**Title:** Neuropathic pain after surgery for major trauma to the lower limb: prevalence, predictors and association with pain severity, disability and quality of life in the UK WHiST trial

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**Ethical review statement**

No ethical approval was sought as this was an analysis of an established dataset and was within the permission of the use of the date from the original ethics approval.

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**Abstract**

**Aims**

To identify the prevalence of neuropathic pain after surgery for lower limb fracture, to assess associations with pain severity, quality of life and disability, and to determine baseline predictors of chronic neuropathic pain, at three and at six months post-injury.

**Patients and Methods**

Secondary analysis of a UK multicentre randomised controlled trial (WHiST) dataset including adults aged 16 years or over following surgery for major trauma to the lower limb. The trial recruited 1547 participants from 24 trauma centres. Neuropathic pain was measured at three and six months using the Doleur Neuropathique Questionnaire (DN4); 933 participants provided DN4 for at least one timepoint. Physical disability (Disability Rating Index; DRI, 0-100) and health-related quality-of-life (EQ-5D-5L) were measured. Candidate predictors of neuropathic pain included sex, age, BMI, injury mechanism, concurrent injury, diabetes, smoking, alcohol, analgesia use pre-injury, index surgery location, fixation type, Injury Severity Score, open injury, and wound care.

**Results**

Participants were median age 51 years (IQR 35 to 64). At three and six months post-injury respectively, 32% (222/702) and 30% (234/787) had neuropathic pain, 53% (413/787) and 56% (396/702) had chronic pain without neuropathic characteristics, the remainder were pain-free. Pain severity was higher amongst those with neuropathic pain. Linear regression analyses found that those with neuropathic pain at 6 months post-injury had more physical disability (DRI adjusted mean difference at 11.49 [95%CI:7.84, 15.14, $p<0.001$) and poorer quality of life (EQ-5D utility -0.15[95%CI:-0.19, -0.11], $p<0.001$) compared to those without neuropathic characteristics. Logistic regression identified that prognostic factors of younger age, current smoker, below knee fracture, concurrent injuries and regular analgesia pre-injury, were associated with higher odds of post-injury neuropathic pain.

**Conclusion**

Pain with neuropathic characteristics is common after lower limb fracture surgery and persists to six months post-injury. Persistent neuropathic pain is associated with substantially poorer recovery. Further attention to identify neuropathic pain after lower limb injury, predicting patients at risk, and targeting interventions, is indicated.

**Clinical relevance of paper:**

- The Wound Healing in Surgical Trauma (WHiST) trial is one of the largest cohorts of major trauma in the UK with neuropathic pain captured over multiple timepoints
- Pain with neuropathic characteristics was common, affecting approximately one in three participants in the six months after surgery for a lower limb fracture and, when compared to those with non-neuropathic pain, was associated with greater pain severity, and poorer outcomes of physical disability and quality of life
- Identification and appropriate management of neuropathic pain is required to support patients that develop these chronic post-injury pain problems

**Introduction**

Persistent pain following surgical treatment of trauma to the lower limb is common.[1, 2] Post-traumatic pain is considered chronic when it persists for at least three months after initial tissue injury, either due to trauma or surgery.[3] Patients sustaining lower limb fractures report severe, persistent and disabling pain well after the acute healing phase,[4] that cannot be explained by simple mechanical pain mechanisms from peripheral nociception. However, there has been limited investigation into the prevalence and impact of chronic neuropathic pain in this patient group. The disability associated with persistent pain has important socioeconomic consequences as traumatic injury largely affects adults of working age.

Neuropathic pain is defined by the International Association for the Study of Pain (IASP) as 'pain arising as a direct consequence of a lesion or disease affecting the somatosensory system'.[5] While this definition encompasses central and peripheral nervous system lesions, surgical treatment of major trauma to the lower limb has the potential to impact upon/damage the peripheral nerve fibres (Aβ, Aδ and C fibres).[6] Traction to the nerve during injury or compression from swelling, implants, and external supports are all potential mechanisms of further aggravating peripheral nerve injury.

Neuropathic pain characteristics are distinct from nociceptive pain as the patient experiences dysesthesias, such as burning and electrical sensations, and can experience pain from a stimulus that is not usually painful (allodynia). A clinically obvious motor or sensory deficit in peripheral nerve function is not required for neuropathic pain to develop.[5] Conversely, patients that have a major deficit of peripheral nerve function do not necessarily always develop neuropathic pain. Given the scale and nature of the problems of pain after musculoskeletal trauma surgery,[7] we aimed to investigate the burden and impact of chronic pain with neuropathic characteristics in a large cohort of participants from a multicentre randomised controlled trial (RCT) recruited from across the UK. The Wound Healing in Surgery for Trauma (WHIST) trial recorded pain data as secondary outcomes. The aims of this study were to:

1. assess prevalence of chronic pain with neuropathic characteristics after lower limb fracture surgery from three to six months from injury;
2. examine associations between neuropathic pain and pain severity, quality of life and disability;
3. explore risk factors associated with chronic neuropathic pain characteristics after lower limb fracture surgery.

## Patients and Methods

### Design

A secondary analysis of the UK WHiST trial cohort[8] was conducted. The WHiST multicentre pragmatic RCT included 1547 adults (aged 16 years or over) who had surgical treatment for major trauma to the lower limb, recruited from 24 major trauma centres across the UK. Recruitment was from July 2016 to April 2018, with participant follow-up to December 2018. The trial compared interventions of incisional negative pressure wound therapy (NPWT) to standard wound dressing not involving negative pressure on outcomes of deep surgical site infection. The full trial results have been published elsewhere.[8, 9]

### Pain assessment

Patient-reported pain severity was measured on an 11-point numerical rating scale (NRS) (from 0 - no pain to 10 – pain as bad as you can imagine) at three and six months post-injury. Presence of chronic pain with neuropathic characteristics (hereafter referred to as "neuropathic pain") after surgery was measured at three and six months post-randomisation using the Doleur Neuropathique Questionnaire (DN4).[10] The DN4 is a validated neuropathic pain screening tool recommended by IASP.[11] We used the self-administered 7-item DN4 screening tool suitable for inclusion within postal questionnaires.[12] Scores range from 0 to 7, where a score of ≥3 indicates neuropathic pain (coded as DN4 positive).[10] Participants that reported any pain on the NRS (>0/10) with DN4 scores lower than 3 (DN4 negative) were classified as having chronic pain without neuropathic characteristics ("non-neuropathic pain"), and those who were DN4 negative and scored zero on the NRS were classified as "pain-free".

The DN4 was added to the trial after recruitment had commenced and was therefore completed at three and/or six months post-randomisation for 933/1547 (60.3%) of trial participants. There were 701 participants with completed DN4 status at three months, and 781 participants with completed DN4 status at six months. Baseline sociodemographic characteristics of those with known DN4 status at three and/or six months were compared with those of the whole trial population to establish whether this group were representative of the recruited WHIST population. We compared demographic and clinical characteristics and other potential predictors by the presence or otherwise of neuropathic pain characteristics (listed below).

### Physical disability and quality of life outcomes

Physical disability was measured using the Disability Rating Index, a self-reported, 12-item visual analogue scale (VAS) questionnaire (range 0–100, higher scores indicate more disability).[13] Health-related quality of life was measured using the EuroQol EQ-5D-5L, a health status classification system which was used to calculate multi-attribute utility scores (range –0.594 to 1, 0 equating to death, higher scores indicate better quality of life).[14]

**Candidate predictors of chronic pain with neuropathic characteristics**

The following baseline variables were explored as potential predictors for chronic neuropathic pain based on previous literature[15] and clinical rationale**:** (i) sex (male or female); (ii) age (continuous); (iii) Body Mass Index [BMI](continuous); (iv) mechanism of injury (high/low energy); (v) other injury in addition to index major trauma fracture (yes/no); (vi) diabetes (yes/no); (vii) current smoker (yes/no); (viii) alcohol (0-14 units or >14 units); (ix) regular analgesia use pre-injury (yes/no); (x) index surgical wound location related to major trauma fracture (acetabulum/femur or patella/tibia, fibula or foot); (xi) fixation type (nail/plate and screws/arthroplasty/other); (xii) Injury Severity Score at presentation [ISS] (<15/≥16; note: an ISS score of exactly 14-5 is not possible); (xiii) open injury (open/closed); and, (xiv) wound care (NPWT/standard wound dressings).

**Statistical Analysis**

Pain status (pain-free, non-neuropathic pain and neuropathic pain) was summarised separately at three and six months. Pain severity (NRS) and DN4 scores were summarised using medians and interquartile ranges (IQRs) and means and standard deviations (SD) by time point. The number and proportion of participants who reported neuropathic pain by time point was summarised; mean (SD) DRI and EQ-5D-5L utility scores were summarized by pain status. Linear regression models were used to compare disability and quality of life scores across the three groups (pain free, non-neuropathic pain, neuropathic pain) for each outcome separately at each time point. Both unadjusted models and models adjusted for allocated trial intervention in the original RCT (standard wound dressings/NPWT), stratification factors, sex, age at randomisation and baseline scores were fitted, consistent with the main analyses of the WHiST trial.

We assessed for collinearity using pairwise correlations and confirmed that none of the candidate predictors were highly correlated with one another. Logistic regression was used to examine potential baseline predictors of the presence of chronic neuropathic pain (DN4≥3) over time. First, potentially important characteristics were identified using univariate logistic regression for each candidate predictor in turn, using a cut-off of

p<0.15. Those characteristics which were identified as individually important were then jointly investigated to build a suitable prognostic risk model using stepwise methods. The probability for removal used was p=0.20 and the probability for addition p=0.05. For each model, the allocated trial treatment was included regardless of statistical significance. This analysis was repeated separately to look at predictors of chronic neuropathic pain at three and six months. In addition, we completed analyses comparing participants with neuropathic pain at either timepoint to those considered to be either pain-free or with non-neuropathic pain .

The use of data from the WHiST trial for these secondary analyses were permitted under the informed consent and research ethics committee approvals for the main trial.[8]

**Results**

The baseline demographic and clinical characteristics of 933 participants completing DN4 scores were similar to the full trial cohort (Table 1). This was anticipated as the main predictor of DN4 completion was timing of recruitment, whereby the DN4 questionnaire was incorporated after the trial had started. Therefore, we did not expect time trends related to participant or surgical characteristics. For participants providing DN4 scores (n=933), median age was 51 years (IQR 35 to 64), 383 (41%) were female, 377 (41%) were full-time employed, and 743 (80%) had an Injury Severity Score (ISS) < 15.

*Prevalence of chronic neuropathic pain after lower limb fracture surgery*

At three months, 32% of participants (222/702) had chronic neuropathic pain, a further 56% (396/702) had chronic non-neuropathic pain and the remainder of participants (84/702; 12%) were pain-free (Table 2). Mean pain severity scores were higher in those with neuropathic pain than in those with non-neuropathic pain (mean NRS 5.2 versus mean 3.6 at three months). At six months, the proportion of participants with neuropathic pain (30%; 234/787) and non-neuropathic pain (53%; 413/787) had each decreased slightly with a corresponding increase in the proportion of participants reporting being pain-free (18%; 140/787). Mean pain severity remained higher in those reporting chronic neuropathic characteristics compared to those without (mean NRS 4.9 versus mean 3.3).

Comparison of reports of chronic neuropathic pain at three and six months are presented in Table 3. Of those participants completing DN4 data at both time points, 11% (104/933) reported chronic neuropathic pain at both three and six months, 6% reported chronic neuropathic pain at three months (52/933) only or six months

(57/933) only, but had missing data for the other time point. 66 of the 222 participants that reported chronic neuropathic pain at three months (30%) had resolution by six months, whilst 73 of the 479 participants that did not have chronic neuropathic pain at three months (15%) reported new, late onset, chronic neuropathic pain at six months.

*Association between chronic neuropathic pain, quality of life and disability*

DRI scores at three and six months by pain status (pain-free, non-neuropathic pain, neuropathic pain) are provided in Table 4. These show that the DRI scores were significantly higher, both clinically and statistically, indicating greater physical disability amongst those reporting chronic neuropathic pain at each time point (Table 4) than for those with either non-neuropathic pain or those who were pain-free (six month DRI adjusted mean difference [MD] 11.49 [95%CI 7.84, 15.14], p<0.001 vs. non-neuropathic pain, MD 18.49 [95%CI 13.67, 23.31], p<0.001 vs. pain-free). Results for quality of life utility scores showed a similar pattern (Table 4), suggesting poorer quality of life amongst those reporting chronic neuropathic pain compared to those with either non-neuropathic pain or pain-free (six month EQ-5D-5L utility adjusted MD -0.15 (95%CI -0.19 to -0.11), p<0.001 vs. non-neuropathic pain, MD -0.24 (95%CI -0.30, -0.19), p<0.001 vs. pain-free).

*Predictors of chronic neuropathic pain after lower limb fracture surgery*

Based on the univariate analyses, the following variables were identified as potential predictors of chronic neuropathic pain after injury (Table 5):

- Male sex, younger age, high energy injury mechanisms, having concurrent injuries, being a smoker, index surgery below the knee, higher ISS score, and open injury were all identified as risk factors associated with chronic neuropathic pain at three months;
- Younger age, high energy injury mechanism, having concurrent injuries, being a smoker, index surgery below the knee, higher ISS score, and open injury were all identified as risk factors for chronic neuropathic pain at six months;
- Younger age, injury mechanism, concurrent injury, being a smoker, regular use of analgesia before injury, index surgery below the knee, and higher ISS score were all identified as risk factors associated with chronic neuropathic pain at both three and six months after injury.

Odds ratios (ORs) and associated 95% confidence intervals (CIs) from the final fitted models selected using stepwise methods are presented in Table 6. The models considering chronic neuropathic pain at three or six months separately were similar; with being a current smoker (vs. not), an injury to the lower leg (tibia, fibula

or foot vs. femur or patella) and having a severe traumatic injury (ISS of >16 vs. <15) and younger age all increasing the odds of having chronic neuropathic pain. When considering those with chronic neuropathic pain at either three or six months, being a current smoker, younger age, an injury to the lower leg and having other concurrent injuries (vs. none) and taking regular analgesia pre-injury (vs. none) were also associated with higher odds of chronic neuropathic pain.

**Discussion**

In this multicentre UK study recruiting patients with major trauma to the lower limb requiring surgical intervention, we found that approximately one in three patients reported chronic pain with neuropathic characteristics over six months follow-up. Chronic neuropathic pain was associated with greater pain severity, greater physical disability and lower quality of life when compared to participants with non-neuropathic chronic pain and those who were pain-free.

Contrary to the expectation that pain intensity and character gradually improves after traumatic injury, approximately one in ten participants developed late onset chronic neuropathic pain, thus were pain-free or had few neuropathic characteristics at three months but these developed by six months post-injury. This has been reported after other surgical conditions, including after breast cancer surgery, whereby late onset pain was reported by 15% of women followed up for six years post-treatment.[16] Very few studies have prospectively examined the frequency and burden of chronic neuropathic pain after traumatic injury to the lower limb. The extent of neuropathic pain characteristics in the WHiST trial cohort were consistent with one small Dutch observational study, whereby 61/271 (23%) respondents reported chronic neuropathic pain in a follow-up survey of 527 patients contacted six years after internal fixation of ankle fractures.[17] The clinical importance of the prevalence of chronic neuropathic pain is emphasised by the association with the notably greater disability and worse quality of life identified in our study. The high prevalence of postal screening for chronic neuropathic pain in post-trauma cohorts contrasts with the relatively low rates of clinically diagnosed peripheral nerve injuries in lower limb trauma patients, for example, 1.8% prevlance reported in a registry cohort of 60,422 patients in central Europe based on hospital diagnostic coding.[18]

Important prognostic risk factors for chronic pain with neuropathic characteristics after injury identified in our study included being of younger age, a current smoker, having an injury to the lower leg involving the tibia, fibula or foot, concurrent injuries and the use of regular analgesia before the traumatic injury. The use of regular analgesics pre-injury is a likely indicator of an existing chronic pain condition pre-injury. Chronic preoperative pain is a known risk factor for chronic postoperative pain, being reported in studies examining

different surgical procedures.[19] Although causal associations cannot be inferred from this analysis, these identified clinical prognostic factors may be important for further work determining which patients are at greater risk of developing persistent neuropathic pain and therefore may require further targeted monitoring and pain management. Screening around time of injury and during the acute postoperative period may also potentially identify those at greatest risk of poorer long-term outcome.

The prevalence of chronic pain with neuropathic characteristics following surgical treatment of major trauma to the lower limb, and the association with poor outcome in terms of ongoing disability and poorer quality of life, are important considerations for clinical practice. First-line medications recommended in the National Institute for Health and Care Excellence (NICE) guidelines on pharmacological management of neuropathic pain are amitriptyline, duloxetine, gabapentin or pregabalin, rather that opioids (with the exception of Tramadol for acute short-term rescue therapy).[20] Non-pharmacological management including physical and psychological therapies are also highlighted in these guidelines, indicating the multifactorial approaches that may need to be considered when supporting people with complex chronic pain problems. There is uncertainty about which pain management strategies are optimal specifically in the post-trauma population, an important area for further research. An under-recognition of neuropathic pain in this patient group may be contributing to sub-optimal pain management. Persistent opioid use has been identified in musculoskeletal trauma patients.[21, 22] There may be a risk of under-recognition of chronic neuropathic pain within fracture services, for those patients where there is not an obvious loss of peripheral nerve sensory or motor function loss. Furthermore, as screening for neuropathic pain after surgical treatment of major trauma to the lower limb is not common place, also routine clinical assessment stops at four to six months follow-up, later manifestations of neuropathic pain may only present in primary care settings or to secondary care pain clinics.

The WHiST trial is one of the largest cohorts of major trauma in the UK to date with neuropathic pain data captured over multiple timepoints. Using this clinical trial dataset was efficient as the resources required to recruit and carefully follow up such a large cohort would have been otherwise unfeasible in the context of the limited evidence available to date. Another strength of our study is that our timing of follow-up adheres to international pain guidance for determining pain chronicity (three months and longer).[3] Limitations include the fact that the choice of potential prognostic factors were restricted to those collected in the trial. Also, cohorts from RCTs can be more selective than the wider clinical population. However, the WHiST trial was a large, multicentre pragmatic study recruiting 1547 patients from the entire Major Trauma Network in the UK thus we are confident that our findings are representative and also reflect contemporary surgical care of lower limb injury. The use of a self-reported screening postal questionnaire without detailed clinical assessment is a

further limitation of this study. The full DN4 questionnaire includes three clinical assessment tests to further establish a diagnosis of clinically confirmed neuropathic pain. The design of the trial did not allow for detailed objective assessment of peripheral nerve function. Whilst that would be ideal to improve diagnostic accuracy, population screening for neuropathic pain in larger cohorts is more feasible with validated, self-reported questionnaires. There is good evidence that the DN4 self-report version has excellent sensitivity and specificity, when compared to the full version with clinical assessment, with the validated cut-offs having a sensitivity of 82% and specificity of 86%, similar to the clinician administered version.[12]

Our study has shown that chronic pain with neuropathic characteristics is common after lower limb fracture surgery, and persists in approximately one in three patients up to six months. A subset of people develop new, late onset chronic neuropathic pain. Chronic pain with neuropathic characteristics is associated with greater pain severity, and substantially poorer recovery in terms of disability and quality of life. Further attention to identifying patients with chronic neuropathic pain, predicting which patients are at risk, and targeting interventions for neuropathic pain after major trauma injury, is indicated.

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**Table 1:** Comparison of baseline demographic and clinical characteristics of trial participants by DN4 completion at 3 and 6 months

| | All participants (n=1547) | Provide DN4 at 3m or 6m (n=933) | Did not provide DN4 at 3m or 6m (n=614) |
|---|---|---|---|
| **ISS < 15**[1] | 1207 (78.0%) | 743 (79.6%) | 464 (75.6%) |
| **Closed injury**[1] | 1259 (81.4%) | 755 (80.9%) | 504 (82.1%) |
| **NPWT**[1] | 784 (50.7%) | 490 (52.5%) | 294 (47.9%) |
| **Female**[1] | 583 (37.7%) | 383 (41.1%) | 200 (32.6%) |
| **Age (years)**[2] | 50.1 (31.7, 63.7) | 51.2 (34.7, 63.8) | 46.9 (27.7, 63.6) |
| **Left leg**[1] | 758 (49.3%) | 460 (49.3%) | 298 (49.3%) |
| **Location**[1] | | | |
| ***Femur/Patella*** | 596 (38.7%) | 344 (36.9%) | 252 (41.5%) |
| ***Hip/Acetabulum*** | 325 (21.1%) | 192 (20.6%) | 133 (21.9%) |
| ***Tibia/Fibula/Foot*** | 619 (40.2%) | 397 (42.6%) | 222 (36.6%) |
| **High energy fall**[1] | 1001 (65.0%) | 604 (64.7%) | 397 (65.5%) |
| **Fixation type**[1] | | | |
| ***Nails*** | 537 (34.9%) | 329 (35.3%) | 208 (34.3%) |
| ***Plate/screws*** | 824 (53.6%) | 505 (54.2%) | 319 (52.6%) |
| ***Arthroplasty*** | 103 (6.7%) | 63 (6.8%) | 40 (6.6%) |
| ***Other*** | 74 (4.8%) | 34 (3.7%) | 40 (6.6%) |
| **Other injuries**[1] | 881 (57.2%) | 475 (50.9%) | 406 (66.9%) |
| **Analgesia pre-injury**[1] | 288 (19.0%) | 158 (17.0%) | 130 (22.2%) |
| **BMI**[2] | 25.6 (22.7, 29.4) | 25.5 (22.7, 29.3) | 25.6 (22.7, 29.5) |
| **Diabetes**[1] | 148 (9.7%) | 84 (9.0%) | 64 (10.8%) |
| **Smoker**[1] | 434 (28.9%) | 242 (26.0%) | 192 (33.7%) |
| **Alcohol consumption**[1] | | | |
| ***0-7 units*** | 1021 (68.7%) | 636 (68.3%) | 385 (69.4%) |
| ***8-14 units*** | 215 (14.5%) | 138 (14.8%) | 77 (13.9%) |
| ***15-21 units*** | 111 (7.5%) | 73 (7.8%) | 38 (6.8%) |
| ***>21 units*** | 139 (9.4%) | 84 (9.0%) | 55 (9.9%) |
| **White**[1] | 1368 (90.4%) | 854 (91.6%) | 514 (88.3%) |
| **Employment status**[1] | | | |
| ***Full-time employed*** | 597 (40.2%) | 377 (40.6%) | 220 (39.6%) |
| ***Full-time student*** | 41 (2.8%) | 25 (2.7%) | 16 (2.9%) |
| ***Part-time employed*** | 109 (7.3%) | 71 (7.6%) | 38 (6.8%) |
| ***Retired/Look after home/inactive*** | 407 (27.4%) | 250 (26.9%) | 157 (28.2%) |
| ***Self-employed*** | 147 (9.9%) | 98 (10.5%) | 49 (8.8%) |
| ***Unemployed*** | 172 (11.6%) | 96 (10.3%) | 76 (13.7%) |
| ***Unpaid work*** | 12 (0.8%) | 12 (1.3%) | 0 (0.0%) |

[1] *Summaries are n (%)*

[2] *Summaries are median (IQR)*

**Table 2:** Chronic pain status, pain score and DN4 scores at three months and at six months

| | No pain[1] | Non-neuropathic pain[2] | Neuropathic pain[3] |
|---|---|---|---|
| **3 months[4]** | 84/702 (12.0%) | 396/702 (56.4%) | 222/702 (31.6%) |
| ***Pain NRS[5]*** | NA | 3 (2, 5), 3.64 (2.25) | 5 (3, 7), 5.21 (2.47) |
| ***DN4 score[5]*** | 0 (0, 0), 0.24 (0.55) | 1 (0, 2), 0.99 (0.83) | 4 (3, 5), 4.35 (1.28) |
| **6 months[4]** | 140/787 (17.8%) | 413/787 (52.5%) | 234/787 (29.7%) |
| ***Pain NRS[5]*** | NA | 3 (1, 4), 3.26 (2.18) | 5 (3, 7), 4.89 (2.55) |
| ***DN4 score[5]*** | 0 (0, 0), 0.29 (0.60) | 1 (0, 2), 1.03 (0.82) | 4 (3, 5), 4.17 (1.18) |

*NRS: Numerical Rating Scale*

*[1] Participants are defined as pain-free if NRS = 0 and DN4 < 3 or missing*

*[2] Participants are defined as having non-neuropathic pain if NRS> 0 and DN4 < 3*

*[3] Participants are defined as having neuropathic pain if they report DN4 3+*

*[4] Summaries are n/available data (%)*

*[5] Summaries are median (IQR), mean (SD)*

**Table 3:** Pattern of DN4 scores at three and six months by neuropathic pain status

| Neuropathic pain at 3m | Neuropathic pain at 6m | n (%) | DN4 scores at 3m[1] | DN4 scores at 6m[1] |
|---|---|---|---|---|
| Yes | Yes | 104/933 (11.1%) | 4 (3, 6), 4.54 (1.35) | 4 (4, 5.5), 4.53 (1.26) |
| No | No | 306/933 (32.8%) | 1 (0, 2), 0.80 (0.82) | 1 (0, 2), 0.80 (0.83) |
| Yes | No | 66/933 (7.1%) | 4 (3, 5), 3.88 (1.05) | 1 (0, 2), 1.14 (0.88) |
| No | Yes | 73/933 (7.8%) | 1 (0, 2), 1.16 (0.85) | 3 (3, 4), 3.67 (0.91) |
| Yes | Missing | 52/933 (5.6%) | 4 (3.5, 5.5), 4.58 (1.29) | NA |
| No | Missing | 100/933 (10.7%) | 1 (0, 2), 0.83 (0.83) | NA |
| Missing | Yes | 57/933 (6.1%) | NA | 4 (3, 5), 4.14 (1.09) |
| Missing | No | 175/933 (18.8%) | NA | 1 (0, 2), 0.82 (0.82) |

[1] *DN4 scores range from 0 to 7. Summaries are median (IQR), mean (SD).*

**Table 4:** DRI and EQ-5D utility scores by neuropathic pain status at 3 and 6 months

| | Pain-free[1] | Non-neuropathic pain[1] | Neuropathic pain[1] | | Unadj. MD (95% CI) | Adj. MD (95% CI) , p-value[2] |
|---|---|---|---|---|---|---|
| ***3 months*** | | | | | | |
| **DRI[3]** | 44.16 (26.74), 80 | 49.11 (23.19), 376 | 57.95 (22.14), 216 | Non-neuropathic pain vs. Pain-free: | 4.95 (-0.68, 10.59) | 5.07 (-0.21, 10.35), p=0.060 |
| | | | | Neuropathic pain vs. Pain-free: | 13.79 (7.80, 19.78) | 14.69 (9.01, 20.36), p<0.001 |
| | | | | Neuropathic pain vs. Non-neuropathic pain: | 8.84 (4.93, 12.75) | 9.61 (5.96, 13.26), p<0.001 |
| **EQ5D utility[4]** | 0.65 (0.32), 84 | 0.53 (0.26), 390 | 0.38 (0.32), 220 | Non-neuropathic pain vs. Pain-free: | -0.12 (-0.19, -0.05) | -0.12 (-0.19, -0.06), p<0.001 |
| | | | | Neuropathic pain vs. Pain-free: | -0.27 (-0.34, -0.20) | -0.28 (-0.35, -0.21), p<0.001 |
| | | | | Neuropathic pain vs. Non-neuropathic pain: | -0.15 (-0.20, -0.10) | -0.16 (-0.20, -0.11), p<0.001 |
| ***6 months*** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **DRI**[3] | 32.21 (27.87), 130 | 38.62 (24.70), 403 | 50.22 (24.06), 230 | Non-neuropathic pain vs. Pain-free: | 6.41 (1.45, 11.38) | 7.00 (2.59, 11.41), p=0.002 |
| | | | | Neuropathic pain vs. Pain-free: | 18.01 (12.61, 23.41) | 18.49 (13.67, 23.31), p<0.001 |
| | | | | Neuropathic pain vs. Non-neuropathic pain: | 11.60 (7.53, 15.66) | 11.49 (7.84, 15.14), p<0.001 |
| **EQ5D utility**[4] | 0.68 (0.33), 137 | 0.61 (0.24), 408 | 0.46 (0.30), 232 | Non-neuropathic pain vs. Pain-free: | -0.08 (-0.13, -0.02) | -0.09 (-0.14, -0.04), p<0.001 |
| | | | | Neuropathic pain vs. Pain-free: | -0.23 (-0.29, -0.17) | -0.24 (-0.30, -0.19), p<0.001 |
| | | | | Neuropathic pain vs. Non-neuropathic pain: | -0.15 (-0.19, -0.10) | -0.15 (-0.19, -0.11), p<0.001 |

[1] *Summaries are mean (SD), N*

[2] *Adjusted for allocated treatment, minimisation factors (ISS and wound closure as fixed effects and centre as a random effect), sex, age at randomisation and baseline scores.*

[3] *DRI scores range from 0 to 100 with higher scores indicating greater physical disability*

[4] *EQ-5D-5L utility scores range from -0.594 to 1 with higher scores indicating better quality of life*

**Table 5:** Univariate predictors of neuropathic pain at three and six months, p-values

| | Neuropathic pain at 3m (n=701) | Neuropathic pain at 6m (n=781) | Neuropathic painat 3m or 6m (n=549) |
|---|---|---|---|
| **Male vs. female** | 0.04 | 0.54 | 0.62 |
| **Age (years)** | <0.001 | <0.001 | <0.001 |
| **BMI** | 0.39 | 0.52 | 0.77 |
| **Low vs. High energy injury** | 0.03 | 0.002 | 0.007 |
| **Concurrent injuries vs. none** | 0.06 | 0.02 | 0.01 |
| **Diabetic vs. non-diabetic** | 0.23 | 0.46 | 0.43 |
| **Smoker vs. non-smoker** | <0.001 | <0.001 | 0.03 |
| **>14 units alcohol vs. 0-14 units alcohol/week** | 0.18 | 0.49 | 0.65 |
| **Regular analgesia before injury vs. not** | 0.47 | 0.22 | 0.13 |
| **Location of injury (reference category = femur/patella)** | | | |
| ***Hip/acetabulum*** | 0.21 | 0.87 | 0.75 |
| ***Tibia/Fibula/foot*** | 0.001 | <0.001 | 0.001 |
| **Fixation type (reference category = nails)** | | | |
| ***Plate/screws*** | 0.99 | 0.53 | 0.81 |
| ***Arthroplasty*** | 0.23 | 0.97 | 0.71 |
| ***Other*** | 0.19 | 0.82 | 0.88 |
| **ISS≥16 vs. ISS<15** | 0.01 | 0.02 | 0.08 |
| **Open vs. closed wound** | 0.05 | 0.13 | 0.62 |
| **NPWT vs. Usual care** | 0.79 | 0.27 | 0.34 |
| **EQ-5D utility score** | 0.16 | 0.96 | 0.87 |

**Table 6:** Prognostic models for pain (defined as DN4 positive) at 3 and 6 months, odds ratios and 95% CIs

| | Neuropathic pain at 3m OR (95% CI ) | Neuropathic pain at 6m OR (95%CI) | Neuropathic pain at 3m or 6m OR (95%CI) |
|---|---|---|---|
| **N participants** | 701 | 781 | 549 |
| **NPWT vs. Usual care** | 0.97 (0.70 ,1.35) | 0.87 (0.64 ,1.20) | 0.84 (0.59 ,1.19) |
| **Smoker vs. non-smoker** | 1.75 (1.21 ,2.53) | 1.76 (1.22 ,2.54) | 1.36 (0.88 ,2.10) |
| **Age (years)** | 0.985 (0.976 ,0.994) | 0.991 (0.982 ,1.000) | 0.981 (0.970 ,0.991) |
| **Location (reference category = femur/patella)** | | | |
| ***Hip/acetabulum*** | 1.39 (0.87, 2.24) | 1.02 (0.64, 1.63) | 1.15 (0.70, 1.83) |
| ***Tibia/fibula/foot*** | 1.77 (1.21, 2.60) | 2.27 (1.57, 3.28) | 1.80 (1.20, 2.70) |
| **ISS≥16 vs. ISS<15** | 1.53 (0.29, 1.06) | 1.57 (1.06 ,2.33) | NA |
| **Concurrent injuries vs. not** | NA | NA | 1.53 (1.07 ,2.19) |
| **Analgesia use pre-injury vs. not** | NA | NA | 2.35 (1.41 ,3.93) |
| **$R^2$** | 0.050 | 0.054 | 0.058 |