cord injury: a population-based study. Spinal Cord. 2009;48(1):45-50.

60. Ahacic K, Kåreholt I. Prevalence of musculoskeletal pain in the general Swedish population from 1968 to 2002: Age, period, and cohort patterns. Pain. 2010;151(1):206-14.

61. Torrance N, Smith BH, Bennett MI, Lee AJ. The Epidemiology of Chronic Pain of Predominantly Neuropathic Origin. Results From a General Population Survey. The Journal of Pain. 2006;7(4):281-9.

62. Gwak YS, Hulsebosch CE. Neuronal hyperexcitability: a substrate for central neuropathic pain after spinal cord injury. Curr Pain Headache Rep. 2011;15(3):215-22.

63. Wasner G, Lee BB, Engel S, McLachlan E. Residual spinothalamic tract pathways predict development of central pain after spinal cord injury. Brain. 2008;131(Pt 9):2387-400.